The Rabbit

The laboratory rabbit is derived from the domestic rabbit, *Oryctolagus cuniculus*, and belongs to the order *lagomorpha.* The commonest strain seen in the laboratory is the New Zealand white, a large outbred rabbit. The smaller Dutch rabbit may also be encountered, and some inbred strains are available. Rabbits with coloured coats may be identified readily by their appearance.

Behaviour

Wild rabbits are crepuscular or nocturnal, becoming active and emerging from their burrows to feed at dusk or during the night. In the laboratory, periods of activity are seen throughout the day and night. Rabbits are social animals which are able to utilise a complex, three dimensional environment. If given sufficient space, domestic and laboratory rabbits will exhibit the full range of behaviours seen in their wild ancestors, including territory marking (chinning), climbing up to a good vantage point, exploratory and tunnelling behaviour, social activity and aggression. Aggressive behaviour is seen most in breeding and pubertal animals, and adult males. Males are most aggressive when competing for food, territory or females. It is usual for them to be separated from 10 weeks of age to prevent fighting.

Housing

It is essential to provide sufficient room for rabbits to perform the majority of their natural locomotory behaviours to prevent skeletal problems. Cages designed to hold rabbits singly are unlikely to provide enough room to allow the rabbit to perform natural behaviour, resulting in prolonged periods of inactivity and increased stereotypic behaviour. This may also lead to hypoplasia of bone tissue and osteoporosis, with the increased risk of fractures and nerve damage leading to cage paralysis. Single caging should be used only where group housing is inappropriate, such as for adult males or if an animal needs to be isolated for measurement of food and water intake. Pair housing in large cages may be an acceptable alternative in many circumstances.

Rabbits like to stretch out, and stand on their hind legs or climb onto ledges to gain a better view. Cages should allow the rabbit to stretch out in at least one direction and be tall enough for the animal to stand or even to house a box they can sit on. Environmental enrichment can be provided by giving hay, chew sticks or cardboard boxes to play with, and animals can be taken to exercise areas for short periods. Rabbits should always be housed where they can see other rabbits. Grid floors are generally provided if rabbits are kept in cages, and should be carefully designed to allow urine and faeces to drain without predisposing to sore hocks (pododermatitis). Trays beneath the grid should be lined with an absorbent pad to lock in the ammonia. Otherwise, high ammonia levels predispose the animal to the development of respiratory disease.

Rabbits thrive when group housed in floor pens with high sides made from smooth impervious material. The incidence of aggressive behaviour depends on many factors, including strain (Dutch rabbits are more aggressive than New Zealand whites), sex, age and weight, pen size and construction, the relatedness of the individuals, and the proximity of other rabbits of the opposite sex. Animals to be group housed should be of similar weights, and it is important to provide ample dividers, cardboard boxes or large tubes within

the pen so nervous or frightened animals have bolt holes where they can hide from aggressive conspecifics. Continued monitoring of newly formed groups for excessive aggression is recommended. Breeding females, siblings or groups put together at weaning, a doe and litter, single sex groups of newly weaned animals, and stable groups of animals on procedure can be successfully housed together.

Rabbits communicate using olfactory cues, so this must be taken into consideration when designing rabbit housing. Rabbits will feel secure and confident if surrounded by their own smell, and are disturbed by excessive cleaning or the use of strong smelling disinfectants etc. Floor pens should be deeply lined with bedding material which does not have a strong smell. In these circumstances, rabbits will urinate and defaecate in latrine areas which can be cleaned frequently, but faecal matter will still become spread throughout the pen. Over-frequent cleaning however will simply result in increased territory marking and upset the animals' confidence.

Group housing in pens has many advantages over traditional single cages. The improved welfare of group housed animals manifests in improved physical and psychological well-being. Animals can exhibit natural behaviour and interact socially which reduces stereotypy, they tend to be calmer and more docile, the increased opportunity for locomotory behaviour reduces osteoporosis and cage paralysis, and improved ventilation leads to fewer respiratory problems. In addition, floor pens are more economic to purchase and maintain than conventional cages. On the other hand, there may be increased aggressive behaviour and stress particularly in unstable and incompatible groups, identification and treatment of individuals is more difficult, and exposure of staff to soiled bedding may increase the risks of allergy.

Rabbit housing should be cleaned at least weekly. They produce copious, turbid urine, which may be yellow to dark red, due to the presence of a varying quantity of porphyrins. The urine tends to leave scale on the litter trays due to the calcium content, and so they may need to be cleaned with acidic agents. Absorbent tray liners help to lock in ammonia and to reduce the scale problem.

Feeding

Rabbits have evolved to survive on a diet with a high fibre content and low nutritional value, and in the wild will spend much of the time nibbling on vegetation. They need a diet high in fibre, and low in fat and soluble carbohydrate. Although much fibre remains undigested, it is required for bulk and reduces the incidence of hairballs and diarrhoea. Rabbits are coprophagic, and this is an important part of their digestion: inappropriate diets affect microbial digestion in the caecum and predispose to diarrhoea. A diet with 12-22 per cent fibre, and 12 per cent protein for maintenance or 15-17 per cent for growth is recommended. Ad lib feeding for rabbits in cages may sometimes result in obesity. Overeating may be a stereotypic behaviour, and is seldom seen in floor housed rabbits. Providing environmental enrichment and a variety of foodstuffs can reduce this problem. Hay may be given to provide additional fibre. High energy diets are required for breeding rabbits and for the dwarf breeds, with 10,500kJ per kg feed. For maintenance, 8,800kJ per kg is sufficient. **Rabbits need 6-8g of high energy food per 100g bodyweight daily.**

As gut flora play an important part in digestion, changes in diet should be done gradually, over a 4-5 day period, to allow the flora to adapt. Failure to do this will result in diarrhoea or anorexia.

Water

Water should be supplied ad lib, and be fresh and clean. Automatic systems are often used. **Rabbits normally consume 10ml water per 100g bodyweight. Lactating does may drink up to 90ml per 100g bodyweight.** Rabbits have a tendency to play with water bottles, so they should be checked frequently to ensure they are not empty, and that the floor has not become wet.

Environment

Rabbits require temperatures between 16-20^{o}C. Neonates cannot maintain their body temperatures until they are seven days old, so they must be kept in a warm environment. Humidity should be kept between 40-60 per cent. Females require 14-16 hours of light daily, and males 8-10, with or without periods of twilight. Shorter light cycles may result in reduced sexual activity in the autumn. Low intensity light should be provided for albino animals. Rabbits can hear in the ultrasound range, from 2-16kHz and possibly up to 42kHz, so care should be taken not to expose them to excessive ultrasound. Background noise can help to prevent the animals from being startled by sudden noises. Ventilation is particularly important for rabbits. They are susceptible to respiratory diseases, and poor ventilation allows a build up of ammonia which predisposes to these. Draughtless ventilation and efficient tray liners for caged animals, reduce the ammonia level. At least 12-15 air changes per hour should be provided.

Breeding

Females begin breeding at 4½-7 months, males from 6-7 months. Rabbits are induced ovulators, and have no oestrus cycle as such. They are receptive for 7-10 days, then inactive for 1-2 days. Does are also receptive at intervals during pregnancy and lactation. There is some seasonal effect, but if daylength is maintained and particularly if the temperature is high breeding will take place all year. Breeding efficiency falls after 7-11 litters, or 3-4 years. Coitus induces ovulation and results in pregnancy in 75% of does. Gestation lasts 31-32 days. Care should be taken in handling the doe during gestation, as the pregnancy is easily aborted. The doe must have a clean nest box in the last week of gestation. A doe will scatter her young if the nest is dirty, or if it smells of disinfectant. The doe will line her nest with hair. Does usually kitten in the morning. Between 1-22 kits may be born, usually 7-8, depending on the breed. It is rare for them to be eaten by the doe unless there is a deformity or they are dead, but it may also happen if the doe is inexperienced or if there is some environmental disturbance. Does will rarely retrieve their young if they crawl out of the nest, hence the need for a good nest box. Young are only suckled for 5-10 minutes once daily, in the morning, and lactation lasts 6-8 weeks. Hand rearing of rabbits is relatively easy. Does may be rebred shortly after parturition, but more usually are mated after weaning.

Handling

Rabbits are generally docile and amenable, can be readily trained to facilitate the performance of procedures, and rarely bite if handled correctly. There are a number of particular considerations when handling rabbits. The animal should NEVER be lifted by the ears, and the back must be supported at all times, otherwise contractions of the strong spinal muscles during struggling can result in injuries to the spine. Rabbits have powerful hind legs, and the handler must be careful to avoid being kicked or scratched. Before removing a rabbit from a cage or floor pen, orientate the rabbit so it is facing you. Grasp the animal by the scruff, avoiding the ears, and lift the front end. Then you can either slide the free hand beneath the rabbit, placing the thumb and little finger in front of the hind legs to extend them, and then lift the animal, or the free hand can be placed behind the animal's hindquarters and the animal scooped towards you. Once the animal has been lifted clear of the cage or pen, it should be carried held against the chest or resting on the arm with it's head tucked under the armpit, with the scruff securely held and the back and hindquarters supported at all times.

To sex adult rabbits, place the animal on a non-slip surface or support it on your knee. Hold the animal by the scruff and lift the head, scooping the hindquarters under the animal so it sits on its haunches. Whilst still holding the scruff, the free hand can be used to expose the genitalia. Alternatively, the head can be controlled by placing the thumb and third finger each side of the head and the index finger between the ears. The other hand can then be placed under the abdomen, and the rabbit turned over onto the knee for sexing, its back being supported by the forearm.

Pain and stress recognition

A rabbit will often react to painful procedures with stoic acceptance. This may relate to feral behaviour where concealment is important for survival. A rabbit in pain is usually characterised by reduced food and water intake and limited movement. There may be apparent photosensitivity and ocular discharge with protrusion of the third eyelid. Faecal staining of the coat, digestive disturbances and dehydration may also be seen.

Common diseases and health monitoring

Rabbits suffer from very few viral diseases, but myxomatosis, commonly encountered in wild and pet rabbits, and viral haemorrhagic disease of rabbits are both potentially fatal. Vaccines are now available for both of these diseases. Protective clothing and a good standard of hygiene is essential to prevent inadvertent transmission of these diseases to laboratory rabbits. Rabbits suffer from a number of bacterial infections, the most important of which is *Pasteurella multocida*. *Pasteurella* is mainly a respiratory pathogen which can be carried subclinically in the upper respiratory tract, causing problems when the animal is stressed. Signs may vary from sudden death, pneumonia, meningitis, generalised septicaemia, or subcutaneous abscesses to snuffles. Recurrent conjunctivitis caused is common. Treatment may reduce the symptoms of *Pasteurella*, but it will not eradicate it. If this organism is present in a colony, it is essential to maintain adequate environmental conditions particularly humidity, ensure meticulous hygiene, keep the stocking density low, and avoid stress. The stress of scientific procedures often precipitates an outbreak of clinical disease, and if this occurs ideally the colony should be culled and clean animals bought in after fumigation of the room.

Diarrhoea is another common disease problem in rabbits. There are many causes including sudden diet changes, coccidial (intestinal parasite) infestation and infectious causes. Mucoid enteropathy is a common, often fatal, finding in growing rabbits. It seems to be associated with an inadequate level of fibre in the diet (less than 15%) and stress. Inappetance is another commonly encountered problem, associated with environment or diet changes, hairballs, or subclinical diseases. This can cause a rapid loss of condition and should be treated promptly. In general, many of the commonest diseases of rabbits are husbandry related, so it is very important that the diet, housing, environment and general management of rabbits are kept up to a high standard.

Anaesthesia in the rabbit – special considerations

In this species the combination of stress and general anaesthesia can lead to cardiac and respiratory arrest. It is therefore very important to keep both the pre and post operative stresses to the absolute minimum. Premedication prior to induction of anaesthesia is common practice in this species and the following drugs can be used:

Medetomidine 250 ug/kg s.c. This can rapidly be reversed with *atipamezole* 0.2 mg/kg into the ear vein.
Diazepam or *midazolam* 0.5-2 mg/kg i.v. or i.m. produces quite good sedation.
Hypnorm 0.2 ml/kg i.m. produces sedation and analgesia but poor muscle relaxation which lasts for about 20 minutes. Full recovery takes more than an hour unless specific reversal with *naloxone* (0.1 mg/kg i.m.) is used.
Ketamine at 50 mg/kg i.m. produces sedation and immobilisation lasting about 30 minutes.
Xylazine at 3 mg/kg i.m. will produce heavy sedation with some analgesia.

Inhaled agents should not be used for induction of anaesthesia since rabbits find this stressful, and hold their breath and show prolonged periods of apnoea. It is better to induce anaesthesia with an injectable agent and then use inhalational agents for maintenance. Endotracheal intubation is relatively straightforward in rabbits and is preferred to the use of a face mask. The larynx can be sprayed with lignocaine before intubation is attempted to reduce the risk of laryngospasm. Visualisation of the larynx in

the rabbit requires the use of a specialised laryngoscope, but it is also possible to intubate the rabbit without seeing the larynx. The rabbit is placed in sternal recumbency, its head gripped and extended upward. The tongue is pulled gently forwards taking care to bring it out to the side of the teeth so that it is not damaged. The endotracheal tube, lubricated with local anaesthetic gel, is advanced over the tongue towards the larynx. Careful observation of the chest wall will indicate when the rabbit breathes in. The tube should be advanced through the larynx on inspiration.

Rabbits are prone to stasis of the gastrointestinal tract and inappetance following general anaesthesia, and may require supplementary feeding or gut motility stimulants to aid recovery.

Anaesthesia in the Small Laboratory Animals

Anaesthesia in small laboratory animals is potentially difficult and presents a significant risk. Their small size makes access to blood vessels difficult and increases heat loss during anaesthesia, resulting in hypothermia. Also, fasting before or after anaesthesia may result in the development of hypoglycemia. Pre-anaesthetic fasting is unnecessary since these animals cannot vomit. It may be required if surgery on the upper GI tract is to be undertaken but even then, since coprophagy is not prevented, removing the animal's food may not result in an empty stomach.

Anaesthesia should only be induced in healthy, stress free animals. Small animals need to be kept warm during and after anaesthesia, to prevent hypothermia, and may need supplementary fluids to prevent dehydration and encourage return to normal physiology in the post anaesthetic period.

Inhalation anasthesia

Isoflurane is the inhalation agent of choice for small animal anaesthesia. It has a very high safety margin for all species and is rapidly excreted from the tissues via the lungs, which results in rapid recovery. There is virtually no biotransformation, making it the most suitable agent for studies that require maintenance of normal drug metabolising ability.

Isoflurane may be used to induce anaesthesia in rodents by exposing them to a high concentration of the agent. This may be administered via a facemask, or more usually via an anaesthetic chamber. These methods are suitable for mice, rats and guinea pigs, but not for rabbits, which breath-hold for a long period and become anoxic.

Alternatively a short-acting injectable agent may be given to produce initial unconsciousness, with anaesthesia then being maintained with a volatile inhalation agent. Once an animal is unconscious, anaesthesia can be maintained by passing an endotracheal tube and administering a low concentration of volatile agent in oxygen. This is safe for both the animal and the operator. However, passing an endotracheal tube in the small laboratory species can be difficult, and it may be necessary to use a facemask.

Injectable anaesthesia

Injectable agents can be given by a number of routes. In all cases, the intra-venous route is to be preferred, as the effect is immediate and the dose can therefore be titrated against the effect, making it much safer. However, difficulty accessing veins in some of the smaller animals, especially guinea pigs and mice, makes intra-peritoneal route more common in these species. With this route, the dose has to be pre-determined against body weight and then administered in one injection. There are several disadvantages to the i/p route: the total dose is always larger than if given i/v, absorption is slower, and therefore induction is slower. Any residual drug effects will persist for longer and so recovery is usually also prolonged. It is also never possible to be absolutely certain that you have administered the injection into the peritoneal space, and occasional mis-injection into other tissues, such as fat, may account for the variable results that may sometimes be seen following injection.

Many injectable agents are available. Some of these are listed in the tables.

Drug dose rates for anaesthesia in rodents and rabbits, all i/p administration unless otherwise stated

Drug	Type of small animal										Comments	Duration of anaesthesia	Sleep time
	Guinea-pig		Mouse		Rabbit		Rat		Hamster				
	mg/kg	Route	mg/kg	Route	mg/kg	Route	mg/kg	Route	mg/kg	Route			
Medetomidine (ug/kg)	-	-	30-100	s.c			30-100	s.c	100	s.c	Sedation only. Reverse with atipamezole 1mg/kg s.c	-	-
Hynorm (ml/kg) (fentanyl/fluanisone)	0.65 20 min	i/m	0.5 60 min +		0.22	i/m	0.4	i/m	0.5	i.m	Sedation only. Good analgesia Poor relaxation	-	-
Alphaxalone (mg/kg)	40	i/v	10-15	i/v	6-9	i/v	10-15	i/v	150	i.p.	Surgical anaesthesia only if i/v	5 mins	10 min
Hypnorm (ml/kg) + diazepam (mg/kg)	1 2.5	i/m	0.4 5		0.3 2.5	i/m i/p or i/v	0.3 2.5	i/m	1 +5	i.m or i.p	Good surgical anaesthesia	45-60 mins	3-4 hours +
Hypnorm (ml/kg) + midazolam (mg/kg)	8*		10*		0.3 2	i/m i/p or i/v	2.7*		4*	i.p	Good surgical anaesthesia	45-60 mins	3-4 hours +
Ketamine (mg/kg_ Diazepam(mg/kg)	100 5		100 5		25 5	i/m i/m	75 5				Light anaesthesia	20 mins	2 hrs
Ketamine (mg/kg) + Medetomidine (mg/kg)	40 1		75 0.5		35 0.5	i/m	75 0.5		100 +0.25		Surgical anaesthesia	20-30 mins	2-4 hrs +
Ketamine (mg/kg) + Xylazine (mg/kg)	40 5	i/m	80-100 10		35 5	i/m	90 +10		50-200 +5-10		Surgical anaesthesia	20-30 mins	2-4 hrs +
Propofol (mg/kg)	10	i.v	26	i/v	10	i/v	10	i/v	10	i.v	Surgical anaesthesia only if i/v	5 mins	10 mins

i/m intramuscular i/p intraperitoneal i/v intravenous

* Mixture of 1 part Hypnorm, 2 parts water for injection and 1 part midazolam.
+ Recovery time reduced if specific antagonists are administered

Suggested dose rates of analgesia in small animals

Analgesic	Type of small animal														
	Mouse			Rat			Guinea-pig			Hamster			Rabbit		
	Dose (mg/kg)	Route	Interval (hourly)	Dose (mg/kg)	Route	Interval (hourly)	Dose (mg/kg)	Route	Interval (hourly)	Dose (mg/kg)	Route	Interval (hourly)	Dose (mg/kg)	Route	Interval (hourly)
Buprenorphine	0.05-0.1	s/c	8-12	0.01-0.05	s/c	8-12	0.05	s/c	8-12	0.5	s/c	8-12	0.01-0.05	s/c, i/v	8-12
Butorphanol	1-5	s/c	4	2	s/c	4	1	s/c	24	0.4	s/c	8-12	0.1-0.5	i/v	4
Flunixin	2.5	s/c, i/m	12	2.5	s/c, i/m	12	-	-	-	2.5	s/c	12	1.1	s/c, i/m	12
Ibuprofen	30	per os	4	15	per os	4	10	i/m	4	-	-	-	10	i/v	4
Meloxicam	5	s/c	24	1.0	s/c, per os	12-24	0.1-0.3	s/c, per os	24						
Morphine	2-5	s/c	2-4	2-5	s/c	2-4	2-5	s/c, i/m	4	-	-	-	2-5	s/c, i/m	2-4
Pethidine	10-20	s/c, i/m	2-3	10-20	s/c, i/m	2-3	10-20	s/c, i/m	2-3	20	s/c	2-3	10	s/c, i/m	2-3

i/m intramuscular i/v intravenous s/c subcutaneous

See Flecknell and Waterman-Pearson (2000) Pain management in animals. WB Saunders.

Biological data, rabbit

Biological Data		Breeding Data	
Adult weight (grams)	900-6000	Puberty (days)	90-120
Diploid number	44	Age to breed male	6-10 months
Food intake	5g/100g bodyweight	Age to breed female	4-9 months
Water intake	10ml/100g bodyweight	Gestation (days)	30-32
Lifespan (years)	6-12	Litter size	4-10
Rectal temperature (^{o}C)	38.5-40	Birth weight (grams)	30-70
Heart rate/min.	130-325	Weaning age (weeks)	4-8
Blood pressure systole (mm Hg)	90-130	Oestrous cycle	Induced Ovulator
Blood pressure diastole (mm Hg)	60-90	Post partum oestrus	Not used
Blood volume (ml/kg)	57-65		
Respiratory rate/min.	30-60		
Tidal volume (ml/kg)	4-6		

Haematological Data		Biochemical Data	
RBC (x10^{6}/mm^{3})	4-7	Serum protein (g/dl)	5.4-7.5
PCV (%)	36-48	Albumin (g/dl)	2.7-4.6
Hb (g/dl)	10-15.5	Globulin (g/dl)	1.5-2.8
WBC (x10^{3}/mm^{3})	9-11	Glucose (mg/dl)	75-150
Neutrophils (%)	20-75*	Blood urea nitrogen (mg/dl)	17-23.5
Lymphocytes (%)	30-85	Creatinine (mg/dl)	0.8-1.8
Eosinophils (%)	0-4	Total bilirubin (mg/dl)	0.25-0.74
Monocytes (%)	1-4	Cholesterol (mg/dl)	35-53
Basophils (%)	2-7		
Platelets (x10^{3}/mm^{3})	250-270		

* Neutrophils often resemble eosinophils due to cytoplasmic granules.

From Wolfensohn and Lloyd (2003).

REFERENCES AND FURTHER READING

BVA Animal Welfare Foundation online tutorials: http://www.bva-awf.org.uk/resources/tutorials/

BVA Animal Welfare Foundation et al. Refinements in rabbit husbandry. Second report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on refinement. **Laboratory Animals**, 27 301-29.

Conlon, K.C., Corbally, M.T., Bading, J.R., and Brennan, M.F. (1990). Atraumatic endotracheal intubation in small rabbits. **Laboratory Animal Science**, 40(2), 221-22.

Davies, A., Dallak, M. and Moores, C. (1996). Oral endotracheal intubation of rabbits (Oryctolagus cuniculus). **Laboratory Animals 30**, 182-183.

FELASA Working Group on Health Monitoring of Rodent and Rabbit Colonies. (2002) Recommendations for the health monitoring of rodent and rabbit colonies in breeding and experimental units. **Laboratory Animals** 36, 20-42

Flecknell and Waterman-Pearson (2000) **Pain management in animals**. WB Saunders

Foster, H.L., Small, J.D., and Fox, J.G. (eds.) (1983). **The mouse in biomedical research** Vol. III. Academic Press, New York.

Harkness J.E. and Wagner J.E. (1989). **The biology and medicine of rabbit and rodents** Lea and Febiger

Hillyer E.V. and Quesenberry K.E. (1997). **Ferrets, Rabbits and Rodents: clinical medicine and surgery** W.B. Saunders

Hubrecht R. and Kirkwood J. (eds) (2010). **The UFAW Handbook on the Care and Management of Laboratory Animals.** Eighth Edition. Wiley, Chichester.

National Research Council (1996). **Laboratory animal management: rodents**. National Academy Press.

Popesko. P., Rajtova, V. and Horak, J. (1992). **A colour atlas of anatomy of small laboratory** animals Volume 1: Rabbit, guinea pig. Volume 2: Rat, mouse, hamster. Wolfe Publishing Ltd.

Rodent Refinement Working Party (1998). Refining rodent husbandry: the mouse. **Laboratory Animals** 32, 233-259

Tuffery AA(ed) (1995). **Laboratory Animals an Introduction for Experimenters** 2nd Edition

Wolfensohn S and Lloyd M (2003). **Handbook of laboratory Animal Management and Welfare** Third edition. Wiley Blackwell.