Review Article

Mapping the Age of Laboratory Rabbit Strains to Human

Abstract

Rabbit strains find immense application in biomedical research with every strain having their discrete advantage in specific research endeavor. Acceptability of rabbit strains as laboratory animals owes to their breeding ease, availability, cost-effectiveness, ethical conveniences, larger size, compared to rats and mice, and responsiveness. With respect to different life phases, the article displays that one human year is equivalent to: (1) in developmental phase, 56.77 days for New Zealand White (NZW) and New Zealand Red (NZR) rabbits, 71.01 days for Dutch belted and Polish rabbits, and 85.28 days for Californian rabbits; (2) in the prepubertal phase, 13.04 days for NZW and Dutch belted, 15.65 days for NZR and Californian, and 10.43 days for Polish rabbits; (3) in the adult phase, 18.25 days for NZW and Californian rabbits, 22.75 days for NZR, and 12 days for Dutch Belted and Polish rabbits; (4) during reproductive senescence, 42.94 days for NZW, NZR and Californian rabbits, 28.62 days for Dutch belted, and 25.05 days for Polish rabbits; (5) in the post-senescence phase, 50.34 days for NZW, 25.17 days for NZR, Dutch Belted and Californian and 31.46 days for Polish rabbits. The laboratory rabbit strains differ in various physiological, developmental and genetic make-ups, which also reflect upon the correlation of their age at different life stages with that of a human. The present article aids selection of laboratory rabbit strain of accurate age as per experimental need, by precisely relating the same with age of human considering different life stages.

Keywords: *Aging, animal models, physiology, rabbits*

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Introduction

Any biomedical experimental design is based upon the selection of an appropriate laboratory animal model that will suit the matched age of the human to which the research aims to cater and the animal strain to fit the research procedures. Therefore, both the age of the laboratory animal corresponding to that of human as well as the strain of the same animal as per experimental requirement, are the primary criteria to be fulfilled prior to any research endeavour.[1] Arriving at a specific laboratory animal model that coincides with all fields of research application is quite arduous. But the variety in strains of particular animal species offers choice to the investigators for selecting the model for their study design. Considering the constraints regarding the expense, availability, legal and ethical aspects of using large mammals, it is feasible to select the most phylogenetically developed animals, closest to human among the smaller mammal species that are available in sufficient quantity. *Lagomorphs* reportedly are closest to human phylogeny after primates, among which rabbits bear the most resemblance.[2] Rabbits also possess advantages over mice and rats for being used as laboratory animals owing to its genetic closeness to human than rodents.[3]

Rabbits are members of family *Leporidae* and order *Lagomorpha*[4] and according to the taxonomists, there are 47 distinct strains of rabbits,[5] but more recently, the American Rabbit Breeders Association (ARBA) has identified 49 rabbit strains.[6] Though New Zealand white (NZW) strains of rabbits (*Oryctolagus cuniculus*) gain more popularity in biomedical research,[7] other vital strains essential for specific research purposes include the Dutch-belted rabbits, Californian white, Polish rabbits and the New Zealand red.[7]

In one of our previous articles[8] based on the amelioration of the selection of appropriate age of laboratory animal for biomedical sciences, it had been mentioned that as per the data of European

How to cite this article: Sengupta P, Dutta S. Mapping the age of laboratory rabbit strains to human. Int J Prev Med 2020;11:194.

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Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.IJPVM_530_18

Quick Response Code:

Union (2010), rabbits had been the third mostly globally used laboratory mammals, just after the usage of mice and rats. There had been a declining trend of use of rabbit from 1950 to 2010[9] as is also evident from data (1973 to 2015) of the United States Department of Agriculture (USDA)/ Animal and Plant Health Inspection Service (APHIS),[10-12] but this is probably owing to the global protest against the use of animal for experimentation, which diverted the biomedical research towards more *in vitro* studies, as an 8% decline in research use of animals, taken as a whole, from 2014 to 2016, has also been shown by USDA/ APHIS.[13-15] This explains the reduction in laboratory use of rabbits from 258,754 in 2000 to 139,391 in 2016.[13] However, rabbits are still indispensable for laboratory use which attributes to its relatively larger size than mice or rats, while a convenient size compared to larger mammals, docile nature, availability of its strains each of which fit for specific experimentation procedures and its cost effectiveness, for which it has been the second highest used animal in research and teaching in 2016 in the Unites States, as per USDA/APHIS[13] [Figure 1].

The objective of this paper was to realize a literature review analysing the age of the laboratory rabbit strains, which holds the most importance in biomedical experimentation, in comparison with men's age. We aim to ameliorate research specificity in selecting appropriate age of any particular rabbit strains for serving as laboratory model by separately correlating different life phases of human with that of every vital laboratory rabbit strain.

Commonly used laboratory rabbits strains

The order *Lagomorpha* comprises of cottontails, hares, pikas and rabbits. Common laboratory rabbit strains are derived from the European rabbit (*Oryctolagus cuniculus*),[7,16] among which the most vital ones for research are the New Zealand White (albino), New Zealand Red, Dutch-belted, Californian White, and Polish.[7] However, as many as about 30 rabbit breeds (including mutant strains) have been identified by ARBA for commercial and experimental uses.[6,7,17] Rabbit strains can be broadly differentiated by their size and body weight in which small refers to less than 2 kg (Polish, Dutch-belted); medium refers to 2-5 kg (New Zealand White, New Zealand Red and Californian); large refers to those greater than even 5 kg (Flemish).[6] Though New Zealand White (albino) is the most commonly used laboratory strains being easy to locate surface veins and arteries in them for blood collection,[18,19] other strains such as the New Zealand red, Dutch-belted, Californian and Polish rabbits find implications in many important research endeavors [Table 1].

Existing theories support that mating of Flemish Giant with Belgian hare produced the NZR rabbit in around 1910. Later, William Preshaw of Rippon, California, in 1919, developed NZW rabbits by using Angoras, white American rabbits as well as the Flemish Giants. American Rabbit Breeders Association (ARBA) has accepted the NZW rabbit in 1920.[20] According to the

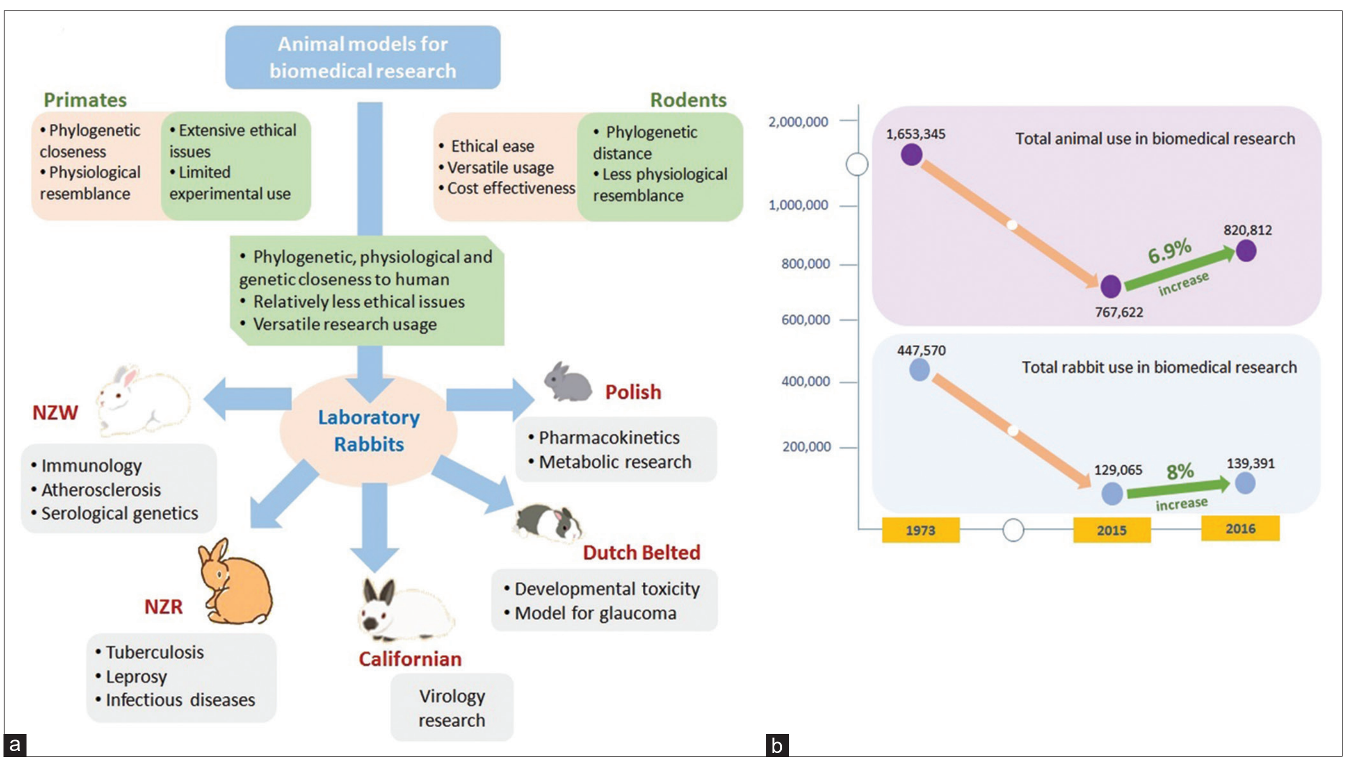

Figure 1: (a) Research benefits of different rabbit strains; (b) trend of total animal and rabbit uses in biomedical research.

British Rabbit Society the NZW and NZR are separate strains of rabbit, while ARBA recognizes them as same stains with colour variations.[20] Dutch rabbits was actually developed in England, since in 1830s, these rabbits were imported from Ostend in Belgium to England.[21]

Polish rabbit is a small compact rabbit strain which finds its origin in England.[22] It is perceived that these rabbits were produced by breeding Himalayan and Dutch rabbit in 1600s. The Polish rabbits arrived in America in around 1912, and soon after the American Rabbit Breeders Association (ARBA) accepted them as a distinguished rabbit strain.[23] The Californian Rabbit originated in the 1923, which was developed by George West of California and were shown as breed in 1928, got individual recognition as a rabbit breed by the American Rabbit Breeders Association (ARBA) in 1939.[24]

Table 1: Commonly used breeds of laboratory rabbits and their research applications

Mostly used breeds	Research applications
New Zealand White	Cancer and other immunology research, atherosclerosis, hypertension, serological genetics and other research related to human diseases
New Zealand Red	Tuberculosis, leprosy and other infectious disease research
Californian White	Virology research
Dutch belted rabbits	Developmental toxicity experiments, model for glaucoma
Polish rabbits	Pharmacokinetics, metabolic research

Biological Data of Rabbit Strains

The benefits using rabbit strains as laboratory model for biomedical research attributes to its ease of handling, cost-effectiveness, breeding convenience and variety of its available strains each of which fits as model in versatile experimentation. Moreover, its higher blood volume, more phylogenetic resemblance to human as compared to mice or rats, suffice the criteria of large mammals.[2] Any commonly used strain of laboratory rabbit permits the researchers to modulate and standardize their experimentation environment according to the particular research need, even allowing genetic standardization.[25] Their short vital cycles also coincide with limited research time-span [Table 2].

Relation between rabbit age and human age

In biomedical experiments with rabbits representing humans, the rabbit age must be precisely determined in relation to human age, in terms of both the lifespan and individual life stages, to attain utmost accuracy and specificity in research. In the following section, we present human age with that of laboratory rabbit at different developmental stages of life [Figure 2].

Relation between their lifespans

A rabbit bears accelerated and shorter early life than humans. The strain type and living conditions are the major

Table 2: General physiology and reproductive data of different laboratory rabbit strains

Common physiological data	NZW	NZR	Dutch belted	Californian	Polish
Birth weight (g)	30-80	~55	35-40	~54	30-35
Ideal mature weight (♂/♀) (kg)	10/11	10/11	2.5/2.5	9/9.5	2.5/2.5
Growth rate (g/day to 8 weeks)	15-20	15-25	10-12	21-24	9-12
Body temperature	38-40°C	38-40°C	38-39°C	38-39°C	38-39°C
Water consumption (ml/day)	100-600	100-500	50-100	85-90	50-80
Food consumption	100-300 g/day	100-300 g/day	0.8 ounces/day	4.2 kg/kg gain	20-25 g/day
Skeletal weight (of BW)	7-8%	7-8%	7-8%	7-8%	~8%
Average litter size	4-10	7-8	5-6	7-9	2-4
Heart rate	130-325	125-320	280-330	123-304	300-330
Blood volume	45-75 ml/kg BW	45-75 ml/kg BW	5.7-6.9 ml/100 g	45-75 ml/kg BW	5-7 ml/100 g
Age at estrous (months)	5-6	5-7	4-5	6-7	~4
Weight at estrous	1.7-3 kg	2-3 kg	500-800 g	1.5-2.5 kg	500-700 g
Frequency of estrous cycle			Induced		
No. oocytes in ovulation	9-14	9-12	7-10	9-12	3-7
Time of ovulation (hrs after mating)	10-12	9-13	10-12	9-13	10-12
Menopause (years)	5-7	5-7	3-5	5-7	3-4
Parturition interval	~79 d	~70 d	~60 d	~65 d	~60 d
Average semen volume (ml)	0.3-0.6	0.5-1.0	0.3-0.6	0.5-1.0	0.3-0.6
Sperm concentration ($\times 10^6$/ml)	150 to 500	200-450	150-300	200-450	150-250
Sperm motility (%)	~ 60	~ 70	~ 60	~ 80	~ 60
Serum testosterone (ng/ml)	2.0-2.5	2.0-2.5	1.5-2.0	2.0-2.5	1.5-2.0
Time of implantation (days of gestation)	8-9	8-9	~8	7-8	~8
Length of gestation (days)	31-32	28-35	30-33	28-32	28-34

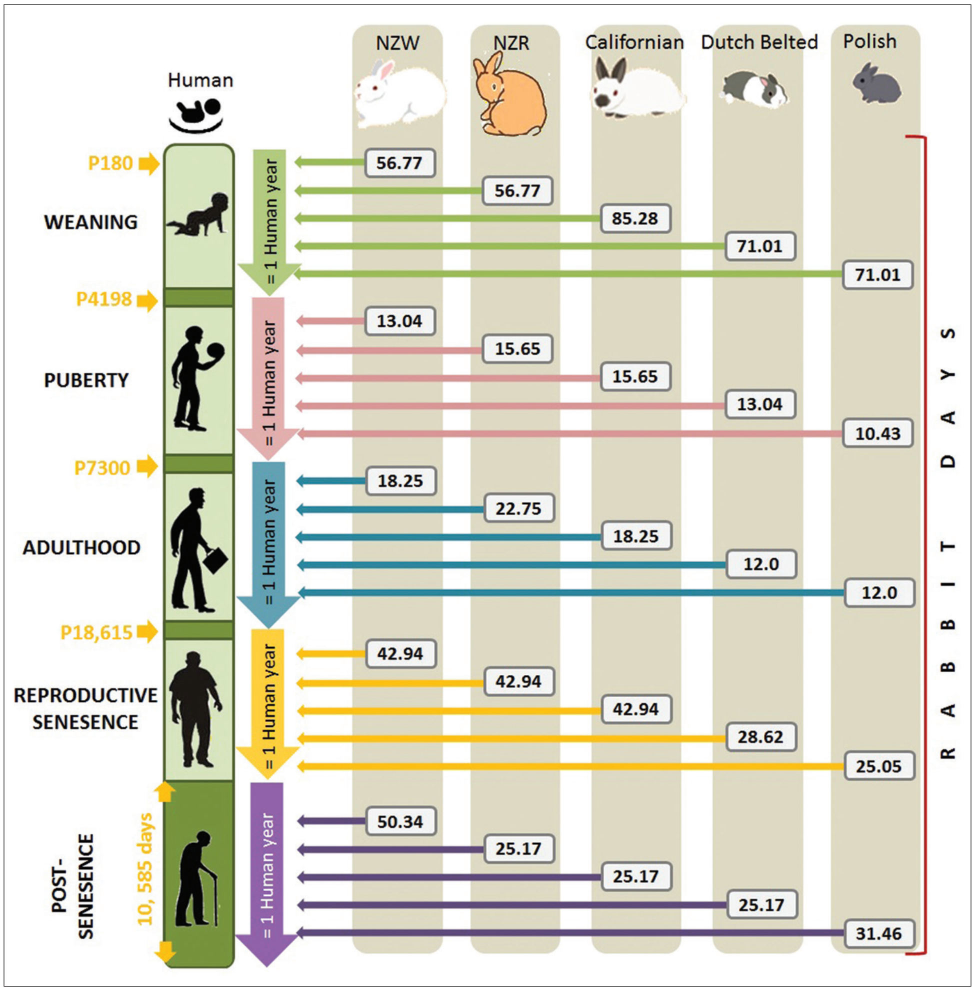

Figure 2: Mapping of ages of different strains of rabbit to human age in different life periods.

determinants of rabbit lifespan. The life-expectancy of rabbits in general is about 8-12 years.[26,27] But, in laboratory and breeding environments, their lifespan is reduced due to stress.[28] Given the disparity between the developmental stages of rabbits and humans, their entire life spans cannot be considered as reliable parameters to calculate human days in terms of rabbit days and thereby, every life phase of different rabbit strains has to be taken into account to correlate with the corresponding life phase in human. The approximation of life expectancy of a human is 80 years and this definitely vary with socio-economic and health conditions in various geographic regions.[8,29,30]

The lifespan of the laboratory rabbit strains and that of human may be correlated as follows:

NZW rabbits may live up to 10 years with proper care, spaying and neutering.[30]

$(80 \times 365) \div (10 \times 365) = 8$ human days = 1 NZW rabbit day

and

$365 \div 8 = 45.625$ NZW rabbit days = 1 human year

NZR rabbits are healthy and robust strains with lifespan of 5-10 years.[20] In this study, the approximation of average life span of NZR rabbits is 8 years.

$(80 \times 365) \div (8 \times 365) = 10$ human days = 1 NZR rabbit day

and

$365 \div 10 = 36.5$ NZR rabbit days = 1 human year

Californian rabbits live a healthy life devoid of any strain specific disease but it can suffer from sore hocks at any phase of life. Their average lifespan is considered as 8 years in the present study.[24]

$80 \times 365) \div (8 \times 365) = 10$ human days = 1 Californian rabbit day

and

$365 \div 10 = 36.5$ Californian rabbit days = 1 human year

The Dutch-belted rabbits live for 5-8 years. They rarely live longer life, one such report being up to 15 years, depending upon the care taken, and if they are neutered or spayed.[31] Approximation of their lifespan for calculation in this study is considered as 6 years.

(80 × 365) ÷ (6 × 365) =13.33 human days = 1 Dutch-belted rabbit day

and

365 ÷ 13.33 = 27.38 Dutch-belted rabbit days = 1 human year

Polish rabbits generally experience a lifespan of 5-8 years but longer in some cases based on neutering, spaying, care and diet,[32] and their average life span may be taken as 6 years.

(80 × 365) ÷ (6 × 365) =13.33 human days = 1 Polish rabbit day

and

365 ÷ 13.33 = 27.38 Polish rabbit days = 1 human year

Weaning in Laboratory rabbit strains and in human

Mammals are altruistic towards their newly born young ones to whom they nurse and feed till they are able to feed themselves and live independently. 'Weaning is the transition of the human infant from breastfeeding or bottle nursing and commencement of nourishment with other food'.[33] For human, the average age of weaning is about 6 months (180 days).[8,34]

Just following birth, baby rabbits are hairless with closed eyes and till the time when they open their eyes and able to walk, their mother continues to nurse them with her milk. The time of weaning varies according to strains and ranges from 4th to 7th week (P28-P49). During the time of weaning, the baby rabbits develop their teeth and fur, they are very active, able to jump, drink and feed on their own and the males (bucks) should be separated from the females (does).[26,28,35]

For New Zealand strains (both albino and red), weaning occurs at around the 4th week (P28).

180 ÷ 28 = 6.43 human days = 1 NZW rabbit day

and

365 ÷ 6.43 = 56.77 NZW rabbit days = 1 human year

180 ÷ 28 = 6.43 human days = 1 NZR rabbit day

and

365 ÷ 6.43 = 56.77 NZR rabbit days = 1 human year

For Californian rabbits, weaning may occur between 5th and 7th week and may be approximated as P42.

180 ÷ 42 = 4.28 human days = 1 Californian rabbit day

and

365 ÷ 4.28 = 85.28 Californian rabbit days = 1 human year

Dutch-belted and Polish rabbits wean at around the 5th week (P35).

180 ÷ 35 = 5.14 human days = 1 Dutch-belted rabbit day

and

365 ÷ 5.14 = 71.01 Dutch-belted rabbit days = 1 human year

180 ÷ 35 = 5.14 human days = 1 Polish rabbit day

and

365 ÷ 5.14 = 71.01 Polish rabbit days = 1 human year

Pubertal age in Laboratory rabbit strains and in human

Puberty is marked by development of the hypothalamo-pituitary-gonadal axis, according to which the gonadotropin levels alter in the circulation and eventually lead to pick in the levels of sex steroids accompanied with various sudden changes in behaviour. In case of humans, pubertal age begins from about 11.5 years (11.5 × 365 = 4198 days).[8,34]

With the onset of puberty, bucks show more aggression and frequently dispense urine at all places as indication of interest in courtship, while doe become more conscious about her personal territory.[28] The age when a rabbit attains puberty depends on its strain with small strains (Polish and Dutch rabbit strains) maturing earlier than the large strains (New Zealand and Californian rabbits).[36] Polish rabbits attain their puberty at around P120, while Dutch rabbits at around P150.

The pubertal age for New Zealand rabbits vary between 5th and 7th months,[28,35] New Zealand white rabbits attain their puberty at around P150, while New Zealand red sexually mature at around P180.

4198 ÷ 150 = 27.98 human days = 1 NZW rabbit day

and

365 ÷ 27.98 = 13.04 NZW rabbit days = 1 human year

4198 ÷ 180 = 23.32 human days = 1 NZR rabbit day

and

365 ÷ 23.32 = 15.65 NZR rabbit days = 1 human year

For the Californian rabbits, onset of puberty ranges from 6 to 7 months and can be taken as P180.

4198 ÷ 180 = 23.32 human days = 1 Californian rabbit day

and

365 ÷ 23.32 = 15.65 Californian rabbit days = 1 human year

Polish rabbits attain their puberty at around P120, while Dutch-belted rabbits at around P150.

4198 ÷ 150 = 27.98 human days = 1 Dutch‑belted rabbit day

and

365 ÷ 27.98 = 13.04 Dutch‑belted rabbit days = 1 human year

4198 ÷ 120 = 34.98 human days = 1 Polish rabbit day

and

365 ÷ 34.98 = 10.43 Polish rabbit days = 1 human year

Adulthood in different laboratory rabbit strains and its relation to human

Adulthood is the age when sexual maturity along with proper social conceptions and awareness are fully attained. In laboratory rabbits, young adulthood is the time when they are the most active and estrous cycle is regularised in doe which is considered continuous.[35,37] In the middle‑adult age, their movements slag down, while in their late adulthood, they begin to suffer from age‑related physiological troubles. Both doe and buck remain fertile in their entire adulthood phase with highest numbers of eggs and sperms.[38,39] Every year, the time spanning from October to December is generally their mounting season.[5] In laboratory rabbit strains, just alike other mammals including humans, the demarcation of the shifting from adolescence to adulthood may be the epiphyseal growth plate closure.[40] For humans, fusion of the last growth plates in the scapula occurs at about 20 years of age (365 × 20 = 7300 days).[40]

The age at which New Zealand Rabbits can be considered as adults varies with strains. NZW Rabbits reach their adulthood approximately at 1 year of age (P365),[28,41] while NZR rabbits attain their adulthood between 52nd and 80th weeks, approximately at around P455.

7300 ÷ 365 = 20 human days = 1 NZW rabbit day,

which indicates that

365 ÷ 20 = 18.25 NZW rabbit days = 1 human year

7300 ÷ 455 = 16.04 human days = 1 NZR rabbit day,

which indicates that

365 ÷ 16.04 = 22.75 NZR rabbit days = 1 human year

Californian rabbits also attain their adulthood approximately at 1 year of age (P365).

7300 ÷ 365 = 20 human days = 1 Californian rabbit day,

which indicates that

365 ÷ 20 = 18.25 Californian rabbit days = 1 human year

The smaller strains (Dutch‑belted and Polish rabbits) owing to their accelerated early life phase, reach their adulthood at comparatively earlier ages (between 6th and 10th months; approximately P240).[20,21,23]

7300 ÷ 240 = 30.41 human days = 1 Dutch‑belted rabbit day,

which indicates that

365 ÷ 30.41 = 12 Dutch‑belted rabbit days = 1 human year

7300 ÷ 240 = 30.41 human days = 1 Polish rabbit day,

which indicates that

365 ÷ 30.41 = 12 Polish rabbit days = 1 human year

Reproductive senescence in rabbits and humans

In humans, menopause in women is a marker of reproductive senescence, which is associated with the termination of the fertility cycle. The average age of menopause in women, according to the American Medical Association, is 51 years (51 × 365 = 18,615 days).[8] Although the biomarkers of ageing are not very authentic to detect reproductive senescence, in rabbits, reproductive functions cease in late middle‑age which is considered to be around 6 years (P2190) for medium‑ and large‑sized rabbits (NZW, NZR and Californian).[28]

18,615 ÷ 2190 = 8.5 human days = 1 NZW rabbit day

and

365 ÷ 8.5 = 42.94 NZW rabbit days = 1 human year

18,615 ÷ 2190 = 8.5 human days = 1 NZR rabbit day

and

365 ÷ 8.5 = 42.94 NZR rabbit days = 1 human year

18,615 ÷ 2190 = 8.5 human days = 1 Californian rabbit day

and

365 ÷ 8.5 = 42.94 Californian rabbit days = 1 human year

While in smaller rabbit strains, it ranges from 3‑4 years. For Polish and Dutch rabbits, the age of reproductive senescence is approximately 3.5 years (P1277.5) and 4 years (P1460) respectively.[20,21,23]

18,615 ÷ 1460 = 12.75 human days = 1 Dutch‑belted rabbit day

and

365 ÷ 12.75 = 28.62 rabbit days = 1 human year

18,615 ÷ 1277.5 = 14.57 human days = 1 Polish rabbit day

and

365 ÷ 14.57 = 25.05 Polish rabbit days = 1 human year

Post‑senescence phase in rabbits and humans

After reproductive senescence and female humans may survive approximately for 10,585 days after senescence.[8] The periods of post‑senescence to death in laboratory rabbit strains ranges from 2 to 4 years depending upon their longevity.

This period is found to be almost uniform in different rabbit strains with 2 years in Dutch-belted, Californian as well as in NZR rabbit; 2.5 years in Polish rabbits; and 4 years in NZW.[20,21,23]

10585 ÷ 1460 = 7.25 human days = 1 NZW rabbit day

and

365 ÷ 7.25 = 50.34 NZW rabbit days = 1 human year

10585 ÷ 730 = 14.5 human days = 1 NZR rabbit day

and

365 ÷ 14.5 = 25.17 NZR rabbit days = 1 human year

10585 ÷ 730 = 14.5 human days = 1 Californian rabbit day

and

365 ÷ 14.5 = 25.17 Californian rabbit days = 1 human year

10585 ÷ 730 = 14.5 human days = 1 Dutch Belted rabbit day

and

365 ÷ 14.5 = 25.17 Dutch Belted rabbit days = 1 human year

10585 ÷ 912.5 = 11.6 human days = 1 Polish rabbit day

and

365 ÷ 11.6 = 31.46 Polish rabbit days = 1 human year

Conclusions

Rabbits are indispensable for biomedical research with different strains finding specific application in various experimentations. Considering the disparities in developmental, physiological and genetic make ups of the commonly used laboratory rabbit strains, the present study separately relates the age of individual strain with that of human at different life stages. Therefore, the study aids the selection of specific laboratory rabbit age relating with corresponding human age, upon which the research outcome aims to be implemented.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 24 Nov 18 **Accepted:** 24 May 19

Published: 11 Dec 2020

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