

Letter to the Editor

The issue of rodent longevity in the UK

A meeting was convened by Charles River UK in October 1992, to explore the issue of the survival of rats in carcinogenicity testing as perceived in the UK.

At that meeting, all factors that could have impact both positive and negative, on longevity were discussed. One of the main conclusions drawn at the meeting was that, not surprisingly, longevity is a multifactorial phenomenon and only one single factor emerged as dominant, namely, overall food consumption. Other factors include strain, health status, number housed per cage, route of administration of the test article, the formulation of the diet, its administration and accessibility. Not surprisingly, with the range of permutations offered by these factors, different survival rates are apparent from different facilities using the same rats operating ostensibly similar methods to conduct carcinogenicity studies for regulatory purposes. In the UK these common factors include gang-housing—usually five animals per cage, low protein (14%) diet, grid bottomed cages (in compliance with Home Office requirements for floor area and height), bottled (usually tap) water, and diet containing the test article administered as a powder.

A postal survey was made of nine major laboratories in Britain enquiring about the survival of rats

in control groups in carcinogenicity studies between 1977 and 1990 (see table).

One factor known for years to have a marked effect on survival is dietary restriction, a phenomenon which has recently been confirmed by Merck in the USA to markedly improve the survival of rats. In the US other husbandry factors operate that are dissimilar from those commonly employed in the UK. Even a small decrease in the amount of food consumed compared to 'ad libitum' intakes has a significant effect on overall food consumption, bodyweight gain (growth) and eventual survival at week 104. Unfortunately, using gang-housed rats, dietary restriction is less easy to adopt without significant increases in study complexity and manpower. In addition, toxicologists express concern over its effects on metabolism and other biological processes. Because limited dietary restriction poses such a marked effect on survival, it makes one wonder what other factors might inapparently affect food consumption to some slight degree and therefore survival.

Obvious factors are the palatability and accessibility of the food offered. The latter is in turn affected by competition within the cage and the design of the food-hopper. In fact, many people have commented that, when competition for food is decreased due to deaths within a cage of gang-housed rats, thereby simulating single housing, few in that cage survive to study termination. On the other hand, when the original incumbents survive most of the way through the study, they often all continue to termination.

Table Percentage survival of group housed control CD rats at 104 weeks in 2 year studies

Start date	Males			Females		
	Mean	n	Range	Mean	n	Range
1977	48	4	40–55	56	4	49–69
78	47	3	42–51	52	3	41–63
79	58	4	55–56	52	4	46–60
80	37	2	30–43	32	2	24–48
81	46	4	37–62	45	4	39–56
82	58	3	54–60	52	3	41–58
83	48	5	42–53	54	5	36–60
84	44	4	33–64	45	4	35–58
85	47	6	33–53	49	6	42–49
86	49	13	34–52	49	13	36–56
87	50	21	26–72	53	21	40–64
88	48	12	22–76	54	12	22–82
89	53	29	16–66	49	29	18–64
90	56	14	39–71	53	14	27–76

n = number of carcinogenicity studies

Toxicologists have considered genetic drift in the CD rat, estimated to be the strain used for 80% of all drug registrations world-wide, to be a causative factor. Whilst some drift might have occurred, it is impossible to determine how much. However, because the drift is subtle its impact on longevity is likely to be considerably less than the environmental/ husbandry factors previously discussed. Nevertheless, Charles River has improved its system for outbred breeding populations which maximises the randomness of matings within the colony and controls genetic diversity by regular infusions of breed-stock from and into established reference colonies for supply to production colonies.

Recent work by Huntingdon Research Centre,¹ published at this year's Society of Toxicology meeting, indicated a slight increase in mortality for gang housed Sprague Dawley rats fed breeding diet during the period 1985 to 1991. However, following a change to maintenance diet, during the period 1987 to 1992 there has been an improvement in survival, with survival for the majority of male and female control groups being in excess of 50% at week 104. This work further strengthens the importance of housing and diet on survival in long term rodent studies.

Some confirmation of these findings was obtained in a survey conducted by the Centre for Medicines

Research,² which showed that no overall decline in survival was apparent for the commonly used strains during the last 20 years.

In conclusion, palatability and accessibility to food are the factors which will probably prove to be pivotal in the issue of longevity of rats used for 2 year carcinogenicity studies. Where facilities are experiencing a decline in survival of rats, it is possible that husbandry changes made in the recent past are contributing to an overall increase in food consumption per rat at their premises, which has resulted in increased obesity and poorer survival.

References

- 1 Hooks WN, Newton DF, Green OP & Harling RJ. A review of mortality in tumorigenicity studies conducted on gang-housed Sprague Dawley rats over the period 1985-1992. *Toxicologist* 1993; **13**: 653.
- 2 Purves D. *A survey of survival on rat strains used for carcinogenicity studies*. (Unpublished data). Centre for Medicines Research: Carshalton, Surrey.

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