Comparison of Historical Control Data in Two Strains of Rat Used in Carcinogenicity Studies

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Introduction

Regulatory guidelines necessitate carcinogenicity testing of potential new human therapeutics intended to be administered to humans for longer than six consecutive months. The assessment of a chemical's ability to induce tumor growth in animals helps predict the relative risk in humans. Further evaluations including survivability and body weight are monitored for the entire lifespan of the species. Therefore, a suitable rat strain for carcinogenicity testing should be selected based on expected survival for the recommended duration of the study (2 years).

Comparative data collected over a 20-year period from Sprague Dawley IGS and Wistar (Hannover) rats housed in a conventional non-barrier facility were assessed. Selected parameters of interest included survival, body weight and body weight gain, and incidence of common neoplastic lesions.

Methods

Animals:

- Sprague Dawley CD® IGS (Crl: CD[SD]) and Wistar (Han) IGS (Crl: WI [Han]) rats obtained primarily from Charles River, Quebec, Canada used as control animals.
- Animals were between six and eight weeks of age at the start of treatment.
- Animals were group or individually housed in conventional wire or perforated steel plate floors, or group housed in polycarbonate bins containing appropriate bedding and maintained under standard laboratory conditions.

Study Design:

- Studies assessed: Dietary, oral gavage, subcutaneous injection, and nose-only inhalation 2-year carcinogenicity studies conducted over a 20-year period. All studies were conducted in accordance with Good Laboratory Practices.
- Diet provided (fed *ad libitum*): Certified rodent diet containing 14, 18 or 21% protein.

Parameters Assessed:

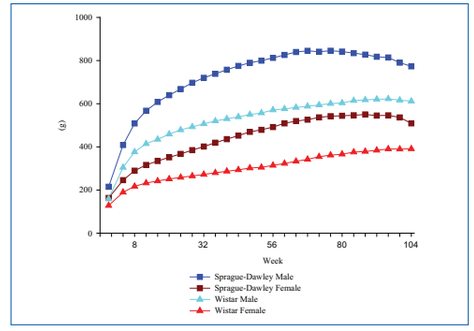
- Survival, body weight and body weight gain, and incidence of common neoplastic and non-neoplastic lesions.

Results

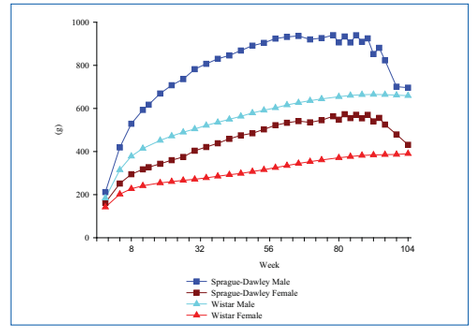
Overall, notable differences among the two strains included lower mean body weights associated with increased survival rates and a lower incidence of spontaneously occurring tumors over a 2-year period in the Wistar (Hannover) rats.

Comparisons of the two housing regimens did not reveal any major differences on the growth rate (body weight) of rats. Mean body weight data from individually housed Sprague Dawley or Wistar male rats were slightly lower than group housed males of the respective strain. The growth curve of Sprague Dawley or Wistar female rats was similar across both housing regimens.

Graph 1: Group mean body weights; individually housed rats

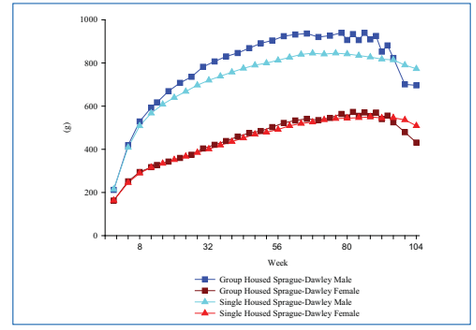


Graph 2: Group mean body weights; group housed rats

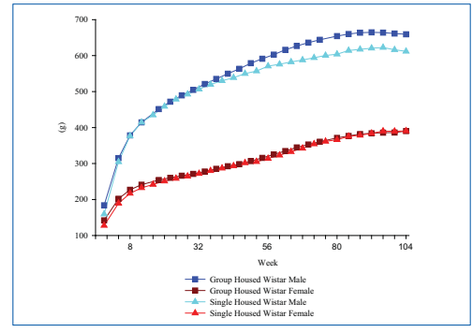


Results (cont'd)

Graph 3: Group mean body weights; group vs individually housed Sprague Dawley rats



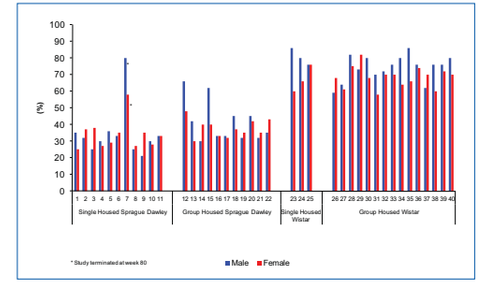
Graph 4: Group mean body weights; group vs individually housed Wistar rats



At the end of a 2-year dosing period, survival was significantly higher in Wistar rats when compared to Sprague Dawley rats. There were no major differences in survival between housing regimens in Wistar rats, whereas group housed Sprague Dawley rats exhibited slightly higher survival than individually housed. In recent studies, early indications of marginally improved survivability in Sprague Dawley rats may be attributed to a reduction in protein content of the diet from up to 21% to 14% at this laboratory.

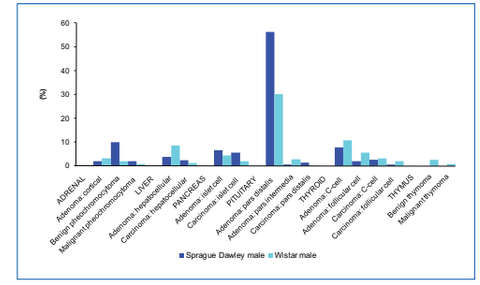
Results (cont'd)

Graph 5: Percentage survival over a 2-year period



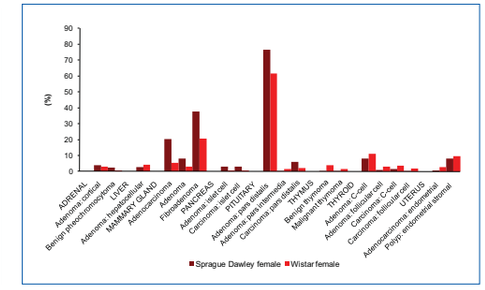
Similar types of neoplastic lesions were seen in both strains; however, at a greater incidence primarily in Sprague Dawley rats. Spontaneously occurring tumor types were seen in many tissues including adrenal, liver, pancreas, pituitary, thyroid, thymus, uterus and/or mammary gland. There was no evidence of significant changes in tumor types in the data evaluated.

Graph 6: Incidence of common neoplastic lesions; males



Results (cont'd)

Graph 7: Incidence of common neoplastic lesions; females



Conclusion

It is concluded that collective data over 20 years demonstrate that both Sprague Dawley and Wistar (Hannover) rats remain appropriate models for use in carcinogenicity studies. However, given the above-mentioned benefits (increased survival, and lower body weights and incidences of spontaneous tumor types), a trend towards the use of Wistar (Hannover) rats in North America has been observed. Prolonged effects of the reduction in protein limits in the diet on survival and body weights changes will continue to be evaluated.

Acknowledgements

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References

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