Overview of the NTP Rat Model Selection: Technical Reports 583-586

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NTP Technical Reports Peer Review
May 22, 2014

Objective

To provide an overview of the rat models used in the NTP studies presented today.

NTP F344/N Rat

- The F344/N rat had several characteristics that made it a good choice for the 2-year rodent bioassay.
  - Used in the rodent bioassay for about 30 years.
  - The historical database was based on a 5-year rolling window and was very robust.
  - Relatively small as compared to other rat strains and stocks.
  - Good survival rate at the end of a 2-year study.
  - Good fecundity for an inbred rat strain, with approximately 6-8 pups produced per litter.

NTP F344/N Rat

- There were several concerns with the F344/N rat as well.
  - High background incidence of:
    - Testicular tumors (interstitial cell tumor)
    - Mononuclear cell leukemia
  - The F344/N rat developed declining fertility, sporadic idiopathic seizures, and spontaneous chylothorax without evidence of trauma.
    - These issues were unique to the NTP F344/N colony.
    - Possibility of genetic drift within the colony.

Strains & Stocks Workshop

- NTP hosted a workshop in June 2005, "Animal Models for the NTP Rodent Cancer Bioassay: Stocks & Strains—Should We Switch?"
  - One of the objectives of the workshop was to determine if the F344/N rat was still an appropriate model in identifying substances that may be a carcinogenic hazard for humans.
  - Included an invited panel of scientists with expertise in rodent genetics, cancer biology, statistics and other related fields.
  - Breakout groups discussed this rodent model and its place in the NTP bioassay.

Strains & Stocks Workshop Summary

- The rat breakout group recommended discontinuing the use of the current F344/N rat strain
  - Proposed 3 options:
    - Re-establish the F344/N strain from another source, however the general concerns about the model would still be present.
    - Create an F1 hybrid such as the F344 X Brown Norway cross, FBNF1.
    - Consider using an alternative model such as an outbred rat like the Wistar Han or Sprague Dawley.

King-Herbert A, Thayer K. NTP workshop: animal models for the NTP rodent cancer bioassay: stocks and strains--should we switch? Toxicol Pathol. 2006;34(6):802-5.

NTP Deliberations

- The NTP discontinued use of the F344/N rat in all new studies and temporarily used the F344/NTac rat from Taconic Farms, Inc.’s commercial colony.
- Scientists within the NTP deliberated the selection of an alternative rat model.

http://www.criver.com/files/pdfs/rms/wistarhan/rm_d_wistar_han_igs_rat.aspx

Other programmatic changes

- The NTP decided to utilize a single rat model for studies of other endpoints.
  - Minimized the need to conduct multiple preliminary and toxicokinetic studies.
  - Enhanced comparability across study endpoints.
- The NTP was moving towards a perinatal exposure design.
  - Some toxicity/carcinogenicity studies would include *in utero* exposure in rat models.
  - More developmental/reproductive toxicology studies to be performed.
    - RACB, MOG and teratology studies
  - Inbred strains were not a good choice for perinatal exposure but outbred stocks were.

Thayer KA, Foster PM. Workgroup report: National Toxicology Program workshop: hormonally induced reproductive tumors—relevance of rodent bioassays. Environ Health Perspect. 2007;115:1351–1356.

General considerations when selecting animal models

Primary

- Availability
- Fecundity
- Survival
- Sensitivity to carcinogens
- Spontaneous tumor rate

Other

- Experience with the model
- Similar metabolic pathways to humans
- Similar pathology to humans
- Sensitivity to other endpoints
- Cost

www.harlan.com

NTP rat model selection

- Desired traits
  - Outbred
  - Long lifespan
  - Moderate size for an outbred rat
  - Good fertility with large litters
- 2007
  - Selected the Wistar Han model [Crl:WI(Han)] but discontinued use due to several issues
    - Low pregnancy rate
    - Litter size smaller than expected
    - Sex ratio in litters appeared skewed
- 2009
  - Changed the rat model to the Harlan Sprague Dawley [HSD:Sprague Dawley (SD)]
  - Currently use this model

King-Herbert, AP, Sills, RC., Bucher, JR. Commentary: update on animal models for NTP studies. Toxicol Pathol. 2010;38(1):180-1.

Brief overview on rodent models - Alike but different

F344/N ≠ **F344/NTac**

N=NIH

- F344/N – NIH rat strain
- F344/NTac – Substrain of the NIH F344 rat; bred at Taconic Farms, Inc.
- In general, historical databases are not combined between substrains

Summary of rat models used in the studies presented today

	2-week study	3-month study	2-year study
Bromodichloroacetic Acid TR 583	F344/N	F344/N	F344/NTac
Indole-3-Carbinol TR 584	N/A	F344/N	Harlan Sprague Dawley
Green Tea Extract TR 585	N/A	F344/NTac	Wistar Han
Cimstar 3800 TR 586	N/A	F344/NTac	Wistar Han

Questions?