



NTP

National Toxicology Program

Overview of the NTP Rat Models

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NTP F344/N Rat

- This rat model had several favorable characteristics that made it a good choice.
 - For over 30 years the NTP used the F344/N rat in the rodent bioassay, so the historical database was very robust.
 - Relatively small as compared to other rat strains and stocks.
 - Good survival rate at the end of a 104 week 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.
 - There were high background incidences of testicular tumors (interstitial cell tumor) and mononuclear cell leukemia in the F344 rat strain.
 - Over a period of time the F344/N rat used in NTP studies developed declining fertility, sporadic idiopathic seizures, and spontaneous chylothorax without evidence of trauma.
 - These issues were unique to the NTP F344/N colony.
 - 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 used in the NTP rodent bioassay was still an appropriate model in identifying substances that may be a carcinogenic hazard for humans.
 - Invited panel of scientists with expertise in rodent genetics, cancer biology, statistics and other related fields convened in one of several breakout groups to discuss this rodent model and its place in the NTP bioassay.

Strains & Stocks Workshop Summary

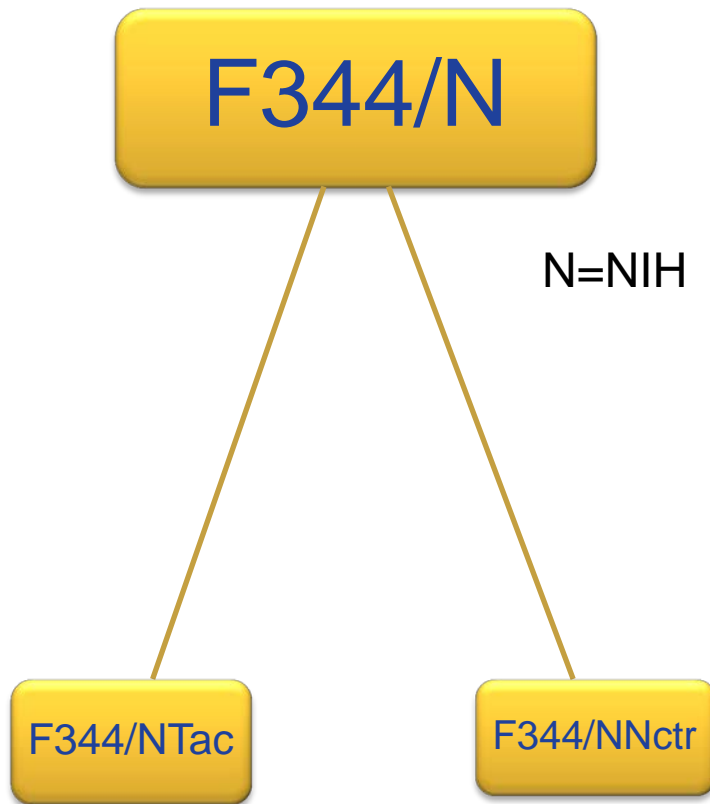
- Rat breakout group recommended discontinue use of the current F344/N rat strain
 - Proposed 3 options:
 - Re-establish the F344/N strain from another source, however the general concerns about the model would still be present.
 - Create an F1 hybrid such as the F344 X Brown Norway cross, FBNF1.
 -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



NTP Deliberations

- Soon after the workshop the NTP discontinued use of the F344/N rat in all new studies and temporarily started using the F344/NTac rat from Taconic Farms, Inc.'s commercial colony.
- Scientists within the NTP deliberated the selection of an alternative rat model.
 - The NTP decided to use a single rat model to study other endpoints in addition to cancer.
 - Introduction of the perinatal exposure paradigm.
 - Outbred model was more appropriate for perinatal exposure studies.

Brief overview on rodent inbred strains: alike but different



- F344/N – NIH rat strain
 - F344/NTac – Substrain of the NIH F344 rat; bred at Taconic Farms, Inc.
 - F344/NNctr – Substrain of the NIH F344 rat; bred at NCTR.
- In general, do not combine historical databases because the three rat strains are more than likely genetically different.

Considerations for Selection of Animal Models

- Availability
- Sensitivity to carcinogens
- Survival
- Spontaneous tumor rate
- Fecundity
- Cost
- Experience with the model
- Stable response
- Similar metabolic pathways to humans
- Similar pathology to humans
- Sensitivity to other endpoints

Selection of the Wistar Han Rat

- In 2007, the Wistar Han rat [Crl:WI(Han)] was selected as the default rat model for NTP studies.
 - Outbred albino rat
 - Long lifespan
 - Moderate size for an outbred rat
 - Good fertility with large litters



Summary of rat models used in the studies presented today

	2-week study	3-month study	2-year study
Vinylidene Chloride TR 581	F344/N	F344/N	F344/N
Cobalt TR 582	F344/N	F344/N	F344/NTac
Tetrabromobisphenol A TR 587	N/A	F344/NTac	Wistar Han (included a 3 month interim evaluation)
Glycidamide TR 588	F344/NNctr	F344/NNctr	F344/NNctr

Questions?

