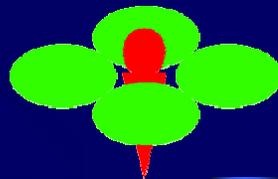


Pathology Evaluation of Long Evans and Wistar Rats in a 2-yr Feeding Study

HANS CHEN

Greenseasons Biotech Co.

Tamshui, Taipei County 251, Taiwan



CROs Safety Assessment in Taiwan

- Developmental Center For Biotech (DCB)
Founded in 1991, first study report issued in 1996
Major study sponsored by institutional research projects
- Green Seasons Biotech Co., Ltd. (GSB)
Founded in 2000 first study report issued in 2001
>500 study reports(health food drugs) issued up to present
Major study include :
 - 1).Acute / subchronic oral toxicity
 - 2).Dermal test, local stimulation and hypersensitivity
 - 3).Others– medical device, etc
 - 4).Special project : MOEA sponsored study

2-yr Feeding Study-MOEA Sponsored Project

Purposes

- Databases for local research organizations
- Under SPF condition, following SOP
- Aimed at GLP lab for credential
- Chronic toxicity/ carcinogenicity databases in Long Evens and Wistar rats; comparison with SD and F344 rats data
- First 2-yr study under barrier system in Taiwan

Protocol

6 time – points

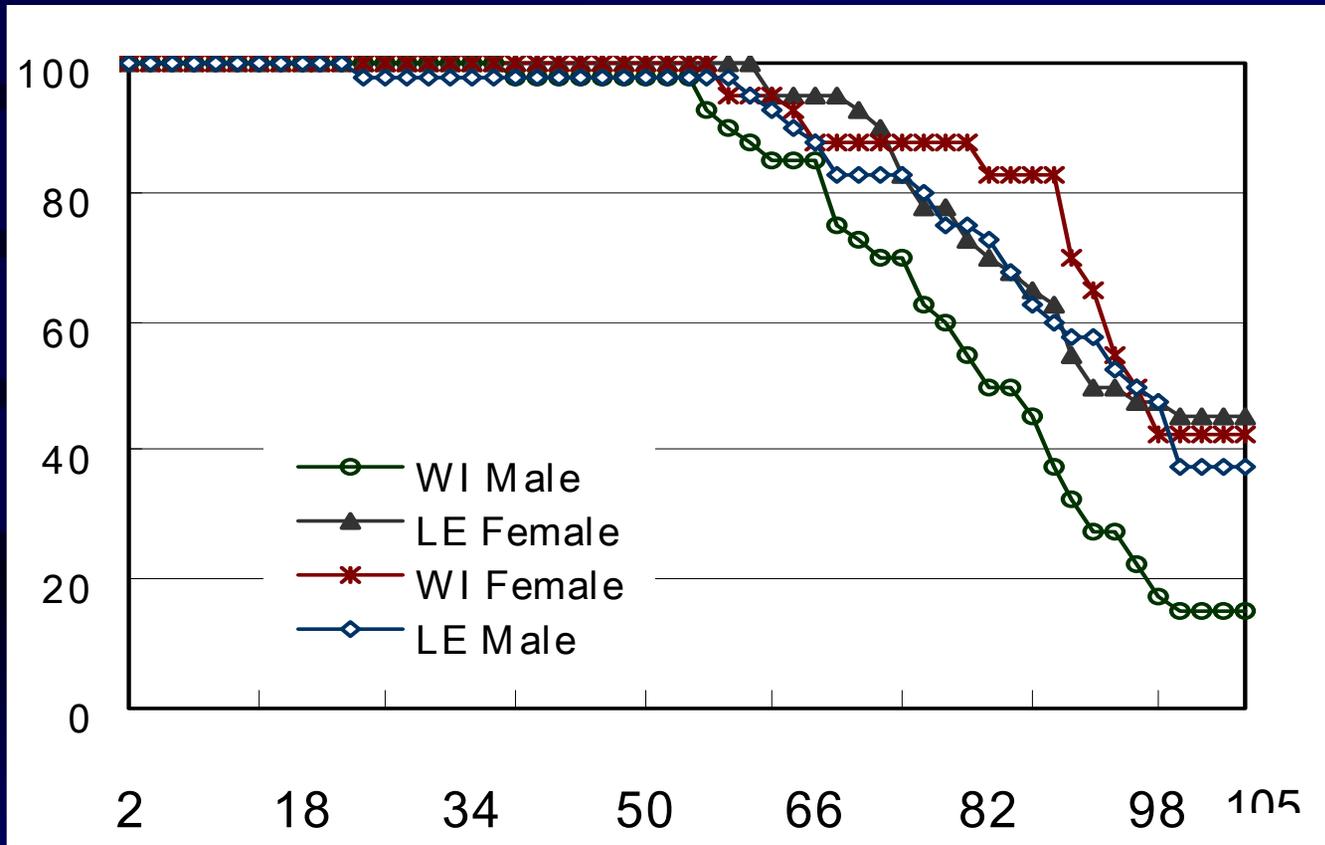
| | 28-d | 90-d | 180-d | 1-yr | 1.5-yr | 2-yr |
|------------------|-------------|-------------|--------------|-------------|---------------|-------------|
| strains | 40 | 40 | 40 | 40 | 60 | 160 |
| LE male | 10 | 10 | 10 | 10 | 15 | 40 |
| LE female | 10 | 10 | 10 | 10 | 15 | 40 |
| WI male | 10 | 10 | 10 | 10 | 15 | 40 |
| WI female | 10 | 10 | 10 | 10 | 15 | 40 |

Table1.– Incidences of animal fates

| Male | | | | | | Female | | | | | |
|-------|------|------|-------|------|------|--------|----|----|-------|------|----|
| 11/LE | | | 12/WI | | | 11/LE | | | 12/WI | | |
| 40 | | | 40 | | | 40 | | | 40 | | |
| FS | KE | FD | FS | KE | FD | FS | KE | FD | FS | KE | FD |
| 14 | 11 | 15 | 6 | 13 | 21 | 18 | 16 | 6 | 17 | 13 | 10 |
| 35 | 27.5 | 37.5 | 15 | 32.5 | 52.5 | 45 | 40 | 15 | 42.5 | 32.5 | 25 |

Fig. 1.--- Survival Curves for LE and WI Rats

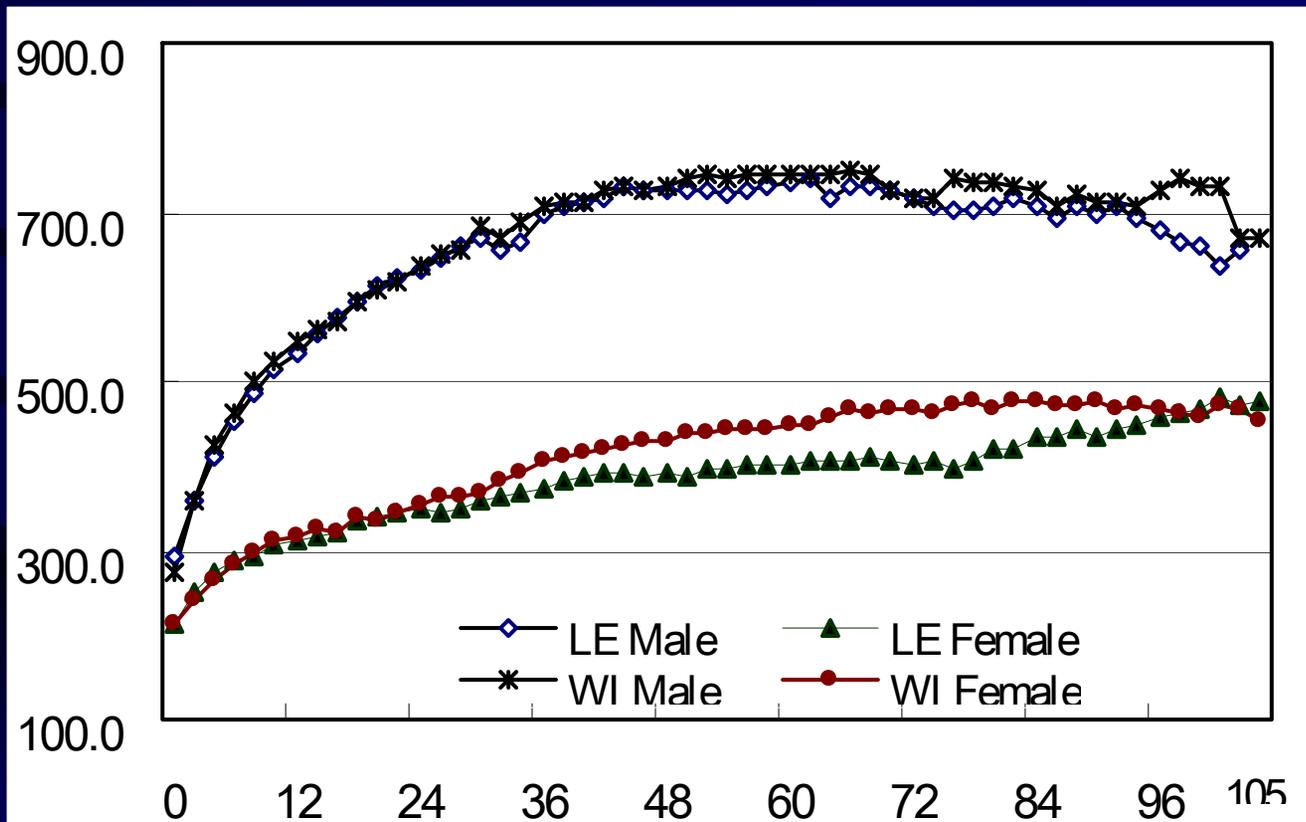
Probability of survival



Weeks on study

Fig. 2.--- Body Weight Curves for LE and WI Rats

Mean Body Weight in Gram



Weeks on study

Table 5.--- Incidences of Death Causes

| Causes | Male | | Female | |
|------------------------------------|----------|----------|----------|---------|
| | 11/LE | 12/WI | 11/LE | 12/WI |
| | 26 | 34 | 22 | 23 |
| Neoplastic Disease (%) | 16(61.9) | 12(35.3) | 15(68.2) | 16(70) |
| Chronic Progressive nephrosis (%) | 5(20) | 17(50) | 6(25) | 4(17.3) |
| Left atrial thrombosis | 0 | 1 | 0 | 0 |
| Murine progressive cardiomyopathy | 0 | 2 | 0 | 0 |
| Stomach: Erosion/ulcer | 0 | 1 | 0 | 0 |
| Fibrinous suppurative pericarditis | 1 | 0 | 0 | 0 |
| Dermatitis, ulcerative | 1 | 0 | 0 | 0 |
| Prostatitis/Abscess | 1 | 0 | 0 | 0 |
| Ovarian hemorrhage | 0 | 0 | 0 | 1 |
| Heart hypertrophy/dilatation | 0 | 0 | 0 | 1 |
| Undetermined | 2 | 1 | 1 | 1 |

Table 6.---Incidences of the Neoplastic Disease in death Causes

| Causes | Male | | Female | |
|--------------------------------|-------------|--------------|-------------|--------------|
| | 11/LE 26 | 12/W I 34 | 11/LE 22 | 12/W I 23 |
| Intestinal Adenocarcinoma | 0 | 0 | 0 | 1 |
| Hemengiosarcoma | 1 | 0 | 0 | 0 |
| Histiocytic sarcoma | 1 | 3 | 0 | 0 |
| Lymphoma, malignant | 1 | 1 | 0 | 0 |
| Malignant hibernoma | 1 | 1 | 0 | 0 |
| Malignant fibrous histiocyoma | 0 | 2 | 0 | 1 |
| Mammary fibroadenoma | 0 | 1 | 1 | 1 |
| Mammary fibrosarcoma | 0 | 0 | 1 | 0 |
| Mammary fibroma | 0 | 0 | 0 | 1 |
| <u>Pituitary adenoma</u> | 9 | 3 | 10 | 9 |
| Heart Schwannoma | 0 | 0 | 0 | 1 |
| Uterus Squamous cell carcinoma | - | - | 1 | 0 |
| Endometrial stromal sarcoma | - | - | 2 | 0 |
| Lieomyosarcoma, eye | 0 | 1 | 0 | 0 |
| Malignant mesenchymal tumor | 1 | 0 | 0 | 0 |
| Islet cell carcinoma | 1 | 0 | 0 | 0 |
| Menigioma | 0 | 0 | 0 | 1 |
| Pinealoma | 0 | 0 | 0 | 1 |
| Astrocytoma | 1 | 0 | 0 | 0 |

Conclusion

There were rather low incidence of lymphoma (including large granular lymphocytic lymphoma), hepatocell adenoma/ adenocarcinoma combined, alveolo-bronchiolar cell adenoma, and renal tubule adenoma noted in these Long Evans and Wistar rats that may reflect some advantagement of using these 2 strains in comparison with SD and F-344 rats that are the most commonly used strain rats for chronic toxicity/carcinogenicity study.