**Presented**
**at the**
**Arthritis Advisory Committee Meeting**
**on**
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**by**

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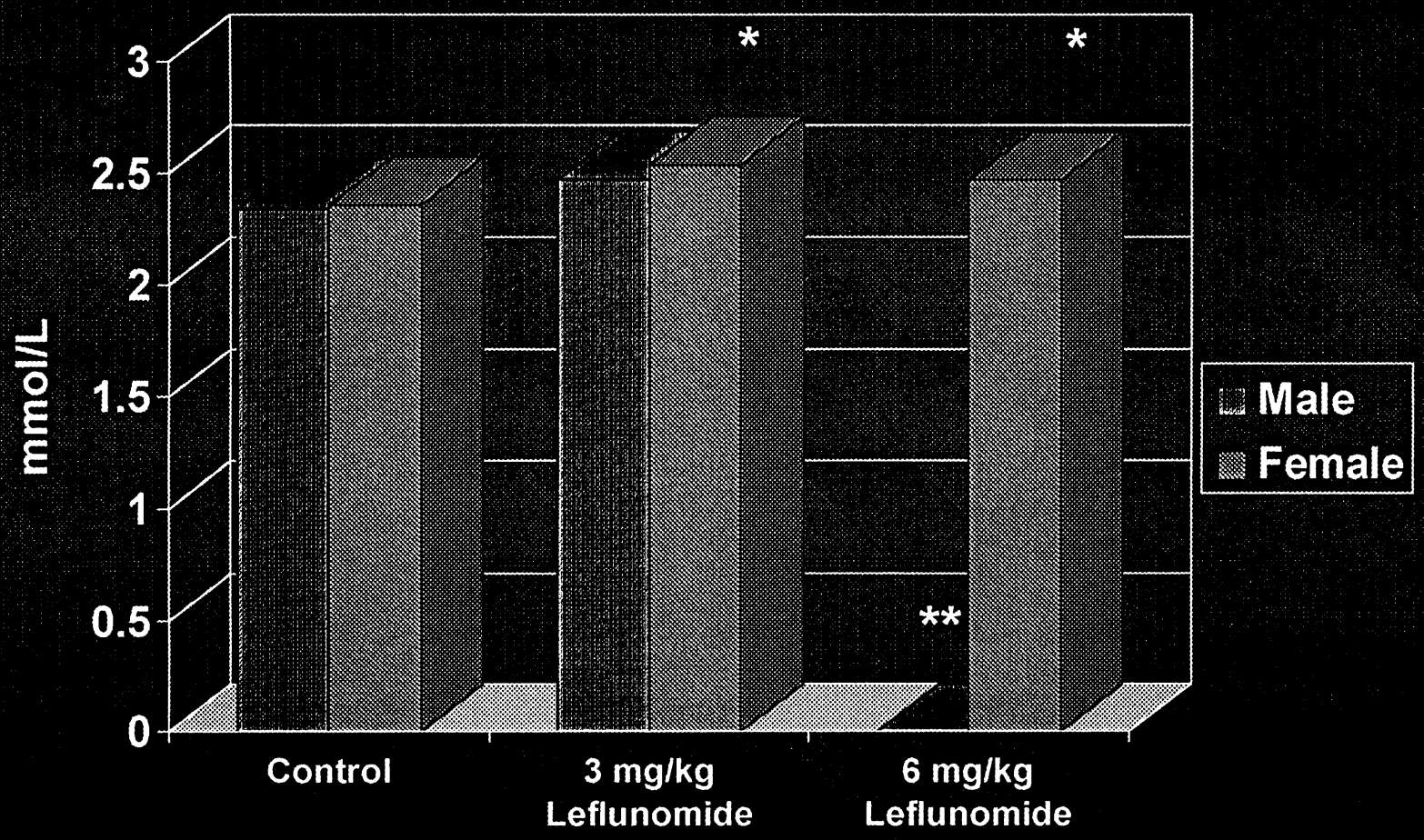
**Analgesic and Ophthalmic Drugs**

# SERUM CALCIUM LEVELS IN WISTAR RATS AT 104 WEEKS

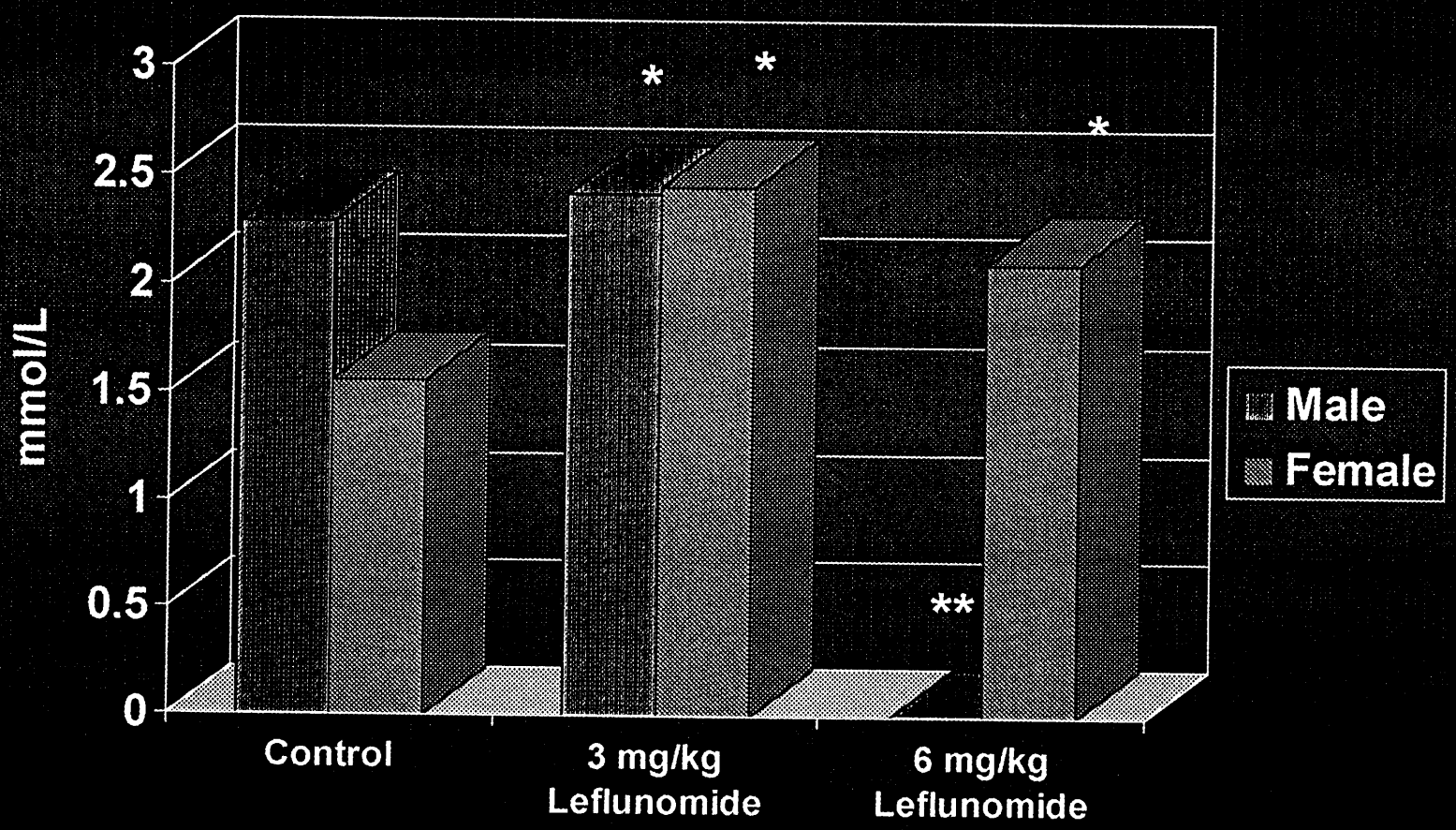



*sig different from the control

** Animals died or killed

PHARMACOLOGY

# SERUM INORGANIC PHOSPHATE LEVELS IN WISTAR RATS AT 104 WEEKS




*sig different from the control

** Animals died or killed

# CONCLUSIONS

- CHRONIC TREATMENT WITH LEFLUNOMIDE SHOWED HIGHER LEVELS OF SERUM CALCIUM AND PHOSPHATE COMPARED TO THE CONTROL AT THE END OF 2nd YEAR IN RATS.
- SIMILAR CHANGES WERE NOT EVIDENT AT THE END OF 1st YEAR.
- SIGNIFICANCE OF THE FINDING IS UNKNOWN

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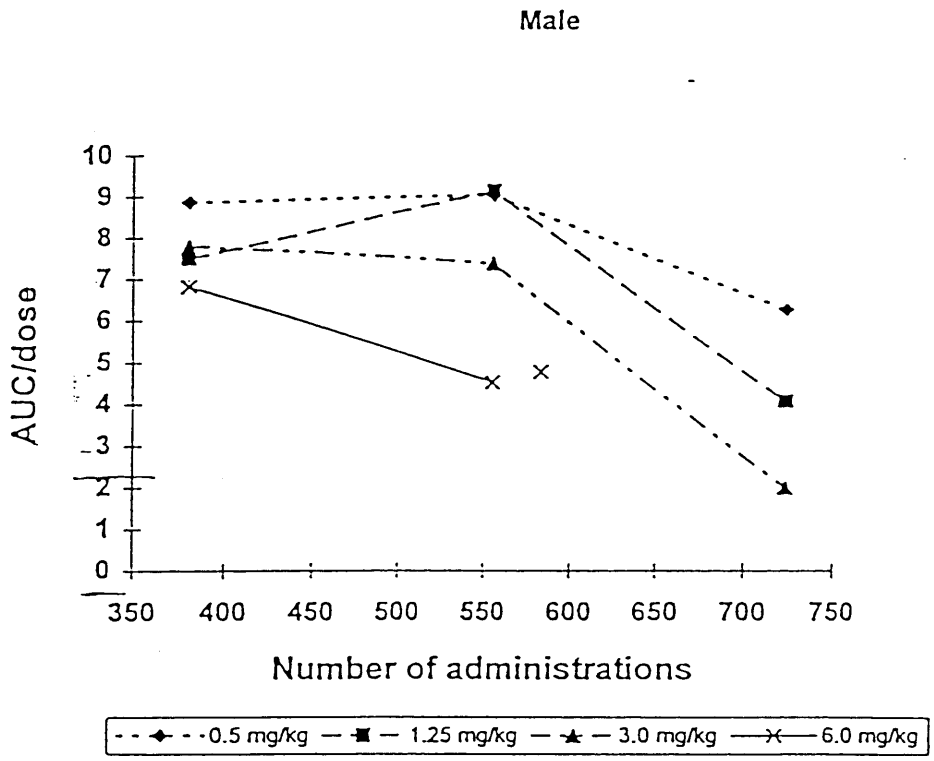
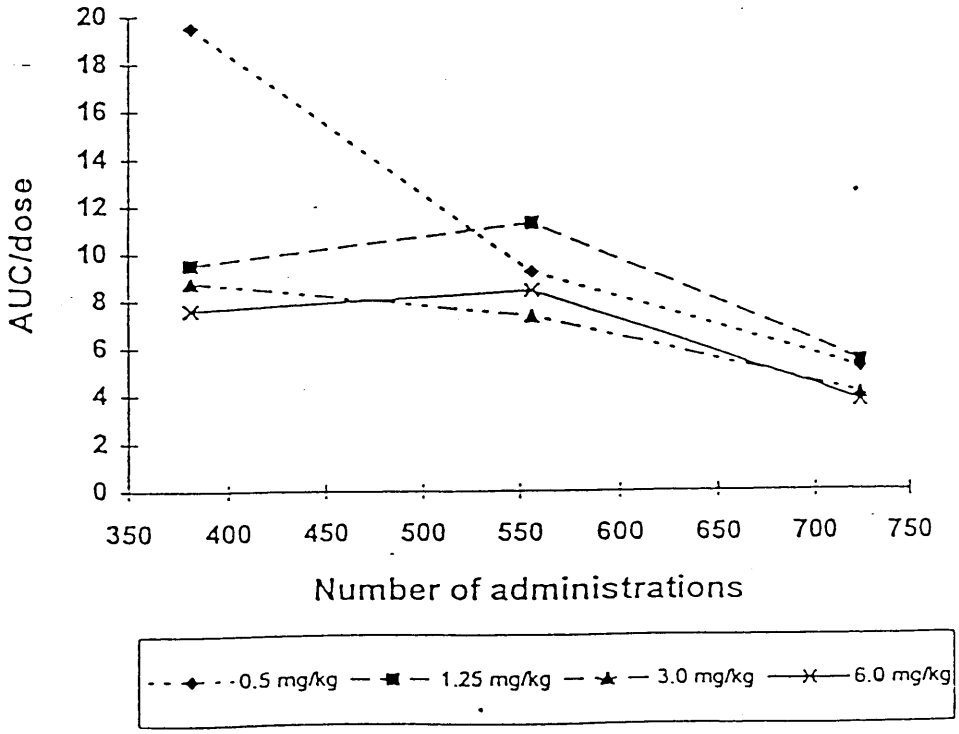
FIGURE 2: Comparison of normalised trapezoidal area (AUC) with the number of dose administrations for serum A77 1726 concentration data from rats dosed in a 2 year carcinogenicity study with HWA 486



Female


20
18
16
14
12
10
8
6
4
2
0
AUC/dose
350
400
450
500
550
600
650
700
750
Number of administrations
0.5 mg/kg
1.25 mg/kg
3.0 mg/kg
6.0 mg/kg

# CHRONIC TOXICITY OF LEFLUNOMIDE IN REPRODUCTIVE ORGANS

## OLIGOSPERMIA

- RATS (0.5-6.0 mg/kg)
- MICE (15 mg/kg)
- DOGS (8 mg/kg)

# GLANDULAR POLYPS OF UTERUS IN WISTAR RATS

| | CONTROL | 0.5 mg/kg | 1.25 mg/kg | 3.0 mg/kg | 6 mg/kg |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS | 100 | 50 | 60 | 80 | 80 |
| NUMBER OBSERVED | 0 | 0 | 1 (1.6%) | 0 | 4 (5%) |

# FIBROSIS OF CERVICAL UTERUS IN CD-1 MICE

| | CONTROL | 1.5 mg/kg | 5 mg/kg | 15 mg/kg |
|---|---|---|---|---|
| NUMBER OF ANIMALS | 100 | 50 | 50 | 70 |
| NUMBER OBSERVED | 2 (2%) | 3 (6%) | 0 (0) | 4 (5.7%) |

# PRECLINICAL REPRODUCTIVE SAFETY STUDIES

| | SEGMENT-I | SEGMENT-II | | SEGMENT-III |
|---|---|---|---|---|
| SPECIES | RAT | RAT | RABIT | RAT |
| DURATION OF TREATMENT | 14 DAYS BEFORE MATING-WEANING | GESTATION DAYS 7-19 | 6-18 | GESTATION DAY 7-POSTPARTUM DAY 21 |
| NO EFFECT DOSE | 0.4 mg/kg | 1 mg/kg | 1 mg/kg | < 0.4 mg/kg |
| $C_{max}$ (μg/ml) | 1.82 (at 0.5 mg/kg) | 3.70 | 4.25 | |
| $C_{24hrs}$ (μg/ml) | 0.54 | 0.97 | 0.30 | |