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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Supplementary Table 1: Incidences of non-neoplastic lesions in bone, eye, forestomach, kidney, lymph node, parathyroid gland, and testes of male F344/N Nctr rats administered 0, 0.02, 0.044, 0.092, 0.2, 0.44, 0.92, or 2 mg furan/kg BW for 2 years. | | | | | | | | | |
| Tissue/Lesion |  | Furan (mg/kg BW) | | | | | | | |
| 0 | 0.02 | 0.044 | 0.092 | 0.2 | 0.44 | 0.92 | 2 |
|  | | | | | | | | | |
| Bone femur fibrous osteodystrophy | Overall ratea | 1/150 (1%) | 1/150 (1%) | 4/100 (4%) | 2/100 (2%) | 1/50 (2%) | 0/50 (0%) | 1/50 (2%) | 3/50 (6%) |
| Poly-3 testb | **P =0.033** | P = 0.757 | P = 0.081 | P = 0.365 | P = 0.514 | P = 0.722N | P =0.477 | **P = 0.033** |
| Average severityc | 2.0 | 2.0 | 2.0 | 2.5 | 2.0 |  | 3.0 | 1.7 |
|  | | | | | | | | | |
| Bone marrow myeloid cell hyperplasia | Overall rate | 36/148 (24%) | 27/150 (18%) | 18/95 (19%) | 20/100 (20%) | 7/49 (14%) | 12/49 (24%) | 15/50 (30%) | 21/49 (43%) |
| Poly-3 test | **P < 0.001** | P = 0.154N | P = 0.213N | P = 0.239N | P = 0.081N | P = 0.491 | P = 0.205 | **P =0.004** |
| Average severity | 2.9 | 2.9 | 2.6 | 3.0 | 2.7 | 2.9 | 3.1 | 3.0 |
|  | | | | | | | | | |
| Eye  cataract | Overall rate | 1/144 (1%) | 2/143 (1%) | 3/92 (3%) | 4/96 (4%) | 2/48 (4%) | 4/45 (9%) | 1/50 (2%) | 6/47 (13%) |
| Poly-3 test | **P < 0.001** | P = 0.490 | P =0.168 | P = 0.084 | P = 0.167 | **P = 0.007** | P =0.487 | **P < 0.001** |
| Average severity | 2.0 | 1.0 | 1.7 | 1.5 | 3.0 | 1.5 | 3.0 | 2.8 |
|  | | | | | | | | | |
| Forestomach edema | Overall rate | 27/149 (18%) | 22/150 (15%) | 13/99 (13%) | 16/100 (16%) | 15/50 (30%) | 12/49 (24%) | 9/50 (18%) | 15/48 (31%) |
| Poly-3 test | **P = 0.004** | P = 0.286N | P = 0.191N | P = 0.413N | P = 0.073 | P = 0.209 | P = 0.487 | **P = 0.032** |
| Average severity | 3.0 | 3.2 | 2.6 | 3.1 | 2.7 | 2.8 | 3.1 | 2.8 |
|  | | | | | | | | | |
| Forestomach epithelium hyperplasia | Overall rate | 41/149 (28%) | 41/150 (27%) | 22/99 (22%) | 24/100 (24%) | 19/50 (38%) | 17/49 (35%) | 15/50 (30%) | 21/48 (44%) |
| Poly-3 test | **P = 0.004** | P = 0.533N | P = 0.215N | P = 0.352N | P = 0.135 | P = 0.214 | P = 0.339 | **P =0.022** |
| Average severity | 2.6 | 2.6 | 2.6 | 2.7 | 2.4 | 2.4 | 2.0 | 2.5 |
|  | | | | | | | | | |
| Forestomach chronic active inflammation | Overall rate | 33/149 (22%) | 31/150 (21%) | 18//99 (18%) | 19/100 (19%) | 14/50 (28%) | 15/49 (31%) | 13/50 (26%) | 19/48 (40%) |
| Poly-3 test | **P < 0.001** | P = 0.473N | P = 0.275N | P = 0.348N | P = 0.308 | P = 0.148 | P = 0.259 | **P = 0.011** |
| Average severity | 2.5 | 2.7 | 2.6 | 2.6 | 3.0 | 2.4 | 2.2 | 2.3 |
|  | | | | | | | | | |
| Forestomach ulcer | Overall rate | 13/149 (9%) | 17/150 (11%) | 11/99 (11%) | 7/100 (7%) | 5/50 (10%) | 9/49 (18%) | 5/50 (10%) | 9/48 (19%) |
| Poly-3 test | **P = 0.027** | P =0.281 | P = 0.359 | P =0.398N | P = 0.570 | P = 0.052 | P = 0.438 | **P = 0.043** |
| Average severity | 3.2 | 3.1 | 3.5 | 3.1 | 2.8 | 3.1 | 3.4 | 2.6 |
|  | | | | | | | | | |
| Kidney transitional epithelium hyperplasia | Overall rate | 27/150 (18%) | 39/150 (26%) | 25/99 (25%) | 23/100 (23%) | 14/50 (28%) | 9/49 (18%) | 12/50 (24%) | 19/50 (38%) |
| Poly-3 test | **P = 0.008** | **P = 0.048** | P = 0.126 | P = 0.202 | P = 0.122 | P = 0.567 | P = 0.155 | **P = 0.001** |
| Average severity | 1.4 | 1.6 | 1.6 | 1.5 | 1.5 | 1.8 | 1.3 | 1.4 |
|  | | | | | | | | | |
| Lymph node pancreatic sinus dilation | Overall rate | 0/59 (0%) | 1/69 (1%) | 1/35 (3%) | 0/38 (0%) | 0/23 (0%) | 0/20 (0%) | 0/26 (0%) | 4/33 (12%) |
| Poly-3 test | **P < 0.001** | P = 0.533 | P = 0.388 |  |  |  |  | **P = 0.010** |
| Average severity |  | 2.0 | 2.0 |  |  |  |  | 3.3 |
|  | | | | | | | | | |
| Parathyroid gland hyperplasia | Overall rate | 38/149 (26%) | 25/150 (17%) | 11/98 (11%) | 15/98 (15%) | 8/50 (16%) | 5/49 (10%) | 7/50 (14%) | 19/50 (38%) |
| Poly-3 test | **P = 0.002** | P = 0.045N | P = 0.003N | P = 0.031N | P = 0.081N | P = 0.019N | P = 0.116N | **P = 0.044** |
| Average severity | 1.5 | 1.6 | 2.0 | 1.9 | 1.6 | 1.6 | 1.7 | 1.7 |
|  | | | | | | | | | |
| Testes mineralization | Overall rate | 1/150 (1%) | 0/149 (0%) | 0/98 (0%) | 1/100 (1%) | 0/50 (0%) | 0/49 (0%) | 0/50 (0%) | 3/50 (6%) |
| Poly-3 test | **P < 0.001** | P = 0.505N | P = 0.585N | P = 0.671 | P = 0.709N | P = 0.724N | P = 0.732N | **P = 0.034** |
| Average severity | 2.0 |  |  | 3.0 |  |  |  | 3.3 |

aNumber of animals with a lesion/number of animals examined microscopically.

bBeneath the 0 mg furan/kg BW incidences are the P-values associated with the trend test. Beneath the treated group incidences are the P-values corresponding to pair-wise comparisons between the 0 mg furan/kg BW group and each treated group. The Poly-3 test accounts for differential mortality in animals that do not reach the terminal sacrifice. P-values < 0.05 were considered significant and are bolded. An N indicates a lower incidence compared to the 0 mg furan/kg BW group.

cAverage severity of the observed lesions. The severity of the lesions was graded as 1, minimal; 2, mild; 3, moderate; and 4, marked.

**Supplementary figure legends**

Supplementary figure 1. Benchmark dose modeling of incidences of epididymis or testes malignant mesothelioma in male F344/N Nctr rats administered 0, 0.02, 0.044, 0.092, 0.2, 0.44, 0.92, or 2 mg furan/kg BW for 2 years. A. Gamma model; B. Logistic model; C. Log-Logistic model; D. Log-Probit model; E. Multistage model; F. Probit model; and G. Weibull model.

Supplementary figure 2. Benchmark dose modeling of incidences of cholangiofibrosis in male F344/N Nctr rats administered 0, 0.02, 0.044, 0.092, 0.2, 0.44, 0.92, or 2 mg furan/kg BW for 2 years. A. Gamma model; B. Logistic model; C. Log-Logistic model; D. Log-Probit model; E. Probit model; and F. Weibull model.

Benchmark dose modeling of incidences of epididymis or testes malignant mesothelioma in male F344/N Nctr rats

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Benchmark dose modeling of incidences of epididymis or testes malignant mesothelioma in male F344/N Nctr rats

Benchmark dose modeling of incidences of cholangiofibrosis in male F344/N Nctr rats

Benchmark dose modeling of incidences of cholangiofibrosis in male F344/N Nctr rats

Benchmark dose modeling of incidences of cholangiofibrosis in male F344/N Nctr rats