A 03

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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National Institute of
Environmental Health Sciences
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February 06, 2001

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Dear Document Control Office:

In compliance with the National Toxicology Program's (NTP) mission to keep our colleagues informed of the current NTP findings during ongoing studies, a copy of the revised Summary Pathology Tables for the chronic Dosed-Feed study on EMODIN (518-82-1) are enclosed for your review.

The NTP assembles a Pathology Working Group to review every study and to resolve any differences between the study laboratory and quality assessment pathology evaluations. Please note that the PWG conclusion of the study results is based solely on the pathology for this study and may not reflect final NTP conclusions. In determining final conclusions, the NTP assesses a broad array of information that includes other results from this study and historical control data.

The Summary Pathology Tables contain the Incidence Rates of Neoplastic and Non-neoplastic Lesion data and the Statistical Analysis of Primary Tumors data pertaining to the laboratory animals. All study data are subject to an NTP retrospective audit and the interpretation may be modified based on the findings.

A wide variety of NTP information is also available in electronic format on the world-wide web, for example, the NTP Annual Plan, abstracts of NTP Reports, study data, and the status of all NTP studies. To view this information requires access to the internet and a Web browser such as Netscape Navigator or Internet Explorer. To access the NTP home page, use the URL http://ntp-server.niehs.nih.gov/. Comments on the usefulness of this site and suggestions for improvement are encouraged.

Please contact Central Data Management (CDM) at (919)541-3419 if you have any questions. You may also fax your requests for information to CDM at (919)541-3687 or send them via e-mail to cdm@niehs.nih.gov.

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Sincerely,

William Eastin

William Eastin, Ph.D.
Head, Information Systems & Central Files
Environmental Toxicology Program

Encls: Revised Pathology Summary Tables for Rats
cc: Central Data Management

# NATIONAL TOXICOLOGY PROGRAM

Revision: The final #3 set incorporated skin neoplasm and nonneoplastic lesion changes from Dr. Nyska per a special PWG.

## TR-493 Emodin

### Pathology Tables - Rats

P03 - Incidence Rates of Non-Neoplastic Lesions - 2 year Study

P05 - Incidence Rates of Neoplasms by Anatomic Site (systemic lesions abridged) - 2 year Study

P08 - Statistical Analysis of Primary Tumors - 2 year Study

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



FINAL#3;REVISION#1

Facility: Southern Research Institute

Chemical CAS #: 518-82-1

Lock Date: 07/30/97

Cage Range: All

Reasons For Removal: 25022 Accidently Killed
25020 Natural Death
25019 Moribund Sacrifice
25021 Terminal Sacrifice

Removal Date Range: All

Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion



A 06

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| **DISPOSITION SUMMARY** | | | | |
| Animals Initially In Study | 60 | 60 | 60 | 60 |
| Early Deaths | | | | |
| Moribund Sacrifice | 12 | 8 | 11 | 15 |
| Natural Death | 5 | 3 | 4 | 1 |
| Survivors | | | | |
| Terminal Sacrifice | 33 | 39 | 35 | 34 |
| Animals Examined Microscopically | 50 | 50 | 50 | 50 |
| **ALIMENTARY SYSTEM** | | | | |
| Intestine Large, Cecum | (49) | (50) | (49) | (50) |
| Edema | | | 1 (2%) | |
| Hemorrhage | | | 1 (2%) | |
| Inflammation, Acute | | | 1 (2%) | |
| Intestine Small, Duodenum | (48) | (50) | (49) | (50) |
| Epithelium, Hyperplasia | | | 1 (2%) | |
| Liver | (49) | (50) | (50) | (50) |
| Angiectasis | | | 2 (4%) | 4 (8%) |
| Basophilic Focus | 39 (80%) | 44 (88%) | 41 (82%) | 45 (90%) |
| Clear Cell Focus | 2 (4%) | 10 (20%) | 4 (8%) | 11 (22%) |
| Eosinophilic Focus | 18 (37%) | 10 (20%) | 18 (36%) | 27 (54%) |
| Hematopoietic Cell Proliferation | 2 (4%) | | 2 (4%) | 2 (4%) |
| Hemorrhage | 1 (2%) | | 1 (2%) | |
| Hepatodiaphragmatic Nodule | 3 (6%) | 9 (18%) | 7 (14%) | 7 (14%) |
| Infiltration Cellular, Mixed Cell | 15 (31%) | 12 (24%) | 9 (18%) | 11 (22%) |
| Mixed Cell Focus | 4 (8%) | 5 (10%) | 6 (12%) | 1 (2%) |
| Necrosis, Focal | 4 (8%) | 4 (8%) | 3 (6%) | |
| Bile Duct, Hyperplasia | 1 (2%) | | 4 (8%) | 1 (2%) |
| Centrilobular, Necrosis | | 1 (2%) | | 1 (2%) |
| Hepatocyte, Vacuolization Cytoplasmic | 3 (6%) | 2 (4%) | 2 (4%) | 2 (4%) |
| Kupffer Cell, Pigmentation | 2 (4%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Mesentery | (1) | (6) | (1) | (6) |
| Accessory Spleen | | 2 (33%) | | 2 (33%) |
| Fat, Necrosis | 1 (100%) | 4 (67%) | 1 (100%) | 5 (83%) |
| Pancreas | (49) | (50) | (49) | (50) |
| Atrophy | 13 (27%) | 15 (30%) | 18 (37%) | 13 (26%) |
| Metaplasia, Hepatocyte | 1 (2%) | | | |
| Salivary Glands | (49) | (50) | (50) | (50) |
| Atrophy | 1 (2%) | | 1 (2%) | 2 (4%) |
| Stomach, Forestomach | (49) | (50) | (50) | (50) |

a Number of animals examined microscopically at site and number of animals with lesion



A 07

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| ALIMENTARY SYSTEM - CONT | | | | |
| Edema | 1 (2%) | 1 (2%) | 1 (2%) | |
| Erosion | | | 1 (2%) | |
| Perforation | | | 1 (2%) | |
| Epithelium, Hyperplasia | 1 (2%) | | | |
| Stomach, Glandular | (49) | (50) | (50) | (50) |
| Edema | | | 1 (2%) | |
| Erosion | | 1 (2%) | 1 (2%) | 1 (2%) |
| Tongue | | (1) | | |
| Epithelium, Hyperplasia | | 1 (100%) | | |
| CARDIOVASCULAR SYSTEM | | | | |
| Heart | (49) | (50) | (50) | (50) |
| Cardiomyopathy | 22 (45%) | 16 (32%) | 17 (34%) | 16 (32%) |
| Inflammation, Chronic Active | | 1 (2%) | | |
| ENDOCRINE SYSTEM | | | | |
| Adrenal Cortex | (49) | (50) | (50) | (50) |
| Accessory Adrenal Cortical Nodule | 6 (12%) | 4 (8%) | 7 (14%) | 10 (20%) |
| Atrophy | | | | 2 (4%) |
| Degeneration, Fatty | 12 (24%) | 9 (18%) | 14 (28%) | 10 (20%) |
| Hemorrhage | 1 (2%) | 1 (2%) | | |
| Hyperplasia, Diffuse | 1 (2%) | | | |
| Hyperplasia, Focal | 3 (6%) | 3 (6%) | 8 (16%) | 7 (14%) |
| Hypertrophy | 1 (2%) | | | |
| Hypertrophy, Focal | 12 (24%) | 7 (14%) | 12 (24%) | 10 (20%) |
| Necrosis | | 2 (4%) | | |
| Adrenal Medulla | (47) | (50) | (50) | (50) |
| Hyperplasia | 2 (4%) | 2 (4%) | 2 (4%) | 3 (6%) |
| Islets, Pancreatic | (49) | (50) | (49) | (50) |
| Hyperplasia | | 1 (2%) | | |
| Pituitary Gland | (49) | (50) | (49) | (49) |
| Pars Distalis, Angiectasis | 9 (18%) | 10 (20%) | 6 (12%) | 5 (10%) |
| Pars Distalis, Cyst | 22 (45%) | 11 (22%) | 13 (27%) | 16 (33%) |
| Pars Distalis, Hyperplasia, Focal | 13 (27%) | 10 (20%) | 3 (6%) | 5 (10%) |
| Pars Intermedia, Cyst | | 1 (2%) | | |
| Thyroid Gland | (49) | (50) | (50) | (50) |
| Ultimobranchial Cyst | 1 (2%) | | 1 (2%) | |
| C-Cell, Hyperplasia | 21 (43%) | 9 (18%) | 11 (22%) | 12 (24%) |
| Follicle, Cyst | 1 (2%) | 1 (2%) | 2 (4%) | 2 (4%) |

a Number of animals examined microscopically at site and number of animals with lesion



A 08

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| **GENERAL BODY SYSTEM** | | | | |
| None | | | | |
| **GENITAL SYSTEM** | | | | |
| Clitoral Gland | (49) | (50) | (49) | (49) |
| Cyst | 1 (2%) | | 4 (8%) | 1 (2%) |
| Hyperplasia | 3 (6%) | 2 (4%) | 6 (12%) | 3 (6%) |
| Inflammation, Chronic | 5 (10%) | 5 (10%) | 6 (12%) | 5 (10%) |
| Ovary | (49) | (50) | (50) | (50) |
| Cyst | 10 (20%) | 6 (12%) | 6 (12%) | 7 (14%) |
| Uterus | (49) | (50) | (50) | (50) |
| Angiectasis | | 1 (2%) | | |
| Hydrometra | 5 (10%) | 3 (6%) | 5 (10%) | 6 (12%) |
| Hyperplasia, Cystic | 1 (2%) | 5 (10%) | 4 (8%) | 7 (14%) |
| Inflammation, Chronic | 1 (2%) | | 1 (2%) | 2 (4%) |
| **HEMATOPOIETIC SYSTEM** | | | | |
| Bone Marrow | (49) | (50) | (50) | (50) |
| Hyperplasia | 5 (10%) | 3 (6%) | 4 (8%) | 6 (12%) |
| Infiltration Cellular, Histiocyte | | 2 (4%) | 4 (8%) | 2 (4%) |
| Lymph Node | (5) | (3) | (4) | (3) |
| Mediastinal, Hemorrhage | | | 2 (50%) | 1 (33%) |
| Mediastinal, Hyperplasia, Lymphoid | | | 1 (25%) | 1 (33%) |
| Mediastinal, Pigmentation | 1 (20%) | 1 (33%) | 1 (25%) | |
| Pancreatic, Hematopoietic Cell Proliferation | | | 1 (25%) | |
| Pancreatic, Hemorrhage | | | 1 (25%) | |
| Lymph Node, Mandibular | (49) | (50) | (50) | (50) |
| Ectasia | 1 (2%) | 2 (4%) | 6 (12%) | 6 (12%) |
| Hemorrhage | 2 (4%) | 4 (8%) | 4 (8%) | 4 (8%) |
| Hyperplasia, Lymphoid | 1 (2%) | | 2 (4%) | 1 (2%) |
| Pigmentation | 18 (37%) | 19 (38%) | 21 (42%) | 25 (50%) |
| Lymph Node, Mesenteric | (49) | (50) | (49) | (50) |
| Hemorrhage | 2 (4%) | 5 (10%) | 2 (4%) | 4 (8%) |
| Pigmentation | 2 (4%) | 2 (4%) | | 2 (4%) |
| Spleen | (50) | (50) | (50) | (50) |
| Angiectasis | | | | 1 (2%) |
| Depletion Cellular | | 1 (2%) | | |
| Developmental Malformation | | | | 1 (2%) |

a Number of animals examined microscopically at site and number of animals with lesion



A 09

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| HEMATOPOIETIC SYSTEM - CONT | | | | |
| Fibrosis | | | | 2 (4%) |
| Hematopoietic Cell Proliferation | 27 (54%) | 24 (48%) | 31 (62%) | 40 (80%) |
| Hemorrhage | 1 (2%) | | 1 (2%) | |
| Hyperplasia, Histiocytic | | | 1 (2%) | |
| Necrosis | 1 (2%) | 1 (2%) | | |
| Pigmentation | 30 (60%) | 30 (60%) | 35 (70%) | 43 (86%) |
| Thymus | (47) | (49) | (49) | (50) |
| Cyst | | | | 1 (2%) |
| INTEGUMENTARY SYSTEM | | | | |
| Mammary Gland | (49) | (50) | (50) | (50) |
| Hyperplasia | 44 (90%) | 44 (88%) | 42 (84%) | 42 (84%) |
| Skin | (49) | (50) | (50) | (50) |
| Hyperkeratosis | 1 (2%) | 1 (2%) | 1 (2%) | 3 (6%) |
| Inflammation, Chronic | 1 (2%) | | 1 (2%) | |
| Ulcer | 2 (4%) | 1 (2%) | 4 (8%) | 3 (6%) |
| Epidermis, Hyperplasia | 4 (8%) | 2 (4%) | 5 (10%) | 5 (10%) |
| MUSCULOSKELETAL SYSTEM | | | | |
| Bone | (49) | (50) | (50) | (50) |
| Cranium, Osteopetrosis | 7 (14%) | 5 (10%) | 6 (12%) | 8 (16%) |
| Femur, Osteopetrosis | 6 (12%) | 8 (16%) | 7 (14%) | 7 (14%) |
| Skeletal Muscle | | | (1) | |
| Atrophy | | | 1 (100%) | |
| NERVOUS SYSTEM | | | | |
| Brain | (49) | (50) | (50) | (50) |
| Compression | 8 (16%) | 7 (14%) | 10 (20%) | 7 (14%) |
| Hydrocephalus | 3 (6%) | | 3 (6%) | 7 (14%) |
| Peripheral Nerve | (2) | (1) | (3) | |
| Atrophy | | | 1 (33%) | |
| RESPIRATORY SYSTEM | | | | |
| Lung | (49) | (50) | (50) | (50) |
| Hemorrhage | 3 (6%) | 1 (2%) | 2 (4%) | 5 (10%) |

a Number of animals examined microscopically at site and number of animals with lesion



A 10

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| RESPIRATORY SYSTEM - CONT | | | | |
| Infiltration Cellular, Histiocyte | 38 (78%) | 37 (74%) | 34 (68%) | 32 (64%) |
| Inflammation, Chronic | 1 (2%) | 1 (2%) | 1 (2%) | |
| Alveolar Epithelium, Hyperplasia | 3 (6%) | 4 (8%) | | 4 (8%) |
| Nose | (49) | (50) | (50) | (50) |
| Foreign Body | 1 (2%) | | 1 (2%) | 2 (4%) |
| Inflammation, Chronic | 6 (12%) | 3 (6%) | 5 (10%) | 5 (10%) |
| Goblet Cell, Hyperplasia | 1 (2%) | | 1 (2%) | |
| Respiratory Epithelium, Hyperplasia | 6 (12%) | 4 (8%) | 4 (8%) | 1 (2%) |
| Respiratory Epithelium, Metaplasia, Squamous | 1 (2%) | 1 (2%) | | 2 (4%) |
| SPECIAL SENSES SYSTEM | | | | |
| Eye | (5) | (2) | (4) | (2) |
| Cataract | 4 (80%) | 2 (100%) | 3 (75%) | 1 (50%) |
| Hemorrhage | | | 2 (50%) | |
| Inflammation, Chronic | | | 1 (25%) | 1 (50%) |
| Retina, Degeneration | 4 (80%) | 2 (100%) | 3 (75%) | 1 (50%) |
| URINARY SYSTEM | | | | |
| Kidney | (49) | (50) | (49) | (50) |
| Cyst | | | 1 (2%) | |
| Glomerulosclerosis | | | 1 (2%) | |
| Hydronephrosis | | | 1 (2%) | |
| Infarct | | | 2 (4%) | 3 (6%) |
| Inflammation, Chronic | | 1 (2%) | 1 (2%) | 3 (6%) |
| Nephropathy | 46 (94%) | 43 (86%) | 45 (92%) | 49 (98%) |
| Papilla, Necrosis | | | 1 (2%) | |
| Renal Tubule, Hyaline Droplet | 22 (45%) | 49 (98%) | 49 (100%) | 50 (100%) |
| Renal Tubule, Hyperplasia, Oncocytic | | | | 2 (4%) |
| Renal Tubule, Necrosis | 1 (2%) | | | |
| Renal Tubule, Pigmentation | 45 (92%) | 49 (98%) | 49 (100%) | 50 (100%) |
| Transitional Epithelium, Hyperplasia | 2 (4%) | | 1 (2%) | 1 (2%) |
| Urinary Bladder | (49) | (50) | (50) | (50) |
| Hemorrhage | | | 1 (2%) | |
| Necrosis | | | 1 (2%) | |

a Number of animals examined microscopically at site and number of animals with lesion



A11

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 630 PPM | 2500 PPM |
|---|---|---|---|---|
| DISPOSITION SUMMARY | | | | |
| Animals Initially In Study | 60 | 60 | 60 | 60 |
| Early Deaths | | | | |
| Moribund Sacrifice | 17 | 26 | 27 | 16 |
| Natural Death | 3 | 3 | 2 | 4 |
| Survivors | | | | |
| Terminal Sacrifice | 30 | 21 | 21 | 30 |
| Animals Examined Microscopically | 50 | 50 | 50 | 50 |
| ALIMENTARY SYSTEM | | | | |
| Intestine Large, Colon | (49) | (50) | (50) | (50) |
| Congestion | | 1 (2%) | | |
| Edema | | 1 (2%) | | |
| Inflammation, Chronic | | | | 1 (2%) |
| Epithelium, Hyperplasia | | | | 1 (2%) |
| Intestine Large, Cecum | (49) | (50) | (50) | (49) |
| Congestion | | 1 (2%) | | |
| Edema | 2 (4%) | 2 (4%) | 3 (6%) | 2 (4%) |
| Inflammation, Chronic | | | | 2 (4%) |
| Epithelium, Hyperplasia | | | | 2 (4%) |
| Intestine Small, Jejunum | (49) | (48) | (50) | (49) |
| Congestion | | 1 (2%) | | |
| Epithelium, Hyperplasia | | | | 1 (2%) |
| Liver | (50) | (50) | (50) | (50) |
| Angiectasis | 5 (10%) | 5 (10%) | | 11 (22%) |
| Basophilic Focus | 20 (40%) | 18 (36%) | 18 (36%) | 23 (46%) |
| Clear Cell Focus | 7 (14%) | 7 (14%) | 9 (18%) | 13 (26%) |
| Degeneration, Cystic | 7 (14%) | 10 (20%) | 11 (22%) | 10 (20%) |
| Eosinophilic Focus | 6 (12%) | 8 (16%) | 6 (12%) | 10 (20%) |
| Hematopoietic Cell Proliferation | 2 (4%) | | | |
| Hemorrhage | | | 1 (2%) | |
| Hepatodiaphragmatic Nodule | 3 (6%) | 5 (10%) | 2 (4%) | 4 (8%) |
| Infiltration Cellular, Mixed Cell | | 2 (4%) | 2 (4%) | 2 (4%) |
| Mixed Cell Focus | 6 (12%) | 4 (8%) | 3 (6%) | 9 (18%) |
| Necrosis, Focal | 2 (4%) | 2 (4%) | 2 (4%) | |
| Bile Duct, Hyperplasia | 33 (66%) | 24 (48%) | 20 (40%) | 14 (28%) |
| Centrilobular, Necrosis | 1 (2%) | 1 (2%) | | |
| Hepatocyte, Vacuolization Cytoplasmic | 3 (6%) | 3 (6%) | 4 (8%) | 2 (4%) |
| Kupffer Cell, Pigmentation | 1 (2%) | 1 (2%) | 2 (4%) | 4 (8%) |
| Mesentery | (8) | (7) | (13) | (15) |

a Number of animals examined microscopically at site and number of animals with lesion



A 12

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| ALIMENTARY SYSTEM - CONT | | | | |
| Accessory Spleen | 4 (50%) | 2 (29%) | 2 (15%) | |
| Fat, Necrosis | 5 (63%) | 6 (86%) | 11 (85%) | 12 (80%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Atrophy | 23 (46%) | 19 (38%) | 16 (32%) | 23 (46%) |
| Metaplasia, Hepatocyte | 1 (2%) | | 1 (2%) | |
| Acinus, Hyperplasia, Focal | 1 (2%) | 1 (2%) | | 1 (2%) |
| Salivary Glands | (50) | (50) | (50) | (49) |
| Edema | | 1 (2%) | | |
| Stomach, Forestomach | (50) | (50) | (49) | (48) |
| Diverticulum | 1 (2%) | | | |
| Edema | 4 (8%) | 3 (6%) | 2 (4%) | 5 (10%) |
| Perforation | | | 1 (2%) | |
| Ulcer | 6 (12%) | 2 (4%) | 4 (8%) | 4 (8%) |
| Epithelium, Hyperplasia | 5 (10%) | 4 (8%) | 7 (14%) | 5 (10%) |
| Stomach, Glandular | (50) | (50) | (49) | (48) |
| Edema | 1 (2%) | 3 (6%) | | |
| Erosion | 1 (2%) | 2 (4%) | 3 (6%) | 1 (2%) |
| Ulcer | 2 (4%) | 3 (6%) | 1 (2%) | 1 (2%) |
| Epithelium, Hyperplasia | | 1 (2%) | | |
| CARDIOVASCULAR SYSTEM | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Cardiomyopathy | 34 (68%) | 31 (62%) | 35 (70%) | 36 (72%) |
| Thrombosis | | 2 (4%) | 4 (8%) | 2 (4%) |
| ENDOCRINE SYSTEM | | | | |
| Adrenal Cortex | (50) | (50) | (50) | (50) |
| Accessory Adrenal Cortical Nodule | 13 (26%) | 18 (36%) | 16 (32%) | 10 (20%) |
| Degeneration, Fatty | 7 (14%) | 9 (18%) | 10 (20%) | 8 (16%) |
| Hyperplasia, Diffuse | | 2 (4%) | 1 (2%) | 1 (2%) |
| Hyperplasia, Focal | 3 (6%) | | 4 (8%) | 2 (4%) |
| Hypertrophy | | | 1 (2%) | |
| Hypertrophy, Focal | 6 (12%) | 9 (18%) | 7 (14%) | 3 (6%) |
| Necrosis | | 1 (2%) | | |
| Adrenal Medulla | (50) | (49) | (50) | (50) |
| Hyperplasia | 10 (20%) | 9 (18%) | 7 (14%) | 17 (34%) |
| Islets, Pancreatic | (50) | (50) | (49) | (50) |
| Hyperplasia | 5 (10%) | | 1 (2%) | 2 (4%) |
| Parathyroid Gland | (48) | (45) | (45) | (47) |

a Number of animals examined microscopically at site and number of animals with lesion



A 13

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| ENDOCRINE SYSTEM - CONT | | | | |
| Hyperplasia, Focal | | 1 (2%) | | |
| Pituitary Gland | (49) | (50) | (48) | (50) |
| Pars Distalis, Angiectasis | 1 (2%) | | 1 (2%) | 1 (2%) |
| Pars Distalis, Cyst | 7 (14%) | 9 (18%) | 5 (10%) | 3 (6%) |
| Pars Distalis, Hyperplasia, Focal | 6 (12%) | 3 (6%) | 5 (10%) | 1 (2%) |
| Pars Intermedia, Cyst | | 1 (2%) | | |
| Thyroid Gland | (50) | (50) | (50) | (50) |
| Ultimobranchial Cyst | | | 1 (2%) | 1 (2%) |
| C-Cell, Hyperplasia | 7 (14%) | 2 (4%) | 7 (14%) | 4 (8%) |
| Follicle, Cyst | 1 (2%) | 3 (6%) | 1 (2%) | 1 (2%) |
| Follicular Cell, Hyperplasia | 1 (2%) | | | |
| **GENERAL BODY SYSTEM** | | | | |
| None | | | | |
| **GENITAL SYSTEM** | | | | |
| Epididymis | (50) | (50) | (50) | (50) |
| Atypia Cellular | 29 (58%) | 26 (52%) | 25 (50%) | 29 (58%) |
| Preputial Gland | (50) | (50) | (50) | (50) |
| Cyst | 1 (2%) | | 1 (2%) | |
| Inflammation, Chronic | 17 (34%) | 20 (40%) | 13 (26%) | 20 (40%) |
| Prostate | (50) | (50) | (50) | (50) |
| Fibrosis | 5 (10%) | 5 (10%) | 4 (8%) | 6 (12%) |
| Inflammation, Chronic | 27 (54%) | 24 (48%) | 28 (56%) | 29 (58%) |
| Epithelium, Hyperplasia | 12 (24%) | 3 (6%) | 10 (20%) | 9 (18%) |
| Testes | (50) | (50) | (50) | (50) |
| Germinal Epithelium, Atrophy | 7 (14%) | 12 (24%) | 3 (6%) | 8 (16%) |
| Interstitial Cell, Hyperplasia | 4 (8%) | 8 (16%) | 3 (6%) | 5 (10%) |
| **HEMATOPOIETIC SYSTEM** | | | | |
| Bone Marrow | (50) | (50) | (50) | (50) |
| Hyperplasia | 3 (6%) | 5 (10%) | 3 (6%) | 11 (22%) |
| Lymph Node | (12) | (21) | (18) | (11) |
| Iliac, Pigmentation | | 1 (5%) | | 1 (9%) |
| Mediastinal, Hemorrhage | 1 (8%) | 1 (5%) | 2 (11%) | 4 (36%) |
| Mediastinal, Hyperplasia, Lymphoid | 1 (8%) | | 1 (6%) | |
| Mediastinal, Pigmentation | | 2 (10%) | 4 (22%) | 2 (18%) |

a Number of animals examined microscopically at site and number of animals with lesion



A 14

| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| **HEMATOPOIETIC SYSTEM - CONT** | | | | |
| Pancreatic, Hemorrhage | | | | 1 (9%) |
| Pancreatic, Pigmentation | | 1 (2%) | | |
| Renal, Hemorrhage | | | 1 (6%) | |
| Renal, Pigmentation | | | 1 (6%) | 1 (9%) |
| Lymph Node, Mandibular | (49) | (50) | (48) | (50) |
| Ectasia | | 3 (6%) | 2 (4%) | 1 (2%) |
| Hemorrhage | | | 1 (2%) | 2 (4%) |
| Hyperplasia, Lymphoid | 1 (2%) | | 1 (2%) | |
| Pigmentation | | 2 (4%) | | 2 (4%) |
| Lymph Node, Mesenteric | (50) | (50) | (50) | (50) |
| Atrophy | | 1 (2%) | | |
| Ectasia | | | | 6 (12%) |
| Hemorrhage | 2 (4%) | 2 (4%) | 2 (4%) | 2 (4%) |
| Hyperplasia, Lymphoid | | | | 1 (2%) |
| Spleen | (50) | (50) | (50) | (50) |
| Accessory Spleen | 1 (2%) | | 1 (2%) | |
| Fibrosis | 8 (16%) | 9 (18%) | 3 (6%) | 3 (6%) |
| Hematopoietic Cell Proliferation | 3 (6%) | 5 (10%) | 4 (8%) | 8 (16%) |
| Necrosis | 1 (2%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Pigmentation | 1 (2%) | 2 (4%) | 4 (8%) | 4 (8%) |
| **INTEGUMENTARY SYSTEM** | | | | |
| Mammary Gland | (49) | (47) | (49) | (49) |
| Hyperplasia | 14 (29%) | 23 (49%) | 10 (20%) | 13 (27%) |
| Skin | (50) | (50) | (49) | (49) |
| Cyst Epithelial Inclusion | | | 3 (6%) | 2 (4%) |
| Hyperkeratosis | 2 (4%) | 3 (6%) | 1 (2%) | |
| Hyperplasia, Basal Cell | | 1 (2%) | | |
| Inflammation, Chronic | 2 (4%) | 2 (4%) | | 1 (2%) |
| Ulcer | | 2 (4%) | | |
| Epidermis, Hyperplasia | 1 (2%) | 3 (6%) | | |
| Subcutaneous Tissue, Fibrosis | | 1 (2%) | | |
| Subcutaneous Tissue, Inflammation, Chronic Active | | | | 1 (2%) |
| **MUSCULOSKELETAL SYSTEM** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Cranium, Osteopetrosis | 1 (2%) | | | |
| Skeletal Muscle | (1) | | | (2) |

a Number of animals examined microscopically at site and number of animals with lesion



R01

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| MUSCULOSKELETAL SYSTEM - CONT | | | | |
| Hemorrhage | | | | 1 (50%) |
| Necrosis | | | | 1 (50%) |
| NERVOUS SYSTEM | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Angiectasis | | | | 1 (2%) |
| Compression | 4 (8%) | 2 (4%) | 5 (10%) | 5 (10%) |
| Hydrocephalus | 1 (2%) | 1 (2%) | 2 (4%) | 1 (2%) |
| Necrosis | 1 (2%) | 1 (2%) | | |
| RESPIRATORY SYSTEM | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Hemorrhage | | 1 (2%) | 2 (4%) | 1 (2%) |
| Infiltration Cellular, Histiocyte | 26 (52%) | 28 (56%) | 27 (54%) | 35 (70%) |
| Inflammation, Chronic | 1 (2%) | | | 2 (4%) |
| Alveolar Epithelium, Hyperplasia | 5 (10%) | 1 (2%) | 2 (4%) | 5 (10%) |
| Nose | (50) | (50) | (50) | (50) |
| Foreign Body | 4 (8%) | 3 (6%) | 1 (2%) | 2 (4%) |
| Inflammation, Chronic | 9 (18%) | 8 (16%) | 9 (18%) | 8 (16%) |
| Respiratory Epithelium, Hyperplasia | 6 (12%) | 7 (14%) | 8 (16%) | 5 (10%) |
| Respiratory Epithelium, Metaplasia, Squamous | 4 (8%) | 3 (6%) | 5 (10%) | 1 (2%) |
| SPECIAL SENSES SYSTEM | | | | |
| Eye | (3) | (1) | (1) | |
| Atrophy | 1 (33%) | | | |
| Cataract | 2 (67%) | 1 (100%) | 1 (100%) | |
| Retina, Degeneration | 2 (67%) | 1 (100%) | 1 (100%) | |
| URINARY SYSTEM | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Cyst | | 1 (2%) | 2 (4%) | 1 (2%) |
| Hydronephrosis | | | | 2 (4%) |
| Infarct | | | | 3 (6%) |
| Inflammation, Chronic | 15 (30%) | 11 (22%) | 13 (26%) | 25 (50%) |
| Nephropathy | 48 (96%) | 50 (100%) | 50 (100%) | 50 (100%) |

a Number of animals examined microscopically at site and number of animals with lesion



B 02

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN



| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| URINARY SYSTEM - CONT | | | | |
| Renal Tubule, Hyaline Droplet | 3 (6%) | 45 (90%) | 43 (86%) | 43 (86%) |
| Renal Tubule, Hyperplasia | | | 1 (2%) | |
| Renal Tubule, Necrosis | | 1 (2%) | | 1 (2%) |
| Renal Tubule, Pigmentation | 35 (70%) | 47 (94%) | 49 (98%) | 50 (100%) |
| Transitional Epithelium, Hyperplasia | 4 (8%) | 4 (8%) | 3 (6%) | 2 (4%) |
| Urinary Bladder | (50) | (50) | (50) | (50) |
| Edema | | | | 1 (2%) |
| Hemorrhage | | | | 1 (2%) |
| Transitional Epithelium, Hyperplasia | | | 1 (2%) | |

a Number of animals examined microscopically at site and number of animals with lesion



B 03

END OF REPORT

B 04

INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
EMODIN



FINAL#3;REVISION#1

Facility: Southern Research Institute

Chemical CAS #: 518-82-1

Lock Date: 07/30/97

Cage Range: All

Reasons For Removal: 25022 Accidently Killed, 25020 Natural Death, 25019 Moribund Sacrifice, 25021 Terminal Sacrifice

Removal Date Range: All

Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion



B 05

| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| **DISPOSITION SUMMARY** | | | | |
| Animals Initially in Study | 60 | 60 | 60 | 60 |
| Early Deaths | | | | |
| Moribund Sacrifice | 12 | 8 | 11 | 15 |
| Natural Death | 5 | 3 | 4 | 1 |
| Survivors | | | | |
| Terminal Sacrifice | 33 | 39 | 35 | 34 |
| Animals Examined Microscopically | 50 | 50 | 50 | 50 |
| **ALIMENTARY SYSTEM** | | | | |
| Intestine Small, Ileum | (48) | (50) | (49) | (50) |
| Liver | (49) | (50) | (50) | (50) |
| Hemangioma | | 1 (2%) | | |
| Hepatocellular Adenoma, Multiple | | | | 1 (2%) |
| Pancreas | (49) | (50) | (49) | (50) |
| Hemangiosarcoma, Metastatic, Spleen | | | 1 (2%) | |
| Stomach, Forestomach | (49) | (50) | (50) | (50) |
| Stomach, Glandular | (49) | (50) | (50) | (50) |
| **CARDIOVASCULAR SYSTEM** | | | | |
| Heart | (49) | (50) | (50) | (50) |
| **ENDOCRINE SYSTEM** | | | | |
| Adrenal Cortex | (49) | (50) | (50) | (50) |
| Adenoma | | 1 (2%) | | |
| Carcinoma | | | | 1 (2%) |
| Adrenal Medulla | (47) | (50) | (50) | (50) |
| Pheochromocytoma Malignant | 1 (2%) | | | |
| Pheochromocytoma Complex | | | | 1 (2%) |
| Pheochromocytoma Benign | 1 (2%) | | 4 (8%) | 1 (2%) |
| Islets, Pancreatic | (49) | (50) | (49) | (50) |
| Adenoma | 1 (2%) | 1 (2%) | 1 (2%) | |
| Carcinoma | | 1 (2%) | 1 (2%) | |
| Pituitary Gland | (49) | (50) | (49) | (49) |
| Pars Distalis, Adenoma | 15 (31%) | 21 (42%) | 25 (51%) | 25 (51%) |



B 06

| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| **ENDOCRINE SYSTEM - cont** | | | | |
| Pars Intermedia, Adenoma | 1 (2%) | | | 1 (2%) |
| Pars Intermedia, Carcinoma | | 1 (2%) | | |
| Thyroid Gland | (49) | (50) | (50) | (50) |
| Bilateral, C-Cell, Adenoma | | 1 (2%) | | |
| C-Cell, Adenoma | 4 (8%) | 5 (10%) | 4 (8%) | 3 (6%) |
| C-Cell, Carcinoma | 2 (4%) | 2 (4%) | | 3 (6%) |
| Follicular Cell, Adenoma | | 1 (2%) | | 1 (2%) |
| Follicular Cell, Carcinoma | | 1 (2%) | 1 (2%) | |
| **GENERAL BODY SYSTEM** | | | | |
| Peritoneum | | | | (1) |
| **GENITAL SYSTEM** | | | | |
| Clitoral Gland | (49) | (50) | (49) | (49) |
| Adenoma | 10 (20%) | 10 (20%) | 8 (16%) | 9 (18%) |
| Carcinoma | 2 (4%) | 3 (6%) | 2 (4%) | |
| Bilateral, Adenoma | | 2 (4%) | | 1 (2%) |
| Ovary | (49) | (50) | (50) | (50) |
| Bilateral, Granulosa Cell Tumor Benign | | 1 (2%) | | |
| Uterus | (49) | (50) | (50) | (50) |
| Leiomyoma | | | 1 (2%) | |
| Polyp Stromal | 10 (20%) | 7 (14%) | 7 (14%) | 10 (20%) |
| Polyp Stromal, Multiple | | 1 (2%) | | |
| Sarcoma Stromal | 1 (2%) | | | |
| Vagina | (2) | (3) | (3) | (5) |
| Granular Cell Tumor Benign | | | 1 (33%) | |
| Squamous Cell Papilloma | | | 1 (33%) | |
| **HEMATOPOIETIC SYSTEM** | | | | |
| Bone Marrow | (49) | (50) | (50) | (50) |
| Lymph Node | (5) | (3) | (4) | (3) |
| Lymph Node, Mandibular | (49) | (50) | (50) | (50) |
| Lymph Node, Mesenteric | (49) | (50) | (49) | (50) |
| Spleen | (50) | (50) | (50) | (50) |
| Hemangiosarcoma | | | 1 (2%) | |
| Osteosarcoma, Metastatic, Bone | 1 (2%) | | | |
| Thymus | (47) | (49) | (49) | (50) |



R 07

| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| HEMATOPOIETIC SYSTEM - cont | | | | |
| Thymoma Benign | 1 (2%) | | 1 (2%) | |
| Thymoma Malignant | | 1 (2%) | | |
| INTEGUMENTARY SYSTEM | | | | |
| Mammary Gland | (49) | (50) | (50) | (50) |
| Carcinoma | | | | 2 (4%) |
| Fibroadenoma | 18 (37%) | 13 (26%) | 20 (40%) | 16 (32%) |
| Fibroadenoma, Multiple | 5 (10%) | 5 (10%) | | 1 (2%) |
| Skin | (49) | (50) | (50) | (50) |
| Basal Cell Adenoma | | | | 1 (2%) |
| Keratoacanthoma | 1 (2%) | | | |
| Schwannoma Malignant | 1 (2%) | | | |
| Subcutaneous Tissue, Fibroma | 2 (4%) | | 1 (2%) | |
| Subcutaneous Tissue, Fibrosarcoma | | 1 (2%) | | |
| Subcutaneous Tissue, Lipoma | | | 1 (2%) | |
| Subcutaneous Tissue, Sarcoma | | | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | | |
| Bone | (49) | (50) | (50) | (50) |
| Osteosarcoma | 1 (2%) | 1 (2%) | | 1 (2%) |
| NERVOUS SYSTEM | | | | |
| Brain | (49) | (50) | (50) | (50) |
| Glioma Malignant | | | 1 (2%) | |
| Granular Cell Tumor Malignant | | 1 (2%) | | |
| RESPIRATORY SYSTEM | | | | |
| Lung | (49) | (50) | (50) | (50) |
| Alveolar/Bronchiolar Adenoma | 1 (2%) | | | |
| Alveolar/Bronchiolar Carcinoma | 1 (2%) | | | |
| Carcinoma, Metastatic, Adrenal Cortex | | | | 1 (2%) |
| Osteosarcoma, Metastatic, Bone | 1 (2%) | 1 (2%) | | 1 (2%) |



B-08

| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| SPECIAL SENSES SYSTEM | | | | |
| Lacrimal Gland | (1) | | | |
| Carcinoma | 1 (100%) | | | |
| Zymbal's Gland | | | | (3) |
| Carcinoma | | | | 3 (100%) |
| URINARY SYSTEM | | | | |
| Kidney | (49) | (50) | (49) | (50) |
| Osteosarcoma, Metastatic, Bone | | | | 1 (2%) |
| Urinary Bladder | (49) | (50) | (50) | (50) |
| SYSTEMIC LESIONS | | | | |
| Multiple Organs | *(50) | *(50) | *(50) | *(50) |
| Leukemia Mononuclear | 14 (28%) | 17 (34%) | 16 (32%) | 3 (6%) |
| Mesothelioma Malignant | | | | 1 (2%) |

* Number of animals with any tissue examined microscopically



B 09

| FISCHER 344 RATS FEMALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| TUMOR SUMMARY | | | | |
| Total Animals with Primary Neoplasms (b) | 45 | 47 | 48 | 43 |
| Total Primary Neoplasms | 94 | 99 | 98 | 85 |
| Total Animals with Benign Neoplasms | 41 | 39 | 41 | 37 |
| Total Benign Neoplasms | 70 | 70 | 75 | 70 |
| Total Animals with Malignant Neoplasms | 22 | 24 | 22 | 15 |
| Total Malignant Neoplasms | 24 | 29 | 23 | 15 |
| Total Animals with Metastatic Neoplasms | 1 | 1 | 1 | 2 |
| Total Metastatic Neoplasm | 2 | 1 | 1 | 3 |
| Total Animals with Malignant Neoplasms Uncertain Primary Site | | | | |
| Total Animals with Neoplasms Uncertain-Benign or Malignant | | | | |
| Total Uncertain Neoplasms | | | | |

a Number of animals examined microscopically at site and number of animals with lesion
b Primary tumors: all tumors except metastatic tumors

| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| DISPOSITION SUMMARY | | | | |
| Animals Initially in Study | 60 | 60 | 60 | 60 |
| Early Deaths | | | | |
| Moribund Sacrifice | 17 | 26 | 27 | 16 |
| Natural Death | 3 | 3 | 2 | 4 |
| Survivors | | | | |
| Terminal Sacrifice | 30 | 21 | 21 | 30 |
| Animals Examined Microscopically | 50 | 50 | 50 | 50 |
| ALIMENTARY SYSTEM | | | | |
| Intestine Large, Cecum | (49) | (50) | (50) | (49) |
| Intestine Small, Duodenum | (48) | (50) | (49) | (50) |
| Carcinoma | 1 (2%) | | | |
| Intestine Small, Jejunum | (49) | (48) | (50) | (49) |
| Schwannoma Malignant, Metastatic, Skin | | | | 1 (2%) |
| Intestine Small, Ileum | (50) | (50) | (48) | (49) |
| Sarcoma | | | | 1 (2%) |
| Liver | (50) | (50) | (50) | (50) |
| Cholangiocarcinoma | | | | 1 (2%) |
| Fibrosarcoma, Metastatic, Spleen | | | 1 (2%) | |
| Hepatocellular Carcinoma | | 3 (6%) | 3 (6%) | |
| Hepatocellular Adenoma | 1 (2%) | 1 (2%) | 1 (2%) | 2 (4%) |
| Histiocytic Sarcoma | | 1 (2%) | 1 (2%) | |
| Mesentery | (8) | (7) | (13) | (15) |
| Sarcoma | | | | 2 (13%) |
| Pancreas | (50) | (50) | (50) | (50) |
| Fibrosarcoma, Metastatic, Spleen | | | 1 (2%) | |
| Mixed Tumor Benign | 2 (4%) | | | |
| Salivary Glands | (50) | (50) | (50) | (49) |
| Schwannoma Malignant | | | 1 (2%) | |
| Stomach, Forestomach | (50) | (50) | (49) | (48) |
| Squamous Cell Papilloma | | | | 1 (2%) |
| Stomach, Glandular | (50) | (50) | (49) | (48) |



D 11

| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| **CARDIOVASCULAR SYSTEM** | | | | |
| Heart | (50) | (50) | (50) | (50) |
| Schwannoma Malignant, Metastatic, Skin | | | | 1 (2%) |
| **ENDOCRINE SYSTEM** | | | | |
| Adrenal Cortex | (50) | (50) | (50) | (50) |
| Adenoma | | | 1 (2%) | |
| Adrenal Medulla | (50) | (49) | (50) | (50) |
| Pheochromocytoma Malignant | 1 (2%) | | 1 (2%) | 1 (2%) |
| Pheochromocytoma Benign | 6 (12%) | 11 (22%) | 5 (10%) | 9 (18%) |
| Bilateral, Pheochromocytoma Benign | 1 (2%) | 2 (4%) | 1 (2%) | |
| Islets, Pancreatic | (50) | (50) | (49) | (50) |
| Adenoma | 2 (4%) | 5 (10%) | 1 (2%) | 1 (2%) |
| Carcinoma | 3 (6%) | 1 (2%) | 1 (2%) | |
| Parathyroid Gland | (48) | (45) | (45) | (47) |
| Adenoma | | | 1 (2%) | |
| Pituitary Gland | (49) | (50) | (48) | (50) |
| Pars Distalis, Adenoma | 15 (31%) | 9 (18%) | 10 (21%) | 13 (26%) |
| Pars Intermedia, Adenoma | | 1 (2%) | 1 (2%) | 1 (2%) |
| Thyroid Gland | (50) | (50) | (50) | (50) |
| C-Cell, Adenoma | 3 (6%) | 5 (10%) | 3 (6%) | 3 (6%) |
| C-Cell, Carcinoma | 1 (2%) | 1 (2%) | 1 (2%) | 1 (2%) |
| Follicular Cell, Adenoma | 1 (2%) | 1 (2%) | | |
| Follicular Cell, Carcinoma | | 2 (4%) | 2 (4%) | |
| **GENERAL BODY SYSTEM** | | | | |
| Peritoneum | (2) | (1) | (3) | (1) |
| **GENITAL SYSTEM** | | | | |
| Preputial Gland | (50) | (50) | (50) | (50) |
| Adenoma | 5 (10%) | 1 (2%) | 2 (4%) | 3 (6%) |
| Carcinoma | 3 (6%) | 2 (4%) | 1 (2%) | 3 (6%) |
| Prostate | (50) | (50) | (50) | (50) |
| Adenoma | 1 (2%) | | 1 (2%) | 3 (6%) |
| Seminal Vesicle | (50) | (50) | (50) | (50) |
| Testes | (50) | (50) | (50) | (50) |
| Bilateral, Interstitial Cell, Adenoma | 34 (68%) | 30 (60%) | 37 (74%) | 35 (70%) |



B 12

| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| GENITAL SYSTEM - cont | | | | |
| Interstitial Cell, Adenoma | 7 (14%) | 13 (26%) | 7 (14%) | 13 (26%) |
| HEMATOPOIETIC SYSTEM | | | | |
| Bone Marrow | (50) | (50) | (50) | (50) |
| Histiocytic Sarcoma | | 1 (2%) | | |
| Schwannoma Malignant, Metastatic, Skin | | | | 1 (2%) |
| Lymph Node | (12) | (21) | (18) | (11) |
| Lymph Node, Mandibular | (49) | (50) | (48) | (50) |
| Lymph Node, Mesenteric | (50) | (50) | (50) | (50) |
| Spleen | (50) | (50) | (50) | (50) |
| Fibrosarcoma | | | 1 (2%) | |
| Schwannoma Malignant, Metastatic, Skin | | | | 1 (2%) |
| Thymus | (46) | (47) | (48) | (48) |
| Thymoma Malignant | 1 (2%) | | | |
| INTEGUMENTARY SYSTEM | | | | |
| Mammary Gland | (49) | (47) | (49) | (49) |
| Fibroadenoma | 1 (2%) | 2 (4%) | 2 (4%) | 3 (6%) |
| Skin | (50) | (50) | (49) | (49) |
| Basal Cell Adenoma | | 1 (2%) | | |
| Basal Cell Carcinoma | | 1 (2%) | | 1 (2%) |
| Keratoacanthoma | 3 (6%) | 3 (6%) | 3 (6%) | 3 (6%) |
| Squamous Cell Carcinoma | | | | 1 (2%) |
| Squamous Cell Papilloma | | 1 (2%) | | 2 (4%) |
| Trichoepithelioma | 1 (2%) | | | 1 (2%) |
| Sebaceous Gland, Adenoma | 1 (2%) | 1 (2%) | | |
| Subcutaneous Tissue, Fibroma | 1 (2%) | 3 (6%) | 2 (4%) | 5 (10%) |
| Subcutaneous Tissue, Fibrosarcoma | | 1 (2%) | | |
| Subcutaneous Tissue, Hemangiopericytoma | 1 (2%) | | | |
| Subcutaneous Tissue, Hemangiosarcoma | 1 (2%) | | | |
| Subcutaneous Tissue, Histiocytic Sarcoma | | | 1 (2%) | |
| Subcutaneous Tissue, Lipoma | 1 (2%) | 1 (2%) | 1 (2%) | |
| Subcutaneous Tissue, Sarcoma | 1 (2%) | | | |
| Subcutaneous Tissue, Schwannoma Malignant | | | | 1 (2%) |



B 13

| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| **MUSCULOSKELETAL SYSTEM** | | | | |
| Bone | (50) | (50) | (50) | (50) |
| Osteosarcoma | | | 1 (2%) | 1 (2%) |
| Skeletal Muscle | (1) | | | (2) |
| Schwannoma Malignant, Metastatic, Skin | | | | 1 (50%) |
| **NERVOUS SYSTEM** | | | | |
| Brain | (50) | (50) | (50) | (50) |
| Astrocytoma Malignant | 2 (4%) | 1 (2%) | | |
| Oligodendroglioma Malignant | | 1 (2%) | | |
| Pineal Gland, Meningioma Malignant | | 1 (2%) | | |
| Spinal Cord | (2) | (5) | (8) | (3) |
| **RESPIRATORY SYSTEM** | | | | |
| Lung | (50) | (50) | (50) | (50) |
| Alveolar/Bronchiolar Carcinoma | | 1 (2%) | | |
| Histiocytic Sarcoma | | 1 (2%) | 1 (2%) | |
| Osteosarcoma, Metastatic, Bone | | | | 1 (2%) |
| Schwannoma Malignant, Metastatic, Skin | | | | 1 (2%) |
| Nose | (50) | (50) | (50) | (50) |
| Squamous Cell Carcinoma | | | | 2 (4%) |
| **SPECIAL SENSES SYSTEM** | | | | |
| Zymbal's Gland | | (1) | | (1) |
| Carcinoma | | 1 (100%) | | 1 (100%) |
| **URINARY SYSTEM** | | | | |
| Kidney | (50) | (50) | (50) | (50) |
| Renal Tubule, Stromal Nephroma | | 1 (2%) | | |
| Urinary Bladder | (50) | (50) | (50) | (50) |



B-14

| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| SYSTEMIC LESIONS | | | | |
| Multiple Organs | *(50) | *(50) | *(50) | *(50) |
| Histiocytic Sarcoma | | 1 (2%) | 1 (2%) | |
| Leukemia Mononuclear | 28 (56%) | 31 (62%) | 29 (58%) | 18 (36%) |
| Mesothelioma Malignant | 2 (4%) | 1 (2%) | 3 (6%) | 1 (2%) |

* Number of animals with any tissue examined microscopically



C 01

NTP Experiment-Test: 05211-05 INCIDENCE RATES OF NEOPLASMS BY ANATOMIC SITE (SYSTEMIC LESIONS ABRIDGED) (a)
Study Type: CHRONIC
Route: DOSED FEED

EMODIN

Report: PEIRPT05
Date: 01/23/01
Time: 12:57:56

| FISCHER 344 RATS MALE | 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|
| TUMOR SUMMARY | | | | |
| Total Animals with Primary Neoplasms (b) | 49 | 50 | 50 | 50 |
| Total Primary Neoplasms | 131 | 141 | 124 | 133 |
| Total Animals with Benign Neoplasms | 45 | 46 | 47 | 49 |
| Total Benign Neoplasms | 87 | 91 | 79 | 98 |
| Total Animals with Malignant Neoplasms | 36 | 38 | 36 | 28 |
| Total Malignant Neoplasms | 44 | 50 | 45 | 35 |
| Total Animals with Metastatic Neoplasms | | | 1 | 2 |
| Total Metastatic Neoplasm | | | 2 | 7 |
| Total Animals with Malignant Neoplasms Uncertain Primary Site | | | | |
| Total Animals with Neoplasms Uncertain-Benign or Malignant | | | | |
| Total Uncertain Neoplasms | | | | |

a Number of animals examined microscopically at site and number of animals with lesion
b Primary tumors: all tumors except metastatic tumors



C 02

C 03

END OF REPORT

FINAL#3;REVISION#1

REASONS FOR REMOVAL:
25022 Accidently Killed
25019 Moribund Sacrifice
25020 Natural Death
25021 Terminal Sacrifice

REMOVAL DATE RANGE: ALL

TREATMENT GROUPS: INCLUDE ALL

C 04

NTP
LAB: Southern Research Inst
EXPERIMENT: 05211 TEST: 05
TEST TYPE: CHRONIC
CONT: N01-ES-85216
PATHOLOGIST: HEATH, JAMES
Rats(FISCHER 344)

STATISTICAL ANALYSIS OF PRIMARY TUMORS
EMODIN

CAGES FROM 0000 TO LAST CAGE
ROUTE: DOSED FEED

REPORT: PEIRPT08
DATE: 01/25/01
TIME: 12:58:05

NTP C#: C62408
CAS: 518-82-1

FOR ALL DOSES THE TUMOR RATES IN THE FOLLOWING TISSUES/ORGANS ARE BASED ON NUMBER OF TISSUES EXAMINED. IN OTHER TISSUES/ORGANS RATES ARE BASED ON THE NUMBER OF ANIMALS NECROPSIED.

Adrenal Cortex
Adrenal Medulla
Brain
Clitoral/Preputial Gland
Islets, Pancreatic
Kidney
Liver
Lung
Nose
Ovary
Pancreas
Parathyroid Gland
Pituitary Gland
Prostate
Salivary Glands
Spleen
Testes
Thymus
Thyroid Gland

C 05

NTP
LAB: Southern Research Inst
EXPERIMENT: 05211 TEST: 05
TEST TYPE: CHRONIC
CONT: NO1-ES-85216
PATHOLOGIST: HEATH, JAMES

STATISTICAL ANALYSIS OF PRIMARY TUMORS
EMODIN

CAGES FROM 0000 TO LAST CAGE
ROUTE: DOSED FEED

REPORT: PEIRPT08
DATE: 01/25/01
TIME: 12:58:05

NTP C#: C62408
CAS: 518-82-1

SUMMARY OF STATISTICALLY SIGNIFICANT (P<=.05) RESULTS
IN THE ANALYSIS OF EMODIN

Male Rats

| Organ | Morphology |
|---|---|
| Adrenal Medulla | Pheochromocytoma Benign |
| Islets, Pancreatic | Carcinoma or Adenoma |
| Mesentery | Sarcoma |
| Nose | Squamous Cell Carcinoma |
| Testes | Adenoma |
| All Organs | Leukemia: Lymphocytic, Monocytic, Mononuclear, or Undifferentiated |
| | Benign Tumors |
| | Malignant Tumors |

Female Rats

| Organ | Morphology |
|---|---|
| Mammary Gland | Carcinoma |
| Pituitary Gland: Pars Distalis or Unspecified Site | Adenoma |
| Zymbal's Gland | Carcinoma |
| All Organs | Leukemia: Lymphocytic, Monocytic, Mononuclear, or Undifferentiated |
| | Malignant Tumors |

C 06

Statistical Analysis of Primary Tumors in Rats(FISCHER 344)

Terminal Sacrifice at 105 weeks

EMODIN

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Adrenal Medulla** | | | | | | | | |
| Pheochromocytoma Benign | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 7/50 (14%) | 13/49 (27%) | 6/50 (12%) | 9/50 (18%) | 1/47 (2%) | 0/50 (0%) | 4/50 (8%) | 1/50 (2%) |
| POLY-3 RATE (b) | 7/41.06 | 13/40.68 | 6/40.39 | 9/43.31 | 1/42.90 | 0/45.74 | 4/45.55 | 1/44.02 |
| POLY-3 PERCENT (g) | 17.1% | 32.0% | 14.9% | 20.8% | 2.3% | 0.0% | 8.8% | 2.3% |
| TERMINAL (d) | 6/30 (20%) | 2/20 (10%) | 2/21 (10%) | 7/30 (23%) | 0/33 (0%) | 0/39 (0%) | 3/35 (9%) | 1/34 (3%) |
| FIRST INCIDENCE | 686 | 511 | 638 | 539 | 704 | --- | 665 | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.407N | P=0.036 * | P=0.519 | P=0.397 | P=0.556 | P=0.479N | P=0.205 | P=0.760N |
| POLY 3 | P=0.465N | P=0.091 | P=0.513N | P=0.437 | P=0.564 | P=0.487N | P=0.197 | P=0.755N |
| POLY 1.5 | P=0.479N | P=0.100 | P=0.495N | P=0.430 | P=0.573 | P=0.488N | P=0.196 | P=0.752N |
| POLY 6 | P=0.453N | P=0.077 | P=0.547N | P=0.437 | P=0.551 | P=0.486N | P=0.200 | P=0.759N |
| LOGISTIC REGRESSION | P=0.465N | P=0.075 | P=0.563N | P=0.419 | P=0.572 | P=0.488N | P=0.197 | P=0.759N |
| COCH-ARM / FISHERS | P=0.520N | P=0.096 | P=0.500N | P=0.393 | P=0.587 | P=0.485N | P=0.201 | P=0.737N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Adrenal Medulla** | | | | | | | | |
| Pheochromocytoma: Benign, Complex, Malignant, NOS | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 8/50 (16%) | 13/49 (27%) | 7/50 (14%) | 10/50 (20%) | 2/47 (4%) | 0/50 (0%) | 4/50 (8%) | 2/50 (4%) |
| POLY-3 RATE (b) | 8/41.37 | 13/40.68 | 7/40.39 | 10/43.31 | 2/43.53 | 0/45.74 | 4/45.55 | 2/44.02 |
| POLY-3 PERCENT (g) | 19.3% | 32.0% | 17.3% | 23.1% | 4.6% | 0.0% | 8.8% | 4.5% |
| TERMINAL (d) | 6/30 (20%) | 2/20 (10%) | 3/21 (14%) | 8/30 (27%) | 0/33 (0%) | 0/39 (0%) | 3/35 (9%) | 2/34 (6%) |
| FIRST INCIDENCE | 646 | 511 | 638 | 539 | 527 | --- | 665 | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.440N | P=0.062 | P=0.489 | P=0.403 | P=0.444 | P=0.226N | P=0.369 | P=0.688N |
| POLY 3 | P=0.514N | P=0.142 | P=0.520N | P=0.438 | P=0.450 | P=0.226N | P=0.358 | P=0.690N |
| POLY 1.5 | P=0.527N | P=0.156 | P=0.497N | P=0.434 | P=0.461 | P=0.226N | P=0.359 | P=0.683N |
| POLY 6 | P=0.506N | P=0.120 | P=0.563N | P=0.433 | P=0.435 | P=0.225N | P=0.360 | P=0.690 |
| LOGISTIC REGRESSION | P=0.506N | P=0.127 | P=0.558N | P=0.427 | P=0.484 | P=0.165N | P=0.383 | P=0.644N |
| COCH-ARM / FISHERS | P=0.559 | P=0.150 | P=0.500N | P=0.398 | P=0.477 | P=0.232N | P=0.369 | P=0.668N |

C 07

Statistical Analysis of Primary Tumors in Rats(FISCHER 344)

Terminal Sacrifice at 105 weeks

EMODIN

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Brain** Astrocytoma Malignant | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 2/50 (4%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/49 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 2/40.89 | 1/40.19 | 0/39.45 | 0/42.44 | 0/44.01 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 4.9% | 2.5% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 2/30 (7%) | 0/21 (0%) | 0/21 (0%) | 0/30 (0%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 729 (T) | 464 | --- | --- | --- | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.162N | P=0.575N | P=0.319N | P=0.238N | (e) | (e) | (e) | (e) |
| POLY 3 | P=0.164N | P=0 506N | P=0.245N | P=0.229N | (e) | (e) | (e) | (e) |
| POLY 1.5 | P=0.167N | P=0.496N | P=0.238N | P=0.229N | (e) | (e) | (e) | (e) |
| POLY 6 | P=0.158N | P=0.526N | P=0.259N | P=0.230N | (e) | (e) | (e) | (e) |
| LOGISTIC REGRESSION | P=0.176N | P=0.508N | (e) | (e) | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.170N | P=0.500N | P=0.247N | P=0.247N | (e) | (e) | (e) | (e) |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Brain** Oligodendroglioma, Glioma, or Astrocytoma | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 2/50 (4%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 0/49 (0%) | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) |
| POLY-3 RATE (b) | 2/40.89 | 2/40.60 | 0/39.45 | 0/42.44 | 0/44.01 | 0/45.74 | 1/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 4.9% | 4.9% | 0.0% | 0.0% | 0.0% | 0.0% | 2.2% | 0.0% |
| TERMINAL (d) | 2/30 (7%) | 0/21 (0%) | 0/21 (0%) | 0/30 (0%) | 0/33 (0%) | 0/39 (0%) | 1/35 (3%) | 0/34 (0%) |
| FIRST INCIDENCE | 729 (T) | 464 | --- | --- | --- | --- | 730 (T) | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.119N | P=0.637 | P=0.319N | P=0.238N | P=0.792N | (e) | P=0.512 | (e) |
| POLY 3 | P=0.119N | P=0.692 | P=0.245N | P=0.229N | P=0.787N | (e) | P=0.506 | (e) |
| POLY 1.5 | P=0.121N | P=0.688N | P=0.238N | P=0.229N | P=0.785N | (e) | P=0.504 | (e) |
| POLY 6 | P=0.116N | P=0.675 | P=0.259N | P=0.230N | P=0.790N | (e) | P=0.509 | (e) |
| LOGISTIC REGRESSION | P=0.132N | P=0.684 | (e) | (e) | (e) | (e) | P=0.512 | (e) |
| COCH-ARM / FISHERS | P=0.124N | P=0.691N | P=0.247N | P=0.247N | P=0.783N | (e) | P=0.505 | (e) |

C 08

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Clitoral/Preputial Gland Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 5/50 (10%) | 1/50 (2%) | 2/50 (4%) | 3/50 (6%) | 10/49 (20%) | 12/50 (24%) | 8/49 (16%) | 10/49 (20%) |
| POLY-3 RATE (b) | 5/42.26 | 1/39.45 | 2/40.26 | 3/42.44 | 10/45.28 | 12/46.07 | 8/44.55 | 10/44.11 |
| POLY-3 PERCENT (g) | 11.8% | 2.5% | 5.0% | 7.1% | 22.1% | 26.1% | 18.0% | 22.7% |
| TERMINAL (d) | 2/30 (7%) | 1/21 (5%) | 0/21 (0%) | 3/30 (10%) | 8/33 (24%) | 10/39 (26%) | 7/34 (21%) | 8/33 (24%) |
| FIRST INCIDENCE | 472 | 729 (T) | 483 | 729 (T) | 497 | 656 | 665 | 529 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.482N | P=0.167N | P=0.296N | P=0.355N | P=0.548N | P=0.559 | P=0.369N | P=0.593N |
| POLY 3 | P=0.517N | P=0.117N | P=0.235N | P=0.353N | P=0.517N | P=0.422 | P=0.411N | P=0.574 |
| POLY 1.5 | P=0.530N | P=0.105N | P=0.220N | P=0.348N | P=0.506N | P=0.420 | P=0.411N | P=0.582 |
| POLY 6 | P=0.498N | P=0.138N | P=0.262N | P=0.365N | P=0.531N | P=0.432 | P=0.406N | P=0.566 |
| LOGISTIC REGRESSION | P=0.549N | P=0.104N | P=0.229N | P=0.354N | P=0.510N | P=0.432 | P=0.398N | P=0.592N |
| COCH-ARM / FISHERS | P=0.544N | P=0.102N | P=0.218N | P=0.357N | P=0.490N | P=0.426 | P=0.397N | P=0.599N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Clitoral/Preputial Gland Carcinoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 3/50 (6%) | 2/50 (4%) | 1/50 (2%) | 3/50 (6%) | 2/49 (4%) | 3/50 (6%) | 2/49 (4%) | 0/49 (0%) |
| POLY-3 RATE (b) | 3/41.36 | 2/39.60 | 1/39.45 | 3/43.22 | 2/44.11 | 3/46.09 | 2/44.55 | 0/43.02 |
| POLY-3 PERCENT (g) | 7.3% | 5.1% | 2.5% | 6.9% | 4.5% | 6.5% | 4.5% | 0.0% |
| TERMINAL (d) | 2/30 (7%) | 0/21 (0%) | 1/21 (5%) | 1/30 (3%) | 1/33 (3%) | 2/39 (5%) | 1/34 (3%) | 0/33 (0%) |
| FIRST INCIDENCE | 590 | 704 | 729 (T) | 617 | 704 | 634 | 665 | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.564 | P=0.617N | P=0.407N | P=0.649N | P=0.131N | P=0.556 | P=0.674N | P=0.246N |
| POLY 3 | P=0.541 | P=0.520N | P=0.322N | P=0.642N | P=0.127N | P=0.520 | P=0.690N | P=0.243N |
| POLY 1.5 | P=0.528 | P=0.502N | P=0.308N | P=0.644N | P=0.124N | P=0.514 | P=0.694N | P=0.241N |
| POLY 6 | P=0.558 | P=0.551N | P=0.347N | P=0.643N | P=0.131N | P=0.529 | P=0.685N | P=0.245N |
| LOGISTIC REGRESSION | P=0.525 | P=0.515N | P=0.316N | P=0.663 | P=0.121N | P=0.511 | P=0.695N | P=0.244N |
| COCH-ARM / FISHERS | P=0.509 | P=0.500N | P=0.309N | P=0.661N | P=0.120N | P=0.510 | P=0.691N | P=0.247N |

C 09

Statistical Analysis of Primary Tumors in Rats(FISCHER 344)

Terminal Sacrifice at 105 weeks

EMODIN

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Clitoral/Preputial Gland Carcinoma or Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 8/50 (16%) | 3/50 (6%) | 3/50 (6%) | 5/50 (10%) | 12/49 (24%) | 15/50 (30%) | 9/49 (18%) | 10/49 (20%) |
| POLY-3 RATE (b) | 8/42.73 | 3/39.60 | 3/40.26 | 5/43.22 | 12/45.38 | 15/46.42 | 9/44.55 | 10/44.11 |
| POLY-3 PERCENT (g) | 18.7% | 7.6% | 7.5% | 11.6% | 26.4% | 32.3% | 20.2% | 22.7% |
| TERMINAL (d) | 4/30 (13%) | 1/21 (5%) | 1/21 (5%) | 3/30 (10%) | 9/33 (27%) | 12/39 (31%) | 8/34 (24%) | 8/33 (24%) |
| FIRST INCIDENCE | 472 | 704 | 483 | 617 | 497 | 634 | 665 | 529 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.379N | P=0.204N | P=0.187N | P=0.274N | P=0.305N | P=0.494 | P=0.285N | P=0.404N |
| POLY 3 | P=0.411N | P=0.121N | P=0.115N | P=0.266N | P=0.275N | P=0.349 | P=0.326N | P=0.433N |
| POLY 1.5 | P=0.429N | P=0.105N | P=0.102N | P=0.262N | P=0.265N | P=0.345 | P=0.326N | P=0.423N |
| POLY 6 | P=0.385N | P=0.152N | P=0.141N | P=0.274N | P=0.289N | P=0.363 | P=0.323N | P=0.445N |
| LOGISTIC REGRESSION | P=0.449N | P=0.100N | P=0.102N | P=0.279N | P=0.268N | P=0.355 | P=0.311N | P=0.401N |
| COCH-ARM / FISHERS | P=0.452N | P=0.100N | P=0.100N | P=0.277N | P=0.251N | P=0.349 | P=0.312N | P=0.405N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Islets, Pancreatic Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 2/50 (4%) | 5/50 (10%) | 1/49 (2%) | 1/50 (2%) | 1/49 (2%) | 1/50 (2%) | 1/49 (2%) | 0/50 (0%) |
| POLY-3 RATE (b) | 2/40.89 | 5/39.80 | 1/38.45 | 1/42.44 | 1/44.01 | 1/45.74 | 1/44.58 | 0/44.02 |
| POLY-3 PERCENT (g) | 4.9% | 12.6% | 2.6% | 2.4% | 2.3% | 2.2% | 2.2% | 0.0% |
| TERMINAL (d) | 2/30 (7%) | 4/21 (19%) | 1/20 (5%) | 1/30 (3%) | 1/33 (3%) | 1/39 (3%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 729 (T) | 630 | 729 (T) | 729 (T) | 730 (T) | 730 (T) | 711 | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.152N | P=0.110 | P=0.641N | P=0.500N | P=0.334N | P=0.724N | P=0.745N | P=0.494N |
| POLY 3 | P=0.170N | P=0.203 | P=0.522N | P=0.487N | P=0.328N | P=0.752N | P=0.758N | P=0.500N |
| POLY 1.5 | P=0.172N | P=0.217 | P=0.509N | P=0.488N | P=0.326N | P=0.754N | P=0.760N | P=0.499N |
| POLY 6 | P=0.169N | P=0.180 | P=0.545N | P=0.490N | P=0.332N | P=0.748N | P=0.754N | P=0.502N |
| LOGISTIC REGRESSION | P=0.160N | P=0.158 | P=0.641N | P=0.500N | P=0.333N | P=0.724N | P=0.756N | (e) |
| COCH-ARM / FISHERS | P=0.184N | P=0.218 | P=0.508N | P=0.500N | P=0.321N | P=0.747N | P=0.753N | P=0.495N |

C 10

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Islets, Pancreatic Carcinoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 3/50 (6%) | 1/50 (2%) | 1/49 (2%) | 0/50 (0%) | 0/49 (0%) | 1/50 (2%) | 1/49 (2%) | 0/50 (0%) |
| POLY-3 RATE (b) | 3/40.89 | 1/39.50 | 1/38.86 | 0/42.44 | 0/44.01 | 1/45.74 | 1/44.53 | 0/44.02 |
| POLY-3 PERCENT (g) | 7.3% | 2.5% | 2.6% | 0.0% | 0.0% | 2.2% | 2.3% | 0.0% |
| TERMINAL (d) | 3/30 (10%) | 0/21 (0%) | 0/20 (0%) | 0/30 (0%) | 0/33 (0%) | 1/39 (3%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 729 (T) | 716 | 609 | --- | --- | 730 (T) | 725 | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.107N | P=0.434N | P=0.416N | P=0.120N | P=0.555N | P=0.533 | P=0.511 | (e) |
| POLY 3 | P=0.105N | P=0.317N | P=0.323N | P=0.112N | P=0.543N | P=0.508 | P=0.502 | (e) |
| POLY 1.5 | P=0.110N | P=0.305N | P=0.312N | P=0.112N | P=0.541N | P=0.506 | P=0.500 | (e) |
| POLY 6 | P=0.099N | P=0.341N | P=0.344N | P=0.112N | P=0.545N | P=0.511 | P=0.506 | (e) |
| LOGISTIC REGRESSION | P=0.108N | P=0.400N | P=0.332N | (e) | P=0.555N | P=0.533 | P=0.509 | (e) |
| COCH-ARM / FISHERS | P=0.116N | P=0.309N | P=0.316N | P=0.121N | P=0.538N | P=0.505 | P=0.500 | (e) |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Islets, Pancreatic Carcinoma or Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 5/50 (10%) | 6/50 (12%) | 2/49 (4%) | 1/50 (2%) | 1/49 (2%) | 2/50 (4%) | 2/49 (4%) | 0/50 (0%) |
| POLY-3 RATE (b) | 5/40.89 | 6/39.86 | 2/38.86 | 1/42.44 | 1/44.01 | 2/45.74 | 2/44.60 | 0/44.02 |
| POLY-3 PERCENT (g) | 12.2% | 15.1% | 5.2% | 2.4% | 2.3% | 4.4% | 4.5% | 0.0% |
| TERMINAL (d) | 5/30 (17%) | 4/21 (19%) | 1/20 (5%) | 1/30 (3%) | 1/33 (3%) | 2/39 (5%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 729 (T) | 630 | 609 | 729 (T) | 730 (T) | 730 (T) | 711 | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.034N* | P=0.285 | P=0.372N | P=0.100N | P=0.261N | P=0.558 | P=0.523 | P=0.494N |
| POLY 3 | P=0.036N* | P=0.482 | P=0.235N | P=0.092N | P=0.253N | P=0.513 | P=0.505 | P=0.500N |
| POLY 1.5 | P=0.038N* | P=0.503 | P=0.223N | P=0.093N | P=0.250N | P=0.510 | P=0.501 | P=0.499N |
| POLY 6 | P=0.034N* | P=0.441 | P=0.259N | P=0.093N | P=0.258N | P=0.519 | P=0.511 | P=0.502N |
| LOGISTIC REGRESSION | P=0.036N* | P=0.375 | P=0.276N | P=0.100N | P=0.259N | P=0.558 | P=0.512 | (e) |
| COCH-ARM / FISHERS | P=0.044N* | P=0.500 | P=0.226N | P=0.102N | P=0.245N | P=0.508 | P=0.500 | P=0.495N |

C11

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Liver** Hepatocellular Adenoma | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 1/50 (2%) | 1/50 (2%) | 1/50 (2%) | 2/50 (4%) | 0/49 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| POLY-3 RATE (b) | 1/40.89 | 1/39.45 | 1/39.45 | 2/42.44 | 0/44.01 | 0/45.74 | 0/45.30 | 1/44.02 |
| POLY-3 PERCENT (g) | 2.5% | 2.5% | 2.5% | 4.7% | 0.0% | 0.0% | 0.0% | 2.3% |
| TERMINAL (d) | 1/30 (3%) | 1/21 (5%) | 1/21 (5%) | 2/30 (7%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 1/34 (3%) |
| FIRST INCIDENCE | 729 (T) | 729 (T) | 729 (T) | 729 (T) | --- | --- | --- | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.420 | P=0.681 | P=0.681 | P=0.500 | P=0.208 | (e) | (e) | P=0.506 |
| POLY 3 | P=0.381 | P=0.753 | P=0.753 | P=0.513 | P=0.213 | (e) | (e) | P=0.500 |
| POLY 1.5 | P=0.375 | P=0.761 | P=0.760 | P=0.512 | P=0.215 | (e) | (e) | P=0.501 |
| POLY 6 | P=0.389 | P=0.738 | P=0.739 | P=0.510 | P=0.210 | (e) | (e) | P=0.498 |
| LOGISTIC REGRESSION | P=0.420 | P=0.681 | P=0.681 | P=0.500 | (e) | (e) | (e) | P=0.506 |
| COCH-ARM / FISHERS | P=0.361 | P=0.753N | P=0.753N | P=0.500 | P=0.217 | (e) | (e) | P=0.505 |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Liver** Hepatocellular Carcinoma | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 0/50 (0%) | 3/50 (6%) | 3/50 (6%) | 0/50 (0%) | 0/49 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 0/40.89 | 3/39.70 | 3/39.91 | 0/42.44 | 0/44.01 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 0.0% | 7.6% | 7.5% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 1/21 (5%) | 1/21 (5%) | 0/30 (0%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | --- | 690 | 605 | --- | --- | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.266N | P=0.080 | P=0.090 | (e) | (e) | (e) | (e) | (e) |
| POLY 3 | P=0.277N | P=0.113 | P=0.114 | (e) | (e) | (e) | (e) | (e) |
| POLY 1.5 | P=0.278N | P=0.119 | P=0.119 | (e) | (e) | (e) | (e) | (e) |
| POLY 6 | P=0.279N | P=0.102 | P=0.104 | (e) | (e) | (e) | (e) | (e) |
| LOGISTIC REGRESSION | P=0.281N | P=0.101 | P=0.118 | (e) | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.297N | P=0.121 | P=0.121 | (e) | (e) | (e) | (e) | (e) |

C 12

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Liver** Hepatocellular Carcinoma or Hepatocellular Adenoma | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 1/50 (2%) | 4/50 (8%) | 4/50 (8%) | 2/50 (4%) | 0/49 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| POLY-3 RATE (b) | 1/40.89 | 4/39.70 | 4/39.91 | 2/42.44 | 0/44.01 | 0/45.74 | 0/45.30 | 1/44.02 |
| POLY-3 PERCENT (g) | 2.5% | 10.1% | 10.0% | 4.7% | 0.0% | 0.0% | 0.0% | 2.3% |
| TERMINAL (d) | 1/30 (3%) | 2/21 (10%) | 2/21 (10%) | 2/30 (7%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 1/34 (3%) |
| FIRST INCIDENCE | 729 (T) | 690 | 605 | 729 (T) | --- | --- | --- | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.468N | P=0.103 | P=0.112 | P=0.500 | P=0.208 | (e) | (e) | P=0.506 |
| POLY 3 | P=0.517N | P=0.168 | P=0.170 | P=0.513 | P=0.213 | (e) | (e) | P=0.500 |
| POLY 1.5 | P=0.522N | P=0.179 | P=0.179 | P=0.512 | P=0.215 | (e) | (e) | P=0.501 |
| POLY 6 | P=0.515N | P=0.151 | P=0.154 | P=0.510 | P=0.210 | (e) | (e) | P=0.498 |
| LOGISTIC REGRESSION | P=0.500N | P=0.132 | P=0.158 | P=0.500 | (e) | (e) | (e) | P=0.506 |
| COCH-ARM / FISHERS | P=0.544N | P=0.181 | P=0.181 | P=0.500 | P=0.217 | (e) | (e) | P=0.505 |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Liver** Hepatocellular Carcinoma, Hepatocellular Adenoma, or Hepatoblastoma | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 1/50 (2%) | 4/50 (8%) | 4/50 (8%) | 2/50 (4%) | 0/49 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| POLY-3 RATE (b) | 1/40.89 | 4/39.70 | 4/39.91 | 2/42.44 | 0/44.01 | 0/45.74 | 0/45.30 | 1/44.02 |
| POLY-3 PERCENT (g) | 2.5% | 10.1% | 10.0% | 4.7% | 0.0% | 0.0% | 0.0% | 2.3% |
| TERMINAL (d) | 1/30 (3%) | 2/21 (10%) | 2/21 (10%) | 2/30 (7%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 1/34 (3%) |
| FIRST INCIDENCE | 729 (T) | 690 | 605 | 729 (T) | --- | --- | --- | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.468N | P=0.103 | P=0.112 | P=0.500 | P=0.208 | (e) | (e) | P=0.506 |
| POLY 3 | P=0.517N | P=0.168 | P=0.170 | P=0.513 | P=0.213 | (e) | (e) | P=0.500 |
| POLY 1.5 | P=0.522N | P=0.179 | P=0.179 | P=0.512 | P=0.215 | (e) | (e) | P=0.501 |
| POLY 6 | P=0.515N | P=0.151 | P=0.154 | P=0.510 | P=0.210 | (e) | (e) | P=0.498 |
| LOGISTIC REGRESSION | P=0.500N | P=0.132 | P=0.158 | P=0.500 | (e) | (e) | (e) | P=0.506 |
| COCH-ARM / FISHERS | P=0.544N | P=0.181 | P=0.181 | P=0.500 | P=0.217 | (e) | (e) | P=0.505 |

C13

Statistical Analysis of Primary Tumors in Rats(FISCHER 344)

Terminal Sacrifice at 105 weeks

EMODIN

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Mammary Gland Carcinoma** | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 2/50 (4%) |
| POLY-3 RATE (b) | 0/40.89 | 0/39.45 | 0/39.45 | 0/42.44 | 0/44.24 | 0/45.74 | 0/45.30 | 2/44.02 |
| POLY-3 PERCENT (g) | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 4.5% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 0/30 (0%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 2/34 (6%) |
| FIRST INCIDENCE | --- | --- | --- | --- | --- | --- | --- | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | (e) | (e) | (e) | (e) | P=0.038 * | (e) | (e) | P=0.245 |
| POLY 3 | (e) | (e) | (e) | (e) | P=0.040 * | (e) | (e) | P=0.236 |
| POLY 1.5 | (e) | (e) | (e) | (e) | P=0.040 * | (e) | (e) | P=0.236 |
| POLY 6 | (e) | (e) | (e) | (e) | P=0.039 * | (e) | (e) | P=0.235 |
| LOGISTIC REGRESSION | (e) | (e) | (e) | (e) | (e) | (e) | (e) | P=0.245 |
| COCH-ARM / FISHERS | (e) | (e) | (e) | (e) | P=0.042 * | (e) | (e) | P=0.247 |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Mammary Gland Fibroadenoma** | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 1/50 (2%) | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) | 23/50 (46%) | 18/50 (36%) | 20/50 (40%) | 17/50 (34%) |
| POLY-3 RATE (b) | 1/40.89 | 2/39.45 | 2/39.74 | 3/42.55 | 23/46.87 | 18/46.52 | 20/46.73 | 17/46.07 |
| POLY-3 PERCENT (g) | 2.5% | 5.1% | 5.0% | 7.1% | 49.1% | 38.7% | 42.8% | 36.9% |
| TERMINAL (d) | 1/30 (3%) | 2/21 (10%) | 1/21 (5%) | 2/30 (7%) | 14/33 (42%) | 15/39 (39%) | 15/35 (43%) | 11/34 (32%) |
| FIRST INCIDENCE | 729 (T) | 729 (T) | 648 | 700 | 596 | 634 | 592 | 529 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.336 | P=0.376 | P=0.401 | P=0.309 | P=0.281N | P=0.109N | P=0.279N | P=0.174N |
| POLY 3 | P=0.291 | P=0.487 | P=0.490 | P=0.319 | P=0.220N | P=0.210N | P=0.343N | P=0.162N |
| POLY 1.5 | P=0.285 | P=0.500 | P=0.500 | P=0.318 | P=0.214N | P=0.208N | P=0.[illegible]47N | P=0.157N |
| POLY 6 | P=0.297 | P=0.464 | P=0.471 | P=0.317 | P=0.236N | P=0.217N | P=0.346N | P=0.177N |
| LOGISTIC REGRESSION | P=0.308 | P=0.376 | P=0.478 | P=0.310 | P=0.219N | P=0.187N | P=0.333N | P=0.154N |
| COCH-ARM / FISHERS | P=0.268 | P=0.500 | P=0.500 | P=0.309 | P=0.209N | P=0.208N | P=0.343N | P=0.154N |

C 14

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Mammary Gland Fibroma, Fibroadenoma, Carcinoma, or Adenoma** | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 1/50 (2%) | 2/50 (4%) | 2/50 (4%) | 3/50 (6%) | 23/50 (46%) | 18/50 (36%) | 20/50 (40%) | 18/50 (36%) |
| POLY-3 RATE (b) | 1/40.89 | 2/39.45 | 2/39.74 | 3/42.55 | 23/46.87 | 18/46.52 | 20/46.73 | 18/46.07 |
| POLY-3 PERCENT (g) | 2.5% | 5.1% | 5.0% | 7.1% | 49.1% | 38.7% | 42.8% | 39.1% |
| TERMINAL (d) | 1/30 (3%) | 2/21 (10%) | 1/21 (5%) | 2/30 (7%) | 14/33 (42%) | 15/39 (39%) | 15/35 (43%) | 12/34 (35%) |
| FIRST INCIDENCE | 729 (T) | 729 (T) | 648 | 700 | 596 | 634 | 592 | 529 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.336 | P=0.376 | P=0.401 | P=0.309 | P=0.361N | P=0.109N | P=0.279N | P=0.224N |
| POLY 3 | P=0.291 | P=0.487 | P=0.490 | P=0.319 | P=0.300N | P=0.210N | P=0.343N | P=0.221N |
| POLY 1.5 | P=0.285 | P=0.500 | P=0.500 | P=0.318 | P=0.292N | P=0.208N | P=0.347N | P=0.214N |
| POLY 6 | P=0.297 | P=0.464 | P=0.471 | P=0.317 | P=0.320N | P=0.217N | P=0.346N | P=0.240N |
| LOGISTIC REGRESSION | P=0.308 | P=0.376 | P=0.478 | P=0.310 | P=0.297N | P=0.187N | P=0.333N | P=0.209N |
| COCH-ARM / FISHERS | P=0.268 | P=0.500 | P=0.500 | P=0.309 | P=0.284N | P=0.208N | P=0.343N | P=0.208N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Mesentery Sarcoma** | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 0/40.89 | 0/39.45 | 0/39.45 | 2/42.44 | 0/44.24 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 0.0% | 0.0% | 0.0% | 4.7% | 0.0% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 2/30 (7%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | --- | --- | --- | 729 (T) | --- | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.062 | (e) | (e) | P=0.238 | (e) | (e) | (e) | (e) |
| POLY 3 | P=0.044 * | (e) | (e) | P=0.245 | (e) | (e) | (e) | (e) |
| POLY 1.5 | P=0.043 * | (e) | (e) | P=0.245 | (e) | (e) | (e) | (e) |
| POLY 6 | P=0.045 * | (e) | (e) | P=0.243 | (e) | (e) | (e) | (e) |
| LOGISTIC REGRESSION | (e) | (e) | (e) | P=0.238 | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.042 * | (e) | (e) | P=0.247 | (e) | (e) | (e) | (e) |

D.01

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Nose** Squamous Cell Carcinoma | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 2/50 (4%) | 0/49 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 0/40.89 | 0/39.45 | 0/39.45 | 2/43.13 | 0/44.01 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 0.0% | 0.0% | 0.0% | 4.6% | 0.0% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 1/30 (3%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | --- | --- | --- | 492 | --- | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.054 | (e) | (e) | P=0.247 | (e) | (e) | (e) | (e) |
| POLY 3 | P=0.045 * | (e) | (e) | P=0.249 | (e) | (e) | (e) | (e) |
| POLY 1.5 | P=0.043 * | (e) | (e) | P=0.247 | (e) | (e) | (e) | (e) |
| POLY 6 | P=0.047 * | (e) | (e) | P=0.249 | (e) | (e) | (e) | (e) |
| LOGISTIC REGRESSION | P=0.033 * | (e) | (e) | P=0.207 | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.042 * | (e) | (e) | P=0.247 | (e) | (e) | (e) | (e) |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Pancreas** Mixed Tumor Benign | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/49 (0%) | 0/50 (0%) | 0/49 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 2/41.51 | 0/39.45 | 0/39.45 | 0/42.44 | 0/44.01 | 0/45.74 | 0/44.51 | 0/44.02 |
| POLY-3 PERCENT (g) | 4.8% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 1/30 (3%) | 0/21 (0%) | 0/21 (0%) | 0/30 (0%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 528 | --- | --- | --- | --- | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.230N | P=0.279N | P=0.276N | P=0.235N | (e) | (e) | (e) | (e) |
| POLY 3 | P=0.226N | P=0.248N | P=0.248N | P=0.232N | (e) | (e) | (e) | (e) |
| POLY 1.5 | P=0.234N | P=0.239N | P=0.240N | P=0.231N | (e) | (e) | (e) | (e) |
| POLY 6 | P=0.213N | P=0.265N | P=0.264N | P=0.235N | (e) | (e) | (e) | (e) |
| LOGISTIC REGRESSION | P=0.248N | P=0.245N | P=0.243N | P=0.251N | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.239N | P=0.247N | P=0.247N | P=0.247N | (e) | (e) | (e) | (e) |

D 02

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Pituitary Gland: Pars Distalis or Unspecified Site Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 15/49 (31%) | 9/50 (18%) | 10/48 (21%) | 13/50 (26%) | 15/49 (31%) | 21/50 (42%) | 25/49 (51%) | 25/49 (51%) |
| POLY-3 RATE (b) | 15/41.14 | 9/41.29 | 10/39.69 | 13/42.98 | 15/46.31 | 21/47.49 | 25/45.54 | 25/46.10 |
| POLY-3 PERCENT (g) | 36.5% | 21.8% | 25.2% | 30.3% | 32.4% | 44.2% | 54.9% | 54.2% |
| TERMINAL (d) | 10/29 (35%) | 4/21 (19%) | 5/20 (25%) | 11/30 (37%) | 8/33 (24%) | 16/39 (41%) | 20/35 (57%) | 15/33 (46%) |
| FIRST INCIDENCE | 604 | 511 | 483 | 645 | 497 | 600 | 648 | 590 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.439N | P=0.315N | P=0.443N | P=0.378N | P=0.044 * | P=0.302 | P=0.072 | P=0.054 |
| POLY 3 | P=0.556 | P=0.107N | P=0.193N | P=0.353N | P=0.042 * | P=0.166 | P=0.022 * | P=0.025 * |
| POLY 1.5 | P=0.541 | P=0.096N | P=0.177N | P=0.350N | P=0.044 * | P=0.164 | P=0.023 * | P=0.026 * |
| POLY 6 | P=0.550N | P=0.134N | P=0.234N | P=0.373N | P=0.041 * | P=0.174 | P=0.021 * | P=0.025 * |
| LOGISTIC REGRESSION | P=0.533N | P=0.117N | P=0.206N | P=0.337N | P=0.047 * | P=0.162 | P=0.032 * | P=0.034 * |
| COCH-ARM / FISHERS | P=0.512 | P=0.109N | P=0.193N | P=0.387N | P=0.052 | P=0.166 | P=0.032 * | P=0.032 * |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Prostate Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 1/50 (2%) | 0/50 (0%) | 1/50 (2%) | 3/50 (6%) | | | | |
| POLY-3 RATE (b) | 1/40.89 | 0/39.45 | 1/39.45 | 3/42.44 | | | | |
| POLY-3 PERCENT (g) | 2.5% | 0.0% | 2.5% | 7.1% | | | | |
| TERMINAL (d) | 1/30 (3%) | 0/21 (0%) | 1/21 (5%) | 3/30 (10%) | | | | |
| FIRST INCIDENCE | 729 (T) | --- | 729 (T) | 729 (T) | | | | |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.119 | P=0.571N | P=0.681 | P=0.304 | | | | |
| POLY 3 | P=0.090 | P=0.507N | P=0.753 | P=0.318 | | | | |
| POLY 1.5 | P=0.087 | P=0.500N | P=0.760 | P=0.318 | | | | |
| POLY 6 | P=0.095 | P=0.520N | P=0.739 | P=0.315 | | | | |
| LOGISTIC REGRESSION | P=0.119 | (e) | P=0.681 | P=0.304 | | | | |
| COCH-ARM / FISHERS | P=0.082 | P=0.500N | P=0.753N | P=0.309 | | | | |

D 03

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** | | | | | | | | |
| Basal Cell Carcinoma, Basal Cell Adenoma, Basosquamous Tumor (benign, malignant or NOS), or Trichoepithelioma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 1/50 (2%) | 2/50 (4%) | 0/50 (0%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| POLY-3 RATE (b) | 1/40.89 | 2/39.45 | 0/39.45 | 2/42.91 | 0/44.24 | 0/45.74 | 0/45.30 | 1/44.02 |
| POLY-3 PERCENT (g) | 2.5% | 5.1% | 0.0% | 4.7% | 0.0% | 0.0% | 0.0% | 2.3% |
| TERMINAL (d) | 1/30 (3%) | 2/21 (10%) | 0/21 (0%) | 1/30 (3%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 1/34 (3%) |
| FIRST INCIDENCE | 729 (T) | 729 (T) | --- | 590 | --- | --- | --- | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.511 | P=0.376 | P=0.571N | P=0.505 | P=0.208 | (e) | (e) | P=0.506 |
| POLY 3 | P=0.480 | P=0.487 | P=0.507N | P=0.517 | P=0.213 | (e) | (e) | P=0.499 |
| POLY 1.5 | P=0.474 | P=0.500 | P=0.501N | P=0.514 | P=0.214 | (e) | (e) | P=0.499 |
| POLY 6 | P=0.485 | P=0.464 | P=0.520N | P=0.517 | P=0.210 | (e) | (e) | P=0.498 |
| LOGISTIC REGRESSION | P=0.483 | P=0.376 | (e) | P=0.506 | (e) | (e) | (e) | P=0.506 |
| COCH-ARM / FISHERS | P=0.460 | P=0.500 | P=0.500N | P=0.500 | P=0.215 | (e) | (e) | P=0.500 |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** | | | | | | | | |
| Basal or Sq. Cell Carcinoma, Carcinoma, Basosq. Tumor (M or B), Basal Cell Adenoma, Adenoma, Papilloma, Sq Papilloma, Keratoacanthoma, Trichoepitheliom | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 4/50 (8%) | 6/50 (12%) | 3/50 (6%) | 8/50 (16%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| POLY-3 RATE (b) | 4/40.99 | 6/39.97 | 3/39.45 | 8/43.01 | 1/44.24 | 0/45.74 | 0/45.30 | 1/44.02 |
| POLY-3 PERCENT (g) | 9.8% | 15.0% | 7.6% | 18.6% | 2.3% | 0.0% | 0.0% | 2.3% |
| TERMINAL (d) | 3/30 (10%) | 4/21 (19%) | 3/21 (14%) | 6/30 (20%) | 1/33 (3%) | 0/39 (0%) | 0/35 (0%) | 1/34 (3%) |
| FIRST INCIDENCE | 704 | 638 | 729 (T) | 590 | 730 (T) | --- | --- | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.233 | P=0.201 | P=0.626 | P=0.183 | P=0.532 | P=0.467N | P=0.488N | P=0.755N |
| POLY 3 | P=0.172 | P=0.352 | P=0.521N | P=0.198 | P=0.533 | P=0.493N | P=0.495N | P=0.760 |
| POLY 1.5 | P=0.164 | P=0.372 | P=0.502N | P=0.196 | P=0.537 | P=0.496N | P=0.498N | P=0.760 |
| POLY 6 | P=0.180 | P=0.316 | P=0.557N | P=0.196 | P=0.528 | P=0.489N | P=0.492N | P=0.759 |
| LOGISTIC REGRESSION | P=0.193 | P=0.289 | P=0.639N | P=0.190 | P=0.532 | (e) | (e) | P=0.755N |
| COCH-ARM / FISHERS | P=0.149 | P=0.370 | P=0.500N | P=0.178 | P=0.541 | P=0.500N | P=0.500N | P=0.753N |

D 04

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** | | | | | | | | |
| Fibroma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 1/50 (2%) | 3/50 (6%) | 2/50 (4%) | 5/50 (10%) | 2/50 (4%) | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) |
| POLY-3 RATE (b) | 1/40.99 | 3/40.48 | 2/39.91 | 5/43.17 | 2/44.26 | 0/45.74 | 1/45.38 | 0/44.02 |
| POLY-3 PERCENT (g) | 2.4% | 7.4% | 5.0% | 11.6% | 4.5% | 0.0% | 2.2% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 3/30 (10%) | 1/33 (3%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 704 | 584 | 631 | 605 | 725 | --- | 711 | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.128 | P=0.266 | P=0.439 | P=0.113 | P=0.277N | P=0.210N | P=0.477N | P=0.240N |
| POLY 3 | P=0.100 | P=0.300 | P=0.491 | P=0.113 | P=0.274N | P=0.230N | P=0.491N | P=0.238N |
| POLY 1.5 | P=0.096 | P=0.309 | P=0.501 | P=0.111 | P=0.270N | P=0.233N | P=0.496N | P=0.238N |
| POLY 6 | P=0.104 | P=0.283 | P=0.472 | P=0.113 | P=0.279N | P=0.225N | P=0.485N | P=0.239N |
| LOGISTIC REGRESSION | P=0.088 | P=0.301 | P=0.498 | P=0.109 | P=0.272N | P=0.217N | P=0.483N | P=0.241N |
| COCH-ARM / FISHERS | P=0.088 | P=0.309 | P=0.500 | P=0.102 | P=0.266N | P=0.247N | P=0.500N | P=0.247N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** | | | | | | | | |
| Fibroma, Fibrosarcoma, Sarcoma, Myxoma, Myxosarcoma, or Fibrous Histiocytoma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 2/50 (4%) | 4/50 (8%) | 2/50 (4%) | 5/50 (10%) | 2/50 (4%) | 1/50 (2%) | 2/50 (4%) | 0/50 (0%) |
| POLY-3 RATE (b) | 2/41.99 | 4/40.67 | 2/39.91 | 5/43.17 | 2/44.26 | 1/45.74 | 2/46.35 | 0/44.02 |
| POLY-3 PERCENT (g) | 4.8% | 9.8% | 5.0% | 11.6% | 4.5% | 2.2% | 4.3% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 3/30 (10%) | 1/33 (3%) | 1/39 (3%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 122 | 584 | 631 | 605 | 725 | 730 (T) | 232 | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.267 | P=0.292 | P=0.644 | P=0.230 | P=0.219N | P=0.449N | P=0.674N | P=0.240N |
| POLY 3 | P=0.227 | P=0.322 | P=0.676 | P=0.226 | P=0.216N | P=0.489N | P=0.677N | P=0.238N |
| POLY 1.5 | P=0.222 | P=0.334 | P=0.687 | P=0.225 | P=0.213N | P=0.494N | P=0.684N | P=0.238N |
| POLY 6 | P=0.233 | P=0.301 | P=0.656 | P=0.226 | P=0.220N | P=0.482N | P=0.670N | P=0.239N |
| LOGISTIC REGRESSION | P=0.175 | P=0.243 | P=0.619 | P=0.166 | P=0.191N | P=0.465N | P=0.664N | P=0.241N |
| COCH-ARM / FISHERS | P=0.211 | P=0.339 | P=0.691N | P=0.218 | P=0.208N | P=0.500N | P=0.691N | P=0.247N |

D 05

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** | | | | | | | | |
| Keratoacanthoma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 3/50 (6%) | 3/50 (6%) | 3/50 (6%) | 3/50 (6%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 3/40.99 | 3/39.97 | 3/39.45 | 3/42.44 | 1/44.24 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 7.3% | 7.5% | 7.6% | 7.1% | 2.3% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 2/30 (7%) | 1/21 (5%) | 3/21 (14%) | 3/30 (10%) | 1/33 (3%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 704 | 638 | 729 (T) | 729 (T) | 730 (T) | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.522N | P=0.534 | P=0.497 | P=0.663 | P=0.479N | P=0.467N | P=0.488N | P=0.494N |
| POLY 3 | P=0.575N | P=0.652 | P=0.645 | P=0.647N | P=0.477N | P=0.493N | P=0.495N | P=0.501N |
| POLY 1.5 | P=0.583N | P=0.660N | P=0.661 | P=0.647N | P=0.475N | P=0.496N | P=0.498N | P=0.501N |
| POLY 6 | P=0.567N | P=0.626 | P=0.615 | P=0.652N | P=0.480N | P=0.489N | P=0.492N | P=0.502N |
| LOGISTIC REGRESSION | P=0.550N | P=0.636 | P=0.548 | P=0.660N | P=0.479N | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.601N | P=0.661N | P=0.661N | P=0.661N | P=0.472N | P=0.500N | P=0.500N | P=0.500N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** | | | | | | | | |
| Squamous Cell Carcinoma, Basal Cell Carcinoma, Basosquamous Tumor (malignant or NOS), or Carcinoma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 0/40.89 | 1/39.45 | 0/39.45 | 2/42.44 | 0/44.24 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 0.0% | 2.5% | 0.0% | 4.7% | 0.0% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 1/21 (5%) | 0/21 (0%) | 2/30 (7%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | --- | 729 (T) | --- | 729 (T) | --- | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.190 | P=0.429 | (e) | P=0.238 | (e) | (e) | (e) | (e) |
| POLY 3 | P=0.156 | P=0.493 | (e) | P=0.245 | (e) | (e) | (e) | (e) |
| POLY 1.5 | P=0.154 | P=0.500 | (e) | P=0.245 | (e) | (e) | (e) | (e) |
| POLY 6 | P=0.156 | P=0.480 | (e) | P=0.243 | (e) | (e) | (e) | (e) |
| LOGISTIC REGRESSION | (e) | P=0.429 | (e) | P=0.238 | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.149 | P=0.500 | (e) | P=0.247 | (e) | (e) | (e) | (e) |

D 06

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** Squamous Cell Papilloma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) | 2/50 (4%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 0/40.89 | 1/39.45 | 0/39.45 | 2/42.54 | 0/44.24 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 0.0% | 2.5% | 0.0% | 4.7% | 0.0% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 1/21 (5%) | 0/21 (0%) | 1/30 (3%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | --- | 729 (T) | --- | 702 | --- | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.190 | P=0.429 | (e) | P=0.243 | (e) | (e) | (e) | (e) |
| POLY 3 | P=0.156 | P=0.493 | (e) | P=0.246 | (e) | (e) | (e) | (e) |
| POLY 1.5 | P=0.155 | P=0.500 | (e) | P=0.245 | (e) | (e) | (e) | (e) |
| POLY 6 | P=0.157 | P=0.480 | (e) | P=0.244 | (e) | (e) | (e) | (e) |
| LOGISTIC REGRESSION | P=0.174 | P=0.429 | (e) | P=0.243 | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.149 | P=0.500 | (e) | P=0.247 | (e) | (e) | (e) | (e) |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** Squamous Cell Papilloma, Papilloma, Squamous Cell Carcinoma or Keratoacanthoma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 3/50 (6%) | 4/50 (8%) | 3/50 (6%) | 6/50 (12%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 3/40.99 | 4/39.97 | 3/39.45 | 6/42.54 | 1/44.24 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 7.3% | 10.0% | 7.6% | 14.1% | 2.3% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 2/30 (7%) | 2/21 (10%) | 3/21 (14%) | 5/30 (17%) | 1/33 (3%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 704 | 638 | 729 (T) | 702 | 730 (T) | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.267 | P=0.353 | P=0.497 | P=0.245 | P=0.479N | P=0.467N | P=0.488N | P=0.494N |
| POLY 3 | P=0.206 | P=0.486 | P=0.645 | P=0.259 | P=0.477N | P=0.493N | P=0.495N | P=0.501N |
| POLY 1.5 | P=0.200 | P=0.503 | P=0.661 | P=0.259 | P=0.475N | P=0.496N | P=0.498N | P=0.501N |
| POLY 6 | P=0.211 | P=0.455 | P=0.615 | P=0.254 | P=0.480N | P=0.489N | P=0.492N | P=0.502N |
| LOGISTIC REGRESSION | P=0.234 | P=0.455 | P=0.548 | P=0.246 | P=0.479N | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.185 | P=0.500 | P=0.661N | P=0.243 | P=0.472N | P=0.500N | P=0.500N | P=0.500N |

D 07

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Skin** | | | | | | | | |
| Squamous Cell Papilloma, Papilloma, or Keratoacanthoma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 3/50 (6%) | 4/50 (8%) | 3/50 (6%) | 5/50 (10%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) |
| POLY-3 RATE (b) | 3/40.99 | 4/39.97 | 3/39.45 | 5/42.54 | 1/44.34 | 0/45.74 | 0/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 7.3% | 10.0% | 7.6% | 11.8% | 2.3% | 0.0% | 0.0% | 0.0% |
| TERMINAL (d) | 2/30 (7%) | 2/21 (10%) | 3/21 (14%) | 4/30 (13%) | 1/33 (3%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 704 | 638 | 729 (T) | 702 | 730 (T) | --- | --- | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.405 | P=0.353 | P=0.497 | P=0.359 | P=0.479N | P=0.467N | P=0.488N | P=0.494N |
| POLY 3 | P=0.343 | P=0.486 | P=0.645 | P=0.376 | P=0.477N | P=0.493N | P=0.495N | P=0.501N |
| POLY 1.5 | P=0.336 | P=0.503 | P=0.661 | P=0.376 | P=0.475N | P=0.496N | P=0.498N | P=0.501N |
| POLY 6 | P=0.351 | P=0.455 | P=0.615 | P=0.371 | P=0.480N | P=0.489N | P=0.492N | P=0.502N |
| LOGISTIC REGRESSION | P=0.372 | P=0.455 | P=0.548 | P=0.363 | P=0.479N | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.315 | P=0.500 | P=0.661N | P=0.357 | P=0.472N | P=0.500N | P=0.500N | P=0.500N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Testes** | | | | | | | | |
| Adenoma | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 41/50 (82%) | 43/50 (86%) | 44/50 (88%) | 48/50 (96%) | | | | |
| POLY-3 RATE (b) | 41/44.33 | 43/45.66 | 44/47.50 | 48/48.74 | | | | |
| POLY-3 PERCENT (g) | 92.5% | 94.2% | 92.6% | 98.5% | | | | |
| TERMINAL (d) | 29/30 (97%) | 21/21 (100%) | 20/21 (95%) | 30/30 (100%) | | | | |
| FIRST INCIDENCE | 528 | 555 | 510 | 449 | | | | |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.488 | P=0.020 * | P=0.022 * | P=0.165 | | | | |
| POLY 3 | P=0.099 | P=0.553 | P=0.662 | P=0.135 | | | | |
| POLY 1.5 | P=0.049 * | P=0.563 | P=0.542 | P=0.071 | | | | |
| POLY 6 | P=0.221 | P=0.472 | P=0.578N | P=0.249 | | | | |
| LOGISTIC REGRESSION | P=0.028 * | P=0.309 | P=0.320 | P=0.044 * | | | | |
| COCH-ARM / FISHERS | P=0.023 * | P=0.393 | P=0.288 | P=0.026 * | | | | |

D 08

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Thyroid Gland: C-Cell Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 3/50 (6%) | 5/50 (10%) | 3/50 (6%) | 3/50 (6%) | 4/49 (8%) | 6/50 (12%) | 4/50 (8%) | 3/50 (6%) |
| POLY-3 RATE (b) | 3/40.89 | 5/39.80 | 3/40.37 | 3/42.44 | 4/44.63 | 6/46.09 | 4/45.77 | 3/44.02 |
| POLY-3 PERCENT (g) | 7.3% | 12.6% | 7.4% | 7.1% | 9.0% | 13.0% | 8.7% | 6.8% |
| TERMINAL (d) | 3/30 (10%) | 4/21 (19%) | 0/21 (0%) | 3/30 (10%) | 3/33 (9%) | 5/39 (13%) | 3/35 (9%) | 3/34 (9%) |
| FIRST INCIDENCE | 729 (T) | 632 | 575 | 729 (T) | 527 | 634 | 592 | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.377N | P=0.196 | P=0.553 | P=0.665 | P=0.320N | P=0.461 | P=0.615N | P=0.484N |
| POLY 3 | P=0.426N | P=0.340 | P=0.657 | P=0.646N | P=0.315N | P=0.390 | P=0.630N | P=0.508N |
| POLY 1.5 | P=0.433N | P=0.358 | P=0.658N | P=0.646N | P=0.307N | P=0.385 | P=0.633N | P=0.501N |
| POLY 6 | P=0.420N | P=0.308 | P=0.637 | P=0.650N | P=0.327N | P=0.399 | P=0.622N | P=0.516N |
| LOGISTIC REGRESSION | P=0.414N | P=0.268 | P=0.658 | P=0.665 | P=0.298N | P=0.381 | P=0.628N | P=0.493N |
| COCH-ARM / FISHERS | P=0.453N | P=0.357 | P=0.661N | P=0.661N | P=0.293N | P=0.383 | P=0.631N | P=0.489N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Thyroid Gland: C-Cell Carcinoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 1/50 (2%) | 1/50 (2%) | 1/50 (2%) | 1/50 (2%) | 2/49 (4%) | 2/50 (4%) | 0/50 (0%) | 3/50 (6%) |
| POLY-3 RATE (b) | 1/40.97 | 1/39.45 | 1/39.45 | 1/42.8[illegible] | 2/44.01 | 2/45.74 | 0/45.30 | 3/44.38 |
| POLY-3 PERCENT (g) | 2.4% | 2.5% | 2.5% | 2.3% | 4.5% | 4.4% | 0.0% | 6.8% |
| TERMINAL (d) | 0/30 (0%) | 1/21 (5%) | 1/21 (5%) | 0/30 (0%) | 2/33 (6%) | 2/39 (5%) | 0/35 (0%) | 1/34 (3%) |
| FIRST INCIDENCE | 711 | 729 (T) | 729 (T) | 617 | 730 (T) | 730 (T) | --- | 646 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.620N | P=0.687 | P=0.682 | P=0.751N | P=0.342 | P=0.634N | P=0.225N | P=0.508 |
| POLY 3 | P=0.650N | P=0.753 | P=0.753 | P=0.751N | P=0.358 | P=0.680N | P=0.231N | P=0.504 |
| POLY 1.5 | P=0.656N | P=0.761 | P=0.760 | P=0.752N | P=0.360 | P=0.683N | P=0.233N | P=0.505 |
| POLY 6 | P=0.643N | P=0.737 | P=0.738 | P=0.752N | P=0.354 | P=0.674N | P=0.227N | P=0.503 |
| LOGISTIC REGRESSION | P=0.650N | P=0.722 | P=0.723 | P=0.762 | P=0.348 | P=0.634N | (e) | P=0.500 |
| COCH-ARM / FISHERS | P=0.668 | P=0.753N | P=0.753N | P=0.753N | P=0.364 | P=0.684N | P=0.242N | P=0.510 |

D 09

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Thyroid Gland: C-Cell Carcinoma or Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 4/50 (8%) | 6/50 (12%) | 4/50 (8%) | 4/50 (8%) | 6/49 (12%) | 8/50 (16%) | 4/50 (8%) | 6/50 (12%) |
| POLY-3 RATE (b) | 4/40.97 | 6/39.80 | 4/40.37 | 4/42.83 | 6/44.63 | 8/46.09 | 4/45.77 | 6/44.38 |
| POLY-3 PERCENT (g) | 9.8% | 15.1% | 9.9% | 9.3% | 13.4% | 17.4% | 8.7% | 13.5% |
| TERMINAL (d) | 3/30 (10%) | 5/21 (24%) | 1/21 (5%) | 3/30 (10%) | 5/33 (15%) | 7/39 (18%) | 3/35 (9%) | 4/34 (12%) |
| FIRST INCIDENCE | 711 | 632 | 575 | 617 | 527 | 634 | 592 | 646 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.371N | P=0.190 | P=0.497 | P=0.637N | P=0.507N | P=0.504 | P=0.339N | P=0.602N |
| POLY 3 | P=0.420N | P=0.350 | P=0.636 | P=0.619N | P=0.489N | P=0.411 | P=0.354N | P=0.617 |
| POLY 1.5 | P=0.431N | P=0.371 | P=0.639N | P=0.622N | P=0.480N | P=0.406 | P=0.359N | P=0.618N |
| POLY 6 | P=0.408N | P=0.311 | P=0.611 | P=0.621N | P=0.499N | P=0.423 | P=0.345N | P=0.612 |
| LOGISTIC REGRESSION | P=0.415N | P=0.266 | P=0.628 | P=0.628N | P=0.481N | P=0.409 | P=0.356N | P=0.616N |
| COCH-ARM / FISHERS | P=0.458N | P=0.370 | P=0.643N | P=0.643N | P=0.467N | P=0.403 | P=0.357N | P=0.606N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Thyroid Gland: Follicular Cell Carcinoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 0/50 (0%) | 2/50 (4%) | 2/50 (4%) | 0/50 (0%) | 0/49 (0%) | 1/50 (2%) | 1/50 (2%) | 0/50 (0%) |
| POLY-3 RATE (b) | 0/40.89 | 2/39.46 | 2/39.46 | 0/42.44 | 0/44.01 | 1/45.74 | 1/45.30 | 0/44.02 |
| POLY-3 PERCENT (g) | 0.0% | 5.1% | 5.1% | 0.0% | 0.0% | 2.2% | 2.2% | 0.0% |
| TERMINAL (d) | 0/30 (0%) | 1/21 (5%) | 1/21 (5%) | 0/30 (0%) | 0/33 (0%) | 1/39 (3%) | 1/35 (3%) | 0/34 (0%) |
| FIRST INCIDENCE | --- | 725 | 725 | --- | --- | 730 (T) | 730 (T) | --- |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.354N | P=0.167 | P=0.167 | (e) | P=0.551N | P=0.533 | P=0.512 | (e) |
| POLY 3 | P=0.370N | P=0.229 | P=0.229 | (e) | P=0.543N | P=0.508 | P=0.506 | (e) |
| POLY 1.5 | P=0.372N | P=0.237 | P=0.236 | (e) | P=0.541N | P=0.506 | P=0.504 | (e) |
| POLY 6 | P=0.373N | P=0.214 | P=0.215 | (e) | P=0.546N | P=0.511 | P=0.509 | (e) |
| LOGISTIC REGRESSION | P=0.353N | P=0.175 | P=0.175 | (e) | (e) | P=0.533 | P=0.512 | (e) |
| COCH-ARM / FISHERS | P=0.386N | P=0.247 | P=0.247 | (e) | P=0.538N | P=0.505 | P=0.505 | (e) |

D 10

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Thyroid Gland: Follicular Cell Carcinoma or Adenoma** | | | | | | | | |
| TUMOR RATES | | | | | | | | |
| OVERALL (a) | 1/50 (2%) | 3/50 (6%) | 2/50 (4%) | 0/50 (0%) | 0/49 (0%) | 2/50 (4%) | 1/50 (2%) | 1/50 (2%) |
| POLY-3 RATE (b) | 1/40.89 | 3/39.46 | 2/39.46 | 0/42.44 | 0/44.01 | 2/45.74 | 1/45.30 | 1/44.02 |
| POLY-3 PERCENT (g) | 2.5% | 7.6% | 5.1% | 0.0% | 0.0% | 4.4% | 2.2% | 2.3% |
| TERMINAL (d) | 1/30 (3%) | 2/21 (10%) | 1/21 (5%) | 0/30 (0%) | 0/33 (0%) | 2/39 (5%) | 1/35 (3%) | 1/34 (3%) |
| FIRST INCIDENCE | 729 (T) | 725 | 725 | --- | --- | 730 (T) | 730 (T) | 730 (T) |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.167N | P=0.190 | P=0.379 | P=0.500N | P=0.602 | P=0.276 | P=0.512 | P=0.506 |
| POLY 3 | P=0.174N | P=0.292 | P=0.488 | P=0.493N | P=0.609 | P=0.246 | P=0.506 | P=0.500 |
| POLY 1.5 | P=0.176N | P=0.305 | P=0.499 | P=0.493N | P=0.612 | P=0.244 | P=0.504 | P=0.501 |
| POLY 6 | P=0.173N | P=0.268 | P=0.466 | P=0.494N | P=0.605 | P=0.249 | P=0.509 | P=0.498 |
| LOGISTIC REGRESSION | P=0.163N | P=0.198 | P=0.395 | (e) | (e) | P=0.276 | P=0.512 | P=0.506 |
| COCH-ARM / FISHERS | P=0.187N | P=0.309 | P=0.500 | P=0.500N | P=0.617 | P=0.253 | P=0.505 | P=0.505 |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Uterus Polyp Stromal** | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | | | | | 10/50 (20%) | 8/50 (16%) | 7/50 (14%) | 10/50 (20%) |
| POLY-3 RATE (b) | | | | | 10/45.55 | 8/45.74 | 7/46.22 | 10/44.48 |
| POLY-3 PERCENT (g) | | | | | 22.0% | 17.5% | 15.2% | 22.5% |
| TERMINAL (d) | | | | | 5/33 (15%) | 8/39 (21%) | 4/35 (11%) | 9/34 (27%) |
| FIRST INCIDENCE | | | | | 630 | 730 (T) | 527 | 592 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | | | | | P=0.411 | P=0.291N | P=0.268N | P=0.583N |
| POLY 3 | | | | | P=0.425 | P=0.393N | P=0.285N | P=0.576 |
| POLY 1.5 | | | | | P=0.438 | P=0.394N | P=0.292N | P=0.587 |
| POLY 6 | | | | | P=0.405 | P=0.395N | P=0.279N | P=0.555 |
| LOGISTIC REGRESSION | | | | | P=0.439 | P=0.374N | P=0.299N | P=0.595 |
| COCH-ARM / FISHERS | | | | | P=0.452 | P=0.398N | P=0.298N | P=0.598N |

D 11

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Uterus** | | | | | | | | |
| Sarcoma Stromal or Polyp Stromal | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | | | | | 11/50 (22%) | 8/50 (16%) | 7/50 (14%) | 10/50 (20%) |
| POLY-3 RATE (b) | | | | | 11/45.57 | 8/45.74 | 7/46.22 | 10/44.48 |
| POLY-3 PERCENT (g) | | | | | 24.1% | 17.5% | 15.2% | 22.5% |
| TERMINAL (d) | | | | | 5/33 (15%) | 8/39 (21%) | 4/35 (11%) | 9/34 (27%) |
| FIRST INCIDENCE | | | | | 630 | 730 (T) | 527 | 592 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | | | | | P=0.477 | P=0.214N | P=0.197N | P=0.489N |
| POLY 3 | | | | | P=0.494 | P=0.300N | P=0.205N | P=0.525N |
| POLY 1.5 | | | | | P=0.506 | P=0.302N | P=0.212N | P=0.513N |
| POLY 6 | | | | | P=0.474 | P=0.302N | P=0.201N | P=0.549N |
| LOGISTIC REGRESSION | | | | | P=0.507 | P=0.281N | P=0.218N | P=0.504N |
| COCH-ARM / FISHERS | | | | | P=0.521 | P=0.306N | P=0.218N | P=0.500N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **Zymbal's Gland** | | | | | | | | |
| Carcinoma | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 3/50 (6%) |
| POLY-3 RATE (b) | 0/40.89 | 1/40.19 | 0/39.45 | 1/42.44 | 0/44.24 | 0/45.74 | 0/45.30 | 3/45.82 |
| POLY-3 PERCENT (g) | 0.0% | 2.5% | 0.0% | 2.4% | 0.0% | 0.0% | 0.0% | 6.6% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 1/30 (3%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | --- | 462 | --- | 729 (T) | --- | --- | --- | 360 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.479 | P=0.517 | (e) | P=0.500 | P=0.010 * | (e) | (e) | P=0.128 |
| POLY 3 | P=0.469 | P=0.497 | (e) | P=0.507 | P=0.008 ** | (e) | (e) | P=0.125 |
| POLY 1.5 | P=0.469 | P=0.502 | (e) | P=0.507 | P=0.008 ** | (e) | (e) | P=0.123 |
| POLY 6 | P=0.468 | P=0.485 | (e) | P=0.506 | P=0.008 ** | (e) | (e) | P=0.127 |
| LOGISTIC REGRESSION | P=0.424 | P=0.363 | (e) | P=0.500 | P=0.007 ** | (e) | (e) | P=0.093 |
| COCH-ARM / FISHERS | P=0.459 | P=0.500 | (e) | P=0.500 | P=0.009 ** | (e) | (e) | P=0.121 |

D 12

Statistical Analysis of Primary Tumors in Rats(FISCHER 344) - EMODIN

Terminal Sacrifice at 105 weeks

| Dose | Males 0 PPM | 280 PPM | 830 PPM | 2500 PPM | Females 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **All Organs** | | | | | | | | |
| Leukemia: Lymphocytic, Monocytic, Mononuclear, or Undifferentiated | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 28/50 (56%) | 31/50 (62%) | 29/50 (58%) | 18/50 (36%) | 14/50 (28%) | 17/50 (34%) | 16/50 (32%) | 3/50 (6%) |
| POLY-3 RATE (b) | 28/45.54 | 31/47.64 | 29/45.54 | 18/46.53 | 14/46.56 | 17/47.71 | 16/47.73 | 3/44.70 |
| POLY-3 PERCENT (g) | 61.5% | 65.1% | 63.7% | 38.7% | 30.1% | 35.6% | 33.5% | 6.7% |
| TERMINAL (d) | 16/30 (53%) | 7/21 (33%) | 11/21 (52%) | 6/30 (20%) | 7/33 (21%) | 12/39 (31%) | 9/35 (26%) | 1/34 (3%) |
| FIRST INCIDENCE | 284 | 491 | 373 | 266 | 448 | 575 | 527 | 603 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.012N* | P=0.129 | P=0.174 | P=0.063N | P=0.002N** | P=0.487 | P=0.477 | P=0.006N** |
| POLY 3 | P=0.003N** | P=0.442 | P=0.500 | P=0.021N* | P<0.001N** | P=0.361 | P=0.445 | P=0.003N** |
| POLY 1.5 | P=0.003N** | P=0.425 | P=0.528 | P=0.021N* | P<0.001N** | P=0.347 | P=0.426 | P=0.003N** |
| POLY 6 | P=0.003N** | P=0.460 | P=0.455 | P=0.021N* | P<0.001N** | P=0.385 | P=0.471 | P=0.004N** |
| LOGISTIC REGRESSION | P=0.007N** | P=0.341 | P=0.505 | P=0.037N* | P<0.001N** | P=0.304 | P=0.401 | P=0.004N** |
| COCH-ARM / FISHERS | P=0.006N** | P=0.342 | P=0.500 | P=0.035N* | P<0.001N** | P=0.333 | P=0.414 | P=0.003N** |

| Dose | Males 0 PPM | 280 PPM | 830 PPM | 2500 PPM | Females 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **All Organs** | | | | | | | | |
| Mesothelioma: Benign, Malignant, NOS | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 2/50 (4%) | 1/50 (2%) | 3/50 (6%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| POLY-3 RATE (b) | 2/41.52 | 1/39.78 | 3/40.35 | 1/42.83 | 0/44.24 | 0/45.74 | 0/45.30 | 1/44.17 |
| POLY-3 PERCENT (g) | 4.8% | 2.5% | 7.4% | 2.3% | 0.0% | 0.0% | 0.0% | 2.3% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 0/30 (0%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 604 | 636 | 603 | 617 | --- | --- | --- | 690 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.436N | P=0.531N | P=0.466 | P=0.489N | P=0.203 | (e) | (e) | P=0.495 |
| POLY 3 | P=0.440N | P=0.515N | P=0.487 | P=0.489N | P=0.213 | (e) | (e) | P=0.500 |
| POLY 1.5 | P=0.450N | P=0.501N | P=0.500 | P=0.489N | P=0.214 | (e) | (e) | P=0.500 |
| POLY 6 | P=0.429N | P=0.539N | P=0.462 | P=0.493N | P=0.211 | (e) | (e) | P=0.499 |
| LOGISTIC REGRESSION | P=0.489N | P=0.508N | P=0.495 | P=0.524N | P=0.216 | (e) | (e) | P=0.500 |
| COCH-ARM / FISHERS | P=0.466N | P=0.500N | P=0.500 | P=0.500N | P=0.215 | (e) | (e) | P=0.500 |

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| Dose | Males 0 PPM | 280 PPM | 830 PPM | 2500 PPM | Females 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **All Organs** | | | | | | | | |
| Mesothelioma: Malignant | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 2/50 (4%) | 1/50 (2%) | 3/50 (6%) | 1/50 (2%) | 0/50 (0%) | 0/50 (0%) | 0/50 (0%) | 1/50 (2%) |
| POLY-3 RATE (b) | 2/41.52 | 1/39.73 | 3/40.35 | 1/42.83 | 0/44.24 | 0/45.74 | 0/45.30 | 1/44.17 |
| POLY-3 PERCENT (g) | 4.8% | 2.5% | 7.4% | 2.3% | 0.0% | 0.0% | 0.0% | 2.3% |
| TERMINAL (d) | 0/30 (0%) | 0/21 (0%) | 0/21 (0%) | 0/30 (0%) | 0/33 (0%) | 0/39 (0%) | 0/35 (0%) | 0/34 (0%) |
| FIRST INCIDENCE | 604 | 636 | 603 | 617 | --- | --- | --- | 690 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.436N | P=0.531N | P=0.466 | P=0.489N | P=0.203 | (e) | (e) | P=0.495 |
| POLY 3 | P=0.440N | P=0.515N | P=0.487 | P=0.489N | P=0.213 | (e) | (e) | P=0.500 |
| POLY 1.5 | P=0.450N | P=0.501N | P=0.500 | P=0.489N | P=0.214 | (e) | (e) | P=0.500 |
| POLY 6 | P=0.429N | P=0.539N | P=0.462 | P=0.493N | P=0.211 | (e) | (e) | P=0.499 |
| LOGISTIC REGRESSION | P=0.489N | P=0.508N | P=0.495 | P=0.524N | P=0.216 | (e) | (e) | P=0.500 |
| COCH-ARM / FISHERS | P=0.466N | P=0.500N | P=0.500 | P=0.500N | P=0.215 | (e) | (e) | P=0.500 |

| Dose | Males 0 PPM | 280 PPM | 830 PPM | 2500 PPM | Females 0 PPM | 280 PPM | 830 PPM | 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **All Organs** | | | | | | | | |
| Benign Tumors | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 45/50 (90%) | 46/50 (92%) | 47/50 (94%) | 49/50 (98%) | 41/50 (82%) | 39/50 (78%) | 41/50 (82%) | 37/50 (74%) |
| POLY-3 RATE (b) | 45/45.79 | 46/47.15 | 47/48.25 | 49/49.05 | 41/49.13 | 39/47.70 | 41/48.10 | 37/47.72 |
| POLY-3 PERCENT (g) | 98.3% | 97.6% | 97.4% | 99.9% | 83.5% | 81.8% | 85.2% | 77.5% |
| TERMINAL (d) | 30/30 (100%) | 21/21 (100%) | 21/21 (100%) | 30/30 (100%) | 26/33 (79%) | 32/39 (82%) | 31/35 (89%) | 26/34 (77%) |
| FIRST INCIDENCE | 472 | 511 | 483 | 449 | 497 | 600 | 527 | 529 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.391N | P=0.036 * | P=0.031 * | P=0.344 | P=0.405N | P=0.134N | P=0.411N | P=0.280N |
| POLY 3 | P=0.292 | P=0.792N | P=0.698N | P=0.656 | P=0.260N | P=0.520N | P=0.515 | P=0.313N |
| POLY 1.5 | P=0.148 | P=0.648N | P=0.752N | P=0.313 | P=0.240N | P=0.470N | P=0.538 | P=0.278N |
| POLY 6 | P=0.589 | P=0.998N | P=0.636N | P=0.991 | P=0.296N | P=0.578N | P=0.487 | P=0.367N |
| LOGISTIC REGRESSION | P=0.099 | P=0.634N | P=0.629 | P=0.281 | P=0.242N | P=0.355N | P=0.597N | P=0.237N |
| COCH-ARM / FISHERS | P=0.078 | P=0.500 | P=0.357 | P=0.102 | P=0.220N | P=0.402N | P=0.602N | P=0.235N |

D 14

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **All Organs Malignant Tumors** | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 36/50 (72%) | 38/50 (76%) | 36/50 (72%) | 28/50 (56%) | 22/50 (44%) | 24/50 (48%) | 22/50 (44%) | 15/50 (30%) |
| POLY-3 RATE (b) | 36/48.14 | 38/49.51 | 36/47.55 | 28/48.03 | 22/47.70 | 24/49.57 | 22/48.96 | 15/47.76 |
| POLY-3 PERCENT (g) | 74.8% | 76.8% | 75.7% | 58.3% | 46.1% | 48.4% | 44.9% | 31.4% |
| TERMINAL (d) | 20/30 (67%) | 10/21 (48%) | 13/21 (62%) | 12/30 (40%) | 12/33 (36%) | 15/39 (39%) | 12/35 (34%) | 5/34 (15%) |
| FIRST INCIDENCE | 122 | 462 | 368 | 266 | 448 | 396 | 232 | 360 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.034N* | P=0.134 | P=0.182 | P=0.134N | P=0.096N | P=0.522N | P=0.496N | P=0.142N |
| POLY 3 | P=0.018N* | P=0.504 | P=0.553 | P=0.063N | P=0.047N* | P=0.491 | P=0.535N | P=0.101N |
| POLY 1.5 | P=0.017N* | P=0.480 | P=0.583 | P=0.062N | P=0.045N* | P=0.461 | P=0.553N | P=0.103N |
| POLY 6 | P=0.020N* | P=0.530 | P=0.513 | P=0.066N | P=0.050N | P=0.529 | P=0.513N | P=0.098N |
| LOGISTIC REGRESSION | P=0.027N* | P=0.443 | P=0.588N | P=0.086N | P=0.025N* | P=0.336 | P=0.528 | P=0.094N |
| COCH-ARM / FISHERS | P=0.019N* | P=0.410 | P=0.588N | P=0.072N | P=0.043N* | P=0.421 | P=0.580N | P=0.107N |

| Dose | Males 0 PPM | Males 280 PPM | Males 830 PPM | Males 2500 PPM | Females 0 PPM | Females 280 PPM | Females 830 PPM | Females 2500 PPM |
|---|---|---|---|---|---|---|---|---|
| **All Organs Malignant and Benign Tumors** | | | | | | | | |
| TUMOR RATES | # | # | # | # | # | # | # | # |
| OVERALL (a) | 49/50 (98%) | 50/50 (100%) | 50/50 (100%) | 50/50 (100%) | 45/50 (90%) | 47/50 (94%) | 48/50 (96%) | 43/50 (86%) |
| POLY-3 RATE (b) | 49/49.03 | 50/50.00 | 50/50.00 | 50/50.00 | 45/50.00 | 47/50.00 | 48/50.00 | 43/50.00 |
| POLY-3 PERCENT (g) | 100.0% | 100.0% | 100.0% | 100.0% | 90.0% | 94.0% | 96.0% | 86.0% |
| TERMINAL (d) | 30/30 (100%) | 21/21 (100%) | 21/21 (100%) | 30/30 (100%) | 28/33 (85%) | 36/39 (92%) | 33/35 (94%) | 27/34 (79%) |
| FIRST INCIDENCE | 122 | 462 | 368 | 266 | 448 | 396 | 232 | 360 |
| STATISTICAL TESTS | | | | | | | | |
| LIFE TABLE | P=0.224N | P=0.052 | P=0.056 | P=0.548 | P=0.450N | P=0.308N | P=0.533 | P=0.404N |
| POLY 3 | P=1.000 | P=1.000 | P=1.000 | P=1.000 | P=0.159N | P=0.357 | P=0.217 | P=0.380N |
| POLY 1.5 | P=1.000 | P=1.000 | P=1.000 | P=1.000 | P=0.159N | P=0.357 | P=0.217 | P=0.380N |
| POLY 6 | P=1.000 | P=1.000 | P=1.000 | P=1.000 | P=0.159N | P=0.357 | P=0.217 | P=0.380N |
| LOGISTIC REGRESSION | P=0.754 | P=0.987 | P=0.949 | P=0.860 | (e) | (e) | (e) | (e) |
| COCH-ARM / FISHERS | P=0.472 | P=0.500 | P=0.500 | P=0.500 | P=0.159N | P=0.357 | P=0.218 | P=0.380N |

(a) Number of tumor-bearing animals / number of animals examined at site.
(b) Number of tumor-bearing animals / Poly-3 number
(d) Observed incidence at terminal kill.
(f) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to

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pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death.
Logistic regression is an alternative method for analyzing the incidence of non-fatal tumors. The Cochran-Armitage and Fishers exact tests compare directly the overall incidence rates
For all tests a negative trend is indicated by N
(e) Value of Statistic cannot be computed.
(g) Poly-3 adjusted lifetime tumor incidence.
(I) Interim sacrifice
(T) Terminal sacrifice
# Tumor rates based on number of animals necropsied.
* To the right of any statistical result, indicates significance at (P<=0.05).
** To the right of any statistical result, indicates significance at (P<=0.01).

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