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SuperUser EPA/ORD/CCTE/SCDCD

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- NDA020667-pramipexole dihydrochlori...

dossier created for substance NDA020667-pramipexole dihydrochloride

816ae1ca-1560-48a4-b74c-711535940ae5

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- Export to i6z
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Type at least 3 characters

OECD Exchange of experimental data
NDA020667-pramipexole dihydrochloride

- 1 General information
  1
- 2 Classification and Labelling
- 4 Physical and chemical properties
- 5 Environmental fate and pathways
- 6 Ecotoxicological information
- 7 Toxicological information
  10
  - 7.1 Toxicokinetics, metabolism and distribution
  - 7.2 Acute Toxicity
  - 7.3 Irritation / corrosion
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    2
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  2
  - Two-Year Rat Carcinogenicity Study_94-0250
  - Two-Year Mouse Carcinogenicity Study_93-0589
- 7.8 Toxicity to reproduction
  5
- 7.9 Specific investigations
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0 2 0

Administrative data | Data source | Materials and methods | Results and discussion | Overall remarks, attachments | Applicant's summary and conclusion

Administrative data

Endpoint
carcinogenicity: oral

Type of information
experimental study

Adequacy of study

☐ Robust study summary

☐ Used for classification

☐ Used for SDS

Study period

Reliability

Rationale for reliability incl. deficiencies

Data waiving

Justification for data waiving

Justification for type of information

Attached justification

Attached justification Reason / purpose Actions

Cross-reference

Reason / purpose for cross-reference Related information Remarks Actions

Data source

Reference

Data access

Data protection claimed

Materials and methods

Test guideline

Qualifier Guideline Version / remarks Deviations Actions

Principles of method if other than guideline

GLP compliance

Test material

Test material information

- NDA020667_TM1 | pramipexole dihydrochloride | (6S)-6-N-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine;dihydrochloride | 104632-25-9

Additional test material information

Specific details on test material used for the study

Specific details on test material used for the study (confidential)

Test animals

Species
mouse

Strain
NMRI

Details on species / strain selection

Sex
male/female

Details on test animals or test system and environmental conditions

Administration / exposure

Route of administration

oral: feed

Type of inhalation exposure (if applicable)

Vehicle
no data

Mass median aerodynamic diameter (MMAD)

Geometric standard deviation (GSD)

Remarks on MMAD

Details on exposure

Analytical verification of doses or concentrations

Details on analytical verification of doses or concentrations

Duration of treatment / exposure
2 years

Frequency of treatment
not specified

Post exposure period
not specified

Doses / concentrations

Dose / conc. Remarks Actions 1
Dose / conc.
mg/kg bw/day (actual dose received)
Remarks
2
Dose / conc.
2 mg/kg bw/day (actual dose received)
Remarks
3
Dose / conc.
10 mg/kg bw/day (actual dose received)
Remarks
4
Dose / conc.
0.3 mg/kg bw/day (actual dose received)
Remarks

No. of animals per sex per dose
250 males, 250 females for toxicology 20 males, 20 females for microbiology 159 males, 159 females for toxicokinetics

Control animals

Details on study design
Methods: Dosages: 0.3, 2.0, 10.0 mg/kg/day PPX dihydrochloride (Batch II) The low dose is three times the ED50 for anti-Parkinsonian effects in monkeys, and 5- 15 times higher than the expected human maintenance dose range of 1.5-4.5 mg/day (70 kg human). The high dose was selected as the highest tolerable dose given the duration of the study and the limitation of excessive CNS stimulation. The reduction in body weight gain by this dose was used as an indicator of drug toxicity.. Route of Administration: Drug-in-diet Species/Strain/Number: Mouse (Chbb:NMRI) 250 males, 250 females for toxicology 20 males, 20 females for microbiology 159 males, 159 females for toxicokinetics Blood was sampled during weeks 2, 40 and 80 at 10.00 to 11.00 AM (4-5 hrs after light onset. Mean initial weights/age: males: 29.3g/37 days females: 24.5g/37 days Parameters monitored/Intervals: Clinical - daily Body weight - weekly (wks 1-26), monthly (wks 27-104) Food consumption - weekly Water consumption - weekly (weeks 14, 26, 39, 52, 65, 78, 91, 104) Effective dose - calculated weekly (wks 1-26); monthly thereafter Hematology - done only prior to sacrifice Plasma Conc - in satellite groups as described above Histopathology - on the following tissues: Stains: Hematoxylin/Eosin - all organs/tissues, tumors/lesions Masson's Trichrome - heart, kidney, liver, gall bladder lung, aorta, tumors/lesions Statistics Routine group comparisons were made by the Bartlett test, one-way ANOVA and Newman-Keuls test. The Exact Log-rank test was used for group comparisons of categorical tumor-bearing animal data, and for between-group comparisons of the number of premature decedents. Plasma

concentration data were evaluated after logarithmic transformation by regression analysis and ANOVA to determine the effects dose, time point and sex. Statistical evaluation of neoplastic lesions was according to Peto et al. (1980) using the trend test with respect to dose. Probability levels for significant findings were 0.05 for rare neoplasms and 0.01 for common neoplasms.

Positive control

Examinations

Observations and examinations performed and frequency

Sacrifice and pathology

Other examinations

Statistics

Any other information on materials and methods incl. tables

Results and discussion

Results of examinations

Clinical signs

Description (incidence and severity)
Alopecia: . Male Female CON 12% 19% LD 14% 20% MD 18% 52% HD 42% 52% Effective dose: Weekly recordings indicated that effective drug intake was usually within 20% of intended intake. Most variations were in the direction of "greater than intended" intakes.

Dermal irritation (if dermal study)

Description (incidence and severity)

Mortality

Description (incidence)
Results: Mortality: 87 males and 101 females died or were sacrificed moribund prior to the end of the study. The increased mortality in treated males was statistically significant ($p = 0.0298$ by a one-tailed positive trend test; $p = 0.0112$ by heterogeneity test). The major factor contributing to the higher mortality rate was sacrifice due to debilitating eczema.

Body weight and weight changes

Description (incidence and severity)
Body Weight Gain (Fig. C.5.a.l): M & HDM - sig. decrease - all time points LDF - sig. increase - wks 1-3, 5-6, 9, 15, 17, 19-70, 78, 86-98 M & HDF - sig. decrease - from wk 3 to end of study Food Intake: LDM - tendency for decrease; effect was significant at several time points M & HDM - tendency for increase; effect was significant at several time points LDF - tendency for decrease at wks 25-78 M & HDF - tendency for increase; effect was significant at several time points Water Intake: LDM - no effect M & HDM - tendency for increase; effect was significant at several time points LDF - no effect M & HDF - tendency for increase; effect was significant at several time points

Food consumption and compound intake (if feeding study)

Description (incidence and severity)

Food efficiency

Description (incidence and severity)

Water consumption and compound intake (if drinking water study)

Description (incidence and severity)

Ophthalmological findings

Description (incidence and severity)

Haematological findings

Description (incidence and severity)
Hematology: A number of animals had abnormal WBC counts at sacrifice. This included several controls as well as PPX-treated animals, and there was no clear dose-relationship. (The sponsor has not indicated their criteria for the noted hematological findings in individual animals). Individual variations in animals with abnormal WBC blood counts at termination (Tab. C.5.a.2): In addition, the following hematological changes were noted in animals with "normal" WBC counts: anemia, slight - 2 0M, 3 OF 3 LDF 2 MDM, 1 MDF 3 HDF " , moderate - 1 0M 1 LDF " , marked - 1 OF erythrocytosis - 1 0M, 1 OF 1 LDF 1 HDM Individual variations in animals with abnormal WBC blood counts sacrificed moribund (Tab. C.5.a,3) The following hematological changes were noted in animals with "normal" WBC counts: anemia, slight - 1 0M, 3 0F 1 LDM, 5 LDF 3 MDM, 5 MDF 3 HDM, 6 HDF " , moderate - 6 0F 1 LDF 2 MDF 3 HDF " , marked - 1 HDF (this animal was also stated to have polycythemia???) Group variations: Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident. At termination: increased Hct - HDM decreased lymphocytes(%) - MDM, HDM increased lymphocytes(%) - LDF Moribund sacrifices: decreased RBC, Hb - trend (N.S.) in males decreased Hct - HDM increased leucocytes - MDM (20 to 1 abnormally high value) increased lymphocytes(%) - MDM (The page containing mean values of RBC parameters for females sacrificed moribund was omitted.)

Clinical biochemistry findings

Description (incidence and severity)

Endocrine findings

Description (incidence and severity)

Urinalysis findings

Description (incidence and severity)

Behaviour (functional findings)

Description (incidence and severity)

Immunological findings

Description (incidence and severity)

Organ weight findings including organ / body weight ratios

Description (incidence and severity)

Gross pathological findings

Description (incidence and severity)

Neuropathological findings

Description (incidence and severity)

Histopathological findings: non-neoplastic

Description (incidence and severity)
Pathology: , Non-Neoolastic Lesions Statistically significant drug effects were: The most notable finding was the fibro-osseous proliferative lesion in the femurs of female mice, which was not described in detail by the sponsor, nor was any potential significance suggested. The lesiorf occurred spontaneously in control animals, but its incidence was significantly increased by PPX treatment; the incidence rates were similar in all dosage groups. A possibly related finding was decreased femoral fat content in MDF and HDF, suggestive of increased hematopoietic activity. Albassam et al. (Vet. Pathol. 28:381, 1991) have reported upon the spontaneous occurrence of an apparently similar osseous lesion in the femurs and sternums of female B6C3F1 mice (but not male B6C3F1 or female CF1 mice). The lesion was characterized by the lining of epiphyseal plates by large osteoblasts and had large vascularized centers. Similar drug-induced lesions have been produced by estrogens (Silberberg and Silberberg, Gerontology, 16:201, 1970; Gaunt and Pierce, Vet. Pathol, 22:403, 1985), and the sponsor speculates that a dopaminergic-induced imbalance in estrogemprogesterone levels may account for this lesion. No experimental support for this mechanism (i.e., estrogen level measurements) was provided. The prostaglandin E analogue misoprostol also produces an osseous lesion in female mice (Dodd and Port, Vet. Pathol. 24:545, 1987), and the finding appears in the labeling of that product.

Histopathological findings: neoplastic

Description (incidence and severity)
Neoplastic lesions According to the sponsor’s analysis, the only statistically significant differences in the incidence of neoplasia between treated and

control animals were decreased occurrences of the following tumors: There was also a non-significant trend for decreased occurrence of hepatocellular adenomas in treated males. Inspection of the Tumor Distribution Summary (Tab. C.5.a,6) and statistical analysis tables (Tab. C.5.a,7) reveals some notable findings or tendencies. The incidence of uterine stromal polyps tended to increase at the higher doses (controls: 2%; LD: 2%; MD: 6%; HD: 6%; p= 0.0778 by the Trend Test), as did the incidence of all mesenchymal/epithelial uterine neoplasms (control: 10%; LD: 10%; MD: 14%; HD: 18%; not statistically analyzed). The Test of Heterogeneity indicated a statistically significant increase in the incidence of histiocytic sarcomas in PPX-treated male mice (p = 0.0018), but the tumors were found only in 4 LD animals and are thus not clearly drug-related. There were no significant differences between PPX-treated and control animals with respect to the number of primary neoplasms, the number of mice with primary neoplasms, mice with more than one neoplasm, mice with metastases, the number of benign and malignant neoplasms per group and sex (Tab. C.5.a.8).

Other effects

Description (incidence and severity)

Details on results

Results: Mortality: 87 males and 101 females died or were sacrificed moribund prior to the end of the study. The increased mortality in treated males was statistically significant (p = 0.0298 by a one-tailed positive trend test; p = 0.0112 by heterogeneity test). The major factor contributing to the higher mortality rate was sacrifice due to debilitating eczema. Causes of death are listed in Table C.5.a,l Body Weight Gain (Fig. C.5.a.l): M & HDM - sig. decrease - all time points LDF - sig. increase - wks 1-3, 5-6, 9, 15, 17, 19-70, 78, 86-98 M & HDF - sig. decrease - from wk 3 to end of study Food Intake: LDM - tendency for decrease; effect was significant at several time points M & HDM - tendency for increase; effect was significant at several time points LDF - tendency for decrease at wks 25-78 M & HDF - tendency for increase; effect was significant at several time points Water Intake: LDM - no effect M & HDM - tendency for increase; effect was significant at several time points LDF - no effect M & HDF - tendency for increase; effect was significant at several time points Alopecia: . Male Female CON 12% 19% LD 14% 20% MD 18% 52% HD 42% 52% Effective dose: Weekly recordings indicated that effective drug intake was usually within 20% of intended intake. Most variations were in the direction of "greater than intended" intakes. Hematology: A number of animals had abnormal WBC counts at sacrifice. This included several controls as well as PPX-treated animals, and there was no clear dose-relationship. (The sponsor has not indicated their criteria for the noted hematological findings in individual animals). Individual variations in animals with abnormal WBC blood counts at termination (Tab. C.5.a.2): In addition, the following hematological changes were noted in animals with "normal" WBC counts: anemia, slight - 2 0M, 3 OF 3 LDF 2 MDM, 1 MDF 3 HDF " , moderate - 1 0M 1 LDF " , marked - 1 OF erythrocytosis - 1 0M, 1 OF 1 LDF 1 HDM Individual variations in animals with abnormal WBC blood counts sacrificed moribund (Tab. C.5.a,3) The following hematological changes were noted in animals with "normal" WBC counts: anemia, slight - 1 0M, 3 0F 1 LDM, 5 LDF 3 MDM, 5 MDF 3 HDM, 6 HDF " , moderate - 6 0F 1 LDF 2 MDF 3 HDF " , marked - 1 HDF (this animal was also stated to have polycythemia???) Group variations: Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident. At termination: increased Hct - HDM decreased lymphocytes(%) - MDM, HDM increased lymphocytes(%) - LDF Moribund sacrifices: decreased RBC, Hb - trend (N.S.) in males decreased Hct - HDM increased leucocytes - MDM (20 to 1 abnormally high value) increased lymphocytes(%) - MDM (The page containing mean values of RBC parameters for females sacrificed moribund was omitted.) Plasma Concentrations: . The concentration of PPX was above the LOQ (0.1 ng⁄ml) in all samples at 4-5 hrs after light onset. Increases in plasma concentrations were approximately dose- proportional except for females during week 2 and both sexes during week 40 where the increases were greater than dose proportional (Fig. C.5.a.2; Tab. C.5.a·4). ANOVA indicated that significantly higher concentrations were present in females, although specific occurrences of this finding were not indicated (Tab. C.5.a·5). There was no evidence of drug accumulation. Pathology: , Non-Neoolastic Lesions Statistically significant drug effects were: The most notable finding was the fibro-osseous proliferative lesion in the femurs of female mice, which was not described in detail by the sponsor, nor was any potential significance suggested. The lesiorf occurred spontaneously in control animals, but its incidence was significantly increased by PPX treatment; the incidence rates were similar in all dosage groups. A possibly related finding was decreased femoral fat content in MDF and HDF, suggestive of increased hematopoietic activity. Albassam et al. (Vet. Pathol. 28:381, 1991) have reported upon the spontaneous occurrence of an apparently similar osseous lesion in the femurs and sternums of female B6C3F1 mice (but not male B6C3F1 or female CF1 mice). The lesion was characterized by the lining of epiphyseal plates by large osteoblasts and had large vascularized centers. Similar drug-induced lesions have been produced by estrogens (Silberberg and Silberberg, Gerontology, 16:201, 1970; Gaunt and Pierce, Vet. Pathol, 22:403, 1985), and the sponsor speculates that a dopaminergic-induced imbalance in estrogemprogesterone levels may account for this lesion. No experimental support for this mechanism (i.e., estrogen level measurements) was provided. The prostaglandin E analogue misoprostol also produces an osseous lesion in female mice (Dodd and Port, Vet. Pathol. 24:545, 1987), and the finding appears in the labeling of that product. Neoplastic lesions According to the sponsor’s analysis, the only statistically significant differences in the incidence of neoplasia between treated and control animals were decreased occurrences of the following tumors: There was also a non-significant trend for decreased occurrence of hepatocellular adenomas in treated males. Inspection of the Tumor Distribution Summary (Tab. C.5.a,6) and statistical analysis tables (Tab. C.5.a,7) reveals some notable findings or tendencies. The incidence of uterine stromal polyps tended to increase at the higher doses (controls: 2%; LD: 2%; MD: 6%; HD: 6%; p= 0.0778 by the Trend Test), as did the incidence of all mesenchymal/epithelial uterine neoplasms (control: 10%; LD: 10%; MD: 14%; HD: 18%; not statistically analyzed). The Test of Heterogeneity indicated a statistically significant increase in the incidence of histiocytic sarcomas in PPX-treated male mice (p = 0.0018), but the tumors were found only in 4 LD animals and are thus not clearly drug-related. There were no significant differences between PPX-treated and control animals with respect to the number of primary neoplasms, the number of mice with primary neoplasms, mice with more than one neoplasm, mice with metastases, the number of benign and malignant neoplasms per group and sex (Tab. C.5.a.8).

Relevance of carcinogenic effects / potential

There were no significant differences between PPX-treated and control animals with respect to the number of primary neoplasms, the number of mice with primary neoplasms, mice with more than one neoplasm, mice with metastases, the number of benign and malignant neoplasms per group and sex (Tab. C.5.a.8).

Effect levels

Key result Dose descriptor Effect level Based on Sex Basis for effect level Remarks on result Actions 1

☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
male/female
Basis for effect level

- haematology

Remarks on result
other: No effect level reported

[default] : No effect level reported

2
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
male/female
Basis for effect level

- histopathology: neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

3
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
male/female
Basis for effect level

- histopathology: neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

4
☐ Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
5
☐ Key result
Dose descriptor
NOAEL
Effect level
Based on
Sex
male/female
Basis for effect level

Remarks on result
other: Not reported by medical writer

[default] : Not reported by medical writer

6
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
female
Basis for effect level

- histopathology: non-neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

7
☐ Key result
Dose descriptor
dose level:
Effect level
10 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
8
☐ Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
9
☐ Key result
Dose descriptor
dose level:
Effect level

>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- food consumption and compound intake

Remarks on result
10
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
male/female
Basis for effect level

- mortality

Remarks on result
other: No effect level reported

[default] : No effect level reported

11
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- body weight and weight gain

Remarks on result
12
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
13
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- clinical signs

Remarks on result
14
☐ Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male
Basis for effect level

- haematology

Remarks on result
15
☐ Key result
Dose descriptor
dose level:
Effect level
Based on
Sex
male/female
Basis for effect level

- histopathology: neoplastic

Remarks on result
other: No effect level reported

[default] : No effect level reported

16
☐ Key result
Dose descriptor
dose level:
Effect level
>= 2 mg/kg bw/day (actual dose received)
Based on
Sex
male/female
Basis for effect level

- water consumption and compound intake

Remarks on result
17
☐ Key result
Dose descriptor
dose level:
Effect level
>= 0.3 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result
18
☐ Key result
Dose descriptor
dose level:
Effect level

10 mg/kg bw/day (actual dose received)
Based on
Sex
female
Basis for effect level

- haematology

Remarks on result

Target system / organ toxicity

Key result Critical effects observed Lowest effective dose / conc. System Organ Treatment related Dose response relationship Relevant for humans Actions

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Any other information on results incl. tables

Overall remarks, attachments

Overall remarks

Attachments

Type Attached (confidential) document Attached (sanitised) documents for publication Remarks Actions

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Illustration (picture/graph)

Applicant's summary and conclusion

Conclusions

Executive summary
Summary: Pramipexole was administered in the diet at doses of 0.3, 2.0, and 10.0 mg/kg/day to Chbb:NMRI mice (50/sex/dose group, 100/sex/control) for two years. Relatively few non- neoplastic and no neoplastic lesions were clearly associated with PPX administration. The rate of premature decedents was higher in PPX-treated animals than in controls; the effect was significant in males. The highest mortality rate was 46% in MDF and HDF. The primary cause of premature deaths were unscheduled sacrifices due to eczema, a condition observed in both control and treated animals. Body weight gain was significantly reduced by % in both sexes at the intermediate and high doses at study termination. A relative increase in the incidence of alopecia was also noted in PPX-treated animals. Spontaneous activity was increased in MD and HD females, and HD males. No statistically significant increases or trends for increases in the incidence of neoplastic lesions in drug-treated animals were apparent according to the sponsor's analysis. A pooled analysis of all mesenchymal/epithelial uterine neoplasms was not presented, but the incidences suggest a possible dose-related positive trend (controls: 10%; LD: 10%; MD: 14%; HD: 16%). Statistically significant decreases in the incidence of adrenal cortical adenomas in HD males, and malignant lymphomas in MD and HD females were noted. For all other neoplastic findings, which included systemic neoplasms of the hemolymphoreticular system, and primary neoplasms in the lung, liver, and adrenals in males, and the reproductive tracts of both sexes, the incidences were low, and equivalent in PPX-treated and control animals. The only histopathological findings that occurred at a higher incidence rate in PPX- treated animals were fibro-osseous proliferative lesions in the femurs of females (all dosage groups). This lesion occurred at a relatively high rate in control females (28%), but approximately doubled in incidence in treated animals .%; similar at the three dosage levels). The more severe lesions were found more frequently in treated animals. This type of lesion is known to occur spontaneously in female mice of other strains including B6C3F1 (Albassam, et al., Vet. Pathol.. 28:381, 1991), and has also been observed in mice after administration of the prostaglandin E analogue misoprostol (Dodd and Port, Vet. Pathol.. 24:545, 1987) and estrogens (Gaunt and Pierce, Vet. Pathol.. 22:403, 1985). The increased incidence in drug-treated animals may be related to stimulation of estrogen release (Sass and Montali, Lab. Anim. Sci.. 30:907, 1980), although no experimental evidence of such a hormonal effect of PPX was presented. Pathological changes that might be expected to accompany a bone abnormality (i.e., blood cell count changes) were not clearly associated with this lesion. Possibly compensatory stimulation of splenic erythropoiesis occurred in both treated and control female mice, and increased hematopoietic activity was noted in the femoral bone marrow of MDF and HDF. Based on plasma level measurements in satellite groups during weeks 2, 40 and 80 at 4-5 hrs after light onset, exposure to PPX in the high dose group ng⁄ml) was fold higher than the Cmaxs, in humans following the expected maintenance dose of 1.5 mg, t.i.d. Thus, administration of PPX in the diet for two years was not significantly carcinogenic in mice. However, conclusive interpretation of these results is hindered by the marked impairment of body weight development at the mid- and high-dose levels. The low exposures at the lowest dose levels cannot be considered adequate for assessing the tumorigenic effects of this compound. The importance of the fibro-osseous proliferative lesion is questionable since similar lesions are known to occur spontaneously in certain strains of mice, and no similar lesion was observed in long-term rat and monkey PPX studies. The "No Effect" dose was considered to be 0.3 mg/kg/day, although a trend for decreased food intake was apparent at this dose.

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