Oxymorphone Hydrochloride, a Potent Opioid Analgesic, Is Not Carcinogenic in Rats or Mice

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Despite their long history of chronic use, little information is available regarding the carcinogenicity of opioid analgesics. Oxymorphone is a potent morphinan-type mu-opioid analgesic used for treatment of moderate-to-severe pain. Oxymorphone was tested for carcinogenicity in Crl:CD IGS BR rats and CD-1 mice. Oxymorphone hydrochloride was administered orally once daily for 2 years to rats at doses of 2.5, 5 and 10 mg/kg/day (males) and 5, 10 and 25 mg/kg/day (females), and mice at 10, 25, 75 and 150 mg/kg/day (65 animals per sex per group; 100 animals per sex in controls). In rats, survival was generally higher than controls in oxymorphone-treated groups, attributable to lower body weight gain. In mice, survival was generally higher than controls in females at all doses and males given \( \leq 25 \text{ mg/kg/day} \) but lower in males given \( \geq 75 \text{ mg/kg/day} \) due to a high incidence of obstructive uropathy. Opioid-related clinical signs and reduced body weight gain occurred in both species throughout the study. Nonneoplastic findings associated with oxymorphone pharmacology included ocular and pulmonary changes in rats considered secondary to inhibition of blinking and mydriasis, and antitussive activity, respectively, and urinary tract and renal findings in mice considered secondary to urinary retention. There was no target organ toxicity, and no increase in any neoplastic lesions attributed to oxymorphone.

Plasma oxymorphone levels achieved in these studies exceeded those in patients taking high therapeutic doses of oxymorphone (Area under the curve \( [AUC]_{0-24 \text{ h}} \) values up to 5.6-fold and 64-fold in rats and mice, respectively). Oxymorphone is not considered to be carcinogenic in rats or mice under the conditions of these studies.

Key Words: opioids; carcinogenicity; analgesics.

Potent mu-opioid agonists are widely used for short- and long-term treatment of pain. Many of these drugs (e.g., oxycodone, hydromorphone, hydrocodone) are structurally related to morphine (i.e., morphinans), whereas fentanyl and related compounds are structurally distinct phenyl-propranamides. Despite their common long-term use, there is no information on the carcinogenic potential of potent opioid analgesics. Codeine, a weak morphinan-type opioid, with potency about 1/10 that of morphine, was not carcinogenic in 2-year feeding studies in F344 rats and B6C3F1 mice (National Toxicology Program, 1996). L-alpha-Acetylmethadol (LAAM) and Dl-methadone, structurally distinct diphenyl-heptane mu-opioid agonists commonly used in opioid replacement therapy for drug addiction, have also been tested in 2-year feeding studies. Methadone exhibited no carcinogenic potential in either rats or mice (Rosenkrantz and Fleischman, 1988a). LAAM was not carcinogenic in mice but increased incidences of liver neoplastic nodules and possibly liver carcinoma occurred in F344 rats in the presence of hepatomegaly, hepatocellular hyper trophy, and nuclear enlargement (Rosenkrantz and Fleischman, 1988b).

Genotoxicity data for mu-opioid agonists are also limited. No information was found in the literature or product information for hydrocodone, hydromorphone, or meperidine. None of the opioid agonists that have been tested are mutagenic in the Ames bacterial mutation test. However, mixed results have been found in \( \text{in vitro} \) cytogenetics assays and \( \text{in vivo} \) micronucleus studies. Morphine induces chromosome damage in peripheral lymphocytes and bone marrow cells of treated mice (Das and Swain, 1982; Sawant and Couch, 1995; Swain et al., 1980). These effects can be partially blocked by administration of the opioid antagonist, naloxone (Sawant and Couch, 1995). Morphine does not induce chromosome aberrations in cultured human lymphocytes (Falek et al., 1972) or mouse splenocytes \( \text{in vitro} \) (Sawant and Couch, 1995). Oxycodone produced chromosome aberrations in human peripheral blood lymphocytes \( \text{in vitro} \) and was positive in the mouse lymphoma assay but did not increase micronuclei in the bone marrow of treated mice (OxyContin Package Insert). Fentanyl has shown no evidence of mutagenic activity, either in \( \text{in vitro} \) chromosome aberrations or in an \( \text{in vivo} \) micronucleus assay (DURAGESIC Package Insert). Collectively, these results suggest that potent mu-opioid agonists, particularly those of the morphinan class, produce chromosomal alterations, through either primary or secondary mechanisms, and may thus raise a concern for potential carcinogenicity.

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Oxymorphone is a potent morphinan mu-opioid agonist used for the treatment of acute and chronic moderate-to-severe pain. When administered parenterally, oxymorphone is generally about 10- to 20-fold more potent than morphine in acute antinociception models in rats (Peckham and Traynor, 2006) and mice (Endo Pharmaceuticals Inc., unpublished results). Oxymorphone is not mutagenic in the Ames bacterial mutation test and does not produce chromosome aberrations in Chinese hamster ovary cells in vitro, either in the absence or presence of metabolic activation (OPANA Package Insert). A single oral dose of oxymorphone resulted in increased micronuclei in the bone marrow of Sprague-Dawley rats at doses of 20 mg/kg and higher, and in CD-1 mice at doses of 250 mg/kg and higher (OPANA Package Insert). Further investigation indicated that these findings may be secondary to body temperature changes associated with oxymorphone administration (Shuey et al., 2006).

The studies reported herein were conducted to evaluate the carcinogenic potential of oxymorphone when administered orally for 2 years to Crl:CD IGS BR (Sprague-Dawley) rats and CD-1 mice. The study designs and dose selection were reviewed and approved by the Food and Drug Administration (FDA) Executive Carcinogenicity Assessment Committee prior to study initiation. To our knowledge, these studies represent the first available carcinogenicity data for a potent mu-opioid analgesic.

**MATERIALS AND METHODS**

**Animals and husbandry.** All animals were received from Charles River Canada, St-Constant, Quebec Canada. Rats (Crl:CD IGS BR) were 6–8 weeks of age and weighed 206–286 g (males) or 6–10 weeks of age and weighed 162–226 g (females) at initiation of dosing. Mice (Crl:CD-1[ICR]BR) were 6–8 weeks of age and weighed 24.8–34.0 g (males) or 19.2–27.3 g (females) at initiation of dosing. Each animal was uniquely identified using the AIMS Tattoo Identification System (AIMS, Hornell, NY) system. Animals were housed individually in stainless steel wire mesh-bottomed cages. Cage racks were rotated every 2 weeks. Rooms were environmentally controlled with targeted temperature and humidity of 22 ± 3°C and 50 ± 20%, respectively, and a 12-h light/dark cycle. Animals had free access to purified water and feed (PMI Certified Rodent 5002: PMI Nutrition International, Inc.). Certified Nylabones were provided as necessary to prevent self-chewing.

**Test article and treatment.** Oxymorphone hydrochloride was obtained from Mallinckrodt Inc (St Louis, MO). Oxymorphone was administered as aqueous solutions (in water) by oral gavage (5 ml/kg) once daily, 7 days per week for 104 weeks. Formulations were adjusted for purity (98.3–99.3%), and salt and water content such that doses represent free base equivalents. Dose formulations were prepared weekly and stored at room temperature; stability under these conditions has been established for at least 21 days. Dose formulations were analyzed every 13 weeks and found to be within 10% of nominal concentrations.

Oxymorphone is a Schedule II controlled substance. Appropriate handling precautions were taken. All unused materials were disposed of in accordance with DEA regulations.

**Study design.** Animals were randomized into four (rats) or five (mice) treatment groups based on a body weight stratification. Males and females were randomized separately. Main study groups consisted of 100 animals per sex (group 1; vehicle control) or 65 animals per sex (groups 2–4 rats; groups 2–5 mice). Additional animals were assigned to groups 2–4 (rats, 12 animals per sex per group) and groups 2–5 (mice, 23 animals per sex per group) for determination of plasma oxymorphone levels after 6 months of dosing; these animals were discarded after sample collection. Doses in rats were 0, 2.5, 5, and 10 mg/kg/day in males and 0, 5, 10, and 25 mg/kg/day in females. Doses in mice were 0, 10, 25, 75, and 150 mg/kg/day for both males and females.

Doses were selected based on results of previous 13-week toxicity studies in these species (Endo Pharmaceuticals Inc., unpublished data); the selected high doses were considered to be the maximum tolerated dose based on mortality, body weight deficits, and behavioral changes observed at higher doses. The doses selected for the mouse carcinogenicity study would not be tolerated in naive animals. Therefore, doses were gradually escalated over the first 4 weeks of the study in mice.

The studies were conducted in accordance with U.S. FDA Good Laboratory Practices (21 CFR 58). The testing facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. The protocol and amendments were reviewed and approved by the faculty Institutional Animal Care and Use Committee. The care and use of animals during the study was conducted in accordance with the U.S. National Research Council (1996), and the Canadian Council on Animal Care.

**In-life parameters evaluated.** All animals were observed twice daily for mortality and morbidity. Cage side observations for drug-related adverse clinical signs were performed daily at approximately 1-hour postdose. Detailed examinations were performed weekly. From week 26 onwards, all animals were examined for the presence of palpable masses (minimal dimensions 1 × 1 × 1 mm) during the detailed examination. Animals were weighed and food consumption determined weekly. Ophthalmoscopic evaluations were performed during pretest and at approximately 1 year. Atropine sulfate (0.5%) was used as a mydriatic agent for these examinations. Total and differential white blood cell (WBC) counts (including blood cell morphology) were performed at approximately 1 year and at the end of the dosing period.

**Toxicokinetics.** During week 26 of the treatment period, blood samples (0.5 ml) were collected into heparinized tubes 0- (predose), 0.5-, 1-, 2-, 4-, 8-, 12-, and 24-h postdose in rats, and at 1-, 2-, 4-, 8-, 16-, and 24-h postdose in mice. Samples were collected from three animals at each time point. Up to three samples were collected from each rat; one sample was collected from each mouse. Samples were collected from the jugular vein in unanesthetized rats, or from the abdominal aorta under isoflurane anesthesia in mice. Plasma was isolated and stored at approximately –20°C. After sample collection, toxicokinetic animals were humanely euthanized and the carcasses were discarded without further examination. Plasma oxymorphone levels were determined using a fully validated liquid chromatography/mass spectrometry/mass spectrometry method. Noncompartmental toxicokinetic analysis was performed.

**Gross pathology.** All main study animals were subjected to necropsy. Animals were fasted overnight before scheduled necropsy. Animals were euthanized by exsanguination under isoflurane anesthesia. The following tissues were preserved: abnormalities, adrenals, animal identification, aorta (thoracic), bone and marrow (sternum), brain (cerebrum, cerebellum, midbrain, medulla oblongata), cecum, colon, duodenum, epididymides, esophagus, eyes, gallbladder (mouse), Harderian glands, heart (including section of aorta), ileum, jejunum, kidneys, lacrimal glands, liver (2 lobes), lungs, lymph nodes (mandibular and mesenteric), mammary gland (inguinal; females only), optic nerve, ovaries, pancreas, pituitary, prostate, rectum, salivary gland, sciatic nerve, seminal vesicles, skeletal muscle, skin (inguinal), spinal cord (cervical), spleen, stomach, testes, thymus, thyroid lobes (and parathyroids), tongue, trachea, urinary bladder, uterus (cervix, horns) vagina. Neutral buffered 10% formalin was used for fixation and preservation for all tissues except for epididymides, eyes, optic nerves, and testes, which were fixed in Zenker’s fluid. Bone was decalcified prior to sectioning. Each clinically observed mass, together with the nearest identifiable drainage lymph node, was preserved.

All collected tissues and all gross lesions were examined histopathologically from all animals (except animals designated for toxicokinetics). Tissues were prepared for histopathological examination by embedding in paraffin wax,
sectioning, and staining with hematoxylin and eosin and examined. Suspected
tumors were diagnosed and incidences of benign and malignant tumors were
tabulated.

Statistical analyses—in-life data. All statistical analyses were conducted
Group means and standard deviations were calculated for all numerical data
collected during the studies. Group variances were compared using Levene’s
test at the 0.05 significance level. When group variances were not significantly
different, a parametric one-way analysis of variance (ANOVA) was performed.
If significant differences among the means were indicated by the ANOVA (p ≤ 
0.05), then pairwise comparisons of each group mean to the control were
performed using Dunnett’s “t”-test. If Levene’s test indicated heterogeneous
group variances (p ≤ 0.05), the nonparametric Kruskal-Wallis test was used to
compare all considered groups. If the Kruskal-Wallis test was significant (p ≤ 
0.05), pairwise comparisons of each group mean to the control were performed
using Dunn’s test (Dunn, 1964).

Statistical analyses—mortality and tumor data. All statistical analyses
were conducted using release 8.1 of the SAS/STAT module (SAS Institute Inc.,
Cary, NC). For mortality data, an initial analysis was conducted in order to
compare the survival curves of all groups. Significance of group effects on
mortality rates was assessed by applying the logrank test to all groups. If the
homogeneity comparison (logrank test) revealed significant differences among
the groups, then the significance of a dose-related trend in mortality was
evaluated using the method of Tarone, 1975). Tarone’s test was implemented as
a Peto two-sided test using the arithmetic dose level scores with all uncensored
deaths coded as 2 and all censored deaths coded as 0. In addition, each treated
group was compared against the control group. These pairwise comparisons
were implemented with Peto’s trend test, which was done in the direction
indicated by the sign of the statistic of the previous overall trend test. Each
statistical test was conducted at the 5% significance level.

Statistical evaluation of tumor data was limited to tissues and groups for
which all animals were examined histopathologically. For statistical analysis
of tumors of the skin and subcutaneous tissue, the incidence of these tumors was
also based on the total number of animals in each group, even though
histopathologic examination was only performed on abnormalities, because it
was assumed that all neoplasias were detected during necropsy at these sites.
Lymphosarcomas (malignant lymphomas), leukemias granulocytic and mast
cell tumors, and histiocytic sarcomas were collectively tabulated under
hemolymphoreticular tissue and were evaluated using the total number of
animals in each group. For the purpose of the statistical analysis, hemangio-
sarcomas were combined across all sites.

Statistical evaluation was performed using the Multtest procedure of the
SAS/STAT module, where each tumor was classified as fatal (i.e., the cause of
death) or incidental. All tumors detected in animals that survived until the
scheduled necropsy were classified as incidental. The analysis of incidental
tumors was conducted by creating a single separate interval for the time period
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RESULTS

Survival, Clinical Signs, Body Weight and Food Consumption

Rats. The survival rate of both male and female rats given
oxy-morphone tended to be higher than the control group at all
doses (Fig. 1a, 1b). There was a statistically significant negative
dose-related trend in mortality in females, and the mortality
rate in group 4 was significantly lower than in the controls (p <
0.05). The lower mortality rate in males did not reach statistical
significance. The higher survival rate in rats given oxymor-
phone may be attributed to decreased numbers of fatal chronic
progressive nephropathy (males) and pituitary tumors (males
and females) observed preterminally in these groups (Table 1),
which was likely related to decreased body weight gain (see
below).

The most prominent treatment-related clinical signs in both
males and females were excessive licking, self-biting/self-
mutilation (which was the likely cause of observed increases in
skin lesions and scabs). Increased activity was also observed
in oxymorphone-treated groups. These behavioral changes are
typical of rodents administered opioid agonists and therefore
considered to be related to the pharmacologic activity of
oxymorphone.

Body weight gain was significantly reduced in both males
and females at all doses of oxymorphone (Fig. 1c, 1d). This
effect was both time and dose dependent.

There were no treatment-related effects on food consump-
tion in males given 2.5 or 5 mg/kg/day oxymorphone. Food
consumption was slightly (<15%) but statistically significantly
reduced over the first 8 weeks of dosing in males given 10 mg/
kg/day and females at all doses. Thereafter, food consumption
was generally similar to controls.

Mice. The survival rate of males given 10 or 25 mg/kg/day
and females at all doses tended to be higher than the survival
rate in the control groups (Fig. 2a, 2b). The higher survival in
males in these groups may be associated with a lower incidence
of amyloidosis observed preterminally (Table 2).

A treatment-related decrease in survival occurred in males
given 75 or 150 mg/kg/day (Fig. 2a). The major treatment-
related effect contributing to early death of males at these doses
was a pronounced increase in the incidence of obstructive
uropathy and, to a lesser extent, renal inflammatory changes
(Table 2). No obvious urinary tract blockages were evident.

Treatment-related increases in mydriasis and behavioral
changes including circling, self-biting, excess grooming,
licking, and/or scratching occurred in both males and females,
generally at all doses, which were considered to be the result of
the pharmacological action of oxymorphone. Other treatment-
related clinical signs in both males and females included firm
internal structure (abdominal), oily fur, and yellow fur staining. An increased incidence of protruding penis, and other urogenital findings (skin lesions, swelling, redness of penis, prepuce, and/or scrotum) were observed in treated males. Other clinical signs (thin fur cover, severed tail, various skin lesions/scabs) were considered secondary to behavioral changes noted above.

Mean body weights were statistically significantly lower than controls generally throughout the treatment period in both males and females administered oxymorphone at all doses (Fig. 2c, 2d). These effects were more pronounced in females than in males.

Variable, dose-related effects on food consumption were noted in males and females at all doses.

**Ophthalmology.** Treatment-related ophthalmoscopic findings after 1 year of dosing in rats included an increased incidence of corneal opacities (superficial punctuate keratopathy) in females at 25 mg/kg/day (11/65 animals vs. 0/100 controls), and a slight increase in the incidence of diffuse retinal degeneration in females at 10 and 25 mg/kg/day (3/65 and 5/65 animals, respectively vs. 1/100 controls). These findings are consistent with histopathologic findings of

![Graphs A, B, C, D representing survival and mean body weight over time.](https://example.com/graphs.png)

**FIG. 1.** Survival and body weights of rats administered oxymorphone for 2 years. (A and B) Survival (%) of male and female rats, respectively. (C and D) Mean body weight of male and female rats, respectively. ◆ = controls; ■ = 2.5 mg/kg/day; ▲ = 5 mg/kg/day; * = 10 mg/kg/day; ◊ = 25 mg/kg/day.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Mortality and Most Common Causes of Preterminal Death in Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>Dose (mg/kg/day)</td>
<td>0</td>
</tr>
<tr>
<td>Number of animals</td>
<td>100</td>
</tr>
<tr>
<td>Number (%) of preterminal deaths</td>
<td>64 (64)</td>
</tr>
<tr>
<td>Cause of death undetermined</td>
<td>13</td>
</tr>
<tr>
<td>Pituitary tumors</td>
<td>20</td>
</tr>
<tr>
<td>Mammary tumors</td>
<td>—</td>
</tr>
<tr>
<td>Subcutaneous tumors</td>
<td>5</td>
</tr>
<tr>
<td>Chronic progressive nephropathy</td>
<td>10</td>
</tr>
</tbody>
</table>
increased acute to chronic corneal inflammation and retinal atrophy observed at the end of the study (Table 2). These findings are likely secondary to pharmacologically induced inhibition of the blink reflex and mydriasis. There were no treatment-related ophthalmoscopic findings in mice.

**Hematology.** After 1 year of dosing, mean total WBC counts were statistically significantly lower than controls in male and female rats (up to 28 and 22%, respectively) and male mice (up to 47%) at all doses of oxymorphone, although there was not a clear dose-response in female rats and male mice. In the differential counts there were statistically significant increases in mean percent neutrophils and decreases in mean percent lymphocytes and monocytes. At study termination, these changes were no longer apparent in male rats. In high-dose female rats, the mean percent lymphocytes remained significantly lower than controls and mean percent neutrophils remained significantly higher than controls, while the total WBC counts were similar to controls. In male mice, total WBC counts and associated changes in neutrophils, lymphocytes, and monocytes were still present at the end of dosing. While there appeared to be a treatment-related effect, all values remained within historical control values for rats and mice of this age, and there were no histopathologic findings at termination which correlated with these findings. Thus, the hematologic changes were not considered to be of toxicological significance.

**Necropsy Findings and Histopathology**

**Rats.** Treatment-related nonneoplastic changes were found in the eyes and lungs of both males and females (Table 3). In the eye, dose-related increases in minimal to moderate retinal atrophy, characterized by a partial to total loss of the outer nuclear layer of the retina, and acute to chronic corneal inflammation were observed. In the lung there were dose-related increases in histiocytosis and granuloma/subacute inflammation (Table 3). Pulmonary granuloma and/or subacute inflammation were often associated with the presence of foreign material (plant material) in the bronchi, bronchioles, and/or alveoli. These results are consistent with aspiration of food.

There was no evidence of treatment-related neoplasia in either male or female rats. In the trend tests for uterine endometrial polyp (females), malignant lymphoma (males), and renal tubular adenoma (males), *p* values were 0.0266, 0.0264, and 0.0414, respectively. However, these trends were not considered statistically significant, because the nominal level of significance was not met (*p* < 0.005 for common tumors [uterine endometrial polyp and malignant lymphoma] and *p* < 0.025 for rare tumors [renal tubular adenoma]) (U.S. FDA, 2001). In pairwise comparisons for adrenal benign pheochromocytoma and mammary gland adenoma and adenocarcinoma in female rats given 10 mg/kg/day versus control,
**TABLE 2**

Mortality and Common Causes of Preterminal Death in Mice

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg/day)</td>
<td>0 10 25 75 150</td>
<td>0 10 25 75 150</td>
</tr>
<tr>
<td>Number of animals</td>
<td>100 65 65 65 65</td>
<td>100 65 65 65 65</td>
</tr>
<tr>
<td>Number (%) of preterminal deaths</td>
<td>50 (50) 26 (40) 24 (37) 39 (60) 42 (65)</td>
<td>62 (62) 30 (46) 33 (51) 30 (46) 36 (55)</td>
</tr>
<tr>
<td>Cause of death</td>
<td>5 3 5 10 7</td>
<td>6 3 4 1 9</td>
</tr>
<tr>
<td>Lymphoma/histiocytic sarcoma</td>
<td>8 4 5 5 1</td>
<td>19 11 9 10 12</td>
</tr>
<tr>
<td>Pulmonary tumors</td>
<td>7 3 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Liver tumors</td>
<td>3 2 2 1 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>13 4 3 4 2</td>
<td>63 35 3 1 0</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>6 7 7 12 26</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>Pyelitis/pyelonephritis</td>
<td>0 1 2 2 4</td>
<td>0 0 1 1 3</td>
</tr>
</tbody>
</table>

*p* values were 0.0449, 0.0231, and 0.0466, respectively. However, as common tumors, the nominal level of statistical significance (*p* < 0.01) was not met. Therefore, based on the lack of statistical significance and absence of similar findings at 25 mg/kg/day, these findings were not considered to be treatment related.

A number of nonneoplastic and neoplastic findings showed apparent dose-related decreases including hepatocellular vacuolation and hepatic cystic degeneration in males and females, adrenal cystic degeneration and parathyroid hyperplasia in males, bile duct hyperplasia in females (Table 3), and pituitary adenoma in males (Table 4), which were likely attributable to dose-related decreases in body weight gain in these animals.

**Mice.** Treatment-related nonneoplastic findings in mice were limited to the urogenital tract (Table 5). An increased incidence and severity of findings consistent with obstructive uropathy was observed in males and females given 75 or 150 mg/kg/day. These changes were more frequently observed in males than in females, and often associated with preterminal

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**TABLE 3**

Nonneoplastic Findings in Rats Administered Oxymorphone for 2 Years

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg/day)</td>
<td>0 2.5 5 10 0</td>
<td>5 10 25</td>
</tr>
<tr>
<td>Number of animals</td>
<td>100 65 65 65 100</td>
<td>65 65 65 65</td>
</tr>
<tr>
<td>Finding</td>
<td>Number with finding (%)</td>
<td></td>
</tr>
<tr>
<td>Adrenal Cystic degeneration</td>
<td>17 (17) 5 (8) 1 (2) 1 (2) 1 (2) 37 (37) 27 (42) 27 (42) 34 (52)</td>
<td></td>
</tr>
<tr>
<td>Eye Lens degeneration</td>
<td>2 (2) 2 (3) 2 (3) 1 (2) 1 (1) 1 (2) 1 (2) 5 (8)</td>
<td></td>
</tr>
<tr>
<td>Retinal atrophy</td>
<td>10 (10) 7 (11) 13 (20) 24 (37) 14 (14) 32 (49) 31 (48) 43 (66)</td>
<td></td>
</tr>
<tr>
<td>Corneal inflammation</td>
<td>4 (4) 3 (5) 1 (2) 9 (14) 6 (6) 6 (9) 5 (8) 15 (23)</td>
<td></td>
</tr>
<tr>
<td>Liver Hepatocellular vacuolation</td>
<td>40 (40) 20 (31) 11 (17) 4 (6) 41 (41) 2 (3) 2 (3) 0 (0)</td>
<td></td>
</tr>
<tr>
<td>Cystic degeneration</td>
<td>30 (30) 13 (20) 8 (12) 2 (3) 4 (4) 4 (6) 2 (3) 0 (0)</td>
<td></td>
</tr>
<tr>
<td>Bile duct hyperplasia</td>
<td>40 (40) 29 (45) 24 (37) 28 (43) 33 (33) 11 (17) 7 (11) 3 (5)</td>
<td></td>
</tr>
<tr>
<td>Lang Histiocytosis</td>
<td>22 (22) 19 (29) 21 (32) 40 (62) 19 (19) 23 (35) 40 (62) 56 (86)</td>
<td></td>
</tr>
<tr>
<td>Granuloma/subacute inflammation</td>
<td>7 (7) 5 (8) 11 (17) 35 (54) 11 (11) 5 (8) 10 (15) 37 (57)</td>
<td></td>
</tr>
<tr>
<td>Parathyroid Hyperplasia</td>
<td>11 (13) 3 (7) 0 (0) 0 (0) 3 (4) 1 (2) 0 (0) 0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* Only findings with an apparent dose-relationship (increase or decrease) in one or both sexes are presented. All other findings showed no apparent relationship to treatment or dose in either species.
morbidity as previously described. Findings consisted of dilatation of the renal pelvis, ureters, and urinary bladder with or without thickening of the urinary bladder wall observed at necropsy. Protrusion of the penis, commonly associated with obstructive uropathy, was also observed in males at these doses. Histopathologic evaluation showed renal pelvic dilatation, renal tubular dilatation, pyelitis/pyelonephritis, dilatation of the ureters with or without inflammation, and dilatation of the urinary bladder with or without inflammation. In males a marginal increase was noted in transitional cell hyperplasia of the urinary bladder, although this may have been secondary to dilatation, inflammation, and presumptive urinary retention. In females an increase was noted in subepithelial edema and/or connective tissue thickening in the urinary bladder which, may also have been secondary to primary urinary retention. In a small number of animals, bacterial colonization was present, particularly in marked cases of pyelonephritis. Increased incidences of prostate and seminal vesicular inflammation were also noted in males given 75 or 150 mg/kg/day.

There was no evidence of treatment-related neoplasia in male or female mice at any dose (Table 6).

A number of gross lesions appeared to be diminished in frequency in treated animals when compared to controls. These included masses/nodules of the liver, lung, ovary, and uterus, and enlargement of lymphoid tissues. A dose-related reduction in a number of normally age-related changes in many organs was noted in both males and females including lipofuscin deposits and cortical hyperplasia in the adrenal in males and females at all

### Table 4

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg/day)</td>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>Number of animals</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>Finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma: cortical</td>
<td>4 (4)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Benign pheochromocytoma</td>
<td>17 (17)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma: tubular cell</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Carcinoma: tubular cell</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoma: hepatocellular</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Adenoma: hepatocellular</td>
<td>4 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mammary gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>0&quot;</td>
<td>1</td>
</tr>
<tr>
<td>Adenoma</td>
<td>1&quot;</td>
<td>0</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0&quot;</td>
<td>1</td>
</tr>
<tr>
<td>Pituitary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma: pars distalis</td>
<td>64 (64)</td>
<td>30 (46)</td>
</tr>
<tr>
<td>Carcinoma: pars distalis</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Uterus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyp: endometrial stromal</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sarcoma: endometrial stromal</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Adenoma: endometrial</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Note. Neoplastic findings with an apparent dose-relationship (increase or decrease) in one or both sexes, selected other findings in these same tissues or target tissues (tissues with treatment-related nonneoplastic findings), and selected findings for comparison to the mouse are presented. All other findings showed no apparent relationship to treatment or dose in either species.

*p < 0.05 (pairwise comparison).

#p < 0.05 (positive dose-related trend).

*Percent of animals was not calculated because mammary glands were only examined in males when there were grossly observed lesions.
doses, glomerulonephritis and renal amyloidosis in males at 10 and 25 mg/kg/day (Table 5). The incidence of hepatocellular adenoma and carcinoma appeared to be decreased in males at all doses, and the incidence of pituitary adenoma was decreased in females. These changes were likely attributable to higher preterminal mortality in males at 75 and 150 mg/kg/day and/or treatment-related reductions in body weight.

Toxicokinetics. Toxicokinetic parameters are summarized in Table 7. The rate of gastrointestinal absorption of the oxymorphone was rapid in both species, with peak plasma concentrations observed within 1–2 h after dosing. In rats, systemic exposure generally increased slightly more than proportionally with dose. Similar elimination half-lives ($t_{1/2}$) were seen in both sexes, ranging from 3.6–6.3 h. Plasma levels were comparable in males and females given the same dose (5.0 or 10 mg/kg/day).

In mice, maximal plasma concentration ($C_{max}$) and area under the plasma concentration vs. time curve ($AUC_{0-24}$ h) increased approximately proportionally with increasing dose from 10 to 75 mg/kg/day, and more than proportionally with increasing dose from 75 to 150 mg/kg/day in both males and females. Shorter elimination half-lives ($t_{1/2}$) were observed in females (1.4–3 h) than in males (3–5.3 h).

### DISCUSSION

There is little information in the published literature on the chronic toxicity of opioid analgesics, despite their long history of use in the treatment of chronic pain. To our knowledge, this is the first report of carcinogenicity testing of a potent morphinan opioid analgesic.

Oxymorphone hydrochloride was administered daily, by oral gavage, for 2 years to rats and mice. Plasma concentrations determined after 6 months of dosing showed rapid absorption and increasing systemic exposure with dose. $C_{max}$ and $AUC_{0-24}$ values were similar to those found in 3-month toxicity studies in rats and mice at comparable doses (unpublished data), indicating that accumulation did not occur over long-term exposure. One exception was in the high-dose mice (150 mg/kg/day), where plasma concentrations increased greater than proportionally with dose between 75 and 150 mg/kg/day, and plasma concentrations at 150 mg/kg/day were higher than expected based on 3-month toxicity studies. Plasma concentrations achieved in these studies are comparable to, or exceed those in patients administered high therapeutic doses of oxymorphone. Healthy subjects administered 40 mg of extended-release oxymorphone every 12 h had a steady-state
Administration of oxymorphone produced deficits in body weight gain in rats and mice at all doses. The reductions in body weight gain exceeded standard definitions of maximum tolerated doses (> 10% reduction in body weight gain) (International Conference on Harmonization, 1995). These reductions, particularly in rats, were not anticipated based on results of previous 13-week toxicity studies (unpublished results). Interestingly, the effects on body weight gain in rats were both dose and time dependent, and became apparent only after prolonged exposure at the low- and mid-doses (~10–12 weeks in female rats and >40 weeks in mid-dose male rats). Moreover, the effects on body weight gain occurred in the absence of consistent reductions in food consumption, which was only minimally and variably affected during the first few weeks of the study. Therefore, the basis for the deficit in body weight gain is unclear. In recent studies we found that oxymorphone produces rapid hyperthermia in rats and mice (Shuey et al., 2006). However, these studies were conducted at doses higher than those used in the carcinogenicity studies. Furthermore, it is unknown if this effect is sustained with repeated dosing, although studies with morphine suggest the development of tolerance to this effect (Mucha et al., 1987). Hyperactivity was observed in both rats and mice throughout the dosing period in the carcinogenicity studies. Thus, it is

### TABLE 6
Neoplastic Findings in Mice Administered Oxymorphone for 2 Years

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>25</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>50</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>150</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>Number of animals</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>100</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>65</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>65</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Finding Number with finding (%)</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Adrenal: Adenoma: cortical</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Benign pheochromocytoma</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hemolymphoreticular tissue: Histiocytic sarcoma</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>9 (9)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Kidney: Adenoma: tubular cell</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Carcinoma: tubular cell</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Liver: Adenoma: hepatocellular</td>
<td>18 (18)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Carcinoma: hepatocellular</td>
<td>13 (13)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Lung: Adenoma: alveolar/bronchiolar</td>
<td>14 (14)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Carcinoma: alveolar/bronchiolar</td>
<td>12 (12)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Pituitary: Adenoma: pars distalis</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urinary bladder: Submucosal mesenchymal tumor</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Note. For nonneoplastic findings, only findings with an apparent dose-relationship (increase or decrease) in one or both sexes are presented. Neoplastic findings with an apparent dose-relationship (increase or decrease) in one or both sexes, selected findings in these same tissues, target tissues (tissues with treatment-related nonneoplastic findings), and selected findings for comparison to the rat are presented. All other findings showed no apparent relationship to treatment or dose in either species.

### TABLE 7
Oxymorphone Toxicokinetic Parameters

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Cmax (ng/ml)</th>
<th>Tmax (h)</th>
<th>AUC0–24 h (ng h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Rats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>3.83</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>5.0</td>
<td>6.98</td>
<td>0.5</td>
<td>37.5</td>
</tr>
<tr>
<td>10</td>
<td>24.0</td>
<td>1.0</td>
<td>92.7</td>
</tr>
<tr>
<td>25</td>
<td>—</td>
<td>1.0</td>
<td>415</td>
</tr>
<tr>
<td>Mice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>37.1</td>
<td>2.0</td>
<td>98.5</td>
</tr>
<tr>
<td>25</td>
<td>14.0</td>
<td>1.0</td>
<td>37.1</td>
</tr>
<tr>
<td>75</td>
<td>325</td>
<td>1.0</td>
<td>1040</td>
</tr>
<tr>
<td>150</td>
<td>919</td>
<td>1.0</td>
<td>4002</td>
</tr>
</tbody>
</table>

Note. Healthy subjects administered 40 mg of extended-release oxymorphone every 12 h had a steady-state AUC0–12 h of 37 ng h/ml. This value was doubled for AUC0–24 h comparison.

AUC0–12 h of 37 ng h/ml (Adams and Ahdieh, 2004). The AUC achieved at the high doses in the carcinogenicity studies were 1.3- and 5.6-fold in male and female rats, respectively, and 54- and 64-fold in male and female mice, respectively, this human exposure (based on 24 h).

Administration of oxymorphone produced deficits in body weight gain in rats and mice at all doses. The reductions in body weight gain exceeded standard definitions of maximum tolerated doses (> 10% reduction in body weight gain) (International Conference on Harmonization, 1995). These reductions, particularly in rats, were not anticipated based on results of previous 13-week toxicity studies (unpublished results). Interestingly, the effects on body weight gain in rats were both dose and time dependent, and became apparent only after prolonged exposure at the low- and mid-doses (~10–12 weeks in female rats and >40 weeks in mid-dose male rats). Moreover, the effects on body weight gain occurred in the absence of consistent reductions in food consumption, which was only minimally and variably affected during the first few weeks of the study. Therefore, the basis for the deficit in body weight gain is unclear. In recent studies we found that oxymorphone produces rapid hyperthermia in rats and mice (Shuey et al., 2006). However, these studies were conducted at doses higher than those used in the carcinogenicity studies. Further, it is unknown if this effect is sustained with repeated dosing, although studies with morphine suggest the development of tolerance to this effect (Mucha et al., 1987). Hyperactivity was observed in both rats and mice throughout the dosing period in the carcinogenicity studies. Thus, it is
possible that the effects of oxymorphone on body weight may be secondary to other physiologic changes, though additional studies would be required to further characterize these effects.

The reductions in body weight gain were likely the basis for increased survival in oxymorphone-treated rats and mice relative to the in-study controls. The association of reduced body weight gain resulting from caloric restriction, with increased survival is well established in rats (Keenan et al., 1999; National Toxicology Program, 1997) and mice (National Toxicology Program, 1997). These effects are related to decreased occurrence, progression, and/or delayed onset of common endocrine tumors and other degenerative diseases associated with obesity and aging in these animals. The results of the rat carcinogenicity study are consistent with these conclusions. The decreased mortality in oxymorphone-treated rats appeared to be associated with a decreased incidence of pituitary tumors in males and females and chronic progressive nephropathy in males observed preterminally. Although the overall incidence of pituitary adenoma in treated females was similar to controls, the lower incidence of this finding observed preterminally suggests a delayed onset for this tumor. The basis for increased survival in mice given oxymorphone was less clear. In males there was clear reduction in fatal amyloidosis observed preterminally but there was no obvious reduction in any findings leading to preterminal death of females. However, there were dose-related reductions in a number of common age-related pathologic findings in both male and female mice.

Tolerance to the analgesic effects of opioids in rodents is well described, where antinociceptive activity is diminished in animals with prolonged dosing such that increasing doses are required to sustain analgesic activity. The mechanism for development of tolerance is not fully understood but appears to involve complex interactions of opioid receptors with other neurotransmitter and second messenger systems (reviewed in Reisine and Pasternak, 1996). Development of tolerance is variable among species, sex, and strains (Craft et al., 1999; Kest et al., 2000; Mas et al., 2000; Roerig and Fujimoto, 1988). Further, different behavioral and physiologic effects of opioids show differential development of tolerance (Ling et al., 1989; Solomon et al., 1987). In the carcinogenicity studies reported here, gradual dose escalation improved tolerability to oxymorphone in mice allowing for testing of doses that would not be tolerated in naïve animals, consistent with development of tolerance. However, clinical signs typical of high-dose opioid administration in rodents (hyperactivity and/or hypoactivity, excessive grooming/biting) continued to be observed throughout the dosing period in both rats and mice, and effects on body weight gain developed only after prolonged dosing at the lower doses. These results indicate incomplete tolerance to the effects of oxymorphone over the course of the study.

There was no evidence of target organ toxicity in mice or rats given oxymorphone. All findings were attributable to the pharmacologic action of oxymorphone (i.e., mu-opioid agonist), including ocular and pulmonary findings in rats, and urogenital changes in mice. The retinal change observed in rats was consistent with light-induced retinal degeneration (i.e., phototoxicity) (Yoshitomi and Boorman, 1990) and was probably secondary to both decreased palpebral closure (inhibition of the blink reflex) and mydriasis. Morphine is known to produce mydriasis in rats (Kamenetsky et al., 1997), although miosis is observed with opioid treatment in humans (Reisine and Pasternak, 1996). Similarly, the increased incidence of corneal inflammation was most likely the result of a pharmacologically induced decrease in palpebral closure and subsequent reduction in corneal lubrication (i.e., chronic dry eye). The increased incidence in pulmonary histiocytosis and inflammatory lesions, and presence of the associated plant material (presumably food), was likely the result of food aspiration. Opioids produce relaxation of the gastroesophageal sphincter (Hall et al., 1987), prolong gastric emptying (reviewed in Gutstein and Akil, 2001), and have antitussive activity (reviewed in Kamei, 1996), which could promote gastroesophageal reflux and aspiration. The observed urogenital findings in mice are consistent with chronic urinary retention. Urinary retention is a known effect of morphine-related mu-opioid agonists, resulting from pharmacologic effects on muscle tone in the urinary bladder, ureter, and external sphincter (reviewed in Gutstein and Akil, 2001). The urogenital findings in this study are thus considered secondary to the pharmacologic effects of oxymorphone and not indicative of a direct toxicologic effect on the urinary tract.

There are a number of reports in the literature, both in animals and humans that suggest potent opioids may affect immune function (Bryant et al., 1987; LeVier et al., 1994; West et al., 1997). In the oxymorphone carcinogenicity studies reported here, total WBC counts and the mean percent lymphocyte counts were slightly decreased in male and female rats and male mice after 1 year of dosing when compared to concurrent control groups, although values remained within historical control ranges. These effects persisted until the end of the study in male mice and in high-dose female rats. However, there were no nonneoplastic or neoplastic lesions in tissues of the immune system in oxymorphone-treated animals indicative of chronic immunosuppression.

In genotoxicity studies, oxymorphone increased bone marrow micronucleated polychromatic erythrocytes (MPCEs) in both rats and mice, which appear to be secondary to pharmacologically mediated increases in body temperature (Shuey et al., 2006). This in vivo genotoxic effect of oxymorphone did not translate into a carcinogenic effect. Investigational studies have indicated a threshold for body temperature changes leading to increased MPCEs (Asanami and Shimono, 1997b; Shuey et al., 2006). Studies with morphine showed that increased MPCEs were observed after a single dose but diminished after repeated administration, indicating the development of tolerance (Swain et al., 1980). Repeat-dose micronucleus studies of oxymorphone have not
been conducted. Either the existence of a threshold and/or development of tolerance for genotoxicity could explain the lack of a carcinogenic response with oxymorphone. These results underscore the importance of understanding genotoxic mechanisms and associated carcinogenic risk, particularly if secondary or indirect mechanisms are indicated.

In conclusion, oxymorphone is not carcinogenic in rats and mice. Doses used in these studies produced deficits in body weight gain that exceeded standard definition of a maximum tolerated dose. Increased survival in rats and female mice likely resulted from the decrease in body weight gain and associated decreases in age-related diseases. There was no evidence of target organ toxicity; all findings were related to the pharmacologic action of oxymorphone.

SUPPLEMENTARY DATA

Supplementary data are available online at http://toxsci.oxfordjournals.org/.

ACKNOWLEDGMENTS

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REFERENCES


