EPA Reviewer: Pamela M. Hurley, Ph.D. Pamela M Hurley 5/10/99
Registration Action Branch 2 (7509C)

Work Assignment Manager: Sanjivani Diwan, Ph.D.
Toxicology Branch I (7509C)

# DATA EVALUATION RECORD

STUDY TYPE: Combined Chronic/Oncogenicity
OPPTS Number: 870.4300
OPP Guideline Number: §83-5

DP BARCODE: D241232
P.C. CODE: 070705
SUBMISSION CODE: S534142
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): KBR 3023 Technical (96.7-98.5% a.i.)

SYNONYMS: 1-(1-methyl-propoxycarbonyl)-2-(2-hydroxyethyl)-piperidine

CITATION: Wahle, B.S., and Christenson, W.R., (1996) Technical Grade KBR 3023: A Combined Chronic Toxicity/Oncogenicity Testing Study in the Rat. Bayer Corporation, Stilwell, KS, Laboratory Project Study ID# 92-222-OM, December 17, 1996. MRID 44408728. Unpublished.

SPONSOR: Bayer Corporation, Box 4913, Hawthorn Road, Kansas City, MO

EXECUTIVE SUMMARY:

In a combined chronic/oncogenicity study (MRID 44408728), undiluted KBR 3023 (technical. 96.7-98.5% a.i.) was administered dermally on the dorsal aspect of the trunk to 50 Sprague Dawley rats/sex/dose at dose levels of 0, 50, 100, or 200 mg/kg/day on 5 consecutive days/week for 24 months. In addition, 10-20 rats/sex/group were terminated at 12 months. The administered dose volumes were based on the mean weekly body weight for each dose group. The exposure site was approximately 10% of the total body surface area.

Survival, body weights, food consumption and efficiency, and absolute and relative organ weights for both sexes at all doses were unaffected by treatment with KBR 3023. Clinical observations, hematological parameters, and gross parameters were also unaffected by treatment. In the 2-year males, there was a dose-dependent increase in the incidence of liver cystic degeneration (8/47, 11/46, 14/49, 20/47, in controls, low-, mid-, and high-dose groups, respectively; statistically significant [$p<0.05$] in the high-dose group only). These findings were not corroborated by changes in organ weight or in blood chemistry parameters.

No increases in the incidences of any neoplasm were observed in the dosed animals.

The dose levels used in this study were from an EPA approved protocol.

**The chronic LOAEL was not observed. The chronic NOAEL is 200 mg/kg/day.**

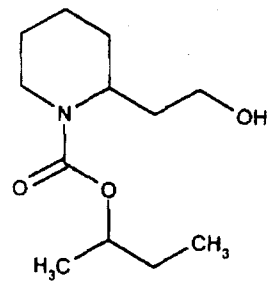
The submitted study is classified as **acceptable (§83-5)** and satisfies the guideline requirements for a combined chronic/oncogenicity study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

# I. MATERIALS AND METHODS

## A. MATERIALS:

1. Test Material: KBR 3023 technical
   Description: Clear liquid
   Lot/Batch #: 030693
   Purity: 96.7-98.5% a.i.
   Stability of compound: The compound is stable for 28 days when stored at room temperature and up to 18 months when stored frozen.
   CAS #: 119515-38-7
   Structure:




   Other comments: The test material was stored under freezer conditions at all times. Dosing aliquots were removed every two weeks and stored under room temperature.

2. Vehicle and/or positive control: None

3. Test animals: Species: Rat
   Strain: Sprague Dawley
   Age and weight at study initiation: Approximately 8 weeks; 180.2-182.8g (males) and 149.7-152.5g (females)
   Source: Charles River Breeders, Portage, MI
   Housing: Suspended stainless steel wire-mesh cages and polycarbonate cages; 1 rat/cage
   Diet: Purina Mills Rodent Lab Chow 5001-4, ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 18-26 C
   Humidity: 40-70%
   Air changes: Not reported
   Photoperiod: 12 hr dark/12 hr light
   Acclimation period: ≥6 days

B. STUDY DESIGN:

1. In life dates - Start: 10/4/93 End: Not specified

2. Animal assignment: Animals were assigned to treatment groups as indicated in Table 1 using a body weight dependent randomization process.

Table 1: Study design

| Test Group | Dose to Animals M/F (mg/kg/day) | Number of Animals [a] | | | |
|---|---|---|---|---|---|
| | | Interim Study (1-year sacrifice) | | Main study (2-year sacrifice) | |
| | | Males | Females | Males | Females |
| Control | 0 | 20 | 20 | 50 | 50 |
| Low | 50 | 10 | 10 | 50 | 50 |
| Mid | 100 | 10 | 10 | 50 | 50 |
| High | 200 | 20 | 20 | 50 | 50 |

a The data were obtained from the study report, Table 2, page 33.

3. Dose Selection: The rationale for dose selection was based on results from a subchronic study in which rats were dosed dermally for 5 consecutive days/week with KBR 3023 at 0, 80, or 200, 500, or 1,000 mg/kg/day for 13 weeks. Acanthosis, hyperkeratosis, and/or hypertrophy of the sebaceous glands around the hair follicle of the dosing site were observed in all treated animals. After a 4 week recovery period, the skin changes were reversed. The changes in the treated skin were not dose-related and were considered an adaptive response to chronic exposure to a liquid compound. Treatment-related increases in liver and kidney weights as well as liver hypertrophy and hyaline degeneration of the kidney tubules were observed in the 500 and 1000 mg/kg/day animals. Based on the observed systemic toxicity, a 5 day/week dosing regime at 50, 100, or 200 mg/kg/day protocol was proposed for all further testing of KBR 3023. In addition, it was determined that no more than 200 mg/kg/day could be administered to each animal because of run-off of the material and possible oral ingestion (personal communication, W. Phang 2/4/99).

The protocol and dose selection for this study were discussed and approved by EPA prior to the start of the study. Copies of the memos reporting the meetings with EPA were submitted with the MRID (Appendix X, pages 4199-4224).

4. Dosage Administration: On 5 consecutive days/week, undiluted technical grade KBR 3023 was applied to a shaved area on the dorsal aspect of the trunk of each treated animal. The administered dose volumes were based on the mean weekly body weight for each dose group. Control animals were shaved, but not treated. The exposure site was approximately 10% of the total body surface area. All animals were fitted with Elizabethan collars (EJAY International, Glendora, CA) for the duration of the study.

5. Test Chemical Analysis: Undiluted technical grade KBR 3023 was stored frozen (-23 °C) and approximately every two weeks, dosing aliquots were provided. From the information provided, it was inferred that the dosing aliquots were stored at room temperature. Prior to commencement of the study and approximately every 6 months, the stability of the test chemical stored at -23 °C was assessed. In addition, stability analyses were performed on samples of KBR 3023 stored at room temperature (22 °C) for 7, 14, 21, or 28 days.

   Results:

   Concentration/Stability Analysis: The chemical purity of KBR 3023 stored frozen was 96.7-98.5% throughout the study. It was stated that the compound is stable for 28 days when stored at room temperature.

   The information provided indicated that the test compound was stable for the duration of the study.

6. Statistics: Bartlett's test of equality or homogeneity of variance was applied to the organ and terminal body weight and clinical pathology data. An analysis of variance (ANOVA) followed by Dunnett's test were applied to group means. In the event of unequal variances, the data were subjected to a Kruskal-Wallis ANOVA followed by the Mann-Whitney-U test. The Chi-Square procedure was applied to the ophthalmology, necropsy, and micropathology data followed by the Fisher exact test if the data indicated a trend. For the Bartlett test, $p \leq 0.001$ was considered significant, $p \leq 0.05$ was considered significant for all other tests.

C. METHODS:

1. Observations: Animals were inspected twice daily for signs of mortality/moribundity. Physical exams, including palpation for masses, were performed weekly. External surface areas, orifices, respiration, excretory products, behavior, and posture were also evaluated during the physical exam.

2. Body weight: Animals were weighed at initiation of dosing, at weekly intervals, and just prior to necropsy.

3. Food consumption: Food consumption for each animal was determined at weekly intervals and calculated on a g/animal/day and g/kg body weight/day basis.

4. Ophthalmoscopic examination: The eyes of all the animals were examined prior to initiation of dosing. In addition, the eyes of all surviving 1-year (10-20 sex/dose) and 2-year animals (19-26 sex/dose) were re-examined prior to their scheduled sacrifice.

5. Blood Analyses: At 3, 6, 12, 18, and 24 months, blood was collected from the 2-year animals (14-20 rats/group) for hematology and differential leukocyte analyses. The animals were fasted overnight prior to blood sampling via the orbital sinus. The following CHECKED (X) parameters were examined.

a. Hematology:

| | | | |
|---|---|---|---|
| X | Hematocrit (HCT) | X | Leukocyte differential count |
| X | Hemoglobin (HGB) | X | Mean corpuscular HGB (MCH) |
| X | Leukocyte count (WBC) | X | Mean corpusc. HGB conc.(MCHC) |
| | Corrected leukocyte count (Cor WBC) | X | Mean corpusc. volume (MCV) |
| X | Erythrocyte count (RBC) | X | Reticulocyte count |
| X | Platelet count | X | Erythrocyte morphology |
| | Blood clotting measurements | | Red cell distribution width |
| | (Thromboplastin time) | | HGB distribution width |
| | (Clotting time) | X | Heinz bodies |
| | (Prothrombin time) | | |

b. Clinical Chemistry:

| | ELECTROLYTES | | OTHER |
|---|---|---|---|
| X | Calcium | X | Albumin |
| X | Chloride | X | Blood creatinine |
| | Magnesium | X | Blood urea nitrogen |
| X | Phosphorus | X | Total Cholesterol |
| X | Potassium | X | Globulins |
| X | Sodium | X | Glucose (fasting) |
| | | X | Total & direct bilirubin |
| | ENZYMES | X | Total serum protein |
| X | Alkaline phosphatase (AP) | X | Triglycerides |
| | Plasma cholinesterase (PL-ChE) | X | Uric acid |
| | Erythrocyte cholinesterase (RBC-CHE) | | |
| | Brain cholinesterase (BR-CHE) | | |
| X | Creatine phosphokinase | | |
| X | Lactate dehydrogenase (LDH) | | |
| X | Serum alanine aminotransferase (ALT) | | |
| X | Serum aspartate aminotransferase (AST) | | |
| X | Gamma glutamyl transferase (GGT) | | |
| | Glutamate dehydrogenase | | |

6. Urinalysis: Urinalyses were performed on the 2 year animals (18-20 sex/group) at 3, 6, 12, 18, and 24 months. The following CHECKED (X) parameters were examined. The animals were not fasted prior to collection of urine.

| | | | |
|---|---|---|---|
| X | Clarity, appearance | X | Glucose |
| X | Volume | X | Ketones |
| X | Specific gravity | X | Bilirubin |
| X | pH | X | Blood |
| X | Sediment (microscopic) | X | Color |
| X | Protein | X | Urobilinogen |
| | Osmolality | X | Nitrite |
| | | | Creatinine |
| | | | Potassium |
| | | | Sodium |
| | | | Urea |

7. Sacrifice and Pathology: All 1-year animals that were sacrificed on schedule and all 2-year animals that died or were killed *in extremis* during the second year and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. Additionally, the (XX) organs were weighed. No necropsy or microscopic data were submitted on animals that died or were killed during the first year, which were 4 animals from the 1-year group and 11 animals from the 2-year group. A complete complement of tissues

was examined histologically for all other animals. Feet lesions from only 5 animals (male and female) and neck (collar) lesions from 5 animals (male and female) from the control and high-dose groups were examined microscopically.

| | DIGESTIVE SYSTEM | | CARDIOVASC./HEMAT | | NEUROLOGIC |
|---|---|---|---|---|---|
| | Tongue | X | Aorta | XX | Brain |
| X | Salivary glands | XX | Heart | X | Peripheral nerve |
| X | Esophagus | X | Bone marrow | X | Spinal cord (3 levels) |
| X | Stomach | X | Lymph nodes | X | Pituitary |
| X | Duodenum | XX | Spleen | X | Eyes (optic n.) |
| X | Jejunum | X | Thymus | | **GLANDULAR** |
| X | Ileum | | **UROGENITAL** | XX | Adrenal glands |
| X | Cecum | XX | Kidneys | X | Harderian gland |
| X | Colon | X | Urinary bladder | X | Mammary gland |
| X | Rectum | XX | Testes | X | Parathyroids |
| XX | Liver | X | Epididymis | X | Thyroids |
| | Gall bladder | X | Prostate | | **OTHER** |
| X | Pancreas | X | Seminal vesicles | X | Bone/skull |
| | **RESPIRATORY** | XX | Ovaries | X | Skeletal muscle |
| X | Trachea | X | Uterus | X | Skin |
| XX | Lungs | X | Vagina | X | All gross lesions and masses |
| | Nose | X | Cervix | X | Lacrimal/exorbital gland |
| | Pharynx | X | Preputial/clitoral | | |
| X | Larynx | | | | |

## II. RESULTS

### A. Observations:

1. Toxicity - All clinical observations were considered to be incidental and were not compound-related. It was stated that open wounds related to the use of the protective collars developed around the necks of approximately 20% of the male rats of each dose group, including the controls. After discussions with the Agency, the Sponsor removed the collars from all of the affected animals and stopped dosing for approximately 3 weeks; the data concerning the open wounds, stating the onset, the animals involved, and the dates when they were not dosed, were not summarized in the report. Corn oil was then applied to the collars until healing of the wounds occurred. Approximately half of the affected animals had a re-occurrence of the neck wounds. The animals from the main study (2-year) that continued to be affected (8, 9, 5, and 10 control, low-, mid-, and high-dose males, respectively and 0, 2, 1, 1 females, respectively) were sacrificed at the interim 1-year sacrifice in exchange for 1-year animals from the same dose group. These 1-year animals that were not sacrificed at the interim sacrifice continued on the study as part of the 2-year main study animals. It was not clear to the reviewers whether the interim 1-year animals that continued on the study were selected

randomly.

Lesions of the hind feet (including alopecia, raised zones, crusty zones, enlarged, and/or ulcers, severity grade, marked) developed in all male groups of the 1-year animals and in all male and female groups of the 2-year animals. The cause of the lesions was postulated to be related to body weight and the wire cage bottom; the incidences were not considered to be treatment-related since they were comparable in all groups. Panalog ointment was applied daily 5 days/week to the hind feet of all affected animals for up to two weeks. The 2-year animals from the main study that did not improve with the Panalog treatment were sacrificed at the interim sacrifice in exchange for 1-year animals from the same dose group; It was not clear to the reviewers how many of the 2-year animals were sacrificed during the interim sacrifice because of feet lesions.

Mortality - In the 1-year animals, two 200 mg/kg/day males and one 100 mg/kg/day female were sacrificed *in extremis* and one control female was found dead. All other 1-year animals survived to the scheduled sacrifice. Nineteen 2-year animals were either sacrificed *in extremis* or found dead during the first year . After 12 months, the survival rate was excellent in males (92-98%) and in females (94-96%) among all 2-year treated animals. Because of the neck and limb lesions discussed above, some animals originally scheduled to be sacrificed at the 1-year interim sacrifice were exchanged with animals originally scheduled to be sacrificed after 2 years of dosing . At 103 weeks, the survival rates in the 2-year animals were 46, 36, 46, and 36% in the controls, low-, mid-, and high-dose males, respectively, and 40, 50, 36, and 34% in the females, respectively. These survival rates exceeded the guideline requirement (not <25%) for this interval. The mortality data are summarized in Table 2 below.

Table 2. Mortality data [a]

| Dosage | | | 0 | 50 | 100 | 200 |
|---|---|---|---|---|---|---|
| 1 Year Animals | | | | | | |
| Male | | Total Animals | 20 | 10 | 10 | 20 |
| | | Found Dead | 0 | 0 | 0 | 0 |
| | | Euthanised | 0 | 0 | 0 | 2 |
| | | Total Mortality | 0 | 0 | 0 | 2 |
| | | % Survival | 100 | 100 | 100 | 90 |
| Female | | Total Animals | 20 | 10 | 10 | 20 |
| | | Found Dead | 0 | 0 | 1 | 0 |
| | | Euthanised | 1 | 0 | 0 | 0 |
| | | Total Mortality | 1 | 0 | 1 | 0 |
| | | % Survival | 95 | 100 | 90 | 100 |
| 2 Year Animals | | | | | | |
| Male | Total Animals | | 50 | 50 | 50 | 50 |
| | 1st Year Mortality | Found Dead | 2 | 2 | 0 | 2 |
| | | Euthanised | 1 | 2 | 1 | 1 |
| | 2nd Year Mortality | Found Dead | 10 | 15 | 14 | 16 |
| | | Euthanised | 14 | 13 | 12 | 13 |
| | Total Mortality | | 27 | 32 | 27 | 32 |
| | % Survival | | 46 | 36 | 46 | 36 |
| Female | Total Animals | | 50 | 50 | 50 | 50 |
| | 1st Year Mortality | Found Dead | 0 | 2 | 1 | 0 |
| | | Euthanised | 1 | 0 | 1 | 3 |
| | 2nd Year Mortality | Found Dead | 5 | 3 | 5 | 5 |
| | | Euthanised | 24 | 20 | 25 | 25 |
| | Total Mortality | | 30 | 25 | 32 | 33 |
| | % Survival | | 40 | 50 | 36 | 34 |

[a] Data extracted from study report, Tables CO-SUM and MORT1-SUM, pages 219, 227, and 295 through 298.

B. Body weight: No treatment-related differences were observed in body weight or body weight gains in either sex of the treated 1-year and 2-year groups throughout the study when compared to the respective control group.

The transient statistically significant differences observed in the treated groups compared to the controls throughout the study were considered to be not biologically significant.

| Mean Body Weight and Monthly Body Weight Gain Data at Selected Time Periods (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Weeks | Males | | | | Females | | | |
| Dose mg/kg/day | 0 | 50 | 100 | 200 | 0 | 50 | 100 | 200 |
| 1 | 248.3 | 244.9 | 241.1 | 241.4 | 188.3 | 182.9 | 186.7 | 183.0 |
| 5 | 388.5 | 380.7 | 377.4 | 373.1 | 246.5 | 239.7 | 249.1 | 244.9 |
| Monthly Gain at 5 | 140.2 | 134.7 | 135.8 | 132.3 | 57.6 | 57.3 | 62.2 | 61.6 |
| 8 | 440.0 | 453.0 | 443.4 | 439.9 | 278.8 | 270.7 | 279.2 | 278.4 |
| Monthly Gain at 8 | 70.5 | 92.4* | 85.1* | 87.1* | 44.4 | 44.2 | 41.9 | 45.3 |
| 13 | 533.8 | 519.6 | 518.2 | 520.0 | 312.5 | 300.5 | 310.5 | 313.7 |
| Monthly Gain at 13 | 61.7 | 47.4* | 54.8 | 58.4 | 26.0 | 21.4* | 24.6 | 25.1 |
| 26 | 601.4 | 603.2 | 598.2 | 592.0 | 356.2 | 350.9 | 351.0 | 361.0 |
| Monthly Gain at 26 | 14.5 | 18.5 | 12.1 | 9.6 | 14.3 | 14.9 | 8.3 | 13.6 |
| 52 | 650.4 | 657.4 | 658.4 | 640.9 | 426.7 | 420.7 | 413.8 | 435.4 |
| Monthly Gain at 52 | 0.8 | 0.1 | 1.8 | 3.8 | 7.4 | 9.5 | 4.2 | 7.5 |
| 101 | 538.8 | 547.3 | 568.9 | 550.7 | 416.3 | 430.4 | 431.0 | 447.5 |
| Monthly Gain at 101 | 7.8 | -7.5 | -11.5 | -12.1 | -24.9 | -1.5 | 1.7 | 5.1 |

* $p \leq 0.05$

C. Food consumption: There were no treatment-related differences in food consumption by the dosed groups compared to the concurrent controls throughout the study. The grand mean food consumption in the 2-year animals was approximately 31 g/male/day and 23-25 g/female/day in all dose groups including the controls. The intermittent statistically significant differences in food consumption by the treated animals compared to controls were considered to be not treatment-related.

D. Ophthalmoscopic examination: There were no treatment-related ophthalmoscopic findings in the 1- or 2-year animals.

E. Blood analyses:

1. Hematology and Differential Counts - No treatment-related effects in hematology parameters, including leucocyte differential counts, were observed after dosing with KBR 3023 at 50, 100, or 200 mg/kg/day for up to 24 months.

2. Clinical Chemistry - At the 3, 12, 18, and 24 month intervals, creatine kinase and lactate dehydrogenase were decreased (↓14-51% and 25-79%, respectively) in the 2-year high-dose males; these values were statistically significant ($p<0.05$) only at 3 and 12 months. The biological significance of these differences is not understood. Occasionally there were statistically significant differences in other clinical chemistry parameters; these transient differences were considered to be not treatment-related.

F. Urinalysis: There were no treatment-related differences observed in urinalysis parameters. At the 12, 18, and 24 month intervals, protein concentration in the high-dose females was consistently increased (↑54-150%). However, the protein values were not statistically significant and there were no indications of dose related and/or chronological trend.

Sacrifice and Pathology:

1. Organ weights - There were no treatment-related differences observed in absolute organ weights or organ weights relative to body weights in the 1- or 2-year dose groups. In the 2-year males, the absolute adrenal weights were decreased (↓36-37%, not statistically significant [NS]) and the absolute heart weights were increased in the 50 and 100 mg/kg/day (↑10% each; $p<0.05$) male dose groups. These findings were considered to be incidental and not related to dosing with KBR 3023.

2. Gross pathology - All gross necropsy findings detected in the treated animals were considered to be incidental. Abscess, alopecia, crusty zones , ulcers, masses, discolored zones, and/or raised zones were noted in the neck region ("skin, other") across all of the dose groups of the 1- and 2-year animals, including the controls. It was concluded that these lesions were as a result of the use of the Elizabethan collars. Missing, crusty

zones, necrotic, ulcer, pitted zones, raised zones, and/or discolored zones of the tail were also noted across all dose groups; these lesions were considered to be associated to grooming problems related to the wearing of the collars. Alopecia, raised zones, crusty zones, edema, enlarged, masses, discolored zones, and/or ulcers of the hindlimbs were noted across all male groups of the 1-year animals and all male and female dose groups of the 2-year animals. The pathology report (pages 4162-4163 of study report) stated that these hindlimb findings were related to the combination of wire cage bottom and the heavy body weights of the rats. Body weights at sacrifice were 406-633g and 392-549g in the 1-year and the 2-year rats, respectively.

3. Microscopic pathology:

a) Non-neoplastic - Microscopic findings were limited to the liver and the treated skin . In the 2-year males, there was a dose-dependent increase in the incidence of liver cystic degeneration (8/47, 11/46, 14/49, 20/47, in controls, low-, mid-, and high-dose groups, respectively; statistically significant [$p<0.05$] in the high-dose group only). These are considered to be age-related lesions and it is considered to be a coincidence that they occurred in a dose-related matter (personal communication (1/26/99, Dr. Dawn Goodman, pathologist with Covance).

An increased incidence ($p<0.05$) of acanthosis was observed in the 1-year males. In the 2-year animals, the incidence of acanthosis and/or hyperkeratosis of the skin were increased ($p<0.05$) in the low- and mid- dose females and in the high-dose males and females. These increased incidences were restricted to the treated skin only and were judged to be not of toxicological concern. Other statistically significant ($p<0.05$) findings, such as an increased incidence of congestion of the adrenals in the 2-year high-dose males and increased incidence of microgranulomas in the lungs of the 2-year low- and high-dose females, were not dose-related and were considered to be not treatment-related.

b) Neoplastic - No significant increases in the incidences of any neoplasm were observed in the dosed animals.

| Microscopic Examination of Selected Tissues (Incidences) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ & Lesion | Males | | | | Females | | | |
| **Dose (mg/kg/day)** | 0 | 50 | 100 | 200 | 0 | 50 | 100 | 200 |
| **Liver** | | | | | | | | |
| Degeneration, cystic | 8/47 | 11/46 | 14/49 | 20/47* | 1/49 | 1/48 | 1/48 | 2/47 |
| Focus/area of cellular alteration | | | | | | | | |
| Hyperplasia/fibrosis, biliary | 16/47 | 7/46 | 17/49 | 12/47 | 12/49 | 6/48 | 7/48 | 2/47 |
| Adenoma, hepatocellular | - | - | - | - | - | 1/48 | - | - |
| Carcinoma, hepatocellular | 1/47 | 2/46 | 1/49 | 2/47 | - | - | - | 1/47 |
| **Kidney** | | | | | | | | |
| Chronic nephropathy | 37/47 | 41/46 | 44/49 | 42/47 | 21/49 | 16/48 | 17/48 | 20/47 |
| Hyperplasia, epithelial cell | 12/47 | 10/46 | 19/49 | 16/47 | 5/49 | - | 4/48 | 3/47 |
| **Lung** | | | | | | | | |
| Congestion | 10/47 | 12/46 | 9/49 | 15/47 | 2/49 | 2/48 | 4/48 | 2/47 |
| Microgranuloma | 8/47 | 2/46 | 4/49 | 5/47 | 1/49 | 8/48* | 4/48 | 10/47* |
| **Mammary Gland** | | | | | | | | |
| Adenocarcinoma | - | - | - | - | 6/48 | 4/48 | 6/48 | 4/47 |
| Fibroadenoma | 2/44 | 2/43 | - | 1/45 | 26/48 | 25/48 | 19/48 | 17/47 |
| **Ovaries** | | | | | | | | |
| Cyst | - | - | - | - | 10/49 | 7/48 | 9/48 | 13/48 |
| **Pituitary** | | | | | | | | |
| Cyst | 16/47 | 13/46 | 12/49 | 8/47 | 30/49 | 25/48 | 29/48 | 24/47 |
| Adenoma | 24/47 | 30/46 | 27/49 | 23/47 | 40/49 | 43/48 | 39/48 | 41/47 |
| **Skin (treated)** | | | | | | | | |
| Acanthosis | - | 5/46* | 4/49 | 16/47* | 1/49 | 4/48 | 6/47* | 12/46* |
| Hyperkeratosis | 22/47 | 24/46 | 32/49 | 37/47* | 3/49 | 10/48* | 10/47* | 22/46* |
| **Brain** | | | | | | | | |
| Compression | 3/47 | 7/46 | 5/49 | 8/47 | 26/49 | 23/48 | 22/48 | 24/47 |
| **Colon** | | | | | | | | |
| Parasitism | 13/47 | 14/46 | 10/49 | 10/47 | 3/49 | 3/48 | 6/48 | 4/47 |
| **Heart** | | | | | | | | |
| Degeneration/Fibrosis/ Cardiomyopathy | 40/47 | 37/46 | 44/49 | 40/47 | 28/49 | 32/48 | 27/48 | 30/47 |

| Microscopic Examination of Selected Tissues (Incidences) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Organ & Lesion | Males | | | | Females | | | |
| **Dose (mg/kg/day)** | 0 | 50 | 100 | 200 | 0 | 50 | 100 | 200 |
| **Adrenals** | | | | | | | | |
| Congestion | 4/47 | 2/46 | 1/49 | 11/47* | 1/49 | - | 1/48 | 2/47 |
| Degeneration, cystic | 4/47 | 3/46 | 10/49 | 5/47 | 43/49 | 41/47 | 44/48 | 34/47 |
| Hemorrhage | 6/47 | 3/46 | 9/49 | 3/47 | 40/39 | 40/47 | 41/48 | 26/47 |
| Hyperplasia, cortical | 10/47 | 2/46 | 7/49 | 11/47 | 5/39 | 5/47 | 4/48 | 4/47 |
| Vacuolization | 12/47 | 18/46 | 17/49 | 17/47 | 18/39 | 21/47 | 17/48 | 21/47 |
| Pheochromocytoma | 10/47 | 3/46 | 9/49 | 12/47 | 1/39 | 1/47 | - | - |

*Statistically significant from control ($p \leq 0.05$)
- means that none were observed in that group.

## III. DISCUSSION

A. Investigators Conclusions - Survival, body weight, food consumption, clinical signs, hematology, organ weights, and gross pathology parameters were unchanged following dermal exposure to KBR 3023 in rats. Cystic degeneration of the liver in the 2-year high-dose males was observed, but no corroborating liver histopathological data were obtained. Acanthosis and/or hyperkeratosis of the treated skin across all doses in the 1- and 2-year animals was also observed. The chronic LOAEL was not observed. The chronic NOAEL is 200 mg/kg/day.

There was no evidence of a carcinogenic effect in rats after repeated dermal exposure to KBR 3023 for up to 24 months.

B. Reviewer's Discussion/Conclusions - Male and female rats (50/dose) were treated dermally with undiluted KBR 3023 (technical, 96.7-98.5% a.i.) at 0, 50, 100, or 200 mg/kg/day on 5 consecutive days/week for 24 months. In addition, 10-20 rats/sex/group were terminated at 12 months.

Survival, body weights, food consumption and efficiency, and absolute and relative organ weights for both sexes at all doses were unaffected by treatment with KBR 3023. Clinical observations, hematological parameters, and gross findings were also unaffected by treatment. In the 2-year males, there was a dose-dependent increase in the incidence of liver cystic degeneration (8/47, 11/46, 14/49, 20/47, in controls, low-, mid-, and high-dose groups, respectively; statistically significant [$p<0.05$] in the high-dose group only). These findings were not corroborated by changes in organ weight or in blood chemistry parameters.

No increases in the incidences of any neoplasm were observed in the dosed animals.

The dose levels used in this study were from an EPA approved protocol.

**The chronic LOAEL was not observed. The chronic NOAEL is 200 mg/kg/day.**

The submitted study is classified as **acceptable (§83-5)** and satisfies the guideline requirements for a combined chronic/oncogenicity study in the rat.

C. Study deficiencies -Data pertaining to the neck and feet lesions should have been more adequately presented. The final in-life date was not specified. These deficiencies are minor and would not change the conclusions of this review.