CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Cumyluron

Chemical Code #: 5986, **Tolerance #:** 53067
SB 950 # NA

Date: 9/8/09

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated
Chronic toxicity, dog:	No data gap, no adverse effect indicated
Oncogenicity, rat:	No data gap, no adverse effect indicated
Oncogenicity, mouse:	No data gap, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect indicated
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, adverse effect indicated
Chromosome effects:	No data gap, adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 240790 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T090908
Revised by R. Pan, 9-8-09

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 53067-0057, 240768, Chronic oral toxicity Study; 835; Rats; Biosafety Research Center, Iwata-Gun, Japan, Experiment Number 1132 (109-013); 3/12/92; Enomoto, M.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Five groups of 80/sex rats were orally administered by diet admixture with 0, 50, 200, 800, and 1600 ppm of JC-940 for 104 consecutive weeks. [Mean chemical uptake: males: 0, 2.67, 10.82, 43.62, 90.82 mg/kg/day; females: 0, 3.40, 13.52, 54.73, 112.57 mg/kg/day]. No access mortality occurred during the study. Body weight decrease was noted in the 1600 ppm group in both sexes, blood chemistry showed decreased GOT, GPT, and LDH in both sexes at weeks 26 and 52 in the 800 and 1600 ppm groups, the effects were less evident at week 78, with only LDH showing a decrease. Absolute and relative organ weights of liver and kidney had treatment related increase at 800 and 1600 ppm groups. **NOEL (M/F):** 50 ppm [M: 2.67 mg/kg/day; F: 3.4 mg/kg/day] for no effect on body weight, blood chemistry, liver and kidney weight, histological findings and nonneoplastic and neoplastic findings. **No oncogenic effects. Study acceptable** (Pan, 5/15/09).

CHRONIC TOXICITY, RAT

Study not submitted.

CHRONIC TOXICITY, DOG

** 53067-0056, 240767, Chronic oral toxicity Study; 831; Beagle Dogs; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki 303, Japan, Laboratory project ID: IET 88-0049; 7/17/91; Ebino, K.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of 5/sex beagle dogs were compulsively administered by gelatinous capsule with 0, 1, 10, and 100 mg/kg/group of JC-940, once daily for 52 weeks. Mortality: one female in 100 mg/kg/day group was killed *in extremis* and 1 male from 1 mg/kg/day group was found dead at week 23. The female animal which was killed *in extremis* showed clinical signs including decreased and loss of appetite, weakness, abnormal respiratory sound and decreased spontaneous motor activity with no recovery. There were other clinical signs that were sporadic and not treatment-related. NOEL: 1 mg/kg/day for the significantly increased incidences of liver centrilobular hepatocellular swelling in both males and females at 10 mg/kg/day group. **Study acceptable** (Pan, 4/29/09).

ONCOGENICITY, RAT

Study not submitted

ONCOGENICITY, MOUSE

** 53067-0058, 240769, Carcinogenicity Study; 832; Mice; Biosafety Research Center, Tokyo, Japan, Experiment Number 1131 (109-102); 4/10/92; Inoue. H.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of 70/sex mice were orally administered by diet admixture with 0, 100, 600, and 1200 ppm of JC-940 for 104 consecutive weeks. [Mean chemical uptake: males: 0, 14.4, 87.3, and 178 mg/kg/day; females: 0, 17.7, 109, and 219 mg/kg/day]. No excessive mortality occurred during the study. Body weight and food consumption was not affected by treatment. Hematology examinations showed decreased white blood cells in 1200 ppm males at 52, 78 and 104 weeks; absolute and relative spleen weight decrease was noted in the 1200 ppm group females at week 104; increased foci/hyperplasia in liver was seen in 1200 ppm group females at week 104; increased hepatocellular adenoma in liver was observed in 1200 ppm group of both sexes at weeks 79-104. **NOEL:** 100 ppm for no effects on any parameters from control was observed. **Study acceptable** (Pan, 5/26/09).

REPRODUCTION, RAT

** 53067-0055, 240766, Two-Generation Reproduction Study; 834; Rat; Biosafety Research Center, Iwata-Gun, Shizuoka 437-12, Japan, Experimental Number 1133 (109-019); 5/15/91; Enomoto, M.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of 25/sex rats were administered by dietary admixture to 0, 100, 600, and 3600 ppm of JC-940, respectively, from days 7-17 of gestation.[Mean test substance intake for males: 0, 8.12- 9.69, 49.3- 58.7, 279.5-315.4 mg/kg/day, for females: 0, 6.89- 14.22, 40.3- 87.8, 246.9- 507.0 mg/kg/day at growth period.]. Mortality: F0: 7/25 males and 3/25 females in the 3600ppm group; F1: 47/49 males and 45/46 females of the 3600 ppm group. The remaining female was found dead after copulation. Accidental deaths including 1 animal at 100 ppm and 3 animals at 3600 ppm were reported. Clinical signs in this group included wasting, subnormal temperature and piloerection in both sexes. In addition, dead or moribund-sacrificed animals showed hypokinesia and tremor. NOEL: 600ppm for general toxicological effect and reproductive effect: due to the mortality, reduced body weight, food consumption, food efficiency, gross and histological findings at sacrifice or necropsies, lowered fertility and gestation indexes at 3600 ppm. NOEL for developmental toxicity: 600 ppm for the decrease of body weight gain in 3600 ppm group. **Study acceptable** (Pan, 4/24/09).

** 53067-0079, 240790, Two-Generation Reproduction Study (Dose-Finding Study); 834; SD (SPF) Rat; Biosafety Research Center, Foods, Drugs, and Pesticides, 1-2-1 Marunouchi Chiyoda-Ku, Tokyo, Japan, Experimental Number 1137 (109-018); 1/31/90; Enomoto, M.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Five groups of 5/sex rats were administered by dietary admixture to 0, 160, 800, 1600 and 4000 ppm of JC-940, respectively, 4 weeks before mating, through mating, gestation, and lactation periods. Mean test material intake (pg 11): [M: 0, 10.43, 52.03, 102.02 and 261.81 mg/kg/day, respectively; F: 0, 12.17-22.15, 52.62-112.99, 108.23-233.14 and 261.75-534.67 mg/kg/day, respectively]. F0: Increased absolute liver weight in the 1600ppm group or higher dose groups females and increased relative liver weight in the 800ppm or higher dose groups. F1: body weight decrease in 4000ppm group in both males and females on day 21 after birth. NOEL for parent animals: 160ppm, for pups: 1600ppm. 4000ppm or lower doses were selected for the two-generation reproduction toxicity study in rats. **Study Supplemental**. (Pan, 8/31/09).

TERATOLOGY, RAT

** 53067-0049 240760, Teratogenicity Study; 833; Rat; Biosafety Research Center, Iwata-Gun, Shizuoka 437-12, Japan, Experimental Number 1134 (109-015); 3/13/91; Agita, K.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of twenty-five rats were administered by gavage (in corn oil) to 0, 14.3, 100, and 700 mg/kg of JC-940, respectively, from days 7-17 of gestation. Since JC-940 did not affect dams or fetuses at the high dose of 700 mg/kg, an additional study was carried out using the maximum possible preparation dose of 1500 mg/kg. **Maternal NOEL** = 1500 mg/kg/day since no treatment related effects were observed in body weights, food consumption, mean absolute and relative organ weights, gross findings at necropsy, mean number of implantation, fetal and placenta weights. **Developmental NOEL** = 1500 mg/kg/day since no treatment related effects were observed in number of live fetus, external, skeletal and visceral examinations of fetuses from this group. **Study acceptable.** (Pan, 4/1/09)

** 53067-0052, 240763, Teratogenicity Study; 833; Rat; Biosafety Research Center, Iwata-Gun, Shizuoka 437-12, Japan, Experimental Number 2691 (109-023); 12/1/95; Tanaka, R.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Two groups of 25 rats were administered by gavage (in

1% methylcellulose) to 0 and 1000 mg/kg/day of JC-940, respectively, from days 7-17 of gestation. Neither death of dams nor treatment-related clinical signs were observed. Body weight change and cumulative food consumption of dams showed no treatment related effects. Gross findings at cesarean section were sporadical and not treatment-related, including red patches/zones in the thymus, reddish thymus, red and colored (brown) patches/zones in the lungs and malformative nodule of the liver in both groups. The mean absolute and relative organ weights showed no treatment-related effects. No treatment related effects on reproductive findings in dams and observations of their fetus. **Maternal NOEL:** 1000 mg/kg due to no treatment related effects in body weight, food consumption, gross findings at C-section and organ weight measurements. **Developmental NOEL:** 1000 mg/kg due to no treatment related effects in external, skeletal and visceral observations. **Study acceptable.** (Pan, 4/9/09)

TERATOLOGY, RABBIT

** 53067-0048 240759, Teratogenicity Study; 833; Rabbit; Biosafety Research Center, Iwata-Gun, Shizuoka 437-12, Japan, Experimental Number 2692 (109-024); 12/15/95; Tanaka, R.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Seventeen, 15, 15, and 16 rabbits were administered by gavage (in 1% methylcellulose) to 0, 100, 300, and 1000 mg/kg/day of JC-940, respectively, from days 6-18 of gestation. **Maternal NOEL** = 300 mg/kg/day due to increased mean absolute and relative spleen weights in the 1000 mg/kg group, the abortion in one of the dams from this group and the resulted necropsy findings of colored patches/zones in the lungs. **Developmental NOEL** = 1000 mg/kg/day since no treatment related effects were observed in number of live fetus, external, skeletal and visceral examinations of fetuses from this group. **Study acceptable.** (Pan, 3/25/09).

** 53067-0050, 0051, 240761&240762, Teratogenicity Study and Amendment; 833; Rabbit; Biosafety Research Center, Iwata-Gun, Shizuoka 437-12, Japan, Experimental Number 1136 (109-017); 10/3/90, 8/22/94; Hagita, K.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of fifteen rabbits were administered by gavage (in corn oil) to 0, 60, 120, and 300 mg/kg/day of JC-940, respectively, from days 6-18 of gestation. **Maternal NOEL** = 300 mg/kg/day since no treatment related effects were observed in body weights, food consumption, mean absolute and relative organ weights, gross findings at necropsy, mean number of implantation, fetal and placenta weights. **Developmental NOEL** = 300 mg/kg/day since no treatment related effects were observed in fetal weight, external, skeletal and visceral examinations of fetuses from this group. **Study acceptable.** (Pan, 4/2/09)

** 53067-0054, 240765, Teratogenicity Study (Dose-Finding Study); 833; Rabbits; Biosafety Research Center, Iwata-Gun, Shizuoka 437-12, Japan, Experimental Number 1135 (109-016); 3/12/90; Hagita, K.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of five rabbits were administered by gavage (in corn oil) to 0, 60, 120, and 300 mg/kg/day of JC-940, respectively, from days 6-18 of gestation. No treatment related mortality was observed. Clinical observations of 1 animal in 300 mg/kg group that died due to administration error showed dyspnea and congestion in the eyes. Body weight change of dams showed no treatment related effects. Gross findings at cesarean section were spontaneous and not treatment-related, including colored patch/zone in lung in some animals of all groups, reddish lung in 1 animal of 300 mg/kg group, and red patch/zone of lung in 1 animal each of the 120 and 300 mg/kg groups. Kidney cyst was observed in 1 animal each of 60 and 300 mg/kg groups. The mean absolute and relative organ weights showed no treatment-related effects No treatment related effects on reproductive findings in dams and observations of their fetus. Therefore, a dose of 300 mg/kg/day (maximum possible dose) was considered appropriated as the high dose in the teratogenicity study of JC-940 in rabbits.

Study supplemental. (Pan, 4/6/09)

** 53067-0053, 240764, Teratogenicity Study (Dose-Finding Study); 833; Rabbits; Biosafety Research Center, Iwata-Gun, Shizuoka 437-12, Japan, Experimental Number 1133 (109-016); 1/10/90; Hagita, K.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of five rats were administered by gavage (in corn oil) to 0, 20, 100, 250, and 500 mg/kg/day of JC-940, respectively, from days 7-17 of gestation. No mortality or clinical signs were observed. Body weight change of dams and gross findings at cesarean section showed no treatment related effects. The mean relative liver weight was increased ($p<0.01$). No treatment related effects on reproductive findings in dams and observations of their fetus. **NO OBSERVED EFFECT LEVEL (NOEL):** 20 mg/kg for maternal since the slightly increased relative liver weight observed in 100 mg/kg and up groups. 500 mg/kg or higher for fetuses since no treatment related effects were observed in fetus. Therefore, 500 mg/kg dose was appropriate as the high dose in the teratogenicity study of JC-940 in rats. **Study supplemental.** (Pan, 4/8/09)

GENE MUTATION

** 53067-0060, 240771, Bacterial Reverse Mutation Assay; 842; Biosafety Research Center, Tokyo, Japan, Experiment Number 1127; 11/28/88; Nakajima, M.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; *S. Typhimurium* strains TA 100, TA 98, TA 1535, TA 1537, and *E. coli* WP2 *uvr* A were treated with JC-940 at concentrations of 156, 313, 625, 2500 and 5000 ug/plate under conditions of direct method and activation method at 37ºC. In the direct method, the tester strains were treated with test material for 20 minutes followed by 48 hours incubation for colony formation on minimum glucose agar plates; in the activation method, the tester strains were treated with S9 fraction of rat liver homogenate and test material for 20 minutes and then incubated further for 48 hours for colony formation. Two replicates were performed for each treatment level. There were increases in numbers of revertant colony in the TA 100 and TA 1535 strains of *Salmonella typhimurium* without dose-response relationship. Confirmation examinations were carried out for these two strains at lower doses. **Possible adverse effects**: Revertant colonies in the TA 1535 strain were increased at 20 ug/plate compared to those of the solvent control, which was judged positive. Therefore, the test material was slightly positive for mutagenicity. Positive controls were functional. **Study acceptable** (Pan, 6/11/09).

CHROMOSOME EFFECTS

** 53067-0059, 240770, *In vitro* Mammalian Chromosome Aberration Test; 843; fibroblast cell line from CHL/IU; Biosafety Research Center, Tokyo, Japan, Experiment Number 1128; 5/29/89; Nakajima, M.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; A fibroblast cell line derived from the lungs of Chinese Hamster (CHL/IU) were treated with JC-940 at concentrations of 110, 220, 440, and 880 ug/mL under conditions of direct method for 24 or 48 hours and activation method at 37ºC. In the direct method, the cells were treated with test material for 24 or 48 hours; in the activation method, the cells were treated with S9 fraction of rat liver homogenate and test material for 6 hours and then incubated further for 18 hours. All of the cells were incubated for an additional 2 hours with Colcemid and fixed and prepared for evaluation. Two replicates were performed for each treatment level. There were no apparent treatment related increase in chromosomal aberration in the direct method treated cells, however, there were slight dose-dependent increases of chromosome aberration and polyploid cells in the activated method treated cells starting from 220 ug/mL. **Possible adverse effects**: Therefore, the test material, once metabolized, was slightly positive for mutagenicity. Positive controls were functional. **Study acceptable** (Pan, 5/29/09).

** 53067-0062, 240773, Micronucleus Test; 843; Mice; Kodaira Laboratories, The Institute of Environmental Toxicology 7-2, Suzuki-cho, Koraira-shi, Tokyo 187, Japan; 12/2/91; Matsumura, H.; JC-940, purity: 97.7%, Lot # 80430; Five male mice/group were dosed by intragastric gavage with 0 (0.5% carboxymethylcellulose sodium salt (CMC·Na) solution), 500, 1000, and 2000 mg/kg of JC-940 or positive control material: Mitomycin C (10mg/kg). The bone marrow smears were prepared 24 hours later based on the preliminary micronucleus test, the frequency of micronuleated polychromatic erythrocytes and ratio of polychromatic erythrocyte were examined. No significant increase in the frequency of micronucleated polychromatic cells or decrease of the polychromatic erythrocyte ratio was observed at any dose of the test substance. Marked increases of the frequency of micronuleated polychromatic erythrocytes were observed in the positive control group treated with mitomycin C. Therefore, JC-940 did not induce micronuclei in bone marrow cells of ICR (Crj: CD-1) male mice under the conditions of this study. **Study acceptable** (Pan, 6/22/09).

DNA DAMAGE

** 53067-0063, 240774, DNA Repair Assay (REC-ASSAY) with JC-940 in *Bacillus Subtilis* Spores- Experiment Number 1126; 844; *Bacillus Subtilis*; Biosafety Research Center, Tokyo, Japan, Experiment Number 1126; 10/17/88; Nakajima, M.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Spores of *Bacillus Subtilis* H17 Rec+ (DNA repair proficient strain) and M45 Rec- (DNA repair deficient strain) were used to investigate ability of JC-940 to induce DNA damage. JC-940 at solubility limit concentration by either direct (8800 ug/disk) or activation method (4400 ug/disk) didn't cause any growth inhibition, while the positive controls produced more than 4 mm-difference in the zone diameters of growth inhibition in both direct and activation methods. Therefore, JC-940 did not induce DNA damage under the conditions of this study. **Study Acceptable** (Pan, 6/23/09).

NEUROTOXICITY

Guideline study not submitted.

METABOLISM STUDY

** 53067-0065 240776, Metabolism study; 851; Rat; Ricerca, Inc., Department of Toxicology and Animal Metabolism, Painesville, Ohio; Project identification:89-0313, 4/2/93; Ho, M.D., Savides, MC, Johnson DB, Killeen JC, Jr.; A series of eight experiments were done to define the metabolism of JC-940 in rats. Each experiment was conducted with [Cl-Ph-^{14}C] JC-940. Some additional animals received [Ph-^{14}C] JC-940, at low (5 mg/kg) or high (500 mg/kg) doses. Both male and female rats were dosed by oral gavage. The distribution of radiolabel was determined 2 (Tmax), 24, 72 and 168 hours after single doses (high or low with 1 or 2 labels). Greater than 83% AD (administered dose) was in GI tract at 2 hours, while less than 12.63% AD, 0.97% AD and 0.12% AD was in tissues at 24, 72 and 168 hours, respectively. At 168 hours, more than 99% AD was excreted. Females excreted more radiolabel in the urine than males at low dose level ([Cl-Ph-^{14}C] JC-940: 28.4% F vs. 19.9% M; [Ph-^{14}C] JC-940: 20.6% F vs. 12.2% M). Similar amount of radiolabel was excreted by male and female animals at high dose ([Cl-Ph-^{14}C] JC-940: 8.9% M vs. 9.7% F; [Ph-^{14}C] JC-940: 3.4% M vs. 5.2% F). More radiolabel was excreted in urine in animals dosed with [Cl-Ph-^{14}C] JC-940 than those with [Ph-^{14}C] JC-940. More percentage of radiolabel was excreted in feces of high dose groups (85.76-96.02% AD) than in low dose ones (70.48-88.34% AD), regardless of radiolabel type. Higher dose groups also had lower radiolabel distribution in total tissues (0.01-0.04% AD) and carcasses (0-0.02% AD) than in low dose ones (tissues: 0.11- 0.12% AD, carcass: 0.05-0.08% AD), regardless of radiolabel type. At Tmax (2 hours after single dose), the tissues with the highest radiolabel besides GI tract and carcass, were

liver and kidney. Seven days after multiple low dose of JC-940 followed with [Cl-Ph-^{14}C] JC-940, less than 0.1%AD of radiolabel was present in any tissue, similar to the single low dose experiment, the radiolabel in carcasses (0.16-0.25% AD) were higher than that of the single doses (0-0.08% AD). The pharmacokinetics experiment was conducted with either high or low doses, at different termination times with [Cl-Ph-^{14}C] JC-940. The Tmax for blood and plasma was about 2 hours, Cmax in whole blood was about 11 to 21 times difference between the low and high doses (M: 0.25 vs. 5.21, F: 0.30 vs. 3.92. unit: ug equiv. / g). Bile duct cannulation was performed to determine the biliary excretion of radiolabel during the first 24 hours following the low dose [Cl-Ph-^{14}C] JC-940 administration. The average total biliary excretion was 7.78% AD for males and 6.52% AD for females. The percentage of radiolabel absorbed was 20.16% AD in male and 14.96% AD in females, 70.31% AD (M) and 82.60% AD (F) in GI tract. The radiolabel profiles for urine samples and feces samples were generated by HPLC analysis and compared between the 2 labeling positions. The profiles of the urine samples from low and high concentration groups with the same radiolabel were similar to each other. The difference between those of the 2 labeling positions suggests a cleavage between the 2 aromatic rings of the molecule in vivo. No parent compound, glucuronide or sulfate conjugates were detected in urines. 2-chlorohippuric acid, 2-chlorobenzoic acid, and cumyl urea have been unequivocally identified, and 2-chlorobenzylurea was identified in urine. Hydroxy JC-940, the sulfonic acid conjugate of JC-940, JC-940 and 2-chlorobenzyl urea were detected in the feces. A metabolic scheme was proposed in which oxidation of JC-940 was followed by a cleavage of the molecule to form two sets of aromatic rings, cumylurea and 2-chlorobenzoic acid, or 2-chlorobenzylurea and 2-phenyl-2-propanol. **Acceptable** (Pan, 7/21/09).

SUBCHRONIC STUDY

Subacute Toxicity Study in Rats

53067-0043 240752, Subacute toxicity; 821; Rat; Biosafety Research Center, Foods, Drugs, and Pesticides, Iwata-Gun, Japan, Experiment Number 1275, 7/11/90; Inoue, H.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of ten Fisher 344 rats/sex/group were exposed orally by dietary admixture to 0, 100, 600 and 3600 ppm JC-940 daily for 13 weeks. [M: 0, 7.0, 42.3, 257.0 mg/kg/day; F: 0, 7.7, 46.8, 280.0 mg/kg/day, respectively]. Mortality: 3/10 males and 7/10 females of the 3600 ppm group. Wasting and piloerection were observed in both sexes in 3600 ppm group; reduction on the mean body weights and food consumption were apparent in the 3600 ppm group since week 1, food efficiency was low until week 5 of dosing. The hematology evaluations showed decrease of red blood cell, hematocrit, hemoglobin values, Mean Corpuscular Volume, Mean Corpuscular Hemoglobin, and increased platelet and Differential leukocyte counts in the 3600 ppm group in both sexes. In the histopathological examination, findings including liver bile duct hyperplasia, kidney edema, fibrosis and transitional cell hyperplasia, dilated follicle in thyroid, atrophy of thymus, salivary gland and seminal vesicle/uterus, ovary and vagina were noted in some or most of the surviving animals in both sexes of the 3600 ppm group. Relative organ weights of brain, heart, liver, kidneys, spleen, adrenals and testis/ovary were increased in 3600 ppm group in both sexes. Blood chemistry showed increases of total cholesterol, total bilirubin, blood urea nitrogen, creatinine, potassium and inorganic phosphate in both sexes of 3600 ppm group. Urinalysis showed increased volume and decreased specific gravity in both sexes of 3600 ppm group. Gross findings at sacrifice included whole body wasting, thymus atrophy, granular kidney and small seminal vesicle/uterus and ovary in both sexes at 3600 ppm group. Autolysis was found in many organs in both sexes of dead or moribund animals. Histological findings of the dead or moribund included congested lung, dilated follicle of thyroid, liver necrosis, bile duct hyperplasia, kidney fibrosis, transitional cell hyperplasia, spleen, thymus and salivary gland atrophy in both sexes, uterus, vagina and ovary atrophy in females. **Rat**

13-Week Subacute Toxicity NOEL for systemic toxicity (M/F): =100 ppm (based on changes in relative liver and kidney weights and hematology parameters). **Study acceptable.** (Pan, 2/19/09)

Four-week Dose Toxicity Study in Rats

53067-0044 240755, Subacute toxicity; 821; Rat; Biosafety Research Center, Foods, Drugs, and Pesticides, Iwata-Gun, Japan, Experiment Number 1130, 11/30/88; Inoue, H.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Five groups of ten Fisher 344 rats/sex/group were exposed orally by dietary admixture to 0, 150, 500, 1500 and 5000 ppm JC-940 daily for 4 weeks. Mean test material intake: [M: 14.1, 47.1, 140.5, 343.3 mg/kg/day; F: 14.3, 47.9, 143.9, 373.9 mg/kg/day]. Mortality: 7/10 males and 7/10 females of the 5000 ppm group including 1/7 moribund females. Wasting and piloerection were observed in both sexes in 5000 ppm group; subnormal temperature and sluggishness was observed in 1 female rat in the 5000 ppm group in week 1 of study; reduction on the mean body weights, food consumption and food efficiency were apparent in the 5000 ppm group during the 4-week study interval. Relative organ weights of brain, heart, liver, kidneys, and adrenals were increased in 5000 ppm group in both sexes; those of liver and kidneys in males increased at dose level 500 ppm or more; in females relative weight of liver showed increase at dose level 1500 ppm or more; relative organ weights of spleen were increased in 1500 ppm or more in both sexes; relative organ weights of ovary were decreased at dose level of 1500 ppm or more. Gross findings at sacrifice included thymus atrophy, granular liver and kidney in 5000 ppm group in both sexes, testis and seminal vesicle atrophy in males and spleen, ovary and uterus atrophy in females at 5000 ppm group. Gross findings of the dead included thymus atrophy, autolysis of small and large intestine of both sexes, brain autolysis in 1/7 males and liver malformative nodule in 1/6 females. **Rat 4-Week Dose Toxicity Study toxic level for chronic toxicity and carcinogenicity study** (M/F): ≤ 1000 ppm. **Study supplemental.** (Pan, 2/25/09)

Subacute Toxicity Study in Mice

53067-0045 240756, Subacute toxicity; 821; Mice; Biosafety Research Center, Foods, Drugs, and Pesticides, Iwata-Gun, Japan, Experiment Number 1129(109-010), 6/16/89; Inoue, H.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Five groups of ten Fisher 344 rats/sex/group were exposed orally by dietary admixture to 0, 100, 400, 1600, 6400 and 25600 ppm JC-940 daily for 13 weeks. [Mean test substance intake M; 0, 16.5, 67.5, 273.0, 1116.0, 4576 mg/kg/day; F: 0, 20.5, 78.8, 322.0, 1273.0, 5295.0 mg/kg/day, respectively.] No mortality. Wasting and piloerection were observed in 1 male in 25600 ppm group for the first 3 weeks; no treatment-related effects on the mean body weights, food consumption and food efficiency in any of the dosing groups. Mean hematology findings in both sexes included treatment-related increase of platelet count and decrease of white blood cells count. Blood chemistry showed decreased total cholesterol and increased alkaline phosphatase, mean absolute and relative liver weights were increased in 25600 ppm group in both sexes; Gross findings at sacrifice included brown liver in 25600 ppm group in both sexes, histological findings included liver cytological alteration in 6400 ppm group in males and 25600 ppm group in both sexes, decreased kidney fatty change in males at 6400 ppm and more, and decreased adrenal spindle cell hyperplasia at 6400 ppm group. No observed effect level (M&F): 400 ppm [based on relative liver weight and histological changes]. **Study acceptable.** (Pan, 3/2/09)

13-Week Subchronic Oral Toxicity Study in Beagle Dogs

53067-0046 240757, Subchronic toxicity; 821; Beagle Dogs; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki 302-02, Japan, Laboratory Project ID: IET 88-0047; 2/26/90; Ebino, K.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Four groups of 4 beagle dogs/sex/group were exposed orally by compulsory administration to 0, 3, 30, and 300

mg/kg/day JC-940 daily for 13 weeks. No mortality. Vomiting and loose stool were observed in both sexes, diarrhea was observed in 1 male; skin hair loss and scab, mucous stool and bloody discharge from vulva in females. No treatment-related effects on the mean body weights, food consumption mean hematology, urinalysis and ophthalmological examinations in any of the dosing groups. Blood chemistry showed increased alkaline phosphatase in the 300 mg/kg/day dosing group at 7 and 13 weeks of treatment in both sexes; increased total bilirubin in 300 mg/kg/day dosing group males at 7 and 13 weeks of treatments. Liver congestion was found in 300 mg/kg/day group females; both absolute and relative liver weight were increased in 300 mg/kg/day group of both sexes and 30 mg/kg/day males at terminal kill; liver centrilobular hepatocellular swelling was found in both sexes of 30 and 300 mg/kg/day groups at the histopathological examinations. No observed effect level (M/F): 3 mg/kg/day based on centrilobular hepatocellular swelling. **Study acceptable.** (Pan, 3/5/09)

Dog Oral Toxicity Dose Range-Finding Study

53067-0047 240758, Subchronic toxicity; 821; Beagle Dogs; Mitsukaido Laboratories, The Institute of Environmental Toxicology, Ibaraki 302-02, Japan, Laboratory Project ID: IET 88-0045; 3/15/89; Ebino, K.; JC-940, a. i.: Cumyluron, purity: 97.7%, Lot # 80430; Five groups of 1 beagle dog/sex/group were exposed orally by compulsory administration to 0, 30, 100, 300 and 1000 mg/kg/day JC-940 daily for 4 weeks. No mortality. Vomiting in the female of the 100 mg/kg/day group at week 4, and loose stool in the female at 1000 mg/kg/day group at week 4 were observed. No treatment-related effects on the mean body weights in males, treatment related decrease of body weight was observed in female beagle dogs. No treatment-related effects on the food consumption, mean hematology, urinalysis and ophthalmological examinations in any of the dosing groups. Blood chemistry showed treatment related increase of alkaline phosphatase at 2 and 4 weeks of treatment in both sexes. Liver congestion was found in 300 mg/kg/day group females and in 1000 mg/kg/day group males and females; both absolute and relative liver weight were increased in 30 mg/kg/day or upper groups of both sexes at terminal kill; liver centrilobular hepatocellular swelling was found in both sexes of 100 mg/kg/day and upper groups at the histopathological examinations. **NOEL (M/F) not determined. Study supplemental.** (Pan, 3/9/09)