CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
COPPER 8-QUINOLINOLATE

Chemical Code # 000159, DPN # 50342
SB 950 # 334
October 15, 2004

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through 144537 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T041015
Stanton Morris, 10/15/04

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

Note: The test article is spelled "copper 8-quinolinoleate" and "copper 8-quinolinolate" by DPR and industry, respectively. The test article is spelled "copper 8-quinolinolate" in the toxicology summary and review sheets.

COMBINED, RAT

50342-025; 144531; "Two-Year Dietary Administration in the Rat, K-37", Project No.854-104; K. Tomono; Hazleton Laboratories America, Inc.; March 26, 1976. Report stamped "rough draft" and not signed. Copper 8-Quinolate (K-37 Technical, 96% stated purity) was fed in dietary mixtures at 0, 5, 20, 100, 500 or 2000 ppm to groups of 5 and 25 albino Charles River rats/sex/group for 52 and 102 weeks, respectively. Kidney and liver copper levels were increased at 2,000 ppm (NOEL = 500ppm). A **possible adverse effect** was indicated by an increased incidence of testicular interstitial tumors in males at 2000 ppm (chi square test, P = 0.399). The study is unacceptable because submissions were inadequate for: analysis of the test article and dosing material; environmental conditions; randomization; dose rationale; body weight; food consumption; hematology; serum chemistry; urinalysis; ophthalmology; organ weights; histopathology; individual data for body weight, food, consumption and survival; no historical control data for tumors; rats had chronic respiratory disease; and QA and GLP sign-offs. The study is not upgradeable (J. Kishiyama and S. Morris, 10/29/03).

50342-19; 051099: Duplicate of DPR doc. # 50342-025, rec. # 144531**.**

50342-011; 026423: 2/18/49; Copper 8-Quinolinolate, 10%, at concentrations of 0 (oleic acid) and 0.2 cc was administered daily for one year to six female rats. Brief summary with no data. Unacceptable (J. Gee, 8/1/85).

CHRONIC TOXICITY, RAT

See COMBINED, RAT above.

SUBCHRONIC TOXICITY, RAT

50342-019; 051098; "A 13-Week Toxicity Study with Ro 17-0099/000 in Mice p.o. (feed admix)," RRB-104 777; S. Buser; F. Hoffman-La Roche & Co., Ltd., Basle, Switzerland; 2/28/83. Groups of 16 SPF Albino mice/sex were fed dietary mixtures of Copper 8-Quinolinolate (Ro 17-0099/00, 99.9% purity) at 0, 100 or 300 mg/kg/day for 13 weeks or stepwise increasing doses of 30 (males, weeks1-5; females, weeks1-4), 600 (males, weeks 6-10; females, weeks 5-9) and 1,000 (males, weeks11-13; females, weeks 10-13) mg/kg/day. Actual average weekly intake for both sexes was 0, 88-113 or 256-323 mg/kg/day or 29-37 (males, weeks1-5; females, weeks1-4), 523-736 (males, weeks 6-10; females, weeks 5-9) and 809-1106 (males, weeks11-13; females, weeks 10-13) mg/kg/day. There were no treatment-related effects on clinical signs, survival, morbidity, body

weight, food consumption, ophthalmology, hematology, urinalysis, gross pathology, organ weights, or histopathology. Serum alkaline phosphatase levels were elevated in males at 30-600-1,000 mg/kg/day. Dysproteinemia was seen in females at 300 mg/kg/day and both sexes at 30-600-1,000. Livers and spleens of both sexes had elevated levels of copper at 30-600-1,000 mg/kg/day. (NOEL = 100 mg/kg/day). No adverse effect was indicated. The study was unacceptable and not upgradeable because of inadequate analysis of the test article and dosing material; rationale for the doses; serum chemistry; organ weights and histopathology (S. Morris and J. Gee, 10/15/04).

CHRONIC TOXICITY, DOG

50342-20; 051100; **"**Two-Year Dietary Toxicity Study in Dogs, K-37 Technical, Final Report," Project No. 854-103; Mulligan, T., Project Director; Hazleton Laboratories America, Inc, Vienna, VA; 2/18/76. Dietary mixtures of Copper 8-Quinolinolate (K-37 Technical, stated purity 96%, no batch No.) were feed to groups of 4 beagle dogs/sex for two years at concentrations of 0, 10, 40, 200, 1,000 or 4,000 ppm. The 4,000 ppm groups were maintained at 4,000 ppm for weeks 1, 2, 8 and 9; 1000 ppm for week 3; 2,000 ppm for week 4; and 3,000 ppm for weeks 5, 6, 7, and 10 thru 104. One dog/sex/group was sacrificed at 52 weeks and the remainder at 104 weeks. Two dogs/sex died or were sacrificed in extremis at 4,000 ppm. All dogs were examined for gross and histopathology abnormalities. Increased organ copper content was seen at interim and terminal sacrifice at 10, 40, 200, 1,000 and 4,000 ppm in both sexes. Treatment-related effects seen in both sexes at 4,000 ppm were decreased body weight gain and food consumption, increased serum liver enzymes, enlarged mesenteric lymph nodes, discolored livers, and distended gall bladders. (NOEL = 1,000 ppm). No adverse effect was indicated. The study is unacceptable but upgradeable with adequate submissions of analytical data for the test and dosing materials, the age of the dogs, environmental conditions of the kennel and ophthalmology data (J. Kishiyama and S. Morris, 5/21/03).

ONCOGENICITY, RAT

See COMBINED, RAT above.

ONCOGENICITY, MOUSE

50342-027; 144533; "K-37: 80 Week Oral (Dietary) Carcinogenicity Study in the Mouse," TOM/2B/93; R.F.A. Husband; Toxicol Laboratories Limited, England; 3/9/94. Groups of 50 Crl: CD-1(ICR)BR mice/sex were fed dietary mixtures of Copper 8-Quinolinolate (K-37 Technical, 97.2% stated purity) at 0, 100, 400, 1500 or 6000 ppm for 80 weeks equivalent to 0, 14.5, 57.2, 207.7 and 855.8 mg/kg/day for males and 0, 16.1, 66.2, 246.2 and 1051.7 mg/kg/day for females. Satellite groups of 10 additional mice/sex were fed diets containing 0 or 6000 ppm for 52 weeks. No significant treatment-related effects were observed on mortality, clinical signs, food consumption and body weight gain. Treatment-related effects included: increased female spleen and kidney weights at 6000 ppm; stomach ulceration , hyperkeratosis and epithelial hyperplasia at 1500 ppm in males and both sexes at 6000; reduced hemoglobin and packed cell volume in both sexes at 1500 and 6000 ppm groups; and

increased platelet count and ALP in females at 6000 ppm (NOEL = 400 ppm). A **possible adverse effect** was indicated by increased uterine endometrial sarcomas in females at 6000 at ppm (3/50 versus 0/50 at 0 ppm). The study was unacceptable but possibly upgradeable with submission of an adequate rationale for the doses used and historical data for uterine endometrial sarcomas (J. Kishiyama and S. Morris, 2/17/04).

50342-026; 144532: "K37, 13 Week Oral (Dietary) Rangefinding Study in the Mouse," TOM/1/90; M. Coleman and P.J.Y. Taupin; Toxicology Laboratories Limited, England; 11/90. Groups of 10 Crl: CD-1(ICR)BR mice/sex were feed dietary mixtures of Copper 8-Quinolinolate (K-37 Technical, 97.2% stated purity) at 0, 300, 1000, 3000, or 6000 ppm for13 weeks. Treatment-related effects included: transient initial decreases in palatability and body weight gain in both sexes at 3000 and 6000 ppm and decreased platelet counts in females at 3000 and 6000 ppm. No worksheet was done (S. Morris, 2/17/04).

REPRODUCTION, RAT

50342-020; 051293; "Final Report, Two Generation Reproduction Study in Rats," Project No. 854-105; T. Mulligan; Hazleton Laboratories America, Inc.; 5/30/75. Copper-8-Quinolinolate (K-37, unstated purity, no batch No.) was continuously fed in the diets of Sprague-Dawley rats for two generations at concentrations of 0, 20,100, or 500 ppm. Twenty-five adult rats/sex/group (P1) were exposed for 13 weeks then through two matings to produce the F1a and F1b litters. Twenty-five F1b weanlings/sex/group (P2) were exposed for nine weeks then through two matings to produce the F2a and F2b litters. Five F1b and 10 F2b litters were delivered by C-section and evaluated for teratological effects. All F1a and F2a, 20 F1b and 10 F2b litters were culled to 4 pups/sex 24 hours after birth and evaluated for postnatal development until sacrifice at weaning except 4 F1b litters and 5 F2b litters were evaluated for growth and development and sacrificed 5 weeks postnatal and 3 months post weaning, respectively. One-third of the F1b offspring, all F2b offspring and all dead moribund animals were examined for gross pathology. There were no treatment-related effects on adult, reproductive, developmental or teratological parameters. No adverse effect was indicated. The study is unacceptable put possibly upgradeable with adequate submissions of analytical and stability data for the test article and dosing materials; the P1 rats' ages; environmental conditions the rats were housed in; a rationale for dose selection; individual data; histopathology data for parental reproductive organs; and a complete and legible copy of the report (J. Kishiyama and S. Morris, 7/15/03).

TERATOLOGY, RAT

50342-024; 143391; "Ro 17-0099/000 (Copper 8-Quinolinolate): Oral (Gavage) Embryo Toxicity in the Rat with the Fungicide Ro 17-0099/000 (Segment II Study with Post Natal Evaluation)," Lab. Proj. I.D. B-154'980: C. Bacchus; F. Hoffmann-La Roche Ltd., Basel, Switzerland; 1/13/92. Copper 8-Quinolinolate (Ro 17-0099/000, stated purity 98.5%, 0.5% carboxymethylcellulose vehicle) given by oral gavage at concentrations of 0, 50, 200, or 800 mg/kg/day to 36 mated female Fu-Albino rats/group on gestations days 6 through 15. At least 20 pregnant females/group (sub-group I) were sacrificed on gestation day 20. The remaining 13 – 15 females/group (sub-group II) were allowed to litter, rear pups to weaning at which time pups and dams were sacrificed. Dams and pups from sub-groups I and II were examined for reproductive, teratological and

developmental effects. Maternal NOEL = 200 mg/kg/day (decreased body weight gain, piloerection and facial encrustation at 800 mg/kg/day). Developmental NOEL ≥ 800 mg/kg/day (no specific findings). There were no adverse effects indicated. The study was unacceptable as but possibly upgradeable with submission of adequate data on analysis of the test article and dosing material and food consumption (J. Kishiyama and S. Morris, 12/8/03).

TERATOLOGY, RABBIT

50342-028; 144534; "K37: Rabbit Teratology Study," Ref. No. AKJ/6/87; P. Ridgway et al.; Toxicol Laboratories Limited, England; August 1987. Groups of 16 mated female New Zealand White rabbits were treated by oral gavage with Copper 8-Quinolinolate (K37 Technical, lot 382 [61.6.3], stated purity 96.5%, 0.5% carboxymethyl cellulose vehicle) at 0, 7, 15, or 30 mg/kg/day on gestation days 7 to 19. Clinical signs, bodyweights and food consumption were recorded. The rabbits were killed on gestation day 28 and necropsied. The fetuses were subjected to detailed external, visceral and skeletal examinations. Decreased food consumption for gestation days 7 thru 11 appeared to be treatment-related at 30 mg/kg/day (maternal NOEL = 15mg/kg/day). No other treatment-related maternal or fetal effects were reported (developmental NOEL ≥ 45 mg/kg/day, from pilot study Ref. No. AKJ/5/87). No adverse effect was indicated. The study is unacceptable but possibly upgradeable with submission of adequate analysis of the test material (J. Kishiyama and S. Morris, 12/8/03).

GENE MUTATION

Although no single study has been evaluated as acceptable, the collective data from the several studies with *Salmonella* indicating a possible mutagenic effect are adequate to fulfill data requirement.

50342-011; 026424; "Mutagenic Evaluation of Cunilate 2174CO, Final Report;" Litton Bionetics, Inc., Kenisington, MD, July 1977. Copper-8-Quinolate (Culinate 2174CO) was evaluated for its effect on the mutation frequency of histidine auxotrophic bacteria strains to prototrophy. Tests were carried out at 0, 0.001, 0.01, 0.1, 1.0 and 5.0 mg/plate, with and without metabolic activation (S9 fraction of Arochlor 1254-induced rat liver homogenates)using *Salmonella typhimurium* strains TA1538, TA98, TA100, Ta1535, and TA1537 and *Saccharomyces* strain D4. Toxicity was observed at 5 µg/plate with and without S-9 Mix. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical date for the test material, no repeat experiment, no individual data and insufficient information (J. Gee, 8/1/85; S. Morris, 2/23/04).

50342-029; 144535; "Mutagenicity Tests of Organic Copper (Copper 8-Quinolinolate) Using Bacteria;" Y. Shirasu, M. Moritani, and K. Kato; Toxicology Division, Institute of Environmental Toxicology; September 12, 1977. Copper 8-Quinolinolate (95% stated purity) was evaluated for its effect on the mutation frequency of histidine auxotrophic strains of *Salmonella typhimurium* (TA1535, TA100, TA1537, TA1538, T98) and a tryptophan auxotrophic strain of *Escherichia coli* (WP2 hcr^-) to prototrophy. One trial was performed with duplicate plates of bacteria that were plated on minimum agar with or without metabolic activation (S9 supernatant of liver homogenates from Aroclor 1254-induced male SD rats) and test material at 0.1, 0.5, 1, 5, and 10 µg/plate. Positive controls were adequate. There was no treatment-related effect on mutation rate.

No adverse effect was indicated. The study was unacceptable and not upgradeable because there were only 1 or 2 plates per concentration per strain (J. Kishiyama and S. Morris, 1/6/04).

50342-029; 144535; "Mutagenicity Tests of Organic Copper (Copper 8-Quinolinolate) Using Bacteria;" Y. Shirasu, M. Moritani, and K. Kato; Toxicology Division, Institute of Environmental Toxicology; September 12, 1977. Groups of 5-6 ICR male mice were given Copper 8-Quinolinolate (95% stated purity) by oral gavage at 0 (5% gum arabic), 200 and 600 mg/kg at 0 and 24 hours. The latter dose was immediately followed by intraperitoneal injection with histidine-requiring *Salmonella typhimurium* strain G46. Three hours later, the mice were and given intraperitoneal lavages of 1/15M phosphate buffer (pH 7.0). The bacterial solution was mixed with biotin-free soft agar, overlaid on minimum agar plates in triplicate, incubated for 2 days at 37˚C and scored for prototrophic colonies. Positive control was adequate. There was no treatment-related effect on mutation rate. No adverse effect was indicated. The study was unacceptable but and not upgradeable (J. Kishiyama and S. Morris, 1/6/04).

50342-029; 144536; "Mutagenicity Tests of Organic Copper (Copper 8-Quinolinolate) Using Bacteria, Report of Additional Test;" Y. Shirasu, M. Moritani, and K. Kato; Toxicology Division, Institute of Environmental Toxicology; 1/12/78. Copper 8-Quinolinolate (95% stated purity) was evaluated for its effect on the mutation frequency of a histidine auxotrophic strain of *Salmonella typhimurium* (TA100) to prototrophy. Four trials were performed with duplicate pates of bacteria plated on minimum agar with or without metabolic activation (S9 supernatant of liver homogenates from Aroclor 1254-induced male SD rats) and test material at 0, 1, 5, 10, 20, 50, or 100 µg/plate. Growth inhibition was reported for 50 and 100 µg/plate with out metabolic activation. A possible adverse effect was indicated by increased revertant colonies at 10 and 20 µg/plate with metabolic activation. Positive controls were adequate. The study was unacceptable and not upgradeable (J. Kishiyama and S. Morris, 1/6/04).

50342-020; 51294; "Metabolic Activation Test to Assess the Potential Mutagenic Effect of Copper 8-oxyquinolate;" D.J.N. Hossack, M. Richold, E. Jones, and R.P. Bellamy; Huntingdon Research Centre, Cambridgeshire, England; 4/17/78. Copper 8-oxyquinolate (unstated purity, DMSO vehicle) was tested at 0 (DMSO), 2, 20, 200, or 2000 µg/well with and without metabolic activation (S9 fraction of liver homogenates from Aroclor 1254-induced CFY rats). The mutation rate of bacteria from histidine auxotrophy to protrotrophy was measured using *Salmonella typhimurium* tester strains TA1535, TA100, TA1538, TA1537 and T98. One sample/treatment/strain with or without S9 was plated in triplicate on histidine deficient media, incubated for 48 hours and scored for prototrophic (revertant) bacterial colonies. A possible adverse effect was indicated by an increased number of revertant colonies of strain TA 1537 seen at 2000 µg/plate. The study was unacceptable and not upgradeable because there were: inadequate analytical data for the test article and dosing materials, inadequate rationale for the doses, no GLP or QA statements, and the portions of report were illegible. (J. Kishiyama and S. Morris, 7/23/2003).

CHROMOSOME EFFECTS

50342-029; 144537; **"Mutagenicity Test on K 37 Technical in the Mouse Bone Marrow Cytogenetic Assay," HLA Study No. 12324-0-451; H. Murli; Hazleton Laboratories America, Inc., Kensington, MD; 3/5/91. Groups of 5 ICR mice/sex were dosed by oral gavage with Copper

8-Quinolinolate (K37 Technical Oxine-Copper, stated purity 97.4%) at 563, 1125, or 2250 mg/kg and sacrificed after 6, 18 or 30 hours. Vehicle (0.5% carboxymethylcellulose, 10 ml/kg) and positive (cyclophosphamide, 80 mg/kg) control groups were sacrificed at 30 and 18 hours, respectively. Animals were injected with colchicine (2 mg/kg, ip) 2 hours prior to sacrifice. Tibiae bone marrow samples were collected, fixed and stained. Fifty metaphase cells/animal were microscopically scored for chromosome aberrations. The mitotic index was calculated as mitotic cells/500 cells scored. Controls were adequate. Diarrhea was seen in some high dose animals. Treatment-related increases in chromosome aberrations were not observed. No adverse effect was indicated. The study was acceptable (J. Kishiyama and S. Morris, 1/6/04).

50342-020; 051295; "Micronucleus Test on Copper 8-oxyquinolate;" D.J.N. Hossack, M. Richold and J.C. Richardson; Huntingdon Research Centre, England; 4/18/78. Copper 8-oxyquinolate (unstated purity) was given by oral gavage (vehicle: 1% methylcellulose, 0.1 ml/10 g body weight) at 0, 1,400, 2,800, or 5,600 mg/kg to 5 fasted CFY rats/sex/dose at 0 and 24 hours. The rats were sacrificed at 30 hours and femural bone marrow smears were prepared and stained for microscopic determination of micronucleated polychromatic erythrocytes. Treatment-related effects on the incidence of micronucleated polychromatic erythrocytes were not seen. No adverse effect was indicated. The study is unacceptable and not upgradeable due to sampling protocol (J. Kishiyama and S. Morris, 9/18/2003).

DNA DAMAGE

50342-029; 144535; "Mutagenicity Tests of Organic Copper (Copper 8-Quinolinolate) Using Bacteria;" Y. Shirasu, M. Moritani, and K. Kato; Institute of Environmental Toxicology, Japan; 9/12/77. Differences in growth inhibition of recombinant repair competent (H-17) and deficient (M-45) strains of *Bacillus subtillus* was measured in the presence of Copper 8-Quinolinolate (95% stated purity, DMSO solvent) by placing 0, 1, 2, 5, 10, 20 or 50 µg (0.02 ml) on 10 mm disks of filter paper. The disks were incubated over night at 37° C on plates containing medium inoculated with bacteria. Differences between the size of the growth inhibition area around the H-17 and M-45 disks were interpreted as DNA damage requiring recombinant repair. Negative and positive controls (kanamyacin and mitomycin C) were adequate. There were no treatment-related differences in the amount of growth inhibition for the two strains. No adverse effect was indicated. The study was unacceptable and not upgradeable because there were no analytical data for the test article or dosing materials, only one trial with one replicate per dose, no rationale for dose selection and no trials with metabolic activation.(J. Kishiyama and S. Morris, 1/6/04).

NEUROTOXICITY

Not required at this time.

These DPR documents have been reviewed.

Rec. #	Doc. #
26423	50342-011
26424	50342-011
51098	50342-019
51099	50342-019
51100	50342-020
51293	50342-020
51294	50342-020
51295	50342-020
143391	50342-024
144531	50342-025
144532	50342-026
144533	50342-027
144534	50342-028
144535	50342-029
144535	50342-029
144535	50342-029
144536	50342-029
144537	50342-029