CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Etoxazole

Chemical Code # 5849, **Tolerance #** 52937
SB 950 # NA

August 26, 2003

I. DATA GAP STATUS

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

Toxicology one-liners are attached.

All record numbers through 205074 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T030826
Revised by Thomas Moore, 8/26/03

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 0050; 203457; "S-1283: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats"; (N. Nakashima; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 303-0043, Japan; Project ID. IET 97-0028; 3/26/01); Fifty Sprague-Dawley [Crj:CD(SD)] rats/sex/group received 0, 50, 5000 or 10000 ppm of S-1283 Technical (lot no. 703900UG, purity: 95.2%) in the diet for 24 months ((M): 0, 1.83, 187, 386 mg/kg/day, (F) 0, 2.07, 216, 445 mg/kg/day). An additional 15 animals/sex/group (satellite animals) were treated for 52 weeks. There was no treatment-related effect upon the survival of the animals. The mean body weights of the females in the 10000 ppm group were less than those of the controls over the course of the study ($p<0.01$ or 0.05). The mean food consumption of the 10000 ppm males and females was less than that of the controls at the beginning of the study ($p<0.01$), diminishing as an effect thereafter. In the hematology examination, the mean hematocrit and hemoglobin levels in the 10000 ppm group were less than those of the controls at various times during the study ($p<0.01$ or 0.05). The mean corpuscular volume and corpuscular hemoglobin values were reduced for both the 5000 and 10000 ppm males below that of the controls ($p<0.01$ or 0.05) at various times during the study as well. In the clinical chemistry evaluation, the total serum protein concentrations of the 10000 ppm males and females and the 5000 ppm males were greater than those of the controls at various time points ($p<0.01$ or 0.05). These increased values were due to either an increase in albumin or globulin concentrations. The γ-glutamyl transpeptidase activities were increased for both the males and females in the 5000 and 10000 ppm groups at various times during the study ($p<0.01$ or 0.05). In the urinalysis, proteinuria was increased for the 10000 ppm females at 25 and 52 weeks ($p<0.05$). In the necropsy examination, the mean absolute and relative liver weights for both sexes in the 5000 and 10000 ppm groups were increased over those of the control at 52 weeks ($p<0.01$ or 0.05) and for the 10000 ppm males at 104 weeks. The mean relative thyroid weight was increased for the males in the 5000 and 10000 ppm groups at both 52 and 104 weeks ($p<0.01$ or 0.05). The mean relative epididymides weights were increased for the 10000 ppm males at 52 and 104 weeks ($p<0.01$). The mean absolute and relative ovary weights for the 10000 ppm females were less than those of the controls at 52 weeks ($p<0.05$). In the histopathology, at 52 weeks, hepatocellular centrilobular hypertrophy of the liver was noted for both sexes in the 10000 ppm group ((M/F) 0: 0/10 vs. 10000: 10/10, $p<0.01$). There was an incidence of abnormal amelogenesis of the upper incisors of the 5000 and 10000 ppm females (0:0/10 vs. 5000:3/10, 10000:6/10, $p<0.01$) at 52 weeks. In addition, there was an increased incidence of chronic nephropathy in the kidneys of the 10000 ppm females (0:2/10 vs. 10000:8/10, $p<0.05$). At 104 weeks, hepatocellular centrilobular hypertrophy was noted for both sexes in the 10000 ppm group ((M) 0:0/50 vs. 10000:8/50, $p<0.01$, (F) 0:0/49 vs. 10000:28/50, $p<0.01$). For the females in the 10000 ppm group, an increased incidence of bile duct hyperplasia was evident (0:17/49 vs. 10000:32/50, $p<0.01$). An increased incidence of abnormal amelogenesis of the upper incisor was noted for both sexes in the 5000 and 10000 ppm groups ((M) 0:1/50 vs. 5000:10/50, $p<0.01$, 10000:32/50, $p<0.01$, (Fl) 0:3/49 vs. 5000:16/50, $p<0.01$, 10000:40/50, $p<0.01$). **No adverse effect indicated. Chronic NOEL (M/F):** 50 ppm ((M): 1.83 mg/kg/day, (F) 2.07 mg/kg/day) (based upon treatment-related effects of abnormal amelogenesis in the 5000 ppm treatment group); **No treatment-related incidence of oncogenicity. Study acceptable.** (Moore, 6/23/03)

**** 0051; 203458;** "YI-5301: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats"; (N. Nakashima; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 92-0148; 6/17/96); Fifty Sprague-Dawley [Crj:CD(SD)] rats/sex/group received 0, 4, 16 or 64 mg/kg/day of YI-5301 Technical (lot no. 921204; purity: 95.39%) in the diet for 24 months. The dietary concentration was adjusted periodically, based on body weight and food consumption. An additional 35 animals/sex/group (satellite animals) were treated for up to 78 weeks. There was no treatment-related effect upon the survival of the animals. The mean body weights, food consumption, ophthalmology, urinalysis and hematology were not affected by the treatment. In the clinical chemistry evaluation, the mean total cholesterol levels of the 16 and 64 mg/kg treatment

males at 26 weeks were increased over that of the control ($p<0.05$). The total bilirubin level for the 64 mg/kg males at 26 weeks was increased as well ($p<0.01$). At 26 weeks, the mean creatine phosphokinase and lactic dehydrogenase activities of the 64 mg/kg females were greater than those of the controls ($p<0.05$). These effects were not evident thereafter. In the necropsy examination, the mean absolute and relative liver weights of the 16 and 64 mg/kg males at 26 weeks were greater than those of the controls ($p<0.05$ or 0.01). In the 64 mg/kg males, centrilobular hepatocellular swelling was evident in 6 of 10 animals in contrast to none of the control animals ($p<0.01$). This effect was not evident thereafter. An increased incidence of tubular atrophy was noted for the 64 mg/kg males overall (0: 6/80 vs. 64: 17/78, $p<0.01$) and for the 16 and 64 mg/kg males which survived to the termination of the study (0: 2/31 vs. 16: 7/23 ($p<05$), 64: 10/28 ($p<0.01$)). An increased incidence of benign interstitial cell tumor in the testes was noted overall for all of the treatment groups (0: 1/80 vs. 4: 10/80, 16: 10/80, 64: 11/78, $p<0.01$). **Possible adverse effect**: increased incidence of benign interstitial cell tumor in the testes. **Chronic NOEL:** (M) 4 mg/kg/day (based upon enlargement of liver in the 16 mg/kg males) (F) 16 mg/kg/day (based upon increased serum enzyme activities for the 64 mg/kg animals). **Study acceptable.** (Moore, 6/26/03)

Note: Although a possible adverse effect was noted in the one rat combined study, the results of second study did not confirm this observation even though higher dose levels were used.

CHRONIC TOXICITY, RAT

See Combined, Rat

CHRONIC TOXICITY, DOG

** 0042; 203449; "YI-5301: 12-Month Oral Chronic Toxicity Study in Dogs"; (T. Kitazawa; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 94-0005; 5/28/96); Four beagle dogs/sex/group received in the diet 0, 200, 1000 or 5000 ppm of YI-5301 technical (lot no. 931027AM, purity: 95.96%) for 12 months ((M): 0, 4.62, 23.5, 116 mg/kg/day, (F): 0, 4.79, 23.8, 117 mg/kg/day). No apparent treatment-related clinical signs were noted in the study. Mean body weights and food consumption were not affected by the treatment. There were no treatment-related effects upon the ophthalmology or urinalysis. In the hematology examination, the mean hemoglobin concentration and red blood cell count were lower for the 5000 ppm males after 13 weeks of treatment than for the controls ($p<0.05$). Likewise, the mean hemoglobin count for the 5000 ppm females were lower than that of the controls after 26 weeks of treatment ($p<0.05$). However, there was no apparent physiological consequence in these lower values. In the clinical chemistry evaluation, the mean serum alkaline phosphatase levels were increased for both the 1000 and 5000 ppm groups ($p<0.01$ or 0.05) throughout the study. The mean serum triglyceride levels were increased for the 5000 ppm group throughout the study as well ($p<0.01$ or 0.05). In the necropsy examination, the livers for the 5000 ppm group were enlarged. The mean absolute and relative liver weights for the 1000 and 5000 ppm animals were greater than those of the controls ($p<0.01$ or 0.05). Although the mean absolute liver weight for the 200 ppm males was also greater than that of the control ($p<0.5$), the relative weight for these animals was not significantly affected. In the liver, centrilobular hepatocellular swelling was noted for all of the animals in the 1000 and 5000 ppm groups. **No adverse effect indicated. Chronic NOEL:** (M/F) 200 ppm ((M) 4.62 mg/kg/day, (F) : 4.79 mg/kg/day) (based upon effects upon the liver of the 1000 ppm group). **Study acceptable.** (Moore, 5/20/03)

ONCOGENICITY, RAT

See Combined, Rat

ONCOGENICITY, MOUSE

** 0043; 203450; "S-1283: 18-Month Oral Oncogenicity Study in Mice"; (N. Nakashima; The Institute of Environmental Toxicology, Mitsukaido-shi, Ibaraki 3003-0043, Japan; Project ID. IET 98-0045; 3/26/01); Fifty ICR (Crj:CD-1) mice/sex/group were fed in the diet 0, 2250 or 4500 ppm of S-1283 technical (lot no. 703900UG, purity: 95.2%) for 18 months ((M) 0, 242, 484 mg/kg/day, (F) 0, 243, 482 mg/kg/day). Satellite groups of 12 animals/sex/group were fed the test material for 52

weeks. There was no treatment-related effect upon survivability, mean body weight, food consumption, or hematology. The mean relative liver weight for the females in the 4500 ppm group was greater than that of the control after 52 weeks of treatment ($p<0.05$). There was an increased incidence of centrilobular fatty change in the liver hepatocytes of the males in the 4500 ppm group at 78 weeks (0: 5/50, 2250: 8/50, 4500: 15/50). This effect was not noted in the females. There was no treatment-related incidence of neoplastic lesions. **No adverse effect indicated. Chronic NOEL (M/F):** 2250 ppm ((M) 242 mg/kg/day, (F) 243 mg/kg/day) (based on the increased incidence of fatty change in the hepatocytes of the males and the increased relative liver weight at 52 weeks of the females in the 4500 ppm treatment group); **No oncogenicity evident. Study acceptable.** (Moore, 5/21/03)

0074; 204625; "YI-5301: 18-Month Oral Oncogenicity Study in Mice"; (T. Kitazawa; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 93-0023; 3/18/96); Fifty two ICR (Crj:CD-1) mice/sex/group were fed in the diet 0, 15, 60 or 240 mg/kg/day of YI-5301 technical (lot no. 921204; purity: 96.01%) for 18 months. Dietary concentrations were adjusted periodically based on body weight and food consumption. Satellite groups of 12 animals/sex/group were fed the test material for 52 weeks. There was no treatment-related effect upon survivability, mean body weight, food consumption, urinalysis or hematology. Serum creatine phosphokinase activities were elevated for the 15 and 240 mg/kg group males at 18 months ($p<0.01$ and $p<0.05$, respectively). No accompanying histopathological lesions in relevant tissues were noted. The mean relative liver weight for the females in the 240 mg/kg group was greater than that of the control after 52 weeks of treatment ($p<0.05$). The mean absolute testes weight of the 240 mg/kg males was greater than that of the control at 52 weeks. However, the difference in the mean relative weights of the two groups was not statistically significant. There was an increased incidence of centrilobular fatty change in the liver hepatocytes of the males in the 240 mg/kg group at 52 weeks (0: 1/10 vs. 240: 7/10, $p<0.01$). The incidence in males at termination was 11/34 for controls and 13/34 for the high dose (NS). There were no comparable findings in the livers of the females at any dose. There was no treatment-related incidence of neoplastic lesions. **No adverse effect indicated. Chronic NOEL (M/F):** 60 mg/kg) (based on the increased incidence of fatty change in the hepatocytes of the males and the increased relative liver weight at 52 weeks of the females in the 240 mg/kg treatment group); **No oncogenicity evident. Study unacceptable,** not upgradeable due to inadequate dose level selection (maximum tolerated dose was not achieved). (Moore, 7/303)

Note: One of the mouse oncogenicity studies (vol. no. 52937-0074, rec. no. 204625) is unacceptable due to inadequate dose level selection. However, the data requirement was fulfilled when data from a second mouse oncogenicity study (vol. no. 52937-0043, rec. no. 203450) were collectively considered.

REPRODUCTION, RAT

** 0049; 203456; "YI-5301: Two-Generation Reproduction Study in Rats"; (N. Hatakenaka; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 93-0047; 2/29/96); Twenty-four Crj:CD (SD) rats/sex/group were treated in the diet with 0, 80, 400, or 2000 ppm of YI-5301-technical (lot no. 921204, purity: 96.01%) for 2 generations. The treatment periods for the F0 generation included 10 weeks prior to mating, mating, 3 weeks of gestation and 3 weeks of lactation. At that time 24 F1 animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. There were no apparent treatment-related deaths among the parents nor treatment-related effects upon mean body weights. The mean relative liver weights for the males in the 2000 ppm treatment group of both generations were greater than those of the controls ($p<0.01$). However, there were no related histological findings. There were no treatment-related effects upon the reproductive parameters. The mean pup weights for both the 2000 ppm males and females in both generations were less than those of the control with statistical significance noted for the F1 males on day 14 ($p<0.05$). **No adverse effect indicated. Parental Systemic NOEL: (M)** 400 ppm (based on the increased mean liver weights for the males in the 2000 ppm group, (M) 21.5 to 48.6 mg/kg/day), **(F)** 2000 ppm (based upon the lack of a treatment-related

effect at the highest dose level, (F) 113 to 427 mg/kg/day); **Reproductive NOEL:** 2000 ppm (based upon the lack of treatment-related effects for the 2000 ppm group, (M) 105 to 233.3 mg/kg/day, (F) 113 to 427 mg/kg/day); **Developmental NOEL:** 400 ppm (based upon the lower mean body weights for the pups in the 2000 ppm group of both generations); (M) 21.5 to 48.6 mg/kg/day, (F) 23.3 to 82.5 mg/kg/day); **Study acceptable**. (Moore, 6/18/03)

52937-0048; 203455; "YI-5301: Two-Generation Reproduction Study in Rats, Preliminary Study"; (N. Hatakenaka; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 92-0079; 10/29/93, amended, 11/4/94); Eight CD rats/sex/group received 0, 100, 300, 1000 or 3000 ppm in the diet of YI-5301 technical (lot no. 920630, purity: 97.99%) for a three week premating period and during the mating, 3 week gestation and 3 week lactation periods ((M) 0, 5.18, 16.1, 53.5, 159 mg/kg/day, (F) premating: 0, 7.44, 22.8, 79.5, 222 mg/kg/day, gestation: 0, 7.35, 21.1, 73.8, 213 mg/kg/day, lactation: 0, 17.2, 49.4, 173.7, 507 mg/kg/day). No deaths resulted from the treatment. There were no treatment-related effects upon mean body weight or food consumption. Mean absolute liver weights were increased for the 1000 and 3000 ppm males and for the 300 ppm females ($p<0.05$, 0.01 or 0.001). The mean relative liver weights were increased for the 1000 and 3000 ppm males and for the 300 ppm females and above ($p<0.01$ or 0.001). There were no treatment-related effects upon the reproductive parameters. The mean body weights of the pups in the 3000 ppm treatment group were lower than those of the controls at 14 and 21 days lactation ($p<0.01$ or 0.001). **No adverse effect indicated. Parental Systemic NOEL:** (M) 300 ppm (16.1 mg/kg/day) (based upon increased mean absolute and relative liver weights for the 1000 ppm males), (F) 100 ppm (range from 7.44 to 17.2 mg/kg/day) (based upon increased absolute and relative liver weights for the 300 ppm females), **Reproductive NOEL:** 3000 ppm (222 mg/kg/day) (based upon the lack of a treatment-related effect at the highest treatment level); **Developmental NOEL:** 1000 ppm (173.7 mg/kg/day) (based upon lower mean pup weights during lactation period in the 3000 ppm treatment group). **Study supplemental.** (Moore, 6/11/03)

TERATOLOGY, RAT

** 0047; 203454; "YI-5301: Teratogenicity Study in Rats"; (N. Hatakenaka; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 93-0007; 4/25/94, amended, 11/4/94); Twenty four mated Crj:CD (SD) female rats/group were dosed orally by gavage with 0 (aqueous 1% CMC), 40, 200 or 1000 mg/kg/day of YI-5301 Technical (lot no. 921204, purity: 95.39%) from day 6 through day 15 of gestation. There were no treatment-related effects upon the mean body weights of the 1000 mg/kg females. The mean food consumption of the 1000 mg/kg females between study days 9 and 12 was less than that of the controls ($p<0.01$). Otherwise, no other treatment-related effects were evident. There were no treatment-related effects upon the development of the fetuses. **No adverse effect was evident.**
Maternal NOEL: 200 mg/kg/day (based upon lower mean food consumption for the 1000 mg/kg treatment group); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of a treatment-related effect upon the fetuses in the highest dose tested), **Study acceptable.** (Moore, 6/10/03)

52937-0046; 203453; "YI-5301: Teratogenicity Study in Rats, Preliminary Study"; (N. Hatakenaka; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 92-0080; 10/29/93); Seven mated female Crj:CD (SD) rats/group were dosed orally by gavage with 0 (1% aqueous CMC), 10, 100, 300 or 1000 mg/kg/day of YI-5301 Technical (lot no. 921204, purity: 95.39%) from day 6 of gestation through day 15. No deaths occurred during the study. No treatment-related clinical signs or treatment-related effects on body weight gain or food consumption were noted. The percentage of fetal resorptions and deaths was increased for the 1000 mg/kg group. However, this greater incidence was largely a function of an unusually low percentage of fetal resorptions and deaths for the control group. **No adverse effect indicated. Study supplemental.** (Moore, 6/5/03)

TERATOLOGY, RABBIT

** 0045; 203452; "YI-5301: Teratogenicity Study in Rabbits"; (H. Hojo; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 93-0049; 12/5/94);

Eighteen artificially-inseminated female Japanese White (Kbl:JW) rabbits/group were dosed orally by gavage with 0 (1% aqueous CMC), 40, 200, or 1000 mg/kg/day of YI-5301 Technical (lot no. 921204, purity: 95.39%) from day 6 through day 18 of gestation. One female was removed from the 1000 mg/kg group due to accidental hind limb paralysis. One animal in both the 40 mg/kg and 200 mg/kg groups aborted. One female in the 1000 mg/kg group died on day 15. The necropsy examination of this animal revealed foamy contents in the trachea and congestion in the lungs. Mean body weight gain and food consumption for the 1000 mg/kg does was lower than that of the controls during the treatment period. There was an increased incidence of the skeletal variation of 27 presacral vertebrae with 13^{th} ribs in the fetuses of the 1000 mg/kg group over that of the control (0: 5/117, 40: 10/121, 200: 5/149, 1000: 14/129, $p<0.05$). **No adverse effect indicated. Maternal NOEL:** 200 mg/kg/day (based upon the lower body weight gain and food consumption in the 1000 mg/kg treatment group); **Developmental NOEL:** 200 mg/kg/day (based upon the increased incidence of skeletal variations for the fetuses in the 1000 mg/kg group); **Study acceptable.** (Moore, 5/27/03)

52937-0044; 203451; "YI-5301: Teratogenicity Study in Rabbits, Preliminary Study"; (H. Hojo; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 92-0149; 11/2/93, amended, 11/7/94); Five artificially-inseminated Japanese White rabbits/group were dosed orally by gavage with 0 (1% aqueous CMC), 10, 100, 300 or 1000 mg/kg/day of YI-5301 Technical (lot no. 921204, purity: 95.39%) from day 6 of gestation through day 18. No deaths occurred during the study. One female each in the 300 and 1000 mg/kg groups did not have any conceptuses. Three of the 1000 mg/kg females exhibited enlarged livers. The mean uterine weight of the 1000 mg/kg females was lower than that of the control ($p<0.05$). The mean number of live fetuses was less than that of the control (0: 10.2 vs. 1000: 4.8, $p<0.05$). This lower number of live fetuses was a consequence of lower mean number of implants in the high dose group (0: 11.4 vs. 1000: 5.0). There were no apparent treatment-related effects upon fetal development. **No adverse effect indicated. Study supplemental.** (Moore, 5/22/03)

GENE MUTATION

**** 0055; 203462**; "S-1283 Mammalian Cell Mutation Assay"; (K. Adams; Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Project ID. SMO 519/952604; 10/21/96); Mouse lymphoma L5178Y cells (clone 3.7.2 ($TK^{+/-}$)) were treated with S-1283 Technical (batch no. 931027AMG, purity: 95.4%) at concentrations ranging from 10 to 100 ug/ml under conditions of non-activation and 0.5 to 20 ug/ml under conditons of activation for 3 hours at 37^{o} C. Two independent trials were performed with duplicate cultures/treatment level and 3 replicates per culture. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. Cell viability and mutation frequency for each treatment level were determined and compared to those of the solvent control. The results for the trials in the absence of the S9 fraction indicated an increased mutant frequency for the test material under conditions of high toxicity with little or no increase in absolute colony counts. In the presence of the S9 fraction, an increase in the mutant frequency was noted with an increase in absolute colony counts. In both instances the colonies were sized. Positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 6/27/03)

** 0058; 203465; "YI-5301: Reverse Mutation Test"; (K. Watanabe; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 92-0017; 4/14/92); *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA were treated for 48 hours at 37^{o} C with YI-5301 technical (lot no. 911118; purity: 96.26%) at concentrations ranging from 313 to 5000 ug/plate with and w/o activation. There were two trials with each treatment level plated in triplicate. A phenobarbital and 5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/1/03)

0059; 203466; "S-1283: Reverse Mutation Test of S-1283 in *Salmonella typhimurium* strain TA 102"; (M. Ota; Sumitomo Chemical Company, Ltd., Environmental Health Science Laboratory,

Konohana-ku, Osaka, Japan; Project ID. 3397; 2/26/99); *S. typhimurium* strain TA 102 was treated with S-1283 technical (lot no. 703900UG; purity: 95.2%) at concentrations ranging from 313 to 5000 ug/plate with a preincubation of 20 minutes and an incubation with plate incorporation for 48 hours at 37^{o} C under conditions of activation and non-activation. One trial was performed with triplicate cultures for each treatment level. A phenobarbital/5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive control was functional. **Study supplemental** (only one test strain was included in the study)**.** (Moore, 7/1/03)

CHROMOSOME EFFECTS

** 0053; 203460; "Micronucleus Test on S-1283 in CD-1 Mice"; (K. Odawara; Sumitomo Chemical Co., Ltd., Environmental Health Science Laboratory, Konohana-ku, Osaka, Japan; Project ID. 3171; 11/27/96); Five CD1 mice/sex/group/time point were treated orally by gavage with 0 (aqueous 1% carboxymethylcellulose), 1250, 2500 or 5000 mg/kg of S-1283 (lot no. 931027AMG; purity: 95.4%) and euthanized at 24, 48 or 72 hours post-dose. As a positive control, another group of 5 mice/sex was treated by oral gavage with 60 mg/kg of cyclophosphamide and euthanized at 24 hours post-dose.. The incidence of micronucleated polychromatic erythrocytes (PCE) in 1000 PCEs and the ratio of PCEs to the total number of erythrocytes were reported. There was no treatment-related increase in the percentage of micronucleated PCEs. **No adverse effect indicated.** Positive control was functional. **Study acceptable.** (Moore, 6/27/03)

** 0057; 203464; "YI-5301: *In Vitro* Cytogenetics Test"; (K. Matsumoto; The Institute of Environmental Toxicology, Kodaira, Tokyo 187, Japan; Project ID. IET 93-0116; 11/7/94); Chinese hamster lung (CHL) cells were exposed to concentrations of YI-5301 Technical (lot no. 921204, purity: 95.39%) ranging from 12.5 to 125 g/ml under conditions of non-activation and 22.5 to 180 ug/ml under conditions of activation at 37^{o} C. For the non-activated cultures, the cells were exposed to the test material for 24 or 48 hours. In the activated samples, the cells were exposed for 6 hours, washed and incubated for an additional 18 or 42 hours. A phenobarbital and 5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. Two trials were performed. Duplicate cultures were performed at each treatment level. There was no treatment-related increase in chromosomal cell aberrations. Positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/1/03)

DNA DAMAGE

** 0056; 203463; "S-1283: Measurement of Unscheduled DNA Synthesis in Rat Liver Using an *In Vivo/In Vitro* Procedure"; (C. Clare; Corning Hazleton (Europe) Harrogate, North Yorkshire, HG3 IPY England; Project ID. 333/72; 1/15/97); Five male rats/group/time point were dosed with 0 (aqueous 1% carboxymethylcellulose), 2500 or 5000 mg/kg of S-1283 technical (batch no. 931027AMG, purity: 95.3%) and euthanized 2 to 4 hours or 12 to 14 hours after dosing. As positive controls, 5 males/group were treated with 75 mg/kg of 2-acetylaminofluorene and euthanized 12 to 14 hours after dosing or 10 mg/kg of dimethynitrosamine and euthanized 2 to 4 hours post-dose. Upon recovery of the hepatocytes, a primary culture was established and the cells were exposed to ^{3}H-thymidine (10 mCi/ml) for 4 hours, followed by further incubation overnight with unlabeled thymidine. Two cultures/animal in one trial, 50 cells/culture, were evaluated for the number of net grains/nucleus. There was no treatment-related increase in unscheduled DNA synthesis. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 6/30/03)

NEUROTOXICITY

Study not submitted.

SUBCHRONIC STUDIES

0034; 203441; "YI-5301: 13-Week Oral Subchronic Toxicity Study in Rats 4-Week Dose Range Finding Study" (Nakashima, N., The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 92-0038, 01/17/95). YI-5301 (Lot No. 911118, purity =

96.26%) was admixed to the diet and fed to 6 Fischer (F344/DuCrj) rats per sex per dose at dose levels of 0 (diet only), 80, 400, 2000, or 10000 ppm (0, 6.1, 30.1, 150.5, 761 mg/kg/day, respectively for males and 0, 6.4, 31.9, 160.5, 732 mg/kg/day, respectively for females) for 28 days. No mortalities occurred. No clinical signs were observed. Treatment-related increases in mean total protein and globulin levels were observed in both sexes at 2000 and 10000 ppm. Significant increases in mean relative liver (males at 2000 and 10000 ppm, females at 400, 2000, and 10000 ppm) and adrenal (males at 400, 2000, and 10000 ppm, females at 10000 ppm) weights were observed. Macroscopic examination revealed treatment-related enlarged livers in both sexes at 2000 and 10000 ppm. Microscopic examination revealed treatment-related centrilobular hepatocellular swelling in both sexes at 2000 and 10000 ppm. **No adverse effects.** NOEL (M) = 30.1 mg/kg/day (400 ppm) and NOEL (F) = 31.9 mg/kg/day (400 ppm) (based on changes in mean relative liver weights and histological changes in the liver). **Supplemental** because 1) only 6 animals per sex per dose were used, 2) no ophthalmological examinations were performed, 3) the animals were treated for only 28 days, and 4) no histopathology was conducted on the test animals except for the examination of the liver of 2 animals per sex per dose level. (Corlett, 05/22/03)

52937-0037; 203444; "YI-5301: 4-Week Supplementary Study in Rats"; (A. Yoshida; The Institute of Environmental Toxicology, Kodaira-shi, Tokyo 187, Japan; Project ID. IET 95-0164; 6/18/96); Fourteen 14 week old male Sprague-Dawley rats/group were fed 0, 4, 16 or 64 mg/kg/day of YI-5301 (lot no. 921204; purity: 95.39%) in the diet for 4 weeks. After 4 weeks of treatment, 10 animals/group were assayed for the serum levels of estradiol, luteinizing hormone, prolactin and testosterone. Testicular weights were recorded and spermatogenesis was examined histologically in the testes and epididymis. The additional 4 animals/group received an intraperitoneal injection of 5-bromo-2'-deoxyuridine (Brdu) 1 hour prior to being euthanized. The number of labeled nuclei per 1000 interstitial cells in the testes was determined for each animal. There was no treatment-related effect upon mean body weight, food consumption and mean absolute testes weights. The serum levels for the various hormones were not affected by the treatment. There was no treatment-related effect upon the cell index for the various stages of spermatogenesis. Brdu labeling was not significantly increased in the treated animals over that of the control. **No adverse effect indicated. NOEL:** (M) > 64 mg/kg/day. **Study supplemental.** (Moore, 5/16/03)

0038; 203445; "YI-5301: 13-Week Oral Subchronic Toxicity Study in Mice 4-Week Dose Range Finding Study" (Enomoto, A., Mitsukaido Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 92-0073, 12/14/92). YI-5301 (Lot No. 911118, purity = 96.26%) was admixed to the diet and fed to 6 Crj:CD-1 mice per sex per dose at dose levels of 0 (basal diet only), 80, 400, 2000, or 10000 ppm (0, 12.1, 58.6, 289.4, 1465 mg/kg/day, respectively for males and 0, 11.8, 59.7, 294.1, 1476 mg/kg/day, respectively for females) for 28 days. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related increase in the mean alkaline phosphatase level was observed in males at 10000 ppm. A treatment-related increase in mean relative liver weight in both sexes at 2000 and 10000 ppm was observed. Macroscopic examination revealed treatment-related darkened livers in both sexes at 10000 ppm. NOEL (M/F) not determined. **Supplemental** because 1) only 6 animals per sex per dose were used, 2) no ophthalmological examinations were performed, 3) the animals were treated for only 28 days, and 4) no histopathology was conducted on the test animals. (Corlett, 05/30/03)

0035; 203442; "YI-5301: 13-Week Oral Subchronic Toxicity Study in Rats" (Nakashima, N., The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 92-0078, 01/17/95). 821. YI-5301 (Lot Numbers 911118 with purity = 96.26% and 911128 with purity = 95.57%) was admixed to the diet and fed to 12 Sprague-Dawley (Crj:CD) rats per sex per dose at dose levels of 0 (diet only), 100, 300, 1000, or 3000 ppm (0, 6.12, 18.28, 61.8, 183.7 mg/kg/day, respectively for males and 0, 6.74, 20.50, 69.0, 204.8 mg/kg/day, respectively for females) for 13 weeks. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related increase in the mean serum γ-glutamyl transpeptidase level was observed in both sexes at

3000 ppm. A treatment-related increase in mean relative liver weight in males at 300, 1000 and 3000 ppm and in females at 1000 and 3000 ppm was observed. Macroscopic examination revealed treatment-related enlarged livers in males at 3000 ppm and in females at 1000 and 3000 ppm. Microscopic examination revealed treatment-related centrilobular hepatocellular swelling in males at 1000 and 3000 ppm and in females at 3000 ppm. **No adverse effects.** NOEL (M) = 18.28 mg/kg/day (300 ppm) and NOEL (F) = 20.50 mg/kg/day (300 ppm) based on increased mean relative liver weight and centrilobular hepatocellular swelling. **Acceptable.** (Corlett, 05/29/03)

0039 (addendum to 0035) ; 203446 (addendum to 203442); "YI-5301: 13-Week Oral Subchronic Toxicity Study in Rats Additional Study of Effect on Proliferative Activity of Testicular Interstitial Cells" (Nakashima, N., Mitsukaido Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 95-0182, 06/27/96). Samples of testis and duodenum (a positive control) tissue preserved at the termination of the 13-week oral subchronic toxicity study with YI-5301 were assayed for proliferating cell nuclear antigen (PCNA). The testis sections from 8 males at 0 ppm and 8 males at 3000 ppm were immunohistochemically stained for proliferating cell nuclear antigen (PCNA) and examined for proliferative activity of testicular interstitial cells. The PCNA labeling index (% mean ± standard deviation) in the testicular interstitial cells was 0.16 ± 0.12 at 0 ppm and 0.19 ± 0.16 at 3000 ppm indicating no treatment-related proliferative activity. **No adverse effects. Supplemental study** (not a guideline study). (Corlett, 06/12/03)

0040 ; 203447; "YI-5301: 13-Week Oral Subchronic Toxicity Study in Rats Biochemical and Pathological Analyses for Hepatomegaly" (Inui, K., Mitsukaido Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 94-0095, 08/22/95). YI-5301 (Lot Number 921204, purity = 95.39%) was admixed to the diet and fed to 6 Sprague-Dawley (Crj:CD) rats per sex per dose for 4 weeks (animals sacrificed at this time) and to 6 rats of the same strain for 13 weeks at dose levels of 0 (diet only), 1000, or 2000 ppm (0, 59.6, 119.5 mg/kg/day, respectively for males and 0, 66.7, 133.5 mg/kg/day, respectively for females). Mortality, clinical signs, body weights, food consumption, and liver weights (absolute and relative) were determined. Livers were examined macroscopically and microscopically. Microsomal protein content, cytochrome P-450 content, and enzyme activities in the livers (ethoxycoumarin O-dealkylase and pentoxyresorufin O-dealkylase) were determined. No treatment-related mortalities or clinical signs were observed. Examination of body weight and food consumption data revealed no treatment-related effects. A treatment-related increase in mean relative liver weight was observed in males at 2000 ppm sacrificed after 4 and 13 weeks of treatment and in females at 1000 and 2000 ppm sacrificed after 4 weeks of treatment. Microscopic examination revealed treatment-related centrilobular hepatocellular swelling in males at 2000 ppm sacrificed after 4 weeks of treatment. A treatment-related increase in microsomal protein content of the liver was observed in males at 2000 ppm after 13 weeks of treatment. **No adverse effects.** NOEL (M) = 59.6 mg/kg/day (1000 ppm), NOEL (F) not determined (based on mean relative liver weight). **Supplemental study** (not a guideline study since only parameters associated with liver and liver function were examined). (Corlett, 06/17/03)

0036; 203443; "YI-5301: 13-Week Oral Subchronic Toxicity Study in Mice" (Inui, K., Mitsukaido Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 92-0111, 8/19/94). 821. YI-5301 (Lot Number 920630, purity = 97.99%) was admixed to the diet and fed to 12 Crj:CD-1 mice per sex per dose at dose levels of 0 (basal diet only), 100, 400, 1600, or 6400 ppm (0, 13.4, 55.1, 213.6, 878.4 mg/kg/day, respectively for males and 0, 15.2, 62.0, 250.5, 994.5 mg/kg/day, respectively for females) for 13 weeks. No mortalities occurred. No treatment-related clinical signs were observed. A treatment-related increase in the mean serum alkaline phosphatase was observed in both sexes at 6400 ppm. A treatment-related increase in mean relative liver weight in males at 1600 and 6400 ppm and in females at 6400 ppm was observed. Microscopic examination revealed treatment-related centrilobular hepatocellular swelling in males at 1600 and 6400 ppm and in females at 6400 ppm, and periportal

hepatocellular necrosis in both sexes at 6400 ppm. **Possible adverse effect: periportal hepatocellular necrosis.** NOEL (M) = 55.1 mg/kg/day (400 ppm) and NOEL (F) = 250.5 mg/kg/day (1600 ppm) based on increased mean relative liver weight and centrilobular hepatocellular swelling. **Supplemental study** (no ophthalmological examinations conducted). (Corlett, 06/04/03)

0074; 205074; "YI-5301: 13-Week Oral Subchronic Toxicity Study in Dogs 4-Week Dose Range Finding Study" (Enomoto, A., Mitsukaido Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 91-0119, 09/28/92). YI-5301 (Lot No. 911118, purity = 96.26%) was admixed to the diet and fed to 1 beagle dog per sex per dose at dose levels of 0 (diet only), 1000, 3000, 10000, or 30000 ppm (0, 30.5, 99.7, 321, 968 mg/kg/day, respectively for males and 0, 35.7, 102, 340, 594 mg/kg/day, respectively for females) for 28 days. No mortalities occurred. Vomiting of feed was observed in males at 10000 and 30000 ppm and females at 30000 ppm. Decreased weight gain was observed in males at 3000, 10000, and 30000 ppm and in females at 3000 and 10000 ppm, and weight loss was observed in the female at 30000 ppm during treatment. A treatment-related increase in serum alkaline phosphatase was observed in both sexes at all dose levels. A treatment-related increase in relative liver weights in both sexes at all dose levels was observed. Macroscopic examination revealed emaciation in the female at 30000 ppm. Microscopic examination revealed treatment-related centrilobular hepatocellular swelling in both sexes at all dose levels. **No adverse effects.** NOEL (M) < 30.5 mg/kg/day (1000 ppm) and NOEL (F) < 35.7 mg/kg/day (1000 ppm) (based on an increase in relative liver weights and centrilobular hepatocellular swelling). **Supplemental** because only 1 animal per sex per dose level was used and the animals were treated for only 28 days. (Corlett, 06/27/03)

0033; 203440; "YI-5301: 13-Week Oral Subchronic Toxicity Study in Dogs" (Kitazawa, T., Mitsukaido Laboratories, The Institute of Environmental Toxicology, Tokyo, Japan, Laboratory Project Identification IET 93-0113, 8/28/95). 821. YI-5301 (Lot Number 921204, purity = 95.39%) was admixed to the diet and fed to 4 beagle dogs per sex per dose at dose levels of 0 (basal diet only), 200, 2000, or 10000 ppm (0, 5.33, 53.7, 268 mg/kg/day, respectively for males and 0, 5.42, 55.9, 277 mg/kg/day, respectively for females) for 13 weeks. No mortalities occurred. Foamy liquid vomit in 3/4 animals in both sexes at 10000 ppm was observed. A treatment-related increase in the mean serum alkaline phosphatase was observed in both sexes at 10000 ppm. A treatment-related increase in mean relative liver weight was observed in both sexes at 2000 and 10000 ppm. A treatment-related decrease in mean relative prostate weight was observed at 10000 ppm. Microscopic examination revealed treatment-related centrilobular hepatocellular swelling in both sexes at 2000 and 10000 ppm and treatment-related acinar cell atrophy in the prostate at 10000 ppm. **No adverse effects.** NOEL (M) = 5.33 mg/kg/day (200 ppm) and NOEL (F) = 5.42 mg/kg/day (200 ppm) based on increased mean relative liver weight and centrilobular hepatocellular swelling. **Acceptable**. (Corlett, 06/27/03)

0041; 203448; "28-Day Repeated Dose Dermal Toxicity Study of S-1283 TG in Rats" (Ichiki, T., Panapharm Laboratories Co., Ltd., Kumamoto, Japan, Laboratory Project Identification 29830, 03/15/99). 822. S-1283 TG (Lot No. 703900UG, purity = 95.6%) was suspended in 0.5% methyl cellulose solution and applied to the clipped and shaved skin of 10 Sprague-Dawley (Crj:CD) rats per sex per dose at dose levels of 0 (0.5% methyl cellulose solution only), 30, 100, or 1000 mg/kg/day for 6 hours per day for 28 consecutive days using an occlusive dressing. No mortalities occurred. No treatment-related clinical signs were observed. Detailed clinical observations and functional observations revealed no treatment-related signs. No dermal reactions were observed. Hematology, serum chemistry, and ophthalmology revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M/F, systemic and skin) = 1000 mg/kg/day based on no treatment-related effects at the highest dose tested. **Acceptable.** (Corlett, 06/23/03)

METABOLISM STUDIES

Study not submitted.