

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Pymetrozine

Chemical Code # 5232, Tolerance # 52326  
SB 950 # NA

January 9, 2006

I. DATA GAP STATUS

<b>Chronic toxicity, rat:</b>	No data gap; no adverse effect indicated
<b>Chronic toxicity, dog:</b>	No data gap; no adverse effect indicated
<b>Oncogenicity, rat:</b>	No data gap; possible adverse effect
<b>Oncogenicity, mouse:</b>	No data gap; possible adverse effect
<b>Reproduction, rat:</b>	No data gap; no adverse effect indicated
<b>Teratology, rat:</b>	No data gap; no adverse effect indicated
<b>Teratology, rabbit:</b>	No data gap; no adverse effect indicated
<b>Gene mutation:</b>	No data gap; no adverse effect indicated
<b>Chromosome effects:</b>	No data gap; no adverse effect indicated
<b>DNA damage:</b>	No data gap; no adverse effect indicated
<b>Neurotoxicity:</b>	No data gap; possible adverse effect*

Toxicology one-liners are attached.

All record numbers through 215681 were examined.

\*\* indicates an acceptable study.

Bold face indicates a possible adverse effect.

## indicates a study on file but not yet reviewed.

File name: T060109

Revised by T. Moore

\* Rat Acute Neurotoxicity Study indicated a possible adverse effect.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

### COMBINED, RAT

**\*\*52326-064 158653** "CGA-215944 Technical 24-Month Carcinogenicity and Chronic Toxicity Study in Rats" (Gerspach, R. 835-Ciba-Geigy Limited, Stein, Switzerland; Study # 901483, 10/19/95). CGA 215944 Technical (Batch # P.102002, purity 98%) was administered in the feed to 80 Tif: RAIf(SPF) rats/sex/dose at levels of 0, 10, 100, 1000 or 3000 ppm for 24 months. Body weights in high-dose males and females were reduced 15% and 24%, respectively, compared to controls; at 1000 ppm, reductions were 4% and 7%, respectively. Food consumption was reduced during the first week in high-dose rats. Clinical signs included hunched posture in high-dose females. Lower RBC counts were reported at week 13 for high-dose males and mean platelet count was increased in high-dose females. Both sexes at 3000 ppm showed decreased ALT values; higher plasma bilirubin and albumin levels were noted in high-dose males and plasma cholesterol and inorganic phosphorus was increased in high-dose females. An increase in liver cysts in high-dose females and increased mottled livers in high-dose males was seen after necropsy; increased liver masses and nodules in the uterus and ovaries were noted in females at this level. Significantly higher organ to body weight ratios were seen in liver and spleen of males and females at 3000 ppm and in kidneys of females at this level. Significantly increased incidence of hepatocellular hypertrophy, mostly seen in the centrilobular and midzonal region of the liver, was noted in both sexes at 1000 and 3000 ppm. Other lesions included hyperplasia of thyroid follicular epithelium in males at 1000 and 3000 ppm and females at 3000 ppm, congestion of the spleen in both sexes at 3000 ppm (interim sacrifice only) and significantly increased dilatation of the uterus in females at 3000 ppm. **Chronic NOEL=100 ppm** (M=3.73 mg/kg; F= 4.45 mg/kg, based on liver pathology at 1000 and 3000 ppm). Neoplastic lesions included slightly increased malignant medullary tumors of the adrenal gland, benign granular cell tumors in the cerebral meninges and primary malignant lymphomas in reticular tissue in males at 3000 ppm. **Possible Adverse Effect:** benign hepatomas in females and malignant medullary tumors of the adrenal gland in males at 3000 ppm. Acceptable. Kellner, 4/24/98.

52326-141 160434 "Liver and Thyroid Medium-Term Bioassay for Tumor Promotion Potential of CGA 215944" (Hagiwara, A.-Daiyu-kai Institute of Medical Science, Ichinomiya, Japan; Project# 9610, 12/26/96). CGA 215944 Technical (Batch # P.102002, purity 97.8%) was administered in the feed to 16 F344 male rats/dose at levels of 0, 25, 50, 100 and 1000 ppm for 18 weeks. Liver and thyroid tumor promotion potential of CGA 215944 was evaluated using N-nitrosodiethylamine (DEN) and dihydroxy-di-N-propylnitrosamine (DHPN) as initiators. After a single injection of DEN (100 mg/kg) i.p. at the start of the study, DHPN (0.1%) was given in the drinking water for 2 weeks; this was followed by the test article in the feed. After necropsy and processing of livers, the number and area per cm<sup>2</sup> of the liver section of glutathione S-transferase placental form positive hepatocytic (GST-P<sup>+</sup>) foci (considered to be preneoplastic lesions) were measured using a color video image processor. Although significantly higher values for liver weight and liver to body weight ratio was observed in 1000 ppm rats, the quantitative values for GST-P<sup>+</sup> foci in animals exposed to the highest dose of the test article were similar to control. There was an increase incidence of follicular cell hyperplasia in the thyroid of high-dose rats and elevated follicular cell adenomas in the 100 ppm group. These data suggest that CGA215944 has weak tumor promotional potential for the thyroid, but not the liver. Supplemental study. Kellner, 6/11/98.

## CHRONIC TOXICITY, RAT

See Combined, Rat above.

## CHRONIC TOXICITY, DOG

52326-056 158629 "12-Month Chronic Dietary Toxicity Study in Beagle Dogs" (Altmann, B. 831-Ciba-Geigy Limited, Stein, Switzerland; Study # 901481, 8/17/94). CGA 215944 Technical (Batch # P.102002, purity 98%) was administered in the feed to 4 Beagle Dogs/sex/dose at levels of 0, 20, 200, 1000 ppm for 12 months (2 additional control and 1000 ppm recovery dogs/sex left untreated for 4 more weeks). There was a slight decrease in body weight gain in high-dose males, mainly due to the weight loss by one male before death at week 33 ( bronchopneumonia, not compound -related). Reduced body weight gains were noted in high-dose females (considered dose-related). Food consumption was reduced in high-dose females. Clinical observations included vomiting in three high-dose males and slight apathy, slightly atactic gait and reduced muscle tone in a single high-dose female. Blood chemistry changes included higher plasma cholesterol and phospholipid levels in high-dose females. Mean relative liver weight was increased in both sexes at 1000 ppm and males at 200 ppm. Mean absolute testes weight was reduced at 200 and 1000 ppm. Treatment-related microscopic lesions at 1000 ppm included myopathy (in skeletal muscle, stomach, small and large intestine), increased inflammatory cell infiltration of the liver, hyperplasia of intrahepatic bile ducts and increased splenic and hepatic hemosiderosis. **NOEL=200 ppm** (M: 5.33 mg/kg; F: 5.03 mg/kg) based on Inflammatory cell infiltration of the liver and hemosiderosis persisting through recovery period. Acceptable. Kellner, 5/6/98.

## ONCOGENICITY, RAT

See Combined, Rat above.

## ONCOGENICITY, MOUSE

**\*\*52326-057 158631** "18-Month Carcinogenicity Study in Mice" (Gerspach, R. 835-Ciba-Geigy Limited, Stein, Switzerland; Study # 901482, 10/30/95). CGA 215944 Technical (Batch # P.102002, purity 98%) was administered in the feed to 60 Tif: MAGf (SPF) mice/sex/dose at levels of 0, 10, 100, 2000 or 5000 ppm for 18 months. Body weights in high-dose males and females were reduced 11% and 24%, respectively, compared to controls; at 2000 ppm, reductions were 4% and 9%, respectively. Food consumption was slightly lower in high-dose females during the first five months of treatment. Clinical signs included hunched posture in high-dose females.

Lower RBC counts, hemoglobin content and hematocrit was reported at week 53 for high-dose males; at week 78, high-dose females showed significantly increased lymphocyte and platelet counts and decreased large unstained cells. Significantly higher absolute and relative organ weights were recorded for the livers (both sexes) and adrenals (males only) at 2000 and 5000 ppm. An increase in liver masses was seen in high-dose mice (both sexes) and males at 2000 ppm after necropsy. Increased incidence of liver nodules and liver mottling was noted in high-dose mice. Splenic enlargement was reported in males at 2000 and 5000 ppm. Significantly increased incidence of hepatocellular hypertrophy were noted in both sexes at 2000 and 5000 ppm. **NOEL (non-neoplastic lesions)=100 ppm** (M=12.0 mg/kg; F= 11.4 mg/kg, based on liver pathology at 2000 and 5000 ppm). Chronic inflammation of the glandular stomach and hyperplasia of the gastric mucosa was increased in males at 5000 ppm. In the spleen, extramedullary hematopoiesis was increased in males and females at 2000 and 5000 ppm. **Possible Adverse Effect:** Neoplastic lesions included hepatocellular carcinoma in males and females at 5000 ppm. **Acceptable.** Kellner, 5/1/98.

52326-038 158603 "CGA 215944 Tech. (Pymetrozine): Effect on Replicative DNA Synthesis in Hepatocytes Following Dietary Administration To Male Mice" (Persohn, E. Ciba-Geigy Limited, Basle, Switzerland; Report# CB 94/28, 5/16/95). CGA 215944 Technical (Batch # P.102002, purity 97.4%) was administered in the feed to 5 Tif: MAGf (SPF) male mice/dose at levels of 0 and 5000 ppm for 4 days or at levels of 0, 10, 100, 500, 2000 and 5000 ppm for 14 or 42 days; one high dose group was allowed 28-day recovery period. Replicative DNA synthesis was

assessed by immunohistochemical staining of liver sections for proliferating cell nuclear antigen (PCNA). PCNA is a diagnostic protein factor which is expressed in the nuclei of DNA replicating S-phase cells. Upon microscopic examination, the total number of hepatocyte nuclei per mm<sup>2</sup> was reduced after treatment with 5000 ppm for 14 and 42 days and after treatment for 42 days with 2000 ppm, indicating hypertrophy. Immunohistochemical staining of liver sections for PCNA revealed a moderate to strong increase in the fraction of DNA synthesizing hepatocytes in S-phase after administration of 2000 and 5000 ppm at all time points (indicating hyperplasia). These effects were reversible when the 14-day treatment (5000 ppm) was followed by a recovery period. These data suggested that at 2000 and 5000 ppm, the test article caused a sustained but reversible stimulation of hepatocyte cell proliferation and the hepatomegaly in the mouse liver at these dose levels was the result of hypertrophy and hyperplasia. With the assumption that these represented threshold effects, the author established a NOEL of 500 ppm [calculated mean daily dose: 70.7 to 83.9 mg/kg/day]. Supplemental study. Kellner, 6/11/98.

52326-039 158604 "Effects on Selected Biochemical and Morphological Liver Parameters Following Dietary Administration to Male Mice" (Waechter, F. and Persohn, E. Ciba-Geigy Limited, Basle, Switzerland; Study# CB 94/24, 3/29/95). CGA 215944 Technical (Batch # P.102002, purity 97.4%) was administered in the feed to 5 or 6 Tif: MAGf (SPF) male mice/dose at levels of 0, 10, 100, 500, 2000 or 5000 ppm for 14 days. Two additional groups dosed at 0 or 5000 ppm for 14 days were followed by a 28-day recovery period. Following treatment, livers were extracted and total microsomal cytochrome P450 and specific P450 isoenzyme content was determined. Moderately increased microsomal cytochrome P450 at 2000 (139% of control) and 5000 ppm (146% of control) were paralleled by 3- and 4-fold increases in microsomal CYP3A protein content at the same dose levels. At the high-dose, cytosolic glutathione S-transferase activity was increased to 188% of control. CGA 215944 was shown to be a moderate and reversible liver enzyme inducer in mice with specific induction of a cytochrome P450 isoenzyme of gene family CYP3A. The test article was classified as a pregnenolone-16 $\alpha$ -carbonitrile-type inducer of foreign compound metabolizing enzymes (3-methylcholanthrene-, phenobarbital- or peroxisome proliferator-type inducer could be excluded). Animals treated with 5000 ppm showed a moderate proliferation of smooth endoplasmic reticulum membranes and deposits of particulate glycogen; following the 28-day recovery period, hepatocytes regained the normal structural and numerical organelle characteristics. A NOEL of 500 ppm (83.5 mg/kg/day) was established for microsomal enzyme induction in male mice. Supplemental study. Kellner, 6/10/98.

### REPRODUCTION, RAT

52326-063 158652 "CGA-215944 Technical Two-Generation Reproduction Study in Rats" (Fitzgerald, R. 834-Ciba-Geigy Limited, Stein, Switzerland, Study #901486, 11/15/93). CGA 215944 Technical (Batch # P.102002, purity 98%) was administered in the diet at levels of 0, 20, 200 or 2000 ppm (mg/kg equivalents ranged from 1 to 4, 10 to 40 and 110 to 440 mg/kg/day, respectively) to 30 Tif: RA1 f (SPF) rats/sex/dose (F0 mating), with 30 weanlings/sex/dose selected for the F1 mating. F0 and F1 animals were treated for 10 weeks prior to mating, and then during mating, gestation and lactation. There were no treatment-related mortalities, clinical signs or necropsy findings in the F0 and F1 adults. Body weights were significantly reduced in the high-dose males and females from the second week of treatment to sacrifice. With the exception of females during lactation, feed consumption was less than control in the high-dose males and females throughout treatment. At necropsy, 2000 ppm F0 females had higher absolute liver and spleen weights and histopathology revealed hepatocellular hypertrophy in 27 of 30 F0 males and 2 of 30 females. Minimal to moderate hyperplasia of lymphatic follicles of splenic white pulp was seen in 25 of 30 females. Minimal hepatocellular hypertrophy was noted in 5 of 30 males at 200 ppm. **Maternal NOEL=200 ppm** (10-40 mg/kg/day, based on hepatocellular effects). **Paternal NOEL=20 ppm** (1 to 4 mg/kg/day, hepatocellular effects). In both the F0 and F1 generations, mating parameters (i.e., mating and fertility indices, mean days till positive mating, gestation, livebirth, viability and lactation indices) were similar to control in all dosage groups. **Reproductive NOEL=2000 ppm** (110-440 mg/kg/day; No effects at HDT). Eye opening was minimally delayed in the high-dose pups (about 0.4 days in the F1 litters and 0.5 days in the F2 groups). F1 litter weights were reduced in the 2000 ppm group compared to controls beginning in the second week of lactation. High-dose F2 litter weights were reduced

from day 7 onward. **Developmental NOEL= 200 ppm** (based on reduced pup weight). There were no treatment-related abnormalities noted after pup necropsy. **No Adverse effects. Acceptable**, Kellner, 3/25/98.

#### TERATOLOGY, RAT

\*\*52326-047, -058, -061 158612, 158634, 158650 "CGA-215944 Technical Rat Oral Teratogenicity"(Fitzgerald, R. 833- Ciba-Geigy Limited, Stein, Switzerland, Study #901484, 9/22/92). CGA-215944 Technical was administered via oral gavage to 24 pregnant Tif : RAI f (SPF) rats/dose at levels of 0, 30, 100 or 300 mg/kg/day on days 6 through 15 of gestation. All surviving dams underwent cesarean sectioning on day 21 post coitum and the uteri were examined for the number and distribution of implantation sites, total resorptions and live and dead fetuses; the ovaries were examined for the number of corpora lutea. No effects on mortality, clinical signs or macroscopic findings were reported. Maternal body weight gain was reduced in the 300 mg/kg group from day 6 to 11. **Maternal NOEL = 100 mg/kg/day** (based on reduced body weight gain). There were no dose-related effects on post-implantation losses, number of live fetuses per litter or fetal weights. Fetal skeletal evaluations revealed variations (probably related to delayed ossification) consisting of asymmetrically shaped sternbra-5, shortened rib 13, absent ossification of metatarsal-1, proximal phalanges of anterior digit 5 and posterior digits 2 to 5 at 300 mg/kg/day and dumbbell-shaped thoracic vertebral centers at 300 mg/kg/day; anomalies in the form of thickening of ischium and displaced pubic bone at 300 mg/kg were also noted. **No Adverse Effect; Developmental NOEL= 100 mg/kg** (based on skeletal anomalies and variations). Acceptable. Kellner, 4/2/98.

#### TERATOLOGY, RABBIT

52326-059, -060, -062, -047 158635, 158649, 158651, 158612 "CGA-215944 Technical Rabbit Oral Teratogenicity"(Fitzgerald, R. 833- Ciba-Geigy Limited, Stein, Switzerland, Study #901485, 9/28/92). CGA-215944 Technical was administered via oral gavage to 20 artificially inseminated Russian, Chbb:HM Rabbits at levels of 0, 10, 75 and 125 mg/kg/day on days 7 through 19 of gestation. Cesarean sectioning occurred on day 29 of pregnancy; uteri were examined for the number and distribution of implantation sites, total resorptions and live and dead fetuses and ovaries were examined for the number of corpora lutea. Body weights were reduced in the 125 mg/kg dose group. **Maternal NOEL = 75 mg/kg/day** (based on mortality and reduced body weight). Gross findings at cesarean section included dose-related increase in early resorptions in the 75 and 125 mg/kg groups. Post-implantation losses showed a dose-related increase in the 75 and 125 mg/kg groups, and mean litter size was lower in the 125 mg/kg dose group. There were no significant differences in mean number of corpora lutea, sex ratio or mean fetal weights. At the high-dose level, fetal external abnormalities included increased incidence of position anomaly of one or both forelimbs and skeletal variations consisted of poor or absent ossification of sternbra-5 and cervical vertebral centers. Also in this group, variations in the form of increased incidence of poor ossification of metacarpal-1, talus, and medial phalanx of anterior digit-5 were seen. An increase in the incidence of additional 13th rib was noted in the 75 mg/kg and 125 mg/kg groups and anomalies in the form of increased incidence of fused sternbrae in the 125 mg/kg group. Reduced pubis in the 75 and 125 mg/kg groups were also reported but was not statistically significant; **no adverse effects. Developmental NOEL=75 mg/kg** (increased fetal skeletal anomalies and variations). **Acceptable**. Kellner, 4/8/98.

#### GENE MUTATION

52326-065 158654 "Salmonella and Escherichia/Liver-Microsome Test" (Hertner, TH. 842-Ciba-Geigy Limited, Basle, Switzerland, Study #911189, 9/18/91). CGA 215944 Technical (Batch # P.102002, purity 98%) was tested for mutagenic potential in the Salmonella and Escherichia coli/Mammalian-Microsome Mutagenicity Assay at levels of 312.5, 625, 1250, 2500 and 5000 ug/plate (triplicate plating) using strains TA98, TA100, TA1535, TA1537 (*S. typhimurium*) and WP2uvrA (*E. coli*) with and without metabolic activation (Aroclor 1254-induced male rat liver S-9 fraction) using triplicate plating in two separate trials (48 hrs at 37°C). The test article was negative for mutagenic potential under the conditions tested. Acceptable. Kellner, 5/12/98.

52326-067 158656 "CGA-215944 Technical Gene Mutations Test with Chinese Hamster Cells V79 (OECD Conform) In Vitro" (Geleick, D. 842- Ciba-Geigy Limited, Basle, Switzerland. Study # 911191, 11/20/91). CGA 215944 Technical (Batch # P.102002, purity 98%) was tested for mutagenic potential in Chinese hamster V79 cells using the V79/HGPRT mutation assay with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) in two trials at dose levels of 5.21, 20.83, 83.33 and 333.33 µg/ml in both trials (with S-9: 5 hr incubation; without S-9: 21 hr). None of the treated cultures exhibited mutant frequencies of more than 23 mutants per 10<sup>6</sup> clonable cells. The test article was negative for mutagenicity under the conditions tested. Acceptable. Kellner, 5/12/98.

#### CHROMOSOME EFFECTS

52326-066 158655 "CGA-215944 Technical Cytogenetic Test on Chinese Hamster Cells In Vitro (EC-Conform)" (Hertner, TH., 843-Ciba-Geigy Limited, Basle, Switzerland, Study #911190, 11/22/91). CGA 215944 Technical (Batch # P.102002, purity 98%) was tested for clastogenic potential in Chinese hamster ovary cells (CCL 61) at 8 concentrations ranging from 2.58 to 330 µg/ml (chromosome analyses performed at 0, 82.5, 165 and 330 µg/ml only) with and without metabolic activation (Aroclor 1254 induced rat liver microsomal enzyme) in two trials. In the absence of S-9 activation, cells were exposed for 18 or 42 hours (3 groups); in the presence of S-9 activation cells were exposed for 3 hours (3 groups). One-hundred metaphase spreads/duplicate flask were scored for chromosomal aberrations. Five of the six groups showed no significant compound-related increase in chromosome aberrations. In the third experiment (without S-9), the percentage of specific chromosomal aberrations was 1%, 2% and 3.5% at the 82.5, 165 and 330 µg/ml concentrations, respectively; values at the two highest dose groups were statistically significantly different from the 0% obtained in the negative control. This probably did not represent compound-related effect (i.e., this was an isolated positive outcome in which the negative control value was unusually low). Therefore, the test compound is negative for chromosome aberrations under the conditions tested. Acceptable. Kellner, 5/18/98

52326-068 158657 "CGA-215944 Technical Micronucleus Test, Mouse" (Hertner, TH., 843-Ciba-Geigy Limited, Basle, Switzerland, Project #911187, 12/17/91). CGA 215944 Technical (Batch # P.102002, purity 98%) was tested for clastogenic activity in polychromatic erythrocytes from bone marrow *in vivo* in two parts: Part 1 had 8 MAGf(SPF) mice/sex/dose/sacrifice time that were administered the test compound (oral gavage) at levels of 0 or 4000 mg/kg and sacrificed at 16, 24, and 48; Part 2 had 8 mice/sex/dose administered 1000, 2000 or 4000 mg/kg and sacrificed at 24 hours; 1000 polychromatic erythrocytes/animal were scored for the presence of micronuclei. Positive control group received cyclophosphamide (64 mg/kg). In part 1, three mice/sex died after treatment in the 16 hour dosage group; the same number died after 24 hours. In the 48 hour group, 3 males and 2 females died. In groups treated with CGA-215944 in part 1, the mean % of micronucleated PCEs was 0.0% (16 h), 0.02% (24 h) and 0.09% (48 h). In part 2, one mouse/sex died at 1000 mg/kg, one male and two females died at 2000 mg/kg and 2 mice/sex died at 4000 mg/kg; there were no dose-related increases in the number of micronucleated polychromatic erythrocytes in bone marrow cells compared to control. No Adverse Effects. Acceptable. Kellner, 5/18/98.

#### DNA DAMAGE

52326-069 158658 "CGA-215944 Technical Autoradiographic DNA Repair Test on Rat Hepatocytes (OECD Conform In Vitro)" (Hertner, TH., 844; Ciba-Geigy Limited, Basle, Switzerland, Study # 911188, 12/10/91). CGA 215944 Technical (Batch # P.102002, purity 98%) was tested for potential DNA damage (UDS) *in vitro* at concentrations of 0.0, 2.78, 8.33, 25, 75, 150 or 300 µg/ml for 16-18 hours in two trials using primary rat hepatocytes from male Tif.RAlf(SPF) rats. The mean net nuclear grain counts for the 75, 150 and 300 µg/ml exposure levels were 0.34, 0.45 and 0.55, respectively in the initial trial and 0.21, 0.33 and 0.46, respectively, in the second trial. These values were comparable to the mean net control values of 0.26 (Trial 1) and 0.61(Trial 2). No Adverse Effects. Acceptable. Kellner, 5/21/98.

#### NEUROTOXICITY

**049, -143; 158614, 160561;** “An Acute Neurotoxicity Study with CGA-215944 Technical in Rats” (Ferkany, J.W., Oread Biosafety, Incorporated, Farmington, CT, Project Number A108-017, Study Number 464-96, 9/3/97). 818. CGA-215944 Technical (Batch Code P.301005, Lot No. FL950247, purity=98.2%), prepared in distilled water, was administered by gavage in a single dose at concentrations of 0 (vehicle), 125, 500, and 2000 mg/kg to 10 Crl:CD(SD)BR rats per sex per dose level. At 2000 mg/kg, 1 male was found dead and 2 males were killed *in extremis*. Treatment-related effects of chromodacryorrhea, chromorhinorrhea, discolored urine (white), infrequent stool, and staining of the head, ventral body, and extremities were observed in both males and females. Tremors and hypothermia were observed in 3 males at 2000 mg/kg. At the peak effect time point (4 hours after dosing) during FOB, treatment-related effects included tremors in the open field in males at 500 and 2000 mg/kg and in females at 2000 mg/kg, a decrease in mean number of rears in the open field in males at all dose levels and in females at 500 and 2000 mg/kg, and a statistically significant decrease in mean rectal temperature in both males and female at all dose levels with all treatment-related effects clearing by Day 8. Statistically significant decreased motor activity counts at the peak effect time point in males at all dose levels and in females at 500 and 2000 mg/kg were observed. Necropsy and microscopic examination revealed no compound-related, neurological lesions in the high dose males or females. **Possible adverse effect: Tremors in males at 500 and 2000 mg/kg and in females at 2000 mg/kg during FOB open field observations at the peak effect time point.** NOEL (M/F)< 125 mg/kg (based on a treatment-related decrease in mean rectal temperature at the peak effect time point). **Acceptable.** (Corlett, 5/4/98)

**035; 158600;** “An Acute Dose Ranging Study of CGA-215944 Technical in the Abbreviated Functional Observational Battery in Adult Male and Female Sprague Dawley Rats” (Ferkany, J.W., Oread Biosafety, Incorporated, Farmington, CT, Project Number A066-017, Study Number 529-97, 5/6/97). CGA-215944 Technical (Batch P.301005, Lot No. FL950247, purity=98.2%), mixed with distilled water, was administered by gavage in a single dose at concentrations of 0, 500, 1000, 2000, 4000, or 6000 mg/kg to 3 Crl:CD(SD)BR rats per sex per dose level. All animals survived through the 5 day observation period except for 2 of 3 males at 6000 mg/kg that were sacrificed *in extremis*. For the abbreviated FOB, treatment-related effects of decreased locomotor activity, decreased arousal level, and immobility beginning at 500 mg/kg in males and at 1000 mg/kg in females 2 hours after dosing, tremors beginning at 2000 mg/kg in both males and females 2 to 8 hours after dosing, and flattened body position beginning in males at 2000 mg/kg and in females at 6000 mg/kg 2 to 8 hours after dosing were observed. **Adverse effect indicated: tremors at 2000 mg/kg in both males and females.** NOEL (M)< 500 mg/kg and (F)=500 mg (both based on decreased locomotor activity, decreased arousal level, and immobility). **Supplemental study** (only 3 animals per sex per dose level used, animals only observed for 5 days following dosing, and no histopathology performed on test animals). (Corlett, 2/25/98)

055, 136, 137; 158625, 160044, 160045; “13-Week Dietary Neurotoxicity Study with CGA-215944 Technical in Rats” (Weiler, M.S., Covance Laboratories Inc., Madison, WI, Project No. 6804-100, Study No. 530-97, 9/3/97). 827. CGA-215944 Technical (Lot No. FL950247, purity=98.2%) was admixed to the feed at concentrations of 0, 500, 1000, or 3000 ppm (0, 35, 68, or 201 mg/kg/day, respectively, for males and 0, 41, 81, or 224 mg/kg/day, respectively, for females) and fed to 10 Crl:CD<sup>®</sup>(SD)BR VAF/Plus<sup>®</sup> rats per sex per dose level continuously for a period of 13 weeks. No animals died. A statistically significant decrease in mean body weight in both males and females at 3000 ppm was observed. During Week 4 FOB assessments, a statistically significant increase in incidences of turning to the stimulus during touch response reflex testing and a treatment-related increase in stereotypy (head continuously moving, excessive sniffing) in males at 3000 ppm were observed. Also during FOB assessments, a statistically significant increase in incidences of avoidance of stimulus during touch response reflex testing were observed in females at 3000 mg/kg during Weeks 4 and 8 was observed. No treatment-related effects were observed at gross necropsy or during microscopic examination. **No adverse effects.** NOEL (M)=68 mg/kg/day (1000 ppm) and (F)=81 mg/kg/day (1000 ppm) (both based on decreased mean body weight and various FOB observations). **Acceptable.** (Corlett, 3/25/98)

52326-0205; 215681; "Pymetrozine Technical (CGA-215944): Preliminary Developmental Neurotoxicity Study in Rats"; (P.J. Pinto; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; Study No. RR0921; 11/20/03); Ten time-mated female Alpk:AP<sub>1</sub>SD (Wistar-derived) rats/group received 0, 500, 1500 or 3000 ppm of Pymetrozine Technical (CGA-215944) (batch no. P301005; purity: 99.3%) in the diet from day 7 of gestation through day 22 *post-partum* (gestation: 0, 40.8, 118, 195 mg/kg/day, lactation: 0, 84.6, 247, 443 mg/kg/day). Two dams in the 3000 ppm treatment group did not have litters. Two other dams in this dose group suffered total litter loss on days 5 and 8 *post partum*. The maternal mean body weights and food consumption of the 3000 ppm treatment group were less than those of the controls throughout the study. The mean body weights of both sexes in the 3000 ppm group of the F1 generation were less than those of the controls from day 5 *post partum* to the termination of the study on day 22 ( $p<0.01$ ). **Study supplemental** (non-guideline dose range-finding study). (Moore, 8/19/05)

52326-0204; 215678; "Pymetrozine Technical (CGA-215944): Developmental Neurotoxicity Study in Rats"; (P.J. Pinto; Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK; Study No. RR9022; 11/21/03); Thirty time-mated female Alpk:AP<sub>1</sub>SD (Wistar-derived) rats/group received 0, 100, 500 or 2500 ppm of Pymetrozine Technical (CGA-215944) (batch no. P.301005; purity: 99.3%) in the diet from day 7 of gestation through day 22 *post-partum* (gestation: 0, 8.1, 38.7, 173.1 mg/kg/day, lactation: 0, 16.8, 82.6 mg/kg/day). The F1 offspring were culled on day 5 *post partum*. One pup/sex/litter/group was examined in the Functional Observational Battery on days 5, 12, 22, 36, 46 and 61 *post partum*. One pup/sex/litter/group was examined for motor activity on days 14, 18, 22 and 60 *post partum*. One pup/sex/litter/group was examined in the auditory startle response assessment on days 23 and 61 *post partum*. One pup/sex/litter/group was assigned to the learning and memory test. The learning phase was performed on days 21 and 59 *post partum*. The memory test was performed on days 24 and 62. Due to excessive maternal toxicity, all of the surviving dams and pups in the 2500 ppm group were euthanized during the lactation period. There was no apparent treatment-related effect upon the mean body weights or food consumption of the 500 ppm treatment group. No apparent treatment-related effect on gestation length was evident although three of the dams in the 2500 ppm group exhibited parturition difficulties. In the FOB for the dams, two of 16 females in the 2500 ppm group exhibited hunched posture and other signs of ill health on day 2 of lactation. These effects were likely due to difficulties related to parturition. No treatment-related effects were noted at the other time points for which the FOB was performed. A dose-related response was evident for the number of dams suffering total litter loss by day 5 of lactation (0: 2/30, 100: 3/30, 500: 5/29, 2500: 4/15). Otherwise, the number of pups/litter was not affected by the treatment. The mean body weights of the F1 offspring in the 500 ppm group were not affected over the course of the observation period. No treatment-related effects were noted in the F1 offspring Functional Observational Battery at any of the time points. The treatment did not result in an effect on the time of preputial separation or vaginal opening of the F1 offspring. The motor activity assessment did not reveal any consistent pattern of a dose-response over the time course of the study. The auditory startle response test did not demonstrate any treatment-related effects at either of the testing time points. The learning and memory tests did not reveal any consistent treatment-related deficits at the two time points of evaluation. In the hematology evaluation, the mean white blood cell count and lymphocyte count for the 500 ppm female F1 offspring were less than those values for the controls ( $p<0.05$ ). No treatment-related effect upon the absolute or relative brain weights was evident at either 12 or 63 days. Isolated areas of the brain from the F1 offspring demonstrated measurements statistically different from those of the controls at either 12 or 63 days. The only site which was consistently different from that of controls at both 12 and 63 days was the increased thickness of the corpus callosum, level 4 in the male offspring (day 12, 500 ppm,  $p<0.05$ , day 63, 100 and 500 ppm,  $p<0.05$ ). **No adverse effect indicated.** Reported **Developmental Neurotoxicity NOEL:** 500 ppm (38.7 mg/kg/day (gestation), 82.6 mg/kg/day (lactation) (based upon the absence of any apparent neurotoxic or behavioral effects upon the F1 offspring); **Study unacceptable**, possibly upgradeable with the submission of positive control data). (Moore, 9/29/05)

## RAT METABOLISM

52326-070 158503 "The Metabolism of [6-<sup>14</sup>C]triazine and [5-<sup>14</sup>C]pyridine CGA-215944 in the Rat" (Schulze-Aurich, J. 851- Ciba-Geigy Limited, Basle, Switzerland, Project # 001AM01, 001AM02, 001AM03, Report 15/93, 2/3/94). Non-radiolabeled: CGA 215944 (Batch # AMS 522/101) purity >99%; Radiolabeled: [6-<sup>14</sup>C]triazine CGA 215944 (Batch #CFQ-6041-2 and CFQ-6041-3) specific activity 2090 kBq/mg (56.5 µCi/mg); [5-<sup>14</sup>C]pyridine CGA 215944 (Batch Ko-10.1A and Ko-10.2A) specific activity 3150 kBq/mg (85.1 µCi/mg) or 2120 kBq/mg (57.3 µCi/mg), purity of > 95%. was administered to 5 Tif: RAIf (SPF) rats/sex at 0.5 mg/kg, to 5 rats/sex at 0.5 mg/kg (after 14 days of unlabeled CGA 215944) and to 5 rats/sex at 100 mg/kg by oral gavage or 5 rats/sex at 0.5 mg/kg by I.V. route. A majority of the oral dose (57-85%) was absorbed from the G.I. tract rapidly, with maximum blood levels 15 minutes and 4 hours at the low and high dose level, respectively. Both sexes excreted more via the kidneys at the high dose level. Half-lives ( $t_{1/2}$ ) for the depuration of the residual radiolabel from the tissues were about 1 to 2 hours at the 0.5 mg/kg level and 3 to 6 hours (fat was longer at 11 hours) and 2 to 11 hours for the triazine and pyridine label, respectively, at the high dose level. Detectable residues were measured in all tissues and organs seven days after administration. Mean values were below 0.025 ppm, except in the heart (0.038 ppm), respectively. The metabolite pattern was complex in urine and feces (i.e. up to 14 metabolite fractions) and the qualitative distribution was largely independent of sex, dose level, pretreatment, route of administration or label. The primary pathway was oxidation of the methyl substituent at the triazine ring leading to metabolite 3U (4,5-dihydro-6-hydroxymethyl-4-[(3-pyridinylmethylene) amino]-1,2,4-triazin-3(2H)-one). Acceptable. (Kellner, 6/1/98).

52326-138 160431 addendum to -070 158503 "The Absorption, Distribution and Excretion of [Triazine-6-<sup>14</sup>C] and [Pyridine-5-<sup>14</sup>C] CGA 215944 in the Rat" (Jack, L. and Dunsire, J. 851- Inveresk Research International, Tranent, Scotland, Report# 777-95, 12/18/95). The fate of CGA 215944 was investigated in 12 groups of male and female Sprague Dawley rats using [Triazine-6-<sup>14</sup>C] and [Pyridine-5-<sup>14</sup>C]-labeled CGA 215944 administered at 2 dose levels (0.5 and 100 mg/kg) ; 16 males had their bile ducts cannulated. Levels of radiolabeled compound in the blood after low dose indicated rapid absorption with maximum concentrations at 1 hour post dose; rapid clearance was achieved with triazine label, with blood levels near background by 24 hours. Independent of both the dose level and the site of labeling, at least 82% of an oral dose was absorbed from the G.I. tract into the general circulation. The highest tissue levels of radioactivity were found in the liver and kidney. The high levels in the liver and kidney reflect that both urine and bile are routes of excretion of the test substance; independent of the site of labeling, biliary excretion seems to be higher at the low dose level at the expense of urinary excretion. Supplemental. (Kellner, 6/10/98).

52326-040 158605 "CGA-215944 tech. (Pymetrozine) Effects on biochemical and morphological liver parameters as well as on plasma thyroid stimulating and thyroid hormones following dietary administration to female rats" (Beilstein, P. -Ciba-Geigy Limited, Basel, Switzerland; Study# CB 94/64, 3/15/96). CGA 215944 Technical (Batch # P.102002, purity 98%) was administered in the feed to 5 to 7 Tif: RAIf (SPF) female rats/dose at levels of 0, 20, 100, 1000 and 3000 ppm for 14 days to identify potential effects on plasma thyroid stimulating hormone (TSH), thyroid hormone concentrations (T3, T4 and rT3) and other biochemical parameters (e.g., microsomal UDP-glucuronosyltransferase, cytosolic glutathione S-transferase and microsomal cytochrome P-450). The reversibility of effects was assessed after treatment with 0 and 3000 ppm for 14 days followed by a 28-day recovery period; the thyroid hormone status in plasma was also determined in rats treated for 4 days with 0 and 3000 ppm as well as for 42 days with 0, 20, 100, 1000 and 3000 ppm. Subchronic treatment caused a strong induction of the phase II liver enzyme UDP-glucuronosyltransferase and a moderate induction of cytosolic glutathione S-transferase. Microsomal cytochrome P-450 was marginally affected. Microscopic changes included moderate proliferation of smooth endoplasmic reticulum membranes. The pattern of hepatic enzyme induction identified the test article as a moderate but reversible inducer of mainly phase II hepatic metabolizing enzymes. Plasma TSH and thyroid hormone determinations indicated a slight stimulatory effect of the test article on the thyroid gland. A NOEL of 100 ppm (about 8 mg/kg) was established for these effects in female rats. Supplemental study. Kellner, 6/11/98.

#### **SUBCHRONIC STUDIES**

##### **Rat Subchronic Toxicity Study**

051; 158617; "3-Month Oral Toxicity in Rats (Administration in Food)" (Gerspach, R., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Study Number 901479, 5/5/92). 821. CGA 215944 tech. (Batch No. P. 102002, purity=98%) was admixed to the pelleted food at concentrations of 0, 50, 500, or 5000 ppm (0, 3.42, 32.5, or 360 mg/kg/day, respectively, for males and 0, 3.63, 33.9, or 370 mg/kg/day, respectively, for females) and fed to 10 Tif: RAlf (SPF) hybrids of RII/1 x RII/2 rats per sex per dose level [with 10 additional rats per sex per dose level at the 0 and 5000 ppm levels to test recovery (4 week recovery period used)] continuously for a period of 3 months. No animals died. No treatment-related clinical signs were observed. A statistically significant decrease in mean body weights was observed in both males and females at 5000 ppm at Weeks 14 and 18. A statistically significant increase in mean alkaline phosphatase levels was observed in both males and females at 5000 ppm at Week 14 but not at Week 18. A statistically significant increase in mean relative liver and mean relative spleen weights was observed in both males and females at 5000 ppm at Weeks 14 and 18. Microscopic examination revealed hypertrophy of centrilobular hepatocytes in males at 5000 ppm at Week 14 but not at Week 18 and atrophy of the thymus at 5000 ppm in both males and females at Week 14 and in males only at Week 18. **No adverse effects.** NOEL (M)=32.5 mg/kg/day (500 ppm) based on decreased mean body weight, an increase in mean alkaline phosphatase level, an increase in mean relative liver and spleen weights, and hypertrophy of centrilobular hepatocytes and (F)=33.9 mg/kg/day (500 ppm) based on decreased mean body weight, an increase in mean alkaline phosphatase level, and an increase in mean relative liver and spleen weights. **Acceptable.** (Corlett, 3/18/98)

#### **Dog Subchronic Toxicity Study**

144; 161052; "3-Month Subchronic Dietary Toxicity Study in Beagle Dogs" (Altmann, B., Ciba-Geigy Limited, Short-/Long-term Toxicology, Stein, Switzerland, Test No. 901480, 11/27/92). 821. CGA 215944 tech. (Batch No. P. 102002, purity=98%) was admixed to the feed at concentrations of 0, 100, 500, or 2500 ppm (0, 3.12, 13.9, and 53.4 mg/kg/day, respectively, for males and 0, 3.24, 14.5, or 60.2 mg/kg/day, respectively, for females) and fed to 4 Beagle dogs per sex per dose level once per day, 7 days per week for 13 weeks. One female at 2500 mg/kg/day was sacrificed in moribund condition. Treatment-related decreases in mean body weight and mean food consumption in males and females at 2500 ppm were observed. Treatment-related decreases in mean red blood cell, hemoglobin, hematocrit, and platelet levels and a treatment-related increase in mean prothrombin time were observed in both males and females at 2500 ppm. At 2500 ppm, treatment-related increases in mean bilirubin, aspartate aminotransferase, and alanine aminotransferase levels in males and females, treatment-related increases in mean gamma-glutamyl transpeptidase and creatine kinase levels in males, and treatment-related increases in mean protein, globulin, and alkaline phosphatase levels in females were observed. At 2500 ppm, treatment-related increases in mean relative liver and spleen weights in males and females and a treatment-related increase in mean relative kidney weights in females were observed. Microscopic examination revealed numerous treatment-related findings including proliferation of intrahepatic bile ducts in both males and females at 500 and 2500 ppm. **No adverse effects.** NOEL (M)=3.12 (100 ppm) and (F)=3.24 (100 ppm) mg/kg/day based on the proliferation of intrahepatic bile ducts in the liver. **Acceptable.** (Corlett, 6/2/98)

#### **Mouse Subchronic Dietary Toxicity Study**

050; 158616; "3-Month Range Finding Study in Mice" (Gerspach, R., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Study Number 901478, 6/22/92). CGA 215944 tech. (Batch No. P. 102002, purity=98%), was admixed to the feed at concentrations of 0, 1000, 3000, or 7000 ppm (0, 143, 429, or 1002 mg/kg/day, respectively, for males and 0, 252, 589, or 1240 mg/kg/day, respectively, for females) and fed to 10 Tif:MAGf (SPF), hybrids of NIH x MAG albino mice per sex per dose level continuously for a period of 3 months. No animals died. No treatment-related clinical signs were observed. A statistically significant and dose-related increase in mean relative liver weights in males at all dose levels and in females at 3000 and 7000 ppm was observed, and a statistically significant increase in mean spleen weights in both males and females at 3000 and 7000 ppm was observed. Microscopic examination revealed dose-related increases in slight focal cell necrosis in the hepatic parenchyma in males at 7000 ppm and in females at all dose levels, in slight to moderate centrilobular hypertrophy of hepatocytes in both

males and females at 3000 and 7000 ppm, and in slight, centrilobular, perivascular-like aggregations of lymphocytes in both males and females at 3000 and 7000 ppm. **No adverse effects.** NOEL (M)< 143 mg/kg/day (1000 ppm) based on an increase in mean relative liver weights and (F)< 252 mg/kg/day (1000 ppm) based on an increase in slight focal cell necrosis in the hepatic parenchyma. **Supplemental study** (no clinical biochemistry determinations on the blood of the test animals and no ophthalmological examinations on the eyes of the test animals were conducted). (Corlett, 3/11/98)

#### **Rat 4-Week Oral Toxicity Study**

052; 158620; "28-Day Oral Cumulative Toxicity Study in Rats (Gavage)" (Frankhauser, H., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Study Number 922002, 10/15/92). CGA 215944 tech. (Batch No. P. 102002, purity=98%) was administered orally by gavage at concentrations of 0 (vehicle, distilled water containing 0.5% carboxymethylcellulose and 0.1% Tween 80), 10, 100, or 600 mg/kg to 10 Tif:RAIf (SPF), hybrids of RII/1xRII/2 rats per sex per dose level daily for 28 days. One female at 600 mg/kg was found dead on Day 26. Reddening of the ears was observed in both males and females at 600 mg/kg. A statistically significant decrease in the mean red blood cell count in both males and females at 600 mg/kg was observed. Statistically significant increases in mean total bilirubin and mean cholesterol levels, and a dose-related increase in the mean alkaline phosphatase level in both males and females at 600 mg/kg were observed. Statistically significant increases in mean relative liver, kidney, and spleen weights in both males and females at 600 mg/kg, and a dose-related decrease in mean relative thymus weights in both males and females at 600 mg/kg were observed. Macroscopic examination revealed incidences of large liver and small thymus in both males and females at 600 mg/kg. Microscopic examination revealed hypertrophy of centrilobular hepatocytes and hyperplasia of splenic white pulp in both males and females at 100 and 600 mg/kg. **No adverse effects.** NOEL (M/F)=10 mg/kg (based on incidences of hypertrophy of centrilobular hepatocytes and hyperplasia of splenic white pulp). **Supplemental study** (study interval only 28 days). (Corlett, 3/30/98)

#### **Rat 4-Week Repeated Dosing Dermal Toxicity Study**

054; 158623; "28-Day Repeated Dose Dermal Toxicity Study in the Rat" (Hagemann, Ch., Ciba-Geigy Limited, Short/Long-term Toxicology, Stein, Switzerland, Study Number 901477, 1/28/93). 822. CGA 215944 tech. (Batch No. P. 102002, purity=98%), suspended in distilled water, was applied to the clipped skin of 5 Tif:RAIf (SPF) hybrids of RII/1 x RII/2 rats per sex per dose at concentrations of 0, 10, 100, or 1000 mg/kg/day for 6 hours per day 5 days per week for 4 weeks using an occlusive dressing. One female at 10 mg/kg was found dead on Day 25. No treatment-related clinical signs or signs of local irritation were observed. Hematology and clinical biochemistry performed on the test animals revealed no treatment-related effects. Macroscopic and microscopic examination revealed no treatment-related findings. **No adverse effects.** NOEL (systemic and dermal, M/F)=1000 mg/kg/day based on the absence of treatment-related systemic effects and the absence of signs of local irritation. **Acceptable.** (Corlett, 4/3/98)