Methylphenidate Gene Toxicity Meeting
Best Pharmaceuticals for Children Act
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
August 29, 2008
6100 Executive Boulevard
Rockville, MD

This meeting was sponsored by the Obstetric and Pediatric Pharmacology Branch (OPPB), Center for Research for Mothers and Children (CRMC), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (HHS), in support of the Best Pharmaceuticals for Children Act (BPCA) Program.

Meeting Goals

The goals of the meeting were to:
- Review genetic toxicity data—consider adequacy of current data and additional experiments that should be conducted
- Review pubertal progression information and ongoing experiments
- Consider late fall meeting/discussion for integrated summary of data and recommendations from public health perspective.

Introductions and Overview of Collaboration

Donald R. Mattison, M.D., Captain, U.S. Public Health Service; Senior Advisor to the Directors of NICHD and CRMC; Chief, OPPB, CRMC, NICHD, NIH

Dr. Mattison thanked the meeting participants for their attendance. He explained that NICHD was given the responsibility for implementing the BPCA Program and that the methylphenidate (MPH) gene toxicity activities evolved out of the BPCA Program. Dr. Mattison thanked his colleagues at the National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), and the National Center for Toxicological Research (NCTR), Food and Drug Administration (FDA), for their collaboration with the MPH gene toxicity activities. The participants then introduced themselves.

Genetic Toxicity of MPH: Additional Studies

Suzanne Morris, Ph.D., Division of Genetic and Reproductive Toxicology, NCTR, FDA

Dr. Morris summarized some findings from a literature review of MPH genetic toxicity and follow-up communications with authors. The studies and findings are as follows:

Dunnick and Hailey (1995):
- Two-year chronic bioassay in F344 rats and B6C3F1 mice
- Doses of 0, 100, 500, or 1,000 ppm in rats
- Doses of 0, 50, 250, or 500 ppm in mice

- Increase in benign liver tumors and liver weights in male and female mice
- Increase in hepatoblastoma in male mice (high dose)
- No increase in tumors in rats.

Teo et al. (2003):
- 90-day toxicity study
  - 2–50 mg/kg/day of D-MPH
  - 100 mg/kg/day of D,L-MPH
  - Changes in clinical chemistry at sacrifice
  - Body and organ weight changes at sacrifice
- D-MPH
  - *In vitro*
    - Ames assay: negative
    - Mouse lymphoma assay (MLA): negative
  - *In vivo*
    - Bone marrow micronucleus (MN) assay: negative.

Suter et al. (2006):
- *In vitro* cytogenetics
  - Human peripheral blood (10 μM)
  - Negative for chromosomal aberrations (CA)
  - Negative for aneuploidy
- *In vivo* bone marrow MN
  - Negative up to 250 mg/kg.

Dr. Suter and colleagues have conducted no additional MPH cytogenetic studies.

Holtmann et al. (2006):
- Position paper on the need for further testing of MPH
- No data presented in this manuscript.

No additional studies are planned by these authors. In a personal communication, they suggested contacting Susanna Walitza and Helga Stopper.

Walitza et al. (2007):
- Pediatric (11- to 15-year-olds) study
  - Determine MN frequency at 1 month, 3 months, and 6 months of treatment
- No increase in the MN frequency.

Additional studies have been completed but not published. Dr. Stopper may provide a draft report before the Environmental Mutagen Society annual meeting in Puerto Rico, October 18–23, 2008. Although additional time points and patients have been added to the studies, the conclusions have not changed.

Andreazza et al. (2007):
- 25- or 60-day-old Wistar rats
- Acute or chronic (28 days)
  - 1, 2, or 10 mg/kg of D,L-MPH (intraperitoneal)
- Comet assay—brain, peripheral blood
  - Positive in brain; negative in peripheral blood
- Micronuclei assay—peripheral blood
  - Negative.

This author has not responded to communication.

Other studies on MPH genetic toxicity include the following:
- Von Gompel et al. (2005)
  - Negative in the yeast GreenScreen assay (activation of RAD54 promoter)
- Snyder et al. (2006)
  - Negative in the 3-D docking study, which suggests that MPH is not an intercalating agent
- Storer et al. (2001)
  - MPH is negative in the 6-month p53+/– mouse tumor study.

The literature search included the following studies on the effect of MPH on pubertal progression:

Martin et al. (2006):
- Pubertal changes and sensation seeking in 11- to 15-year-olds with attention deficit/hyperactivity disorder (ADHD)
- Patients with current or past history of uncomplicated stimulant medication use for ADHD
- Significant association ($p < 0.01$) between Tanner staging (sexual maturation staging), testosterone, and dehydroepiandrosterone sulfate (DHEAS).

Adriani et al. (2006):
- Injected male rats with 2 mg/kg of MPH or saline
- Postnatal day (PND) 44, sacrifice at 2 hours
- PND 30–44, sacrifice at 2 hours
- PND 30–44, sacrifice at 2 months
- Testis recovered
- Testis weight reduced in all three groups *($p < 0.05$); reductions in
  - Sperm head count
  - Total sperm/testis *($p < 0.05$)
  - Intratesticular testosterone levels
  - Testosterone/testis *($p < 0.05$).

Hibel et al. (2007):
- Saliva collected three times a day (morning, noon, and evening)
- 432 children, 6–13 years old
- Measured salivary cortisol, testosterone, and dehydroepiandrosterone (DHEA)

- Diurnal decline in salivary testosterone level in controls between 10:00 a.m. and 4:00 p.m.
- No decline in testosterone levels in MPH-treated subjects.

Dr. Morris explained that reproductive measurements have been collected as part of ongoing MPH studies in nonhuman primates (NHPs). A group from the National Institute for Occupational Safety and Health (NIOSH) is conducting the reproductive assessments, including spermatocrits, sperm motility, and sperm morphology. Sperm chromatin assays will be included to measure strand breaks in the sperm. Data are not yet available. However, preliminary findings indicate differences in sexual maturity and the ability to collect samples in MPH-treated versus untreated subjects.

Lois Winsky, Ph.D., mentioned another source of MPH data: A study currently being conducted by Linda Perrino at Wake Forest University. The study is funded by the National Institute on Drug Abuse.

Genotoxicity Studies in Big Blue Mice Fed MPH

Mugimane G. Manjanatha, Ph.D., NCTR, FDA

Many genotoxicity assays (for example, Ames, MLA, and MN) conducted in rodents have been negative. However, B6C3F1 mice fed MPH showed increase in liver adenomas (NTP CAS # 298-59-9 feed studies, 1995). The NTP investigators hypothesized that the tumors arose through cell proliferation rather than mutation. Mutations were not measured in the target tissue (liver). Comparisons to human studies are difficult because pharmacokinetic (PK) studies have not been performed in the mouse.

Findings from a subsequent dose–range study are as follows:

- Mice tolerated MPH doses up to 4,000 ppm.
- Ritalinic acid (RA) was the reactive metabolite of MPH.
- The average weights for kidneys, seminal vesicle, testes, and urinary bladder were significantly lower than control mice ($p \leq 0.05$).
- MPH-treated mice showed liver hypertrophy.
- *HPRT* and MN assays were negative.

The NPT investigators conducted a study of MPH mutagenicity in the Big Blue Mouse model. The investigators hypothesized that if MPH or its reactive metabolite RA could cause mutations in Big Blue mice, MPH or RA could potentially cause mutations in humans. Details of the study are as follows:

- Selected doses included
  - Cancer bioassay (500 ppm)
  - Additional doses to inform the dose–response curve
- *cII* mutant frequency determined in the liver
- MN frequency determined in peripheral blood
- *HPRT* mutant frequency measured in spleen lymphocytes
- Mode of action for mouse liver tumor formation by MPH (genotoxic or nongenotoxic mechanism).

Summary results are as follows:

- There was no significant difference in food consumption between control and MPH-treated groups.
- Body weights of mice fed higher doses of MPH were significantly lower than those of controls ($p \leq 0.01$).
- Lymphocyte *HPRT* mutant frequency did not increase.
- Erythrocyte MN frequency did not increase.
- *cII* mutant frequencies in the livers of Big Blue mice were not elevated compared with controls.

These results suggest that MPH is nonmutagenic. The induction of liver tumors by MPH is probably due to a nonmutagenic mode of action. With regard to lower body weights of mice fed higher doses of MPH, there is anecdotal evidence that these mice were hyperactive, but no data on metabolism were collected.

Genetic Toxicity of MPH in NHPs

Dr. Morris

This study of the genetic toxicity of MPH is funded by the NICHD through an interagency agreement. The chromosome painting (measures chromosome damage) has been performed under a contract between the NCTR (Dr. Morris) and Wayne State University (James Tucker, Ph.D., and Dayton Petibone, M.S.). The experimental design includes:

- Health monitoring
- Behavioral assessments
- Exposure assessments and PK studies
  - Determine MPH and RA levels in serum at monthly intervals
  - Evaluate PK at 3- to 6-month intervals
- Genetic toxicology evaluation.

The genetic toxicology evaluation included MN frequency, *HPRT* mutant frequency in T-lymphocytes, and chromosome painting (translocation frequency in T-lymphocytes). The chromosomal paintings were performed at Wayne State University. The other assays were conducted at NCTR.

Test subjects were approximately 2-year-old, male rhesus monkeys (*Macaca mulatta*) obtained from the FDA's Center for Biologics Evaluation and Research free-ranging colony in South Carolina. Test subjects passed all health checks and were released from quarantine. They underwent preliminary training for dosing, blood withdrawal, and behavioral testing. Dosing started May 15, 2006. MPH was administered via dosing syringe in a Prang vehicle. Animals were dosed two times per day, in three dose groups:

- Control (10 NHPs)
- Low: 0.15 mg/kg two times per day (10 NHPs) increased to 2.5 mg/kg two times per day
- High: 1.5 mg/kg two times per day (10 NHPs) increased to 12.5 mg/kg twice per day

After 4 months of exposure, the low and high doses were increased to 2.5 mg/kg and 12.5 mg/kg, respectively, to achieve therapeutic serum levels.

Because of the potential for anemia due to the number of blood draws for the cytogenetic and mutation studies, hemocrits, white blood cell (WBC) concentration, and complete blood counts were monitored.

Exposure assessments included:
- Serum MPH concentration
- Serum RA concentration
- Average body weight
- WBC concentration
- Lymphocyte concentration
- Red blood cell (RBC) concentration
- Alanine transaminase (ALT) concentration
- Aspartate transaminase (AST) concentration
- MN-reticulocyte (RET) frequency
- *HPRT* mutation frequency
- Chromosome aberrations (full cytogenetic analysis).

Results for the exposure assessments are as follows:
- Average body weight: no significant difference between treated subjects and controls
- WBC concentration: initially different (months 0–4) but not significantly different from 6 to 12 months on dose
- Lymphocyte concentration: no statistically significant difference
- RBC concentration: no statistically significant difference
- ALT concentration: statistically significant effect of dose (due primarily to high dose)
- AST concentration: no statistically significant difference
- MN- RET frequency: no statistically significant difference either overall or at individual time points
- Chromosome aberrations: no statistically significant difference.

Future studies include exposure assessment and PK, bone growth, cardiac function, and reproductive function (but not breeding performance).

Gene Mutation Detection in Rhesus Monkeys: The *HPRT* and *PIG-A* Story

Vasily Dobrovolsky, Ph.D., NCTR, FDA

Dr. Dobrovolsky explained the rational for including lymphocyte gene mutation detection in the NCTR/WSU rhesus monkey study:
- CA and gene mutations may lead to cancer.
- CA is indicative of DNA damage, which may lead to gene mutations.
- Measuring mutation in cancer-relevant genes is difficult (no phenotype).
- Surrogate targets, such as endogenous genes and transgenes, allow phenotypic selection (in clonal assays).

The *HPRT* assay was used to assess gene mutation in the MPH gene mutation study. The *HPRT* gene is

- X-linked (one functional copy in males and females)
- Present in all mammalian species
- Disposable *in vitro* (important for clonal assay in primary cell cultures)
- An established and verified model (mouse, rat, human, and cynomolgus monkey).

Dr. Dobrovolsky described the procedures for clonal selection of *HPRT* mutants, detection of *HPRT* mutation in peripheral lymphocytes, and automated plate scoring.

The study results indicated that:

- MPH is not mutagenic in the *HPRT* gene of the NHP model.
- There is no increase in *HPRT* mutant frequency.
- The spectrum of *HPRT* mutation in MPH-treated animals is consistent with the spectrum of spontaneous mutation in the *HPRT* gene of other species.

There are several limitations of the *HPRT* assay:

- It does not detect loss of heterozygosity/large deletion mutation.
- It is limited to T-lymphocytes.
- There is negative selection against *HPRT* mutants.
- The culture medium is not commercially available.
- Indirect mutant frequency calculation requires establishing two dissimilar types of cultures.
- The assay is time consuming and does not produce enough lymphocytes.

The *PIG-A* assay provides an alternative to the *HPRT* assay. Endogenous X-linked phosphatidyl inositol glycan (complementation group A) gene (*PIG-A*) is a novel target for mutation detection. *PIG-A* mutation leads to an acquired genetic disorder, paroxysmal nocturnal hemoglobinurea (PNH), which is a surface protein (glycosylphosphatidylinositol [GPI]) deficiency.

Dr. Dobrovolsky described the GPI anchor, the wild-type cell versus *PIG-A* mutant, and the procedure for detecting the *PIG-A* mutation. A study of *PIG-A* mutation frequency in rat RBCs showed that at doses used in the study and within detection sensitivity of the *HPRT* and *PIG-A* gene-based models, MPH is not a gene mutagen.

Cytogenetic Effects of Stimulus Medications for ADHD in Periadolescent Rhesus Monkeys

Michael Weed, Ph.D., Assistant Professor, Psychiatry and Behavioral Science, Behavioral Biology Research Center, Johns Hopkins University (JHU)

This study is funded by the National Institute of Mental Health (NIMH) and is being conducted by JHU. The study is designed to look at the effects of stimulant drugs used to treat ADHD: MPH and amphetamine (75 percent dextro, 25 percent levo). There were 24 study animals, which were taught to voluntarily drink about 100 ml of fluid at 9:00 a.m. and 12:00 p.m. The fluid is Tang or Tang plus drug. The monkeys drink a characteristic amount, and the drug is

titrated so that the monkeys receive roughly the same dose every day. The drug dose was increased slowly over a 6-week period and titrated to target blood plasma levels of 15–20 ng/ml. The final dosing was 15 mg/kg per drinking session. The monkeys are all juvenile males. They were about 2.6 years of age at the start of treatment. The study will have an 18-month exposure period. Cytogenetic data are from 3 months and 6 months of exposure. The 12-month samples have been collected and are being analyzed. The study of cytogenetic effects is an add-on to a larger study, which includes behavioral measures and positron emission tomography studies of brain dopamine function.

All assays were conducted by SRI International in a blinded analysis. The samples were analyzed as collected. The analyses included CA, SCE, and MN. Dr. Weed presented data on change from pretreatment baseline for CA, SCE, and MN. Each animal was compared with its own baseline. There was no change for CA (that is, a very strong no effect). For SCE, there were pronounced, tight increases at 3 and 6 months for both MPH and amphetamine. The increases were not large, but they are statistically significant. The increases for MN at 3 and 6 months were also significantly different and statistically reliable.

The baseline SCE frequency for untreated animals was 2.57 per cell. The baseline frequencies were established 5 months before the treatment. Bromodeoxyuridine concentration was 19.5 μM (6 μg/ml culture media). There was good differentiation. Rupa Doppalapudi, Ph.D., explained the procedures for analyzing CA, SCE, and MN.

The 24-hour activity patterns for drug-treated monkeys are different from untreated monkeys, but the overall amount of activity is not very different. Hyperactivity is not apparent with visual observation. There is a delay to sleep onset in the treated monkeys, but there is not an overall significant increase in activity. The level of hyperactivity is probably not enough to cause free-radical damage increase SCE.

The rhesus monkeys (*M. mulatta*) in the study were of Chinese origin, not Indian origin. It has been proposed that the Chinese monkeys are a subspecies. The Chinese monkeys are known to respond differently to stress and are considered friskier than the Indian monkeys. The two types of monkeys are immunologically different and are slightly different in physical appearance. As far as is known, the two types have the same life expectancy.

With regard to SCE data, there is a strong trend among control animals of increases from baseline at 3 and 6 months. The gap between 0 month and 3 months sampling was 8 months. Baseline frequency was 2.57, 3-month frequency was 3.07, and 6-month frequency was 3.83. These increases are statistically significant. There are few data on aging effects on SCE in monkeys, but there are data showing increases in SCE in rodents and humans with age.

CA, SCE, and MN in Lymphocytes of Pediatric ADHD Patients Treated with Stimulant Drugs

Kristine Witt, Ph.D., Toxicology Branch and Biomolecular Screening Branch, NTP, NIEHS, NIH

Dr. Witt summarized findings on genotoxicity of MPH in nonhuman test systems:

- Negative in bacterial and mammalian cell mutagenicity assays (Mortelmans et al., 1986; Teo et al., 2003)
- Mixed results in *in vitro* CA and SCE assays in Chinese Hamster Ovary cells (Galloway et al., 1987)
- Negative results in *in vivo* rodent erythrocyte MN tests (NTP, 1995; Teo et al., 2003; Suter et al., 2006).

Dr. Witt summarized findings on genotoxicity of MPH in human studies *in vitro* and *in vivo*

- Positive results for CA, SCE, and MN in lymphocytes of 12 ADHD children after 3 months of MPH exposure (El Zein et al., 2005)
- Negative results for CA in human lymphocytes (*in vitro*) (Suter et al., 2006)
- Negative results for MN in lymphocytes of ADHD children after treatment with MPH (Walitza et al., 2007).

The only clearly positive findings, in either nonhuman or human studies, were those reported by El Zein et al. An independent evaluation of the El Zein report revealed numerous protocol deficiencies, including small sample size (12 subjects), no SCE seen in 6 subjects, and critical lack of protocol details. But, due to widespread use of MPH for prolonged periods of time in children, there was a clear need to further investigate the potential for MPH-induced cytogenetic damage. There was a particular need to try to independently reproduce the findings. Therefore, NIEHS and NICHD funded a study of CA, SCE, and MN in lymphocytes of pediatric ADHD patients treated with stimulant drugs.

The specific study design considerations for the NIEHS/NICHD study included:

- Adherence to Good Laboratory Practices and international guidelines for cytogenetic analyses
- Sufficient statistical power to provide high-confidence data with a larger study population
- Comparable data on the two most frequently prescribed ADHD medications, MPH and mixed amphetamine salts (MAS)
  - Almost 50 percent of new prescriptions for ADHD are for MAS
  - More than 2 million annual prescriptions in the United States
  - No information on genotoxicity of MAS
- Clinical work conducted at an ADHD center highly experienced in research, diagnosis, and treatment.

The Duke ADHD Program—a nationally recognized leader in ADHD research—conducted the study for NIEHS and NICHD. The study was a parallel-group, open-label study of 60 children with ADHD, with randomized placement of 30 ADHD children into either MPH or MAS therapy. Baseline values of CA, SCE, and MN in lymphocytes were established before therapy

began. After 3 months of continuous exposure, CA, SCE, and MN in lymphocytes were reanalyzed.

Inclusion criteria were as follows:
- Age 6–12 years inclusive, either sex, any ethnicity/race
- Physically healthy, based on comprehensive physical exam
- Diagnosed at Duke University Medical Center with ADHD, any subtype, using rigorous comprehensive criteria
- Stimulant-drug naïve
- Appropriate candidate for stimulant therapy.

Exclusion criteria were as follows:
- Not meeting one or more inclusion criteria
- Comorbid psychological conditions requiring additional pharmacological treatment
- Diagnostic x-rays within the past 3 months
- Clinically significant electrocardiogram.

Per routine clinical practice, concomitant medications for common childhood conditions were permitted; these were recorded along with the indications for use. Compliance with medication regimen assessed by parent report and drug accountability logs were completed at each clinic visit; more than 96 percent compliance was achieved in both groups.

Dr. Witt summarized the data as follows:
- No treatment-related increases in CA, SCE, or MN
- No significant differences in CA, SCE, or MN between MPH and MAS treatment groups
- CA, SCE, and MN not influenced by age, medication group, gender, body weight, height, race, or ADHD subtype ($p > 0.06$)
- Final dose/body weight not correlated with CA, SCE, MN ($p > 0.35$ for MAS, $p > 0.20$ for MPH)
- CA, SCE, and MN not associated with concomitant medications or indication for use
- All analyses repeated for all subjects (including early terms and switchers); no treatment-related effects.

Summary Discussion of Presentations

Mike Shelby, Ph.D., Director, Center for the Evaluation of Risks to Human Reproduction, NIEHS, NIH

Differences between the NCTR/WSU and NIMH/JHU NHP studies are as follows:
- Subspecies or strain of rhesus monkeys (Chinese origin vs. Indian origin)
- Dosing volumes (100 ml vs. 1 ml/kg)
- Dosing intervals (3 hours vs. 6 hours)
- Number of dosing days per week (5 vs. 7)
- Blood levels/bioavailability of drug
- Cytogenetic endpoints
- Sample handling, storing, shipping, and processing

- Isolated lymphocyte cultures vs. whole blood cultures
- Blood-draw methods (ketamine anesthesia vs. no anesthesia).

The meeting participants agreed to the following:
- The slides from the NCTR/WSU and NIMH/JHU NHP studies that are available and that can be reevaluated will be sent to a central location (for example, a commercial lab), coded, and independently scored or rescored.
- Study investigators will review the inventories of slides and determine what slides should be scored or rescored.
- Drs. Mattison and Shelby will discuss the arrangements for conducting the scoring.

Unresolved issues are:
- What commercial lab will conduct the scoring
- How the lab will be selected
- How the samples sent to the lab will be organized
- What the lab will be asked to do.

Dr. Shelby agreed to draft a general protocol for an independent evaluation of the studies' findings. He will circulate the draft for comment.

The meeting participants agreed that a comparison study should be conducted on the NIMH/JHU samples. The samples will be drawn, half will be processed/cultured immediately per the current protocol, and half will be stored for 24 hours and then processed/cultured per the same protocol. The samples will be processed by Covance (the lab that processed the NIEHS/Duke human samples). However, the samples should ideally be scored by the same scorers for the NIMH/JHU and NCRT/WSU monkey studies.

For the 18-month blood draw for the NIMH/JHU study, samples will be divided (portions from each animal) and shipped to SRI (the NIMH/JHU study lab) and Litron (NCRT/WSU study lab) for separate processing and MN analysis. The samples will also be sent to Covance for CA, SCE, and MN analyses.

Dr. Mattison summarized:
- Create a list of available slides
- Draft a protocol for managing distribution and scoring of the slides
- Send NIMH/JHU samples to NCTR/WSU/Litron for MPH, RA, and MN analyses
- Send 18-month NIMH/JHU samples to
  - Litron for MN analysis
  - Convance for quality assurance of methodology
    - Process/culture half immediately
    - Process/culture half after storing at room temperature for 24 hours.

Future Plans and Closing

Dr. Mattison

The NCRT/WSU investigators will analyze the 18-month samples for endocrine consequences of MPH exposure. The results of the analysis will determine next steps. The NIOSH reproductive assessment data will be available to inform next steps.

Dr. Tucker proposed the consideration of the effects of long-term MPH exposure in young adults. A cross-sectional epidemiologically based study of chronic exposure would analyze any factors deemed relevant, including molecular cytogenetics. The study could include three groups: children with ADHD treated with MPH, children with ADHD not treated with MPH, and children without ADHD. Dr. Tucker noted that the fourth quadrant of the 2 x 2 design would be the MPH-treated monkeys, which do not have ADHD.

The meetings participants agreed to:

- A conference call in September
- An in-person meeting in late 2008 or early 2009.

Participants

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