NATIONAL TOXICOLOGY PROGRAM
US Department of Health and Human Services

Center For The Evaluation Of Risks To Human Reproduction

NTP-CERHR EXPERT PANEL REPORT on the REPRODUCTIVE and DEVELOPMENTAL TOXICITY of METHYLPHENIDATE

March, 2005 **NTP-CERHR- -**

PREFACE

The National Toxicology Program (NTP) and the National Institute of Environmental Health Sciences (NIEHS) established the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) in June 1998. The purpose of the Center is to provide timely, unbiased, scientifically sound evaluations of human and experimental evidence for adverse effects on reproduction and development caused by agents to which humans may be exposed.

Methylphenidate was selected for expert panel evaluation because of widespread usage in children, availability of studies on developmental effects in children and experimental animals, and public concern about the effects of these stimulants on child development. Methylphenidate is a central nervous system stimulant approved by the Food and Drug Administration for the treatment of ADHD and narcolepsy in persons six years and older. *d,l*-Methylphenidate is marketed under the names Ritalin®, Metadate®, Methylin®, and Concerta®. The *d*-enantiomer is marketed under the name Focalin™.

To obtain information about methylphenidate for the CERHR evaluation, the PubMed (Medline) and Toxline databases were searched with CAS RNs for methylphenidate (113-45-1) and methylphenidate hydrochloride (298-59-9), and relevant keywords. Searches were limited to studies indexed prior to December 31, 2004. References were also identified from databases such as REPROTOX®, HSDB, IRIS, and DART and from report bibliographies.

This evaluation resulted from the effort of a thirteen-member panel of government and non-government scientists that culminated in a public expert panel meeting held January 10–12, 2005. This report is a product of the Expert Panel and is intended to (1) interpret the strength of scientific evidence that methylphenidate is a reproductive or developmental toxicant based on data from in vitro, animal, or human studies, (2) assess the extent of human exposures to include the general public, occupational groups, and other sub-populations, (3) provide objective and scientifically thorough assessments of the scientific evidence that adverse reproductive/developmental health effects may be associated with such exposures, and (4) identify knowledge gaps to help establish research and testing priorities to reduce uncertainties and increase confidence in future assessments of risk. This report has been reviewed by CERHR staff scientists, and by members of the Amphetamines and Methylphenidate Expert Panel. Copies have been provided to the CERHR Core Committee, which is made up of representatives of NTP-participating agencies.

This Expert Panel Report will be a central part of the subsequent NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Methylphenidate. This monograph will include the NTP-CERHR Brief, the Expert Panel Report, and all public comments on the Expert Panel Report. The NTP-CERHR Monograph will be made publicly available and transmitted to appropriate health and regulatory agencies.

The NTP-CERHR is headquartered at NIEHS, Research Triangle Park, NC and is staffed and administered by scientists and support personnel at NIEHS and at Sciences International, Inc., Alexandria, Virginia.

Reports can be obtained from the web site (http://cerhr.niehs.nih.gov**) or from:**

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Note to Reader:

This report is prepared according to the Guidelines for CERHR Panel Members established by NTP/NIEHS. The guidelines are available on the CERHR web site (http://cerhr.niehs.nih.gov/). The format for Expert Panel Reports includes synopses of studies reviewed, followed by an evaluation of the Strengths/Weaknesses and Utility (Adequacy) of the study for CERHR evaluation. Statements and conclusions made under Strengths/Weaknesses and Utility evaluations are those of the Expert Panel and are prepared according to the NTP/NIEHS guidelines. In addition, the Panel often makes comments or notes limitations in the synopses of the study. Bold, square brackets are used to enclose such statements. As discussed in the guidelines, square brackets are used to enclose key items of information not provided in a publication, limitations noted in the study, conclusions that differ from those of the authors, and conversions or analyses of data conducted by the Panel.

Abbreviations

AAP	American Academy of Pediatrics
ADHD	attention/deficit-hyperactivity disorder
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the concentration versus time curve
BMD_{10}	benchmark dose, 10% effect level
BMDL	benchmark dose 95th percentile lower confidence limit
BMI	body-mass index
BUN	blood urea nitrogen
bw	body weight
CAS RN	Chemical Abstracts Service Registry Number
CERHR	Center for the Evaluation of Risks to Human Reproduction
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
CYP	cytochrome P450
DAPI	4',6-diamidino-2-phenylindole
DEA	Drug Enforcement Agency
EEG	electroencephalogram
EKG	electrocardiograph
EPA	Environmental Protection Agency
Eq	equivalent
f	female
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, Rodenticide Act
g	gram(s)
FSH	follicle stimulating hormone
GABA	γ-amino-butyric acid
GC	gas chromatography
GD	gestation day(s)
GLP	Good Laboratory Practice
GSH	glutathione
h	hour(s)
HPLC	high performance liquid chromatography
HSDB	Hazardous Substances Data Bank
IGHD	idiopathic growth hormone deficiency
ip	intraperitoneal
ISS	idiopathic short stature
iv	intravenous
kg	kilogram(s)
K_{ow}	octanol-water partition coefficient
L	liter(s)
LD_{50}	lethal dose, 50% mortality
LH	luteinizing hormone

LOAEL	low observed adverse effect level
m	male
M	molar
MAOI	monoamine oxidase inhibitor
max	maximum
mM	millimolar
mmol	millimole(s)
mol	mole(s)
mRNA	messenger ribonucleic acid
n or no	number
N/A	non-applicable
ND	not determined
ng	nanogram(s)
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIOSH	National Institute of Occupational Safety and Health
nmol	nanomole(s)
NOAEL	no observed adverse effect level
NOEL	no observed effect level
ns	non-significant
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
PHS	Public Health Service
PND	postnatal day(s)
ppm	parts per million
RACB	Reproductive Assessment by Continuous Breeding
RIA	radioimmunoassay
RR	relative risk
sc	subcutaneous
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SMVCE	sperm morphology and vaginal cytology examinations
$t_{1/2}$	half-life of elimination
T_{max}	maximum time
US	United States
USP	United States Pharmacopoeia
v	volume
V_d	volume of distribution
wk	week(s)
µg	microgram(s)
µL	microliter(s)
µm	micrometer(s)
µM	micromolar
µmol	micromole(s)

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1.0 CHEMISTRY, USE, AND HUMAN EXPOSURE

This section is initially based on secondary review sources. Primary study reports are addressed by the Expert Panel if they contain information that is highly relevant to a CERHR evaluation of potential human developmental or reproductive toxicity or if the studies were released subsequent to the reviews.

1.1 Nomenclature

Methylphenidate drugs consist of a 50/50 mixture of the *d*-threo- and *l*-threo-enantiomers *(1)* or only the *d*-threo-enantiomer *(2)*. The chemical name is methyl alpha-phenyl-2-piperidineacetate (CAS RN 113-45-1). Synonyms listed in ChemIDplus *(3)* include:

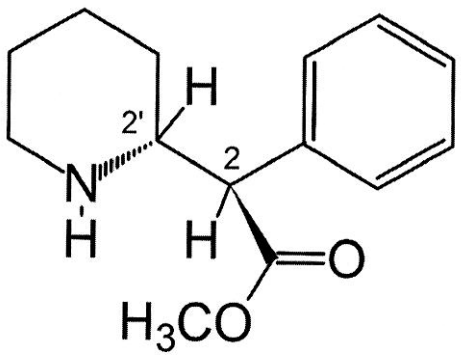
2-Piperidineacetic acid, alpha-phenyl-, methyl ester
Methyl (2-phenyl-2-(2-piperidyl)acetate)
Methyl alpha-phenyl-alpha-(2-piperidyl)acetate
Methyl phenidylacetate
Methylofenidan
Methylphenidan
Methylphenidate
alpha-Phenyl-2-piperidineacetic acid methyl ester

d,l-Methylphenidate hydrochloride (CAS RN 298-59-9) is marketed under the names of Ritalin®, by Novartis Pharmaceuticals Corporation *(4)*, Metadate® by Celltech Pharmaceuticals, Inc. *(5)*, Methylin® by Mallinckrodt, Inc. *(6)*, and Concerta® by Alza Corporation *(7)*. The products are available as immediate-acting and/or extended-release formulations. *d*-Methylphenidate is marketed under the name of Focalin™ by Novartis Pharmaceuticals Corporation *(2)*. The Expert Panel recognizes that the active medicinal compound in all these formulations is methylphenidate.

1.1.2 Formula and molecular mass

The chemical formula for methylphenidate is $C_{14}H_{19}NO_2$ *(4)*. The molecular mass is 233.31. The structure is shown in Figure 1. The chemical formula for methylphenidate hydrochloride is $C_{14}H_{19}NO_2 \cdot HCl$ and it has a molecular mass of 269.77.

Figure 1. Methylphenidate structure.
The *d*-enantiomer is shown with the chiral centers numbered.



1.1.3 Chemical and physical properties

As stated above, methylphenidate used in drug therapy consists of a 50/50 racemic mixture of *d*- and *l*-enantiomers or the *d*-enantiomer. The *d*-enantiomer has greater pharmacologic potency than the *l*-enantiomer. Unless specified otherwise, the information in this exposure section applies to both enantiomers.

Methylphenidate hydrochloride is a white, odorless, crystalline powder *(4)*. Solutions of the compound are acidic to litmus. Methylphenidate hydrochloride has a pK_a of 8.5 and it is relatively stable in acidic solutions (reviewed in *(8)*). Methylphenidate hydrochloride is freely soluble in methanol and water, soluble in alcohol, and slightly soluble in chloroform and acetone *(4)*. The melting point for methylphenidate hydrochloride is 212–216ºC *(8)*.

1.1.4 Technical products and impurities

Methylphenidate hydrochloride medications are available as capsules, tablets, and solutions. Table 1 summarizes the amount of active ingredient and lists the inactive ingredients in each marketed brand of methylphenidate hydrochloride tablets or capsules. Mallinckrodt Baker markets solutions under the name of Methylin *(9)*. Solutions contain methylphenidate hydrochloride at 5 mg/mL and 10 mg/mL; information on inactive ingredients is not available.

Table 1. Active and Inactive Ingredients in Various Methylphenidate Hydrochloride Brands

Brand	Enantiomers	Methylphenidate hydrochloride	Inactive ingredients	Reference
Ritalin	50/50 *d*,*l*-	5, 10, or 20 mg	D&C Yellow No. 10, FD&C Green no. 3, lactose, magnesium stearate, polyethylene glycol, starch, sucrose, talc, and/or tragacanth.	Novartis *(4)*
Ritalin SR	50/50 *d*,*l*-	20 mg	Cellulose compounds, cetostearyl alcohol, lactose, magnesium stearate, mineral oil, povidone titanium dioxide, and zein.	Novartis *(4)*
Ritalin LA	50/50 *d*,*l*-	10, 20, 30, or 40 mg	Ammonio methacrylate copolymer, black iron oxide, gelatin, methacrylic acid copolymer, polyethylene glycol, red iron oxide, sugar spheres, talc, titanium dioxide, triethyl citrate, and/or yellow iron oxide.	Novartis *(10)*
Metadate ER	50/50 *d*,*l*-	10 or 20 mg	Cetyl alcohol, ethylcellulose, anhydrous lactose, and magnesium stearate.	Celltech *(11)*
Metadate CD	50/50 *d*,*l*-	10, 20, or 30 mg	Sugar spheres, povidone, hydroxypropylmethylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, FD&C Blue No. 2, FDA/E172 Yellow Iron Oxide, and/or FDA/E172 Red Iron Oxide.	Celltech *(5)*
Methylin	50/50 *d*,*l*--	5, 10, or 20 mg	Lactose, monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and talc USP.	Mallinckrodt *(6)*
Methylin chewable tablets	50/50 *d*,*l*-	2.5, 5, or 10 mg	Aspartame NF, maltose, microcrystalline cellulose NF, guar gum NF, grape flavor, pregelatinized starch NF, and stearic acid NF.	Mallinckrodt *(12)*
Methylin ER	50/50 *d*,*l*-	10 or 20 mg	Hydroxypropyl methylcellulose 2208 USP, magnesium stearate NF, microcrystalline cellulose NF, and talc USP.	Mallinckrodt *(6)*
Concerta	50/50 *d*,*l*-	18, 27, 36, or 54 mg	Butylated hydroxytoluene, carnauba wax, cellulose acetate, hydroxypropyl methylcellulose**,** lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin	ALZA *(7)*
Focalin	*d*-	2.5, 5, or 10 mg	Pregelatinized starch, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, FD&C Blue No. 1 #5516 aluminum lake, and/or D&C Yellow Lake #10.	Novartis *(2)*

1.2 Use and Human Exposure

1.2.1 Production information

Manufacture of methylphenidate hydrochloride begins with hydrolysis of α-phenyl-2-pyridineacetonitrile in dilute sulfuric acid (reviewed in *(8)*). The hydrolysis product, α-phenyl-2-pyridineacetamide, is hydrogenated to form a diastereoisomeric mixture of α-phenyl-2-piperidineacetamide. The diastereoisomeric mixture is heated in sodium hydroxide to convert it to a threo racemic mixture; in the same reaction, it is hydrolyzed to α-phenyl-2-piperidineacetic acid and reacted with methanol to form the methyl ester free base. The free base is converted to methylphenidate hydrochloride. **[No information was located on manufacture or isolation of the *d*-enantiomer.]**

Companies that are FDA-approved to manufacture brand name methylphenidate drugs include Novartis Pharmaceuticals Corporation, Celltech Pharmaceuticals, Inc., Mallinckrodt, Inc.; Alza Corporation Novartis Pharmaceuticals' Focalin and Ritalin LA brands and Celltech Pharmaceuticals' Metadate CD brand are currently under patent *(9)*.

Companies that have FDA approval to produce unbranded (generic) methylphenidate include Able, Purepac Pharma, Watson Labs, Celltech MFG, and Mallinckrodt *(9)*.

The US Drug Enforcement Agency (DEA) determines a yearly aggregate production quota based on sales and inventory data from manufacturers and information provided by the Food and Drug Administration (FDA) *(13)*. The production quota for methylphenidate was reported at 1768 kg **[3898 pounds]** in 1990 and at 14,957 kg **[32,975 pounds]** in 2000. The United Nations *(14)* reported US methylphenidate production at 12,638 kg **[27,862 pounds]** in 2000, 15,009 kg **[33,089 pounds]** in 2001, and 20,725 kg **[45,690 pounds]** in 2002. From 2000 to 2002, no methylphenidate was imported into the US, but exports totaled 193 kg **[425 pounds]** in 2000, 329 kg [**725 pounds]** in 2001**,** and 501 kg **[1105 pounds]** in 2002 *(14)*. The DEA *(13)* stated that according to a United Nations report, the US produced and consumed about 85% of the global supply of methylphenidate in 1999. US sales of methylphenidate remained stable at ~2000 kg **[4409 pounds]** prior to 1991, but increased nearly 500% by 1999 *(13)*.

1.2.2 Use

Methylphenidate is a central nervous system (CNS) stimulant that is approved by the FDA for treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy in persons 6 years and older. Safety and efficacy have not been established in children younger than 6 years old. In 2000, the DEA *(13)* stated that "After sharp increases in the use of methylphenidate in the early 1990s, methylphenidate prescriptions have leveled off at about 11 million per year for the past four years." Most methylphenidate prescriptions are written for treatment of children diagnosed with ADHD. Although the product label recommends against the use of medication in children younger than 6 years of age, in 1998 it was estimated that 4000 prescriptions were written for children 2 years old and younger, reflecting a difference between clinical practice and approved labeling (Scialli JV, personal communication October 18, 2004). Boys are about four times more likely than girls to be diagnosed with ADHD and prescribed stimulant medication. The DEA *(13)* found the use of methylphenidate to vary greatly among states and communities within each state. While estimates of the prevalence of ADHD in the US are 3–5%, analysis of prescription data and epidemiologic studies found some communities with almost no methylphenidate use and others in which 10–20% of students were given methylphenidate. It has been stated that 10–60% of people with childhood ADHD will have the full or residual syndrome persisting into adulthood *(15-17)*. Methylphenidate could potentially be used to treat ADHD or narcolepsy in pregnant women, but there is no information on the numbers of pregnant women prescribed the drug.

The Expert Panel is aware of off-label uses of methylphenidate to treat depression, primarily as an adjunct to antidepressant medication, and to treat patients with post-stroke cognitive impairment (Scialli JV, Lusskin S, personal communication, September 22, 2004). Similar uses have been documented in reviews *(18*). While depression is common in men and women of reproductive age, strokes most often occur in older individuals. The number of prescriptions written for off-label use is not known. There is an increase in diagnosis and treatment of both ADHD and depression in adolescents and adults. More exposures in people of reproductive age can therefore be expected.

The Expert Panel is also aware of off-label use of methylphenidate in children younger than 6 years of age.

The National Institute on Drug Abuse (NIDA) *(19*) states that addiction to stimulant medications does not occur when medicines are taken in the form and dosage prescribed. However, there is potential for methylphenidate abuse due to its stimulant-related effects such as appetite suppression, increased wakefulness, improved focus/attentiveness, and euphoria associated with somatic sensations called "tweaking." Under the Controlled Substances Act, methylphenidate is listed as a Schedule II drug, a medically utilized drug with high potential for abuse *(13*).

Methylphenidate is available for illegal use only through diversion from legitimate channels, not through illicit manufacture *(13*). Diversion occurs through drug thefts, illegal sale, prescription forgery, and fraudulent presentation with ADHD symptoms to multiple doctors. The DEA reports incidences of methylphenidate stolen from pharmacies or schools, teachers or school nurses personally using methylphenidate prescribed for students, children selling or giving their prescribed methylphenidate to other children, and children taken to numerous physicians by parents in order to obtain the drug for themselves or for "therapeutic trials" for other children at home. The DEA presents the following statistics on methylphenidate diversion:

- Methylphenidate was one of the ten most frequently reported stolen controlled drugs from January 1990 to May 1995;
- About 700,000 dosage units of methylphenidate were reported to the DEA drug theft database from January 1996 to December 1997; and
- In 1998, there were 376 reported thefts of methylphenidate from pharmacies.

The DEA *(13*) receives anecdotal reports of methylphenidate misuse in children daily. The following survey data were reported by the DEA *(13*):

- A 1999 national high school survey reported that about 3% of US high school seniors illicitly used methylphenidate;
- A 1998 university survey reported that almost 7% of high school students illicitly used methylphenidate at least once and 2.5% used it more often;
- In 1998, the Drug Abuse Warning Network reported 1727 methylphenidate emergencies, 56% for 10–17 year olds; and
- A 1996 DEA survey of 3 states found that 30–50% of adolescents in treatment centers reported "non-medicinal" use of methylphenidate, although it was not the primary drug of abuse.

There are concerns that students are using methylphenidate to prolong study time *(20)*. In a 1993 survey of 48,500 students in grades 8–12 of 392 US schools, methylphenidate use during the past year was reported by ~3–4% of students; methylphenidate use during the past month was reported by 1–2% of students *(21)*. Usage rates were higher among students not planning to attend college. However, compared to age peers, college students reported a higher usage rate for methylphenidate, with use during the past year reported at 5% for college students and 3% for young adults.

Although methylphenidate is abused, it is less likely to be abused than other, more bioavailable euphorigenic drugs such as cocaine; emergency department mentions for methylphenidate in the Drug Abuse Warning Network are $1/40^{th}$ of those for cocaine (reviewed in *(22)*).

1.2.3 Human Exposure

For the treatment of ADHD or narcolepsy, dose levels for methylphenidate range from 10 to 60 mg/day in children older that 6 years and in adults *(4-7)*. Average doses in adults range from 20 to 30 mg/day. Manufacturers recommend an initial dose of 10 mg/day in children with weekly incremental increases of 5–10 mg/day until optimal dosages are obtained. According to the American Academy of Pediatrics (AAP) *(23)*, the recommended dosage for methylphenidate in children **[age unspecified]** is 0.3 mg/kg bw twice daily, gradually increased to 0.6–0.8 mg/kg bw twice daily. It has been reported that children continue to respond to the same dose of methylphenidate and there is little evidence that tolerance or behavioral sensitization develops (reviewed in *(18, 22)*). Methylphenidate is administered 1–3 times daily, depending on the required dose and the form of medication *(24)*. Methylphenidate is available in short-acting, intermediate-acting (e.g. Ritalin SR, Metadate ER, and Methylin ER), and extended-release (e.g., Concerta, Metadate CD, and Ritalin LA) formulations *(24)*. Generally, dosing occurs 2–3 times/day with short-acting formulations, 1–2 times/day with intermediate-acting formulations, and 1 time/day with extended-release formulations. Dose schedules can be individualized to meet the need of the patient. For example, if symptom relief is required only during school hours, dosing 5 days/week may be sufficient.

The AAP *(24)* notes that studies examining the safety and efficacy of stimulants involve a period of weeks to months. Due to the lack of long-term studies, manufacturers of methylphenidate recommend occasional discontinuation of treatment and evaluation of symptoms in children *(4-7)*. Manufacturers report that treatment can often be discontinued at puberty. According to a 1988 report, average methylphenidate therapy durations are 2, 4, and 7 years when treatments commence during elementary, middle, and high school stages, respectively (reviewed in *(8)*). However, it has been reported that 10–60% of patients may continue to have symptoms of ADHD as adults (reviewed in *(15-17)*). In some cases, continued treatment through adulthood is recommended due to persistence of symptoms. Treatment of ADHD in adults and children is increasing and is an emerging area of study.

As stated in Section 1.2.2, methylphenidate is also encountered as a drug of abuse. In addition to orally ingesting methylphenidate, abusers often inhale crushed tablets or inject themselves with a solution of methylphenidate dissolved in water *(19)*. Some users inject methylphenidate with cocaine or heroin. Typical abuse patterns include increased dosing, binging followed by depression, and an overpowering urge to continue drug use despite medical or social consequences *(13)*.

1.3 Utility of Exposure Data

Human exposure data include dose ranges for approved therapeutic uses of methylphenidate. Blood levels of methylphenidate measured in children on therapy are presented in Section 2.

There are no data on blood levels in pregnant women or blood or milk values in nursing women using the drug. It is not known how many pregnant or nursing women are exposed. There are no data on human exposures resulting from unapproved use or abuse of methylphenidate.

1.4 Summary of Human Exposure Data

Methylphenidate is a medication marketed for treatment of ADHD and narcolepsy in children 6 years and older and in adults. It is available as a 50/50 mixture of the *d*-threo- and *l*-threo-enantiomers *(1)* or only the *d*-threo-enantiomer *(2)*. It is believed that human exposures are primarily through medication use and to a lesser extent, drug abuse. No information was identified on possible environmental or occupational exposure. Recommended oral doses are 10–60 mg/day for children older than 6 years and for adults. Methylphenidate is available in short-acting, intermediate-acting, and extended-release formulations and is administered 1–3 times daily, depending on the required dose and the form of medication. Dose schedules can be individualized according to patient needs. For example, if symptom relief is required only during school hours, dosing 5 days/week may be sufficient or discontinuation over the summer months is possible. In some cases of ADHD, treatment may be discontinued at puberty; in other cases, continued treatment through adulthood is recommended due to persistence of symptoms. Treatment of ADHD in teenagers and adults is increasing and is an emerging area of study.

In 2000, the DEA *(13)* stated that about 11 million methylphenidate prescriptions per year were written in the past 4 years, most for treatment of ADHD in children. According to the DEA *(13)*, production of methylphenidate was reported at 14,957 kg [32,975 pounds] in 2000. The United Nations *(14)* reported US methylphenidate production at 12,638 kg **[27,862 pounds]** in 2000, 15,009 kg **[33,089 pounds]** in 2001, and 20,725 kg **[45,690 pounds]** in 2002.

The Expert Panel is aware of off-label uses of methylphenidate to treat depression, primarily as an adjunct to antidepressant medication, and to treat patients with post-stroke cognitive impairment. Since depression and ADHD are common in men and women of reproductive age, there is a potential for methylphenidate exposure in that population. There is no information on the numbers of pregnant or lactating women prescribed the drug.

The Expert Panel is also aware of off-label use of methylphenidate in children younger than 6 years of age.

The DEA is aware of cases of methylphenidate diversions for illicit use, including by children or adolescents *(13)*. One review reported that methylphenidate is less likely to be abused than drugs that induce euphoria, such as cocaine; emergency department mentions for methylphenidate in the Drug Abuse Warning Network are $1/40^{th}$ those for cocaine (reviewed in *(22)*). In addition to orally ingesting methylphenidate, abusers often inhale crushed tablets or inject themselves with a solution of methylphenidate dissolved in water *(19)*.

2.0 GENERAL TOXICOLOGY AND BIOLOGIC EFFECTS

Information in Section 2 is initially based upon reviews. The Panel reviewed primary studies if the information in reviews was inadequate; if the information presented in the primary studies is highly relevant for the evaluation of developmental or reproductive effects; or if the studies were published subsequent to reviews.

2.1 Pharmacokinetics and Pharmacodynamics

Unless otherwise specified, the information discussed in this section pertains to the racemic mixture of methylphenidate. Information on stereospecificity is discussed when available.

Pharmacokinetic information obtained from drug labels is summarized in Table 2. Details on protocols and results presented in drug labels are very limited. In addition, it is not known if the values presented are for *d*- or *d,l*-methylphenidate. Most likely, the majority of information in Table 2 is for racemic methylphenidate. Due to the limited amount of information presented in drug labels, and because children are a highly relevant population for this CERHR evaluation, the Expert Panel reviewed primary data on pharmacokinetics of methylphenidate in children. Information on pharmacokinetics in children given single oral doses of racemic methylphenidate is summarized in Table 3. The information in Table 3 is not specific for either enantiomer and represents the *d*- and *l*-enantiomers combined. In addition to the information in Table 3, one study reported that methylphenidate treatment of boys twice daily for 1 week resulted in mean plasma methylphenidate levels of 10.95 ng/mL at 0.25 mg/kg bw, 19.39 ng/mL at 0.50 mg/kg bw, and 41.75 at 1.0 mg/kg bw *(25)* **[the time period between dosing and sampling was not specified]**. A limited number of studies reported pharmacokinetic information for the *d*- and *l*-enantiomers separately, and those studies are reviewed in detail below.

2.1.1 Human

2.1.1.1 Pharmacodynamics

Methylphenidate is classified as a non-catecholamine sympathomimetic that is a direct and indirect adrenergic agonist (reviewed in *(26)*). No information was found on therapeutic mode of action for treatment of narcolepsy. Stimulatory effects presumably occur through methylphenidate activation of the brain stem arousal system and cortex *(11, 12)*. The mode of action for therapeutic treatment of ADHD is not known. It is thought that methylphenidate blocks reuptake of norepinephrine and dopamine by the presynaptic neuron, thus increasing levels of these monoamine neurotransmitters in the extraneuronal space *(5, 7, 10, 12)*. A study in adults demonstrated that orally administered methylphenidate occupies the dopamine transporter in the striatal region of the brain, but binds the transporter at a slower rate than observed with intravenous (iv) cocaine exposure (reviewed in Greenhill et al. *(22)*). Methylphenidate may also inhibit monoamine oxidase to a limited extent (reviewed in *(27)*).

Although stimulants decrease locomotor activity in children, an increase in activity is observed in experimental animal studies. A review by Solanto *(27)* discussed possible reasons for discordance between children and laboratory animals. One theory is that reduced activity and increased attention in children compares to decreased activity as a secondary effect of stereotypy in experimental animals given high doses of methylphenidate. However, several studies examining divergent thinking and cognitive perseverance indicated inconsistent or no associations between therapeutic effects and cognitive constriction or stereotypic thinking (reviewed in *(27, 28)*). An alternate theory of mechanism of action in children is that stimulation of inhibitory presynaptic autoreceptors decreases dopamine activity, thus compensating for excessive dopamine activity in those children with ADHD (reviewed in *(27)*).

Because most pharmacodynamic information was developed from experimental animal studies, more information is presented below in Section 2.1.2.

2.1.1.2. Absorption

Methylphenidate is available in immediate-release and long-acting formulations. Some long-acting formulations consist of capsules containing a mixture of immediate-release and enteric-coated delayed-release beads *(5, 29)*. One long-acting preparation is also available as a tablet containing an outer membrane of drug for immediate release and a layered core of drug and osmotically-active component *(7)*.

Immediate-release formulations of methylphenidate are rapidly absorbed and reach peak values within 1–3 hours following oral ingestion *(2, 10, 12, 30)*. Extended-release (long-acting) formulations usually produce two peak blood levels in children with ADHD and in healthy adults *(7, 10)*. A sharp initial slope to reach peak levels occurs during the first 1–3 hours and is similar to that for immediate-release formulations. A more gradual peak occurs 3–4 hours later. Extended-release formulations minimize variability between peak and trough levels that occur with multiple dosing of immediate-release formulations.

Intermediate-acting formulations, such as Ritalin SR and Metadate are absorbed more slowly, but as completely, as immediate-acting formulations *(4)*. Bioavailability was reported to be the same upon administration of equivalent doses of immediate- or intermediate-acting formulations.

Data on the effects of food on absorption are variable. While one manufacturer reported that a high fat breakfast does not affect pharmacokinetics *(7)*, other manufacturers reported that a high fat breakfast may slow absorption *(4, 5, 10, 12)*. Although food may slow the absorption of methylphenidate, it appears to have little to no effect on C_{max} and AUC *(2, 30)*. One study reported that ingestion of food accelerated methylphenidate absorption in hyperactive children (T_{max} = 1.60±0.42 versus 1.00±0.38 hours [mean ± SD] when taken while fasting versus with a meal) without reducing bioavailability *(31)*. However, the FDA *(29)* noted that studies reporting no effects or more rapid absorption with food had design flaws including use of low calorie and low fat meals, very few subjects, and inadequate blood sampling.

Dosing with *d*-methylphenidate resulted in plasma *d*-methylphenidate levels similar to those obtained with twice the dose of *d,l*-methylphenidate *(30)*. The pharmacokinetics of *d*-methylphenidate were not different from those of the racemic mixture *(30, 32)*.

Table 2. Pharmacokinetics in Humans for Various Brands of Methylphenidate

Brand name (reference) • dose • activity • test subjects (n)	C_{max1} Mean±SD (range), ng/mL	C_{max2} mean±SD (range), ng/mL	T_{max1} mean±SD (range), hours	T_{max2} mean±SD (range), hours	$AUC_{0-\infty}$ mean±SD (range), ng-h/mL	Half-life mean±SD (range), hours
Ritalin *(10)* • 20 mg (2 10-mg doses, 4 hours apart) • immediate acting • children	10.2±4.2 (4.2–20.2)	15.3±7.0 (6.2–32.8)	1.8±0.6 (1–3)	5.6±0.7 (5–8)	102.4±54.6 (40.5–261.6)	2.5±0.8 (1.8–5.3)
Ritalin *(10)* • 20 mg (2 10-mg doses, 4 hours apart) • immediate acting • adults	4.3±2.3 (1.8–7.5)	5.3±1.4 (3.6–7.2)	1.9±0.4 (1.3–2.7)	5.9±0.5 (5.0–6.5)	37.8±21.9 (14.3–85.3)	3.5±1.9 (1.3–7.7)
Methylin Chewable Tablets *(12)* • 20 mg • immediate acting • NS except for half-life in adults	10 (NS)	N/A	(NS) 1–2	N/A	NS	3
Ritalin LA *(10)* • 20 mg • long acting • children	10.3±5.1 (5.5–26.6)	10.2±5.9 (4.5–31.1)	2.0±0.8 (1–3)	6.6±1.5 (5–11)	86.6±64.0 (43.3–301.44)	2.4±0.7 (1.5–4.0)
Ritalin LA *(10)* • 20 mg • long acting • adults	5.3±0.9 (3.8–6.9)	6.2±1.6 (3.9–8.3)	2.0±0.9 (1.3–4.0)	5.5±0.8 (4.3–6.5)	45.8±10.0 (34.0–61.6)	3.3±0.4 (3.0–4.2)
Concerta *(7)* • 18 mg • long acting • adults	NS	3.7±1.0	NS	6.8±1.8	41.8±13.9	3.5±0.4

Brand name (reference) • dose • activity • test subjects (n)	C_{max1} Mean±SD (range), ng/mL	C_{max2} mean±SD (range), ng/mL	T_{max1} mean±SD (range), hours	T_{max2} mean±SD (range), hours	$AUC_{0-\infty}$ mean±SD (range), ng-h/mL	Half-life mean±SD (range), hours
Metadate CD *(5)* • 20 mg • long acting • children	8.6±2.2[b]	10.9±3.9[b]	~1.5	~4.5	63.0±16.8 (AUC_{0-9})	6.8 hours (age NS)
Metadate CD *(5)* • 40 mg • long acting • children	16.8±5.1[b]	15.1±5.8[b]	~1.5	~4.5	120±39.6 (AUC_{0-9})	6.8 hours (age NS)
Focalin *(30)*[c] • 2.5 mg • immediate-acting • children	5.2±1.5	N/A	1.7±1.1	N/A	23.9±6.7	2.4±0.4
Focalin *(30)*[c] • 5 mg • immediate acting • children	10.5±3.4	N/A	1.3±0.7	N/A	50.1±15.5	2.5±0.5
Focalin *(30)*[c] • 10 mg • immediate acting • children	20.6±7.7	N/A	1.8±1.3	N/A	98.7±27.7	2.4±0.4
Focalin *(2, 30)*[c] • 20 mg • immediate acting • adults	22.1±6.9 (fed)[d] 23.7±9.9 (fasting)	N/A	2.9±0.8 (fed) 1.5±0.5 (fasting)[a]	N/A	131.9±49.7 (fed) 120.9±55.3 (fasting)	2.8±0.3 (fed) 2.7±0.3 (fasting)

NS = Not specified; N/A = Not applicable
[a]Values for adults administered 2 10-mg doses.
[b]Values are questionable because the text and figure in product label do not appear to correspond.
[c] Focalin consists solely of the *d*-enantiomer.
[d]Values were measured following ingestion of a high fat breakfast or in the fasting state.

Table 3. Summary of Pharmacokinetic Data for Racemic Methylphenidate in Children Given Single Oral Doses

Number of children	Dosage	Half-life mean±SD (range), hours	T_{max} mean±SD (range), hours	C_{max} mean±SD (range), ng/mL	$AUC_{0-\infty}$ mean±SD (range), ng-h/mL	Clearance mean±SD (range), L/h/kg	Reference
6[b]	0.3 mg/kg bw	2.43	1.5±0.2[a]	10.8±1.9[a]	NS	10.2±2.2	*(33)*
8–14	0.34 mg/kg bw	2.53±0.59	2.5±0.65	11.2±2.7	59.5±13.9	NS	*(34)*
5	10 mg **[0.21–0.41 mg/kg bw]**	3.15±1.04 (2.17–4.62)	NS	NS	33.48±10.38 (18.32–44.06)	9.22±3.56 (7.27–15.26)	*(35)*
5	0.25–0.68 mg/kg bw (taken while fasting)	2.10±0.36 (1.6–2.6)	1.60±0.42 (1.0–2.0)	NS	NS	NS	*(31)*
5	0.25–0.68 mg/kg bw (taken with meal)	2.14±0.32 (1.7–2.5)	1.0±0.35 (0.5–1.5)	NS	NS	NS	*(31)*
4	10–15 mg **[0.30–0.48 mg/kg bw]**	2.56±0.162 (2.37–2.75)	NS	17.6±6.0 (7.71–22.5)	86.93±34.55 (36.26–133.82)	NS	*(36)*
4–5	0.65 mg/kg bw	2.61±0.29	1.90±0.82	20.2±9.1	103.7±55.9	NS	*(34)*
8	0.89±0.14–0.91±0.7[c]	3.33±0.65–4.09±1.8[c]	**[1.63±0.77–1.67±0.68]**[c]	20.17±6.4–23.2±14.4[c]	116.3±45.4–126.9±47.2[c]	8.6±2.9–8.5±4.9[c]	*(37)*

NS = Not specified.
[a]Variances are standard error.
[b]One child was given 2 mg/kg bw methylphenidate; though not explicitly stated, it does not appear that that the child was included in the analysis.
[c]Values were obtained following 0 and 6 months on methylphenidate.

2.1.1.3 Distribution

Apparent volume of distribution following intravenous (iv) exposure to methylphenidate is 6 L/kg (reviewed in *(10, 38)*). Volume of distribution was reported as 10.7–33.2 L/kg in 4 children given 10–15 mg methylphenidate orally *(36)* and ~40 L/kg in children given ~0.9 mg/kg bw (~28 mg) orally *(37)*. According to information presented in a review article *(38)*, a volume of distribution exceeding extracellular fluid and total body water indicates substantial tissue binding. Binding of methylphenidate to plasma protein is low (10–33%) (*(28)*; reviewed in *(1, 10)*). Methylphenidate disposition is stereospecific after oral dosing, resulting in higher plasma levels of the *d*- versus the *l*-enantiomer (reviewed in *(1)*). Peak plasma levels of the *d*-enantiomer are reportedly 8 times higher than the *l*-enantiomer following oral dosing with 10 mg methylphenidate (reviewed in *(8)*). Following iv or oral administration, total body clearance is higher for the *l*-enantiomer, while mean residence time, volume of distribution, AUC, and half-life are higher for the *d*-enantiomer (reviewed in *(1)*). **[Differences between *l*- and *d*-methylphenidate pharmacokinetic parameters by route of administration are attributable to the extensive intestinal clearance of the *l*-enantiomer after oral dosing. Iv dosing by-passes this intestinal clearance.]**

The proportionality of pharmacokinetic parameters to administered dose was reported in children administered 2.5–10 mg *d*-methylphenidate or 5–20 mg *d,l*-methylphenidate *(30)*. One manufacturer reported that C_{max} and AUC values increased proportionally to dose in children given once-daily oral doses of 20 or 40 mg for 1 week or adults given single oral doses of 10–60 mg *(5)*. However, a study in 4 healthy individuals and 1 narcolepsy patient reported disproportionate increases in AUC between 20 and 40 mg and dose-related decreases in oral clearance, most likely due to saturated presystemic metabolism at the level of the intestine, at doses between 10 and 60 mg methylphenidate *(39)*. **[The Panel notes that author conclusions are reasonable, but with so few humans involved, firm conclusions cannot be made.]** The FDA *(29)* reported the possibility of "nonlinearity" at a dose of 60 mg. Modi et al. *(40)* postulated that linearity may be affected by drug formulation due to higher blood concentrations obtained with immediate- versus sustained-release formulations.

Human studies demonstrated uptake of radiolabeled *d,l*-methylphenidate in the striatum of the brain, with peak concentrations occurring 5–15 minutes following iv injection (reviewed by *(1)*). Following iv dosing, methylphenidate has a half-life of ~90 minutes, much longer than the half-life of cocaine in the brain, which is 20 minutes (reviewed in *(41)*).

Because methylphenidate is a basic compound (pK_a 8.8), accumulation in the acid environment of the stomach due to ion trapping has been observed, even following iv exposure (reviewed in *(16)*).

2.1.1.4 Metabolism

Figure 2 illustrates the metabolism of methylphenidate. In the predominant human metabolic pathway for methylphenidate, nonmicrosomal hydrolytic esterases found throughout the body rapidly biotransform methylphenidate to α-phenyl-piperidine acetic acid (commonly called ritalinic acid) *(10)*. The metabolite is believed to have little to no pharmacologic activity *(8)*. The *d*- and *l*- enantiomers are converted to their respective *d*- and *l*-metabolite enantiomers, with no substantial interconversion between enantiomers *(30)*. Less than 2% of methylphenidate is metabolized in minor pathways involving aromatic hydroxylation to *p*-hydroxy compounds, microsomal oxidation to oxo- compounds, and conjugation; none of the minor metabolites are believed to be pharmacologically active (reviewed in *(1, 8)*). Small amounts of hydroxylated metabolites, such as hydroxymethylphenidate and hydroxyritalinic acid, have been detected in plasma *(10)*. Table 4 lists metabolites detected in humans, rats, and dogs. The metabolite ethylphenidate was recently identified in overdose victims and volunteers given methylphenidate

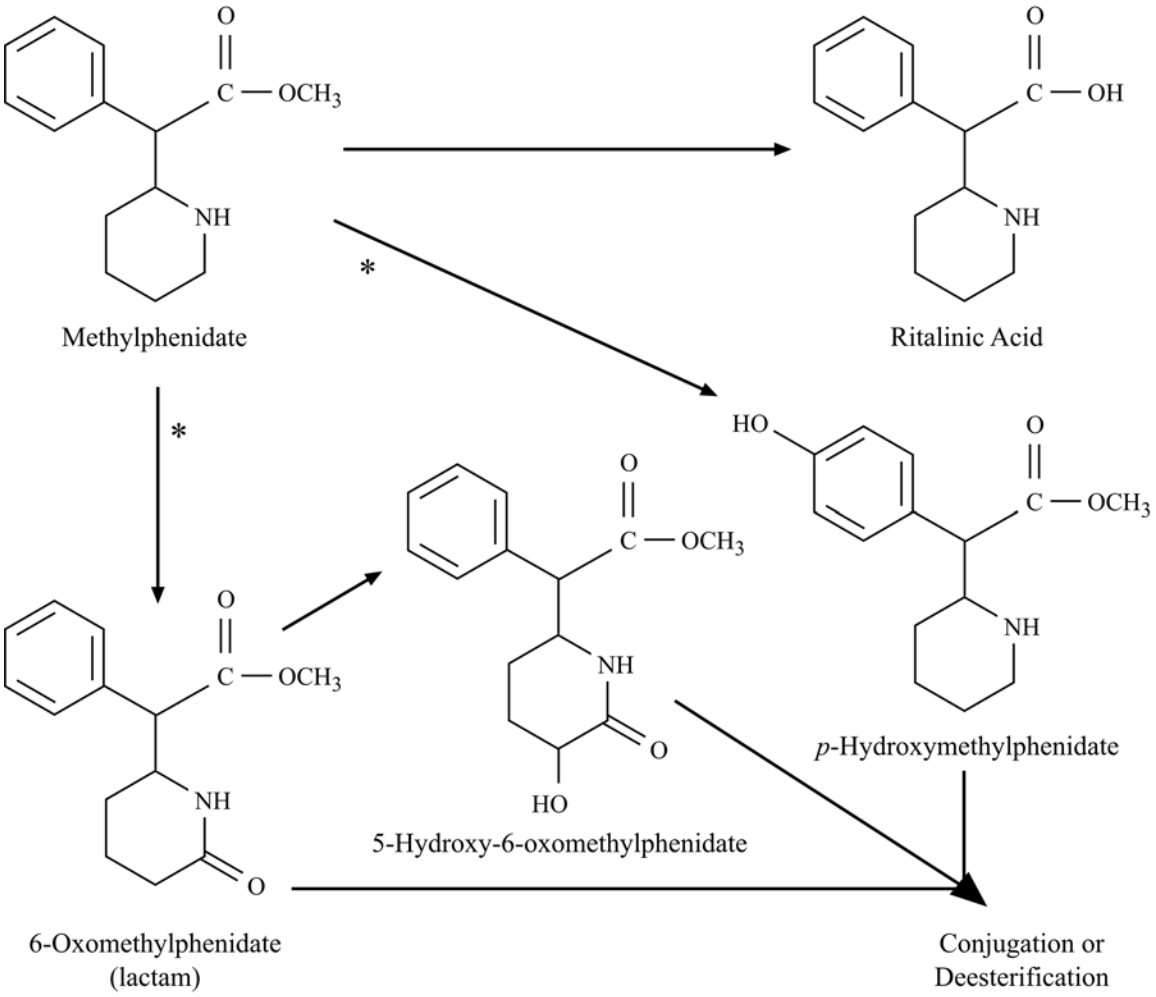
in combination with alcohol (reviewed in *(16)*). Ethylphenidate, which is possibly formed through a transesterification reaction, is of unknown pharmacodynamic significance. No metabolism by or inhibition of cytochrome P450 (CYP) isoenzymes was observed in in vitro studies with the *d,l*-enantiomer *(5)*. A lack of cytochrome CYP isoenzyme inhibition in vitro was also reported for the *d*-enantiomer *(2)*. However, a recent review of drug interaction reports concluded that methylphenidate is involved in pharmacokinetic interactions that suggest inhibition of one or more hepatic CYP enzymes *(42)*.

The low absolute oral bioavailability of methylphenidate in children (~30%, range: ~10–52%) implies extensive presystemic biotransformation *(10, 31)*. There is evidence of stereospecific differences in oral bioavailability of methylphenidate, reported at 23% for the *d*-enantiomer and 5% for the *l*-enantiomer (reviewed in *(1)*).

Table 4. Methylphenidate Urinary Metabolites in Humans, Rats, and Dogs

Species/Dose	Route	Time (hours)	Percent drug or metabolite in urine
Human 20 mg/kg bw	Oral or iv	0–24	Ritalinic acid (80%); *p*-hydroxyritalinic acid (2%); 6-oxoritalinic acid (< 1%, 1.5% iv); methylphenidate, *p*-hydroxymethylphenidate, 6-oxomethylphenidate, and *p*-hydroxyritalinic acid glucuronide (all < 1%)
Rat 20 mg/kg bw	Oral	0–24	Ritalinic acid (35–40%); methylphenidate (1%); 6-oxomethylphenidate (1.5%); 6-oxoritalinic acid (7–10%); 5-hydroxy-6-oxomethylphenidate (2%); 5-hydroxy-6-oxoritalinic acid (15–17%); carbamide methylphenidate (1%); *p*-hydroxyritalinic acid glucuronide (10%); unknown (20%)
		0–48	Ritalinic acid (36%); 6-oxoritalinic acid (1.8%); *p*-hydroxymethylphenidate (3%); p-hydroxyritalinic acid (19%); p-hydroxyritalinic acid glucuronide (10%); methylphenidate and 6-oxomethylphenidate (both < 1%)
	ip	0–48	Ritalinic acid (27%); 6-oxomethylphenidate (1.2%); 6-oxoritalinic acid (3%); *p*-hydroxymethylphenidate (15%); p-hydroxyritalinic acid (20%); p-hydroxyritalinic acid glucuronide (10%); methylphenidate (< 1%)
Dog 5 mg/kg bw	Oral	0–8	Ritalinic acid (23%); 6-oxomethylphenidate (1%); 6-oxoritalinic acid (26.5%); 6-oxoglucoronide (20%); 5-hydroxy-6-oxomethylphenidate glucuronide (12%); 4-hydroxy-6-oxomethylphenidate glucuronide (1%); 5-hydroxy-6-oxoritalinic acid (4%); carbamide methylphenidate (1%); *p*-hydroxy-6-oxoglucuronide (2–3%); *p*-hydroxy-6-oxosulfonic acid (1%); unknown (3%); methylphenidate (0.3%)
	iv	0–5	Ritalinic acid (44%); *p*-hydroxymethylphenidate (1.2%); *p*-hydroxyritalinic acid (2%); 6-oxomethylphenidate (7%); 6-oxoritalinic acid (30%); methylphenidate and *p*-hydroxyritalinic acid glucuronide (both < 1%)

Adapted from NTP *(8)*.



* Minor pathways in human. Adapted from NTP *(8)*.

Figure 2. Metabolic Pathways of Methylphenidate in Human, Rat, and Dog.

2.1.1.5 Excretion

Methylphenidate plasma half-lives of ~2–8 hours (mean ~2.5–3.5 hours) were reported for oral administration of immediate- or extended-release *d*- or *d,l*-formulations after doses of up to 20 mg in adults and children *(2, 5, 7, 10, 12, 30)*. Celltech *(5)* stated that half-life for Metadate CD (6.8 hours) is longer than the half-life for sustained-release tablets (3.4 hour) and immediate-release tablets (2.9 hours); it was suggested that half-life differences resulted from controlled release from extended-release tablets and absorption as the rate-limiting process. Mean total body clearance was calculated at 2.52 L/kg-hour in children administered 10–15 mg methylphenidate by iv infusion (reviewed in *(38)*); according to study authors, a total body clearance value exceeding average blood flow to the liver (1.4 L/kg-hour) is consistent with the extrahepatic metabolism associated with the widespread distribution of hydrolytic esterases. Mean clearance rates of ~9–10 L/kg-hour were reported in children orally exposed to methylphenidate at up to 0.41 mg/kg bw *(33, 35)* and 0.9 mg/kg bw *(37)*.

Oral dosing with radiolabeled methylphenidate results in recovery of 80–90% of the radioactivity in urine *(7, 12)*. Novartis *(10)* reports that 78–97% of a methylphenidate dose is excreted in urine

and 1–3% is excreted in feces as metabolites within 48–96 hours. Ritalinic acid is the main urinary metabolite and represents about 60–86% of the dose *(7, 10)*. Less than 1% of the methylphenidate dose is excreted unchanged in urine *(10)*. Due to the small percentage of methylphenidate excreted unchanged, urinary pH is not expected to affect excretion *(16)*.

The half-life of ritalinic acid is 3–5 hours following dosing with racemic methylphenidate *(10, 31)* and ~3–8 hours with intake of *d*-methylphenidate *(30)*. One study reported a half-life of ~9 hours for *d*-ritalinic acid and ~7 hours for *l*-ritalinic acid following oral intake of sustained-release racemic methylphenidate at doses of 18-54 mg *(40)*. Repeated dosing of children with *d*-methylphenidate did not result in significant accumulation *(30)*.

2.1.1.6 Stereoselective pharmacokinetics

A series of studies from the laboratory of Srinivas examined the stereoselective pharmacokinetics of methylphenidate in children. A study in adults was also reviewed in detail because it examined linearity of pharmacokinetic parameters at multiple doses.

In a pilot study by Srinivas et al. *(35)*, 6 boys (ages 8–13 years) took their regular dose of methylphenidate (10 mg for 5 subjects and 5 mg for 1 subject) prior to eating a light breakfast. Results from the child taking 5 mg were not used in calculations of mean values. Based on the reported body weights for the children, the doses ranged from 0.21 to 0.41 mg/kg bw in the children taking 10 mg and the dose was 0.21 mg/kg bw in the child taking 5 mg. Blood samples were collected prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, or 8 hours following dosing. Plasma levels of *d*-, and *l*-methylphenidate were measured using capillary column gas chromatography (GC) with electron capture detection. Results of the study are listed in Table 5. Plasma *d*-methylphenidate levels were 5 or more times higher than plasma *l*-methylphenidate levels in all children.

Table 5. Pharmacokinetic Parameters in Children Orally Administered *d,l*-Methylphenidate

Parameter	Enantiomer	Results
C_{max} (ng/mL)	*d*	7.07±1.23
	l	1.00±0.19
T_{max} (hours)	*d*	2.15±0.50
	l	2.01±1.16
$AUC_{0-\infty}$ (ng-h/mL)	*d*	30.46±9.57
	l	6.66±1.38
Half-life (hours)	*d*	3.10±1.07
	l	5.59±1.07

Results presented as mean±SD for 5 children given 10 mg methylphenidate. From Srinivas et al. *(35)*.

Hubbard et al. *(43)* examined enantioselective pharmacokinetics of sustained-release *d,l*-methylphenidate. Six children (5 boys and 1 girl 8–14 years old; mean age 11) received an oral dose of 20 mg methylphenidate. Doses on a body weight basis ranged from 0.34 to 0.88 mg/kg. Blood samples were taken prior to dosing and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.5, 6, 8, and 12 hours after dosing. Methods of analysis were referenced, but not described in this paper. Results are listed in Table 6. Peak plasma levels of the *d*-enantiomer were 8- to 10-fold higher than the *l*-enantiomer. Plasma levels of both *d*- and *l*-methylphenidate were sustained for at least 8 hours. Clearance and volume of distribution were greater for the *l*-enantiomer. Citing a study that found higher levels of *d*- versus *l*-enantiomer in the urine of a human dosed with racemic

methylphenidate, the study authors postulated that lower systemic exposure to the *l*-enantiomer is most likely due to reduced bioavailability and not selective urinary excretion of the *l*-enantiomer.

Table 6. Pharmacokinetic Parameters in Children Orally Dosed with Sustained-Release *d,l*-Methylphenidate

Parameter	Enantiomer	Results
C_{max} (ng/mL)	*d*	18.79±9.92
	l	1.60±1.23
T_{max} (hours)	*d*	2.83±1.69
	l	3.13±1.86
$AUC_{0-\infty}$ (ng-h/mL)	*d*	132.78±92.47
	l	12.73±7.37
Oral clearance	Ratio of *l*:*d*-enantiomer	10.18±3.08
Apparent volume of distribution	Ratio of *l*:*d* -enantiomer	14.91±13.19

Results presented as mean±SD for 6 children given 20 mg methylphenidate. From Hubbard et al. *(43)*.

Srinivas et al. *(32)* conducted a double-blind, four-way, randomized, crossover study to further examine enantioselective pharmacokinetics in children. Nine boys (mean age 11 years) orally received 10 mg *d,l*-methylphenidate, 5 mg *d*-methylphenidate, and 5 mg *l*-methylphenidate on 3 separate days, separated by a 1-week interval. Blood was collected prior to dosing and at 1, 2, 3, 4, 5, 6, and 7 hours after dosing. Plasma levels of *d*-, and *l*-methylphenidate were measured using a capillary column GC with electron capture detection. Results are listed in Table 7. The study authors reported no evidence of interconversion between enantiomers. Administration of the racemic compound resulted in higher plasma levels of *d*- than *l*-methylphenidate **[3–8 times higher]**, but T_{max} and half-life were similar for the 2 enantiomers. Citing a manuscript in press, the authors attributed the lower level of *l*-methylphenidate to preferential presystemic metabolism. Pharmacokinetic parameters for *d*-methylphenidate did not differ significantly when the drug was administered in racemic or pure form. However, C_{max} and AUC for *l*-methylphenidate were significantly lower when the drug was administered in pure versus racemic form. Sustained attention of the children was improved only upon administration of *d*- or *d,l*-methylphenidate.

Table 7. Pharmacokinetics in Children Orally Administered *d,l*-, *d*-, or *l*-Methylphenidate

Parameter	Enantiomer	Result for each treatment regimen		
		10 mg *d,l*	5 mg *d*	5 mg *l*
C_{max} (ng/mL)	*d*	6.42±2.17	5.60±2.79	N/A
	l	1.27±0.53	N/A	0.78±0.55
T_{max} (hours)	*d*	2.3±0.5	2.44±0.53	N/A
	l	2.4±0.5	N/A	2.1±0.3
$AUC_{0-\infty}$ (ng-h/mL)	*d*	27.71±9.53	23.55±12.14	N/A
	l	4.61±1.77	N/A	2.0±1.16
Half-life (hours)	*d*	1.87±0.65	1.84±0.83	N/A
	l	1.43±0.76	N/A	0.98±0.21

Results presented as mean±SD for nine children receiving each treatment.
N/A = non-applicable
From *(32)*.

Modi et al. *(40)* conducted a randomized three-way cross-over study to examine pharmacokinetics of *d*- and *l*-methylphenidate in adults (n = 35) orally administered continuous-release methylphenidate (Concerta) at doses of 18, 36 (2 × 18), and 54 (3 × 18) mg/kg bw. Blood

samples were collected over a 30-hour period for measurement of methylphenidate and ritalinic acid levels. Pharmacokinetic parameters are summarized in Table 8. Plasma levels of *d*-methylphenidate were ~40-fold higher than *l*-methylphenidate. In contrast, plasma levels of *d*- and *l*-ritalinic acid were similar. Dose-normalized pharmacokinetics for methylphenidate and ritalinic acid demonstrated linear and dose-proportional values. The ratio of AUC for *d*-methylphenidate to *d*-ritalinic acid was similar in all dose groups (~0.04), indicating no dose-related effects on metabolism.

Modi et al. *(40)* noted that nonlinear pharmacokinetics were observed at doses of 10–60 mg methylphenidate (immediate-release) in a study by Aoyama et al. *(39)*. Modi et al. postulated that nonlinearity may have resulted from the higher blood levels obtained with the immediate-release versus continuous-release formulations.

Table 8. Pharmacokinetics of Methylphenidate and Ritalinic Acid in Adults

		Results at each dose level		
Parameter	Enantiomer	18 mg	36 mg	54 mg
Methylphenidate				
C_{max} (ng/mL)	*d*	3.87±1.8	7.28±2.8	10.6±3.4
	l	0.095±0.2	0.17±0.2	0.36±0.5
T_{max} (hours)	*d*	7.9±2	7.5±1	7.2±1.5
	l	7.1±2	7.0±2	6.1±1
Half-life (hours)	*d*	3.8±0.8	3.9±0.7	3.9±0.7
	l	-	-	-
$AUC_{0-\infty}$	*d*	42.2±16	80.9±31	120±46
(ng-h/mL)	*l*	0.43±0.7	0.96±1	1.82±2.7
Ritalinic acid				
C_{max} (ng/mL)	*d*	53.3±14	105±36	155±37
	l	69.7±19	132±36	192±31
T_{max} (hours)	*d*	8.8±2	8.8±1	8.5±2
	l	8.1±2	7.6±1	7.8±2
Half-life (hours)	*d*	9.1±2	8.8±2	9.1±2
	l	6.9±2	6.7±1	6.8±1
$AUC_{0-\infty}$ (ng-	*d*	989±240	1880±360	2880±660
h/mL)	*l*	961±130	1870±260	2780±350

Data presented as mean±SD.
- = Insufficient data for calculation.
From *(40)*.

2.1.2 Experimental Animal

2.1.2.1 Pharmacodynamics
The National Toxicology Program (NTP) *(8)* reviewed experimental animal studies modeling the pharmacologic action of methylphenidate in the treatment of human ADHD. Methylphenidate stimulatory effects in rodents are thought to occur through stimulation of dopaminergic neurons, releasing stored catecholamines into the synaptic cleft. In neonatal rats, methylphenidate ameliorated hyperactivity induced by depletion of brain dopamine. Dosing of rats with methylphenidate metabolites (ritalinic acid, *p*-hydroxymethylphenidate, and 6-oxomethylphenidate) resulted in no pharmacologic activity, thus indicating that the parent compound is most likely the pharmacologically active species.

A series of studies using dopamine transporter knock-out mice demonstrated that reduction of hyperactivity was modulated through the serotonergic system; however, the relevance of the studies to humans was questioned because serotonin reuptake inhibitors were found to be ineffective in the treatment of children with ADHD (reviewed in *(18)*).

The experimental animal studies suggesting that *d*-methylphenidate is the active enantiomer were reviewed by Teo et al. *(44)*. A rat locomotive activity study demonstrated that potency of *d*-methylphenidate is greater than *d,l*-methylphenidate, which in turn is greater than *l*-methylphenidate. In a rat behavioral study, *d*-methylphenidate was more potent than *l*-methylphenidate, which produced little effect. One study demonstrated that depletion of catecholamine stores in brain neurons reduced locomotive response to *d*-methylphenidate. Studies in human and baboon brains revealed specific binding and uptake of *d*- but not *l*-methylphenidate in the striatum. *d*-Methylphenidate and *d,l*-methylphenidate, but not *l*-methylphenidate, reduced motor hyperactivity in juvenile rats with dopamine projection lesions induced during the neonatal period; *d*-methylphenidate was more potent than *d,l*-methylphenidate *(45)*.

2.1.2.2 Pharmacokinetics

Methylphenidate is readily absorbed and distributed in rats, mice, and monkeys. In rats, 19% of a 10 mg/kg bw methylphenidate hydrochloride dose given orally was absorbed within 1 hour and the peak plasma concentration within that hour was 200 ng/mL (reviewed by *(8)*). Methylphenidate was found at the highest levels in liver, kidney, and lung of rats gavaged with 7–70 mg/kg bw and mice gavaged with 2.1–35 mg/kg bw methylphenidate. In rats given 1 mg/kg bw methylphenidate hydrochloride orally or iv, the brain tissue to serum ratio of methylphenidate was 8 within 1–5 minutes. In another study, the brain to plasma ratio of methylphenidate in rats was 3.4 (reviewed by *(1)*). Methylphenidate brain levels in baboons peaked at 8–10 minutes following iv administration and 60–120 minutes following oral administration (reviewed in *(41)*).

Methylphenidate metabolites in rats and dogs exposed by various routes are outlined in Table 4. Major biotransformation pathways in rats and dogs exposed orally or parenterally are microsomal oxidation of methylphenidate to oxomethylphenidate and aromatic hydroxylation to *p*-hydroxymethylphenidate, in addition to de-esterification to ritalinic acid (Figure 2) (reviewed by *(8)*). More than 50% of metabolites in rats and dogs are derived from microsomal oxidation or aromatic hydroxylation reactions. Percentage of orally administered methylphenidate believed to be biotransformed to ritalinic acid is ~35–40% in rats and 23% in dogs. Less than 1% of methylphenidate is excreted unchanged in all species. Many of the metabolites undergo further conjugation and de-esterification reactions. It was reported that one dog study demonstrated evidence of CYP inhibition by methylphenidate (reviewed in *(42)*).

Elimination half-life of methylphenidate from plasma was reported at 2–3 hours in rats orally administered 10 mg/kg bw and monkeys orally administered 3 mg/kg bw (reviewed in *(8)*). Urinary excretion is the major elimination route in mice, dogs, and rats (reviewed in *(8)*). Oral dosing of rats with radiolabeled methylphenidate resulted in urinary elimination of 50–60% of a ≤20 mg/kg bw dose over an unspecified time period and 80% of a ≤70 mg/kg bw dose over 24 hours. Oral dosing studies in mice and dogs demonstrated 50–60% urinary elimination of an unspecified dose over 48 hours. In another mouse study, 80% of an oral methylphenidate dose ≤35 mg/kg bw was excreted in urine over 24 hours. In rats dosed with 10–20 mg/kg bw methylphenidate orally or by intraperitoneal (ip) injection, 30–40% of elimination occurred through feces and a significant amount of the dose was also excreted in bile (reviewed in *(8)*).

A brief section in the FDA medical review for Focalin reported similar pharmacokinetic values for *d*-methylphenidate in rats, rabbits, and dogs when the drug was administered as the *d*- or *d,l*-enantiomer at equimolar concentrations of *d*-enantiomer *(30)*. T_{max} for *d*-methylphenidate was 30 minutes at doses providing up to 25 mg/kg bw *d*-enantiomer. AUC of *d*-methylphenidate was comparable at equimolar concentrations of *d*- or *d,l*-enantiomers and plasma half-life was reported at 1–2 hours in rats, rabbits, and dogs. Plasma half-life for *d*-ritalinic acid was reported at 1–3 hours in rats and 4–8 hours in rabbits.

A number of studies were described in detail because they examined pharmacokinetics of methylphenidate in pregnant animals. Also notable in these studies is that the *d*- and *l*-enantiomers were analyzed separately.

Teo et al. *(46)* performed a perinatal/postnatal toxicology study of *d*-methylphenidate (98–102% pure) and *d,l*-methylphenidate (chiral purity 50/50) in Sprague-Dawley rats, discussed in Section 3. Satellite groups of pregnant rats were used for pharmacokinetic assessment. Equal treatments were given by gavage twice/day, 6 hours apart, for total daily doses of *d*-methylphenidate of 2 and 20 mg/kg bw/day and a total daily dose of *d,l*-methylphenidate of 40 mg/kg bw/day on GD 7–17. An unspecified number of animals were evaluated on GD 7 and 17 with plasma sampled just prior to the morning dose and at times 0, 0.25, 0.5, 0.75, 1, 2, 4, and 12 hours post-dose (the afternoon dose was omitted on the day of sampling). *d*-Methylphenidate determinations were by liquid chromatography-tandem mass spectroscopy. AUC exposures to *d*-methylphenidate were 500 ng-h/mL after dosing with 20 mg/kg bw/day *d*-methylphenidate and 800 ng-h/mL after dosing with 40 mg/kg bw/day *d,l*-methylphenidate. **[It is not stated whether these data were from GD 7 or 17 samples and no data were given for the 2 mg/kg bw/day dose of *d*-methylphenidate.]** The authors stated that both compounds behaved in a dose-proportional manner without evidence of accumulation. **[No data were shown; the Expert Panel questions whether dose-proportionality could be shown for *d,l*-methylphenidate for which only a single dose appears to have been used.]**

A subsequent developmental toxicity study from the same group *(46)* also included satellite pharmacokinetic assessments in Sprague-Dawley rats and New Zealand White rabbits. The developmental toxicity results are discussed in Section 3. In the pharmacokinetic component, pregnant rats (n = 4/group/time point) were given twice daily gavage doses of *d*-methylphenidate and *d,l*-methylphenidate at the same dose levels and on the same days of pregnancy (GD 7–17) as in the first study *(47)*. Pregnant rabbits (n = 4/group/time point) were given 4 or 100 mg/kg bw/day *d*-methylphenidate or 200 mg/kg bw/day *d,l*-methylphenidate on GD 6–18. As in the rat study, the rabbits received the total daily dose in 2 equal doses 6 hours apart. On the last day of treatment, only the morning dose was given and plasma was sampled 0, 0.25, 0.5, 0.75 (in the rabbits), 1, 2, 4, 8, and 24 hours after the dose. Samples were assayed by liquid chromatography-tandem mass spectroscopy for *d-, l-,* and *d,l*-methylphenidate. **[The authors indicated that based on unpublished data, there is no interconversion of the *d*- and *l*-enantiomers in human plasma.]**

Results are given in Table 9. and Table 10 **[The Expert Panel notes that the methods of Teo et al. *(46)* do not describe the collection of some of the data presented in the paper; these data correspond to the methods given in Teo et al. *(47)*.]** The authors called attention to the higher concentrations of *d*-methylphenidate after administration of *d,l*-methylphenidate than after administration of *d*-methylphenidate, in spite of equal amounts of administered *d*-enantiomer. The lower concentration of *l*- compared to *d*-methylphenidate after administration of *d,l*-methylphenidate in a 50/50 ratio was attributed by the authors to a possible greater rate of elimination of the *l*-enantiomer.

Bakhtiar and Tse *(48)* of the Novartis Institute for Biomedical Research performed a pharmacokinetic study in pregnant Sprague-Dawley rats and New Zealand White rabbits. Treatments were by single daily gavage with "high purity" racemic methylphenidate on GD 6–17 in rats (plug = GD 0) and GD 7–20 in rabbits. Doses in rats were 0, 7, 25, or 75 mg/kg bw/day, and in rabbits 0, 20, 60, or 200 mg/kg bw/day, with 5 animals in each dose group. Blood was obtained from the retro-orbital sinus in rats and the marginal ear artery or vein in rabbits 0.5, 1 ,3, 8, and 24 hours after the last dose. Analysis of *d*- and *l*-methylphenidate was performed using chiral liquid chromatography-tandem mass spectroscopy. No methylphenidate was detected in any of the samples from control animals. Pharmacokinetic parameters are shown in Table 9 and Table 10. **[These tables display data from Teo et al. *(46)* and Bakhtiar and Tse *(48)*; the Expert Panel notes that there were differences between these studies in dosing intervals (twice/day versus daily dosing) and rat strain, pregnancy days of administration and sampling, and sampling intervals.]** The authors reported C_{max} corrected for dose in rats as ranging from 9.69 to 12.6 (ng/mL)/(mg/kg bw/day) for *d*-methylphenidate and 3.29 to 5.50 (ng/mL)/(mg/kg bw/day) for *l*-methylphenidate. In rabbits, the C_{max} corrected for dose ranged from 0.127 to 2.83 (ng/mL)/(mg/kg bw/day) for *d*-methylphenidate and 0.193 to 0.400 (ng/mL)/(mg/kg bw/day) for *l*-methylphenidate. The authors considered C_{max} to be dose-proportional in rats with respect to both enantiomers and in rabbits with respect to *l*-methylphenidate. AUC, however, was not dose-proportional in either species, with greater increases in AUC for both enantiomers in rats and for *d*-methylphenidate in rabbits than would have been predicted based on dose-proportionality. The authors believed these findings were consistent with saturability of metabolic processes.

Table 9. Pharmacokinetic Results in Pregnant Rats Given *d*- or *d,l*-Methylphenidate

Treatment (mg/kg bw/dose)	GD	Enantiomer measured	T_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (ng-h/mL)
d-Methylphenidate						
2[a]	7	*d*	0.25	13.90	0.23	4.93
	17	*d*	0.25	11.08	0.80	8.15
20[a]	7	*d*	0.25	463	0.83	356
	17	*d*	0.25	546	0.66	519
d,l-Methylphenidate						
7[b]	17	*d*	0.5	88.4±16.7	1[c]	120±18.5
		l	0.5	38.5±4.14	1[c]	65.7±9.14
25[b]	17	*d*	0.5	293±28.8	1.5	781±128
		l	0.5	134±35.6	1[c]	329±92.5
40[a]	7	*d*	0.25	536	0.72	674
		l	0.25	488	0.65	500
	17	*d*	0.25	390	1.17	792
		l	0.25	313	0.95	554
75[b]	17	*d*	1.33	727±533	4[c]	3104±2469
		l	1.33	247±164	4[c]	1139±802

[a]Dose divided, given twice daily, GD 7–17, Sprague-Dawley strain. Results were from pooled plasma from 4 rats/group. *l*-Methylphenidate was undetectable after administration of *d*-methylphenidate. From Teo et al. *(46)*.
[b]Dose given once daily GD 6–17, Wistar-Hannover IGS strain. Data from 5 rats/group expressed as mean ± SD.
[c]Estimated from a graph.
From Bakhtiar and Tse *(48)*.

Table 10. Pharmacokinetic Results in Pregnant New Zealand White Rabbits Given *d*- or *d,l*-Methylphenidate

Treatment (mg/kg bw/day)	GD	Enantiomer measured[b]	T_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (ng-h/mL)
d-Methylphenidate						
4[a]	6	*d*	0.25±0.00	1.63±0.53	1.09 (n = 2)	3.25 (n = 2)
	18	*d*	0.31±0.13	3.13±1.49	1.23±0.27	5.84±0.26
100[a]	6	*d*	0.44±0.38	39±34	1.88±0.37	88±50
	18	*d*	0.31±0.13	101±78	1.19±0.08	146±73
d,l-Methylphenidate						
20[b]	20	*d*	0.90	3.98±1.70	2[c]	8.40±4.53
		l	0.90	8.00±3.08	3[c]	47.9±11.6
60[b]	20	*d*	2.3	7.60±2.26	4.5[c]	63.1±22.6
		l	1.4	11.6±1.70	3.5[c]	83.3±11.3
200[b]	20	*d*	0.50	565±213	1[c]	776±124
		l	0.50	86.3±35.1	2[c]	263±50.5
200[a]	6	*d*	0.38±0.14	142±91	1.38±0.45	268±166
		l	0.44±0.13	16.28±9.84	1.39±0.40	35.85±9.51
	18	*d*	0.25±0.00	158±61	1.27±0.32	253±50
		l	0.56 = 0.31	16.10±3.20	1.66±0.51	36.85±4.22

[a]Dose divided, given twice daily, GD 6–18. *l*-Methylphenidate was undetectable after administration of *d*-methylphenidate. Mean±SD (n = 4 except where noted). From Teo et al.*(46)*. [b]Dose given once daily GD 7–20.. Data from 5 rabbits/group expressed as mean ± SD. [c]Estimated from a graph. From Bakhtiar and Tse *(48)*.

Teo et al. *(44)* conducted a satellite pharmacokinetic assessment as part of a subchronic study in Sprague-Dawley rats. The subchronic toxicity results are discussed in Section 2.2.2. In the pharmacokinetic component, rats (n = 4/group/sex/time point) were given twice daily gavage doses of *d*-methylphenidate (1 or 25 mg/kg bw/dose) or *d,l*-methylphenidate (50 mg/kg bw/dose), except on sampling days (day 1 and 80 of the dosing period), when only 1 dose was given. During the 2 days of sampling, blood was collected before dosing and at 0.25, 0.5, 0.75, 1, 2, 4, and 12 hours after dosing. Plasma samples from four rats/time period were pooled and assayed for *d*-methylphenidate by liquid chromatography-tandem mass spectroscopy. Pharmacokinetic endpoints were modeled using noncompartmental analysis. Results are listed in Table 11. Data indicate no accumulation of *d*-methylphenidate. The authors stated that rats dosed with *d,l*- versus *d*-methylphenidate had higher exposure to the *d*-enantiomer.

Table 11. Pharmacokinetic Results for *d*-Methylphenidate in Nonpregnant Rats Given *d*- or *d,l*-Methylphenidate

Treatment (mg/kg bw/dose)[a]	Sex	T_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (ng-h/mL)
d-Methylphenidate					
1	M	ND	ND	ND	ND
	F	0.50/0.25	2.78/9.95	1.53/1.42	3.34/6.57
25	M	0.50/0.50	460/599	0.81/0.74	367/788
	F	0.50/0.50	668/612	0.75/0.72	699/880
d,l-Methylphenidate 50	M	0.50/0.25	675/574	0.74/0.72	692/890
	F	0.25/0.50	946/621	0.72/0.71	1224/1657

n = 1 since data were pooled for 4 rats/sex/time period; ND = not determined since concentrations below limit of quantification (< 1ng/mL).
[a]Dose given twice daily except on the day of sampling when given once daily; results are listed for day 1/day 80 of dosing. From *(44)*.

Teo et al. *(49)* also conducted a satellite pharmacokinetic assessment as part of a subchronic study in Beagle dogs. The subchronic toxicity results are discussed in Section 2.2.2. In the pharmacokinetic component, dogs (n = 4/group/sex/time point) were given twice daily gavage doses of *d*-methylphenidate (0.5 or 5 mg/kg bw/dose) or *d,l*-methylphenidate (10 mg/kg bw/dose), except on days of sampling (day 1 and the first day of week 12 of dosing), when only 1 dose was given. During the 2 days of sampling, blood was collected before dosing and at 0.25, 0.5, 0.75, 1, 2, 4, and 12 hours after dosing. Plasma samples were assayed for *d*-, and *l*-methylphenidate by liquid chromatography-tandem mass spectroscopy. Pharmacokinetic endpoints were modeled using noncompartmental analysis. **[Again, the authors indicated that based on unpublished data there is no interconversion of the *d*- and *l*-enantiomers in human plasma.]** Results are listed in Table 12. Data indicate no accumulation of *d*- or *l*-methylphenidate. According to further analyses presented in a manuscript in preparation, pharmacokinetic parameters were reported to be dose proportional. Differences in AUC according to sex could not be evaluated due to large standard deviations.

Table 12. Pharmacokinetic Results in Dogs Given *d*- or *d,l*-Methylphenidate

Treatment (mg/kg bw/dose)[a]	Sex	Enantiomer measured[b]	T_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (ng-h/mL)
d-Methylphenidate						
0.5	M	*d*	0.42±0.14/ 0.50±0.25	2.40±1.21/ 3.53±3.02	0.43[c]/ 1.31[c]	1.27±0.83/ 2.43±1.89
	F	*d*	0.38±0.14/ 0.50[c]	11.25±13.89/ 1.85[c]	0.42[c]/ ND	7.72±11.60 / 0.64[c]
5	M	*d*	1.50±1.67/ 2.31±1.95	85.40±55.14/ 10.15±6.16	0.85±0.25/ 2.67[c]	114±59/ 19±15
	F	*d*	1.25±1.84/ 1.00±0.87	71.25±68.25/ 38.00±44.50	0.89±0.32/ 3.64±5.09	77±70/ 45±44
d,l-Methylphenidate 10	M	*d*	1.38±1.75/ 1.44±1.74	255±147/ 183±229	0.85±0.11/ 0.83[c]	346±195/ 132±130
	M	*l*	1.25±1.84/ 1.44±1.74	333±174/ 252±286	1.23±0.34/1.74±0.94	479±238/ 218±162
	F	*d*	1.69±1.72/ 5.13±4.87	136±95/ 27.53±29.10	1.42±0.87/ND	155±79/ 41±26
	F	*l*	1.69±1.72/ 5.13±4.87	215±133/ 58±62	1.45±0.78/ND	262±119/ 95±60

Mean±SD (n = 4 except where noted); ND = not determined because concentrations below limit of quantification (< 1ng/mL).
[a]Dose given twice daily except on the day of sampling when given once daily; results are listed for day 1/week 12 of dosing. [b]*l*-Methylphenidate was undetectable after administration of *d*-methylphenidate. [c]No SD reported. From *(49)*.

The Teo et al. *(49)* study in dogs indicated that administration of the racemic mixture resulted in higher blood levels of the *l*-enantiomer. The findings are consistent with a study that also demonstrated higher levels of the *l*-enantiomer in 1 dog orally administered 1.0 mg/kg bw *d,l*-methylphenidate *(50)*. AUCs were 5.96 ng-hr/mL for the *d*-enantiomer and 7.77 ng-hr/mL for the *l*-enantiomer. The half-life for the *d*-enantiomer was 3.07 hours compared to 2.86 hours for the *l*-enantiomer, an unimportant difference. The relevancy of using dogs to study methylphenidate toxicity in humans was questioned by Srinivas et al. *(50)*, who noted that levels of the *d*-enantiomer are higher in humans following ingestion of racemic methylphenidate (see Section 2.1.1.6).

2.2 General Toxicity

2.2.1 Human

2.2.1.1 Side effects of medication therapy

Adverse effects emerging in ≥1% of patients treated with *d*- or *d,l*-methylphenidate were included in an FDA *(30)* review and those effects are summarized in Table 13. A meta-analysis of published placebo-controlled studies of methylphenidate effectiveness for ADHD included an evaluation of adverse effects (Table 14) *(51)*. Briefer reports of adverse effects were presented in methylphenidate product labels *(5, 7)*, but the incidence of effects appears similar to the values reported by the FDA *(30)*. Methylphenidate manufacturers report nervousness and insomnia as the most common adverse effects *(4, 5, 7, 12)*. The adverse effects occurring most frequently in

children include reduced appetite, abdominal pain, weight loss with prolonged therapy, insomnia, and tachycardia *(4, 7, 11, 12*). The AAP *(24*) also reported jitteriness and social withdrawal as common side effects associated with stimulant treatment. Irritability, anxiety, and proneness to crying were reported as common side effects of methylphenidate therapy in a review by Kimko et al. *(1*). The AAP *(24*) states that most effects associated with stimulant treatment occur during early therapy and are mild and transient. However, it has also been reported that some adverse effects such as anorexia, weight loss, headaches, insomnia, and tics may not resolve during methylphenidate treatment in children (reviewed in *(22*)). An effect that has been inconsistently documented in controlled studies of stimulants is "cognitive constriction," which is characterized by interference of cognitive tasks requiring divergent thinking (reviewed by *(28*)). Controlled studies on adverse medication effects in children are discussed in detail in Section 3.1.2.1.

According to drug labels for methylphenidate, its use is contraindicated in individuals with marked anxiety, tension, and agitation, since the drug may aggravate such symptoms *(4, 5, 7, 12*). Use of methylphenidate is also contraindicated in individuals with glaucoma, motor tics, or family history of Tourette syndrome, and hypersensitivity to the drug.

Table 13. Treatment-Emergent Adverse Effects in ≥1% of Patients in Double-Blind Methylphenidate Studies

	Percentage of unique patients reporting the effect		
Body system/adverse effect	*d*-Methylphenidate (n = 79)	*d,l*-Methylphenidate (n = 46)	Placebo (n = 82)
Body as whole			
Abdominal pain	15.2	4.3	6.1
Accidental injury	5.1	8.7	6.1
Chest pain	2.5	0	0
Fever	5.1	6.5	1.2
Flu syndrome	2.5	0	3.7
Headache	12.7	23.9	8.5
Pain	5.1	2.2	3.7
Viral infection	2.5	8.7	6.1
Digestive			
Anorexia	6.3	10.9	1.2
Diarrhea	3.8	2.2	1.2
Gastroenteritis	0	0	2.4
Nausea	8.9	13.0	1.2
Vomiting	5.1	6.5	3.7
Metabolic			
Ketosis	2.5	0	0
Musculoskeletal			
Myalgia	0	2.2	2.4
Nervous			
Emotional lability	3.8	4.3	1.2
Insomnia	2.5	4.3	3.7
Nervousness	2.5	2.2	1.2
Personality disorder	2.5	2.2	0
Somnolence	3.8	4.3	2.4
Respiratory			

Body system/adverse effect	Percentage of unique patients reporting the effect		
	d-Methylphenidate (n = 79)	*d,l*-Methylphenidate (n = 46)	Placebo (n = 82)
Increased cough	2.5	4.3	1.2
Epistaxis	3.8	2.2	1.2
Pharyngitis	2.5	4.3	2.4
Rhinitis	10.1	4.3	7.3
Skin and appendages			
Eczema	2.5	0	0
Herpes simplex	0	0	2.4
Special senses			
Ear pain	0	0	2.4

Adapted from FDA *(30)*.

Table 14. Adverse Events in Published Studies of Methylphenidate in Children

Symptom	Total subjects	Percent parent/self reporting side effect (95% CI)		
		Methylphenidate	Placebo	Methylphenidate–placebo difference
Decreased appetite	675	44.8 (36.8–52.7)	14.4 (5.1–23.8)	30.3 (18.0–42.6)*
Insomnia	663	47.7 (42.1–53.3)	30.7 (23.9–37.5)	17.0 (8.3–25.8)*
Headache	581	18.4 (15.3–21.5)	12.5 (8.9–16.0)	5.9 (1.4–10.4)*
Stomachache	290	24.0 (19.0–28.9)	14.9 (8.7–21.1)	9.0 (1.2–16.9)*
Drowsiness	201	24.3 (16.6–32.0)	14.5 (4.5–24.6)	9.8 (–2.8–22.3)
Anxiety	482	31.1 (24.8–37.5)	38.4 (29.9–46.8)	–7.2 (–17.8–3.3)
Dizziness	383	7.3 (5.5–9.1)	2.2 (0.0–4.6)	5.1 (2.2–8.1)*

Total subjects does not distinguish patients randomized to placebo versus methylphenidate; however, most studies used a cross-over design. The number of studies reporting individual symptoms ranged from 4 to 10. *Statistically significant. From *(51)*.

2.2.1.2 Overdose symptoms

Symptoms of methylphenidate overdose are similar to those of other amphetamine-like drugs. Signs and symptoms result primarily from overstimulation of the CNS and include vomiting, headache, agitation, confusion, euphoria, delirium, tremors, muscle twitching, hyperreflexia, seizures, and possibly coma. Cardiovascular manifestations include tachycardia, chest pain, hypertension, and dysrhythmia. Patients also present with mydriasis, diaphoresis, fever, and abdominal pain. Severe intoxication can result in hyperthermia, dysrhythmia, and seizures *(5, 7, 10, 12)*).

Abuse of methylphenidate by iv injection can result in intoxication. Many of the complications and toxicity of iv administration are related to insoluble excipients in methylphenidate tablets. Reported toxicity has included retinopathy, emphysema, hepatic dysfunction, and multiple organ system failure *(52-56)*.

Symptoms observed with methylphenidate overdose in various age groups were reported in a retrospective review of reports submitted to a certified regional poison information center during 1998 (Table 15) *(57)*. As noted in Table 15, some of the patients ingested other drugs in combination with methylphenidate and the clinical findings were not discussed in terms of

methylphenidate exposures alone. More severe effects were observed in patients ≥13 years, who had larger mean exposures, increased time between overdose and contact with a poison control center, and more frequent co-exposure to other drugs. Known outcomes in patients were classified as no effects to moderate effects. There was no significant morbidity or mortality.

Table 15. Symptoms Reported in Methylphenidate Poisonings

Patient ages (years)	*N*	Intake, mg (mean ± SD)	Mean dose, mg/kg bw	Percent with clinical symptoms	Percent co-exposed to other drugs[a]	Symptoms
< 6	35	13.6 ± 8.2	0.94	16	1	Drowsiness or hyperactivity
6–12	26	26.8 ± 18.7	0.89	30.8	37.5	Drowsiness, hyperactivity, hyperventilation, and/or "feeling hot"
13–19	30	106.8 ± 177	1.70	50.0	46.7	Tachycardia, agitation, uncontrolled movements, hydriasis, confusion, hyperactivity, hypertension, drowsiness, and/or hypokalemia
> 19	22	70.0 ± 73.9	Unknown	54.5	~53	Tachycardia, agitation, uncontrolled movements, confusion, hyperactivity, hypertension, drowsiness, psychosis, and/or slurred speech

[a]Percentages based on number of patients with clinical signs, with the exception of the >19 year-old group which is based on number of patients admitted to the emergency department.

2.2.1.3 Drug Interactions

Methylphenidate may decrease the hypotensive effect of guanethidine and may inhibit metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, diphenylhydantoin, and primidone), phenylbutazone, and tricyclic drugs (e.g., imipramine, clomipramine, and desipramine); although causality has not been established, co-administration of methylphenidate with clonidine may lead to serious adverse effects *(4-6, 10, 16*). Possible inhibition of sertraline (a serotonin reuptake inhibitor) metabolism and possible interactions with phenytoin and antipsychotics (haloperidol and thioridazine) have also been reported *(42*). Hypertensive crises could occur if methylphenidate is used concurrently or within 14 days of treatment with monoamine oxidase inhibitors *(5, 12*).

Gastrointestinal pH changes resulting from antacid or acid suppressant use could potentially alter methylphenidate release from Ritalin LA tablets, but the effect of gastrointestinal pH on absorption has not been studied *(10)*.

2.2.1.4 Drug Abuse

Chronic methylphenidate abuse can lead to tolerance, psychic dependence, and abnormal behavior *(11)*. Methylphenidate abuse has resulted in symptoms similar to those observed with amphetamine toxicity, including psychotic episodes, paranoid delusions, hallucinations, and bizarre behavior *(13)*. Abuse has resulted in death. Depression and symptoms of underlying disorders can be unmasked during withdrawal *(11)*.

Experimental animal and human studies indicate that methylphenidate can substitute for methamphetamine and cocaine in models used to predict abuse potential *(58)*. There has been concern that methylphenidate use by children will increase susceptibility to abuse of stimulants in later life. Evidence for and against this proposition is summarized in Section 3.1.2.7

2.2.2 Experimental Animal

An FDA review *(30)* of Focalin summarized toxicity in rat and dog studies. Weight loss was reported as a consistent finding in dog studies. In rats, decreased platelet count, increased prothrombin time in males, and increased eosinophils in females were reported following dosing with *d*- or *d,l*-methylphenidate for 14 but not 90 days. No observed effect levels (NOEL) for *d*-methylphenidate were identified at < 20 mg/kg bw/day in rats and 1 mg/kg bw/day in dogs. NOELs for *d,l*-methylphenidate were < 40 mg/kg bw/day for rats and 2 mg/kg bw/day for dogs. A maximum tolerated dose of 100 mg/kg bw/day for *d*-methylphenidate in rats was based upon hyperactivity, hypersensitivity, and self-mutilation. The maximum tolerated dose of 10 mg/kg bw/day in dogs was based upon hyperactivity, salivation, and elevated body temperature.

A review by Greenhill *(28)* reported hyperactivity and hyperexcitability but no signs of reduced appetite, growth suppression, convulsions, or changes in liver tissue in dogs treated with 120 mg/kg bw/day methylphenidate for 120 days.

Unlike amphetamine and methamphetamine, there is no evidence that methylphenidate damages neurons (reviewed in *(59)*).

LD_{50} values are summarized in Table 16. Death following exposure to high dose levels of methylphenidate is most probably due to "excessive central adrenergic stimulation" **[not otherwise specified]** *(8)*. Additional effects reported in experimental animals exposed to methylphenidate include lowered brain and serum cholesterol levels and decreased serum thyroxine and triiodothyronine (reviewed in *(8)*).

A review by Greenhill *(28)* reports that methylphenidate has a 100:1 margin of safety for an approximate single human therapeutic dose and a dose producing lethality in two species of animals.

Table 16. LD_{50} Values for Methylphenidate

Species	Exposure route	LD_{50} (mg/kg bw)
Mouse	oral	60–450[a,b]
	ip	32–96.5[a,c]
	sc	150–218[a,c]
	iv	41[a]
Rat	oral	180–350[b]
	ip	430[a]
	sc	170[c]
	iv	50[c]
Rabbit	oral	900[c]
	sc	170[c]
	iv	30[c]

Reviewed in [a]HSDB *(60)*, [b]NTP *(8)*, [c]NIOSH *(61)*.
[The enantiomers were not specified, but based on the CAS RNs provided (298-59-9 or 113-45-1) and the listing of Ritalin as a synonym, it appears that *d,l*-methylphenidate was used in these studies.]

NTP toxicity studies and studies by Teo et al. *(49)* were reviewed in detail because reproductive organs were examined in a subchronic and in a carcinogenicity study and growth was measured in the subchronic study. The carcinogenicity study is described in Section 2.4.2.

The NTP *(8)* conducted 14-day and 13-week studies to examine toxicity of *d,l*-methylphenidate in F344/N rats and $B6C3F_1$ mice. The studies used pharmacopoeia grade methylphenidate hydrochloride, which has a purity of >99%. The drug was mixed in feed; stability, homogeneity, and target concentrations were verified. Statistical analyses included Cox method and Tarone life table test for survival, Fisher exact test and Cochran-Armitage trend test for lesion incidence, and the Dunnet, Williams, Dunn, or Shirley test for continuous variables.

In a 14-day study, no toxicity was observed at doses up to 1000 ppm (80 mg/kg bw in rats and 160 mg/kg bw in mice, as determined by study authors). The study was repeated by exposing 7-week-old animals (5/sex/group) to 0, 16, 62, 250, 1000, or 4000 ppm methylphenidate hydrochloride in feed for 14 days. Doses were 0, 1, 5, 20, 90, or 380 mg/kg bw/day in male rats and 1, 5, 20, 90, and 360 mg/kg bw/day in female rats. The highest dose in rats was approximately equal to the LD_{50} for methylphenidate. Doses in mice were 0, 2, 10, 40, 120, or 460 mg/kg bw/day in males and 0, 2, 10, 40, 140, or 410 mg/kg bw/day in females. Animals were observed daily and weighed before, during, and after treatment. Clinical chemistry and histopathology of liver and kidney were examined in all animals.

In male and female rats exposed for 14 days, body weight gain and final body weight were significantly reduced in the 4000 ppm group. Slightly lower feed intake was observed only during the first 5 days of the study. Clinical signs included hyperactivity in females exposed to ≥250 ppm and males exposed to 4000 ppm. Significant, treatment-related changes in clinical chemistry included decreased serum creatinine levels (≥16-ppm males), increased serum urea nitrogen (≥62 ppm females, ≥1000 ppm males), and decreased aspartate aminotransferase activity (4000 ppm males). In the 4000 ppm group, significant increases were observed for absolute and relative (to body weight) liver weight in males and females, and relative kidney weights in males. Other significant organ weight changes indicated in Table F1 of the NTP report were increased relative brain weight (4000 ppm males and females) and increased absolute heart weight (≥1000-ppm

males). Centrilobular hepatocellular hypertrophy was observed in males and females of the 4000-ppm group **[data not shown]**.

In mice exposed for 14 days, body weight gain was reduced in males and females administered ≥1000 ppm. Final body weight of females in the 4000 ppm group was lower than controls. Feed intake was decreased in the 1000 and-4000 ppm groups only during the first week of the study. During the second week of the study, hyperactivity was observed in some males from the 4000 ppm group. Three males from the 4000 ppm group died during the study. Treatment had no effect on clinical chemistry. Significant, treatment-related effects on organ weights included increased absolute and relative (to body weight) liver weight (≥16 ppm males, 4000 ppm females) and decreased absolute and relative thymus weight (4000 ppm females). According to Table F5 in the NTP report, relative liver weights were significantly increased and absolute thymus weights were significantly decreased in female mice from the 1000 ppm group. Centrilobular hepatocellular hypertrophy was observed in males exposed to ≥250 ppm and females exposed to ≥1000 ppm; the effect was dose-related and more severe in males. Two males that died during the study had slight multifocal tubule epithelial cell degeneration and necrosis in the kidneys **[histopathologic data not shown]**.

The 13-week NTP study was conducted according to FDA Good Laboratory Practices (GLP). Six-week-old rats and mice (10/sex/group) were fed diets containing 0, 125, 250, 500, 1000, or 2000 ppm methylphenidate hydrochloride; exposures occurred for 90 days in rats and 92 days in mice. Study authors estimated doses at 0, 7, 15, 30, 70, or 130 mg/kg bw/day in male rats and 0, 9, 18, 30, 70, and 150 mg/kg bw/day in female rats. Author-estimated doses in mice were 0, 15, 30, 70, 115, and 230 mg/kg bw/day in males and 0, 15, 30, 70, 125, and 260 mg/kg bw/day in females. Dose selection was based on results of the 14-day study. Animals were examined daily and weighed before, during, and after treatment. Growth was assessed in rats by measuring crown-rump length and bone density. After rats were killed they were necropsied and organs were weighed. Livers and kidneys from all animals, major systems organs from control and 2000 ppm animals, and animals that died before the study ended were collected and fixed in 10% neutral buffered formalin for histopathologic evaluation. Included in the organs examined were clitoral gland (rat only), mammary gland, ovary, prostate gland, testis, epididymis, seminal vesicle, and uterus.

In the 13-week rat study, 4 deaths in the 125 ppm group and 1 death in the 250 ppm group were not believed to be treatment-related by authors. Body weight gain was significantly reduced in females exposed to ≥250 ppm and males exposed to ≥500 ppm, but final body weights did not differ significantly from controls. Feed intake was lower in the 2000 ppm group during the first week of the study. During weeks 1 and 2 of the study, females exposed to ≥1000 ppm were slightly hypersensitive to touch and displayed increased activity and vocalization. Increased activity was observed in female rats of the 2000 ppm group during weeks 9–13 of the study. Significant organ weight changes included increased absolute liver weight (2000 ppm male and female), relative liver weight (≥1000 ppm male and female), relative kidney weight (≥1000 male and female), absolute brain weight (≥500 ppm male), and relative brain weight (≥500 ppm male, ≥1000 ppm female). Also reported were a decrease in absolute heart weight in female rats exposed to ≥1000 ppm and an increase in relative testis weight at ≥1000 ppm**.** No increase in histopathologic lesions was observed at the high dose **[data not shown]**. Methylphenidate did not decrease nose-rump length, bone length, or bone density in males or females.

In the 13-week mouse study, body weight gain was significantly reduced in males exposed to ≥125 ppm and females exposed to ≥2000 ppm. Final body weight was significantly lower in males exposed to ≥250 ppm and females exposed to 2000 ppm according to Table 11 in the NTP report. According to Table F6 in the NTP report, necropsy body weights were significantly

reduced in males of all dose groups but there were no significant effects in females. Relative liver weights were reduced in males exposed to ≥250 ppm and absolute and relative liver weights were significantly increased in mice of both sexes exposed to ≥1000 ppm. The study authors stated that only relative weights increased in other organs and the effect was attributed to reduced body weight. **[According to Table F6 in the NTP report, absolute and relative brain weights were increased in the 2000 ppm males.]** Liver lesions were significantly increased in males exposed to ≥500 ppm and the lesions included centrilobular hypertrophy, degeneration, and necrosis.

The NTP tables reporting organ weight effects contain a footnote about organ collection for sperm morphology and vaginal cytology examinations. The results for sperm analyses and male organ weight measurements are addressed in a separate publication *(62*), which is discussed in Section 4.2.

Teo et al. *(44*) examined the subchronic toxicity of *d,l*- and *d*-methylphenidate in Sprague-Dawley rats. In a 14-day dose range-finding study, 10 rats/sex/group were gavage dosed with 0, 1, 10, or 50 mg/kg bw *d*-methylphenidate or 0, 2, 20, 100 mg/kg bw *d,l*-methylphenidate twice daily, 6 hours apart, for a total dosage of 0, 2, 20, or 100 mg/kg bw/day *d*-methylphenidate or 0, 4, 40, or 200 mg/kg bw/day *d,l*-methylphenidate. Significant differences in body weight changes **[not specified but assumed reduced]** and reduced feed consumption were observed in the 200 mg/kg bw/day *d,l*-methylphenidate and 100 mg/kg bw/day *d*-methylphenidate groups. There were 2 moribund rats in the 200 mg/kg bw/day *d,l*-methylphenidate group and clinical signs in that group included self-mutilation, abrasions, and missing portions of front paws. Similar clinical signs were observed in females of the 100 mg/kg bw/day *d*-methylphenidate group, but at a lower incidence and lesser severity. Changes in hematology and clinical chemistry endpoints occurred in the ≥40 mg/kg bw/day *d,l*-methylphenidate and 100 mg/kg bw/day *d*-methylphenidate groups, but the effects were not specified. Organ weight changes included increased absolute and relative liver weight in females of the 200 mg/kg bw/day *d,l*-methylphenidate group and decreased absolute spleen weights in females of the 20 mg/kg bw/day and males of the 100 mg/kg bw/day **[*d*-methylphenidate]** group. Based on the findings of this study, the authors selected high doses of 50 mg/kg bw/day for *d*-methylphenidate and 100 mg/kg bw/day for *d,l*-methylphenidate in the subchronic study.

For the subchronic study, 7-week-old Sprague-Dawley rats were gavage dosed with hydrochloride salts of *d*- or *d,l*-methylphenidate (98–102% purity) in water for 90 days. Doses (number of rats/sex/dose) were 0 (15), 1.0 (10), 10.0 (10), and 25.0 (15) mg/kg bw for *d*-methylphenidate and 50 (15) mg/kg bw for *d,l*-methylphenidate. Doses were administered twice daily, 6 hours apart, for total dosages of 0, 2.0, 20.0, or 50.0 mg/kg bw/day *d*-methylphenidate or 100 mg/kg bw/day *d,l*-methylphenidate. Animals were observed daily and measurements included feed intake, body weight, ophthalmology examination, and body temperature. Blood was collected before and during the study, and just prior to kill for hematologic and clinical chemistry evaluations. After rats were killed, organs were weighed and major organs were collected for a histopathologic evaluation of all animals. The organs analyzed were not generally specified, but testes were reportedly collected and fixed in Bouin solution. Ten rats/sex/group were killed 1–2 days after the last treatment. Five rats/sex group in the control, 50 mg/kg bw/day *d*-methylphenidate, and 100 mg/kg bw/day *d,l*-methylphenidate groups were killed following a 30-day recovery period. Statistical analyses included analysis of variance (ANOVA) followed by Dunnett test.

One male and 1 female in the 50 mg/kg bw/day *d*-methylphenidate group and 1 male in the 100 mg/kg bw/day *d,l*-methylphenidate died during the study. Clinical signs stated to be most likely treatment-related included material around eyes or nose, scabbing, foot swelling, localized alopecia, and abrasions in rats treated with 50 mg/kg bw/day *d*-methylphenidate or 100 mg/kg

bw/day *d,l*-methylphenidate. Dose-related reductions in body weight changes were observed in males, with statistical significance obtained at numerous time points with ≥20 mg/kg bw/day *d*-methylphenidate and 100 mg/kg bw/day *d,l*-methylphenidate. There were no consistent reductions in female body weight gain or feed intake in males or females. There were no eye lesions or significant changes in body temperature. No significant hematologic changes were observed **[data not shown]**. Significant changes in clinical chemistry parameters in males of the 50 mg/kg bw/day *d*-methylphenidate and 100 mg/kg bw/day *d,l*-methylphenidate groups included increased blood urea nitrogen, sodium, and chloride, and decreased albumin, creatinine, and triglycerides; changes in females from the same dose groups included increased chloride and decreased albumin and albumin/globulin ratio. In the 20 mg/kg bw/day *d*-methylphenidate group, significant reductions were observed for triglyceride levels in males and albumin levels in females. Protein in urine was increased in 1 male from the 100 mg/kg bw/day *d,l*-methylphenidate group and 4 females from the 50 mg/kg bw/day *d*-methylphenidate group **[data not shown]**. The only absolute organ weight changes were observed in rats treated with *d,l*-methylphenidate; they included increased pituitary (male only) and ovary weight and decreased prostate weight **[data not shown]**. Significant increases in organ to body weight ratios were observed in rats treated with the high dose of either compound and organs affected included brain, heart, kidney, and liver in *d*-methylphenidate-treated males; liver, ovary, and spleen in *d*-methylphenidate-treated females; adrenals, brain, heart, kidneys and pituitary in *d,l*-methylphenidate-treated males; and brain, kidney, liver, ovary, and spleen in *d,l*-methylphenidate-treated females. When expressed as percent brain weight, only ovarian weights in rats treated with both drugs and prostate and pituitary weights in rats treated with *d,l*-methylphenidate remained increased **[data not shown]**. No abnormal histopathologic changes were observed **[data not shown]**. All effects were resolved or improved during the 30-day recovery period in control and high-dose animals. Based upon body weight changes, the authors identified a no observed adverse effect level (NOAEL) of 20 mg/kg bw/day for *d*-methylphenidate; they concluded that toxicity of *d*- and *d,l*-methylphenidate is comparable at equimolar doses of the *d*-enantiomer under the conditions of this study.

Teo et al. *(49*) examined the subchronic toxicity of *d,l*- and *d*-methylphenidate in Beagle dogs. In a 14-day dose range-finding study, an unspecified number of dogs were treated with 0, 0.5, 1.5, or 5 mg/kg bw *d*-methylphenidate or 1, 3, or 10 mg/kg bw *d,l*-methylphenidate twice daily, 6 hours apart, for a total dosage of 0, 1, 3, or 10 mg/kg bw/day *d*-methylphenidate or 2, 6, or 20 mg/kg bw/day *d,l*-methylphenidate. Hyperactivity and increased salivation were observed in dogs dosed with ≥3 mg/kg bw/day *d*-methylphenidate and 20 mg/kg bw/day *d,l*-methylphenidate. Reduced body weight and food intake were reported for dogs exposed to ≥3 mg/kg bw/day *d*-methylphenidate and ≥6 mg/kg bw/day *d,l*-methylphenidate. The maximum tolerated dose was considered to be 10 mg/kg bw/day for *d*-methylphenidate and 20 mg/kg bw/day for *d,l*-methylphenidate; those dose levels were selected as the high dose for the 90-day study.

In the GLP-compliant subchronic study, Teo et al. *(49*) gavage dosed 6-month-old Beagle dogs (6/sex/group) for 93 days with vehicle **[unspecified]**, 0.5, 1.5, or 5.0 mg/kg bw *d*-methylphenidate, or 10 mg/kg bw *d,l*-methylphenidate twice daily, 6 hours apart for total doses of 1, 3, or 10 mg/kg bw/day *d*-methylphenidate or 20 mg/kg bw/day *d,l*-methylphenidate. Drug purities were reported to be 98–102%. Animals were observed daily and measurements included feed intake, body weight, ophthalmology, body temperature, and electrocardiogram (EKG). Blood was collected before and during the study, and just prior to kill for hematologic and clinical chemistry evaluation. After animals were killed, organs were weighed and major organs were collected for a histopathologic evaluation of all animals. The organs analyzed were not generally specified, but testes were reported to have been collected and fixed in 3% glutaraldehyde. Four dogs/sex/group were killed at the end of treatment, while 2 dogs/sex/group

were killed following a 1-month recovery period. Statistical analyses included ANOVA followed by Dunnett test.

No mortality was observed in the 93-day study. Clinical signs in dogs dosed with 10 mg/kg bw/day *d*-methylphenidate or 20 mg/kg bw *d,l*-methylphenidate included salivation, hyperactivity, and loose stool or diarrhea. Significant reductions were observed for feed intake in males during the first 3–4 weeks of the study and male body weights in the 10 mg/kg bw/day *d*-methylphenidate and 20 mg/kg bw *d,l*-methylphenidate groups; weight loss was also observed in dogs from the highest *d*- and *d,l*-methylphenidate dose groups during the first few weeks of the study. Significant effects on hematology included reduced hemoglobin and hematocrit in males from the 10 mg/kg bw/day *d*-methylphenidate and 20 mg/kg bw/day *d,l*-methylphenidate groups; red blood cell count was also reduced in the males given 20 mg/kg bw/day *d,l*-methylphenidate. **[The results section reported that the only clinical chemistry findings were significant decreases in serum albumin and albumin/globulin ratio at week 4 in males given *d,l*-methylphenidate. However, Table 4 of the report indicates significantly increased blood urea nitrogen in females dosed with 10 mg/kg bw/day *d*-methylphenidate and reduced creatine phosphokinase in males dosed with 20 mg/kg bw/day *d,l*-methylphenidate.]** Significant decreases in absolute organ weights (*d*-: lung; *d,l*-: lung and spleen), increases in organ to body weight ratios (*d*-: brain, heart, and testes; *d,l*-: brain and liver), or decreases in organ to brain weight ratios (*d*-: lung; *d,l*-: lung and spleen) were observed in high-dose males treated with both drugs, but the study authors did not consider the changes to be treatment-related. No abnormal urinalysis results or histopathology were observed **[data not shown]**. Ophthalmologic and EKG testing was also reported to be normal. All effects were reversed or improved during the recovery period **[data not shown]**. The study authors selected a NOAEL of 3 mg/kg bw/day for *d*-methylphenidate based on body weight changes; they concluded that at equimolar concentrations of *d*-methylphenidate, the repeat-dose toxicity of *d*-methylphenidate was slightly less than or similar to that of *d,l*-methylphenidate.

2.3 Genetic toxicology

Results and details of study protocols for in vitro genetic toxicity tests are summarized in Table 17.

Based on results of their mutagenicity studies in *Salmonella* and chromosomal aberration and sister chromatid exchange tests in Chinese hamster ovary cells (Table 17), the NTP *(8)* concluded that methylphenidate ". . . is not a gene mutagen in bacteria or mammalian cells, but . . . might have some potential for inducing clastogenic damage in mammalian cells." However, it was noted that increases in sister chromatid exchange occurred at doses causing severe toxicity and increases in chromosomal aberrations did not correlate well with dose.

Additional genetic toxicity studies were identified. Teo et al. *(26)* demonstrated that *d,l*-, *d*-, and *l*-methylphenidate do not induce mutations in *Salmonella typhimurium*, *Escherichia coli*, or mouse lymphoma cells (Table 17). In an in vitro study available only as an abstract, therapeutic doses of methylphenidate caused a slight but significant increase in sister chromatid exchanges in lymphocytes in two of four pediatric patients [**presumably without metabolic activation**] *(63)*. Methylphenidate tested negative in a cell transformation assay *(64)*.

One in vivo genetic toxicity study was identified. In that study, no increase in bone marrow cell micronucleus formation was observed in 6–8-week-old male and female CD-1 mice treated orally with 25–250 mg/kg bw *d*-methylphenidate, 125–500 mg/kg bw *l*-methylphenidate, or 50–250 mg/kg bw *d,l*-methylphenidate *(26)*. The study included vehicle and positive controls.

Table 17. Genetic Toxicity Studies of Methylphenidate

Reference	Enantiomers tested/concentration	Testing with metabolic activation	Species or cell type/strain	Endpoint	Results
In vitro tests					
NTP *(8)*	*d,l*/≤10,000 µg/plate	Yes	*Salmonella typhimurium* strains TA100, TA1535, TA1537, TA98	Mutagenicity at the histidine operon	↔ with and without metabolic activation
NTP *(8)*	*d,l*/≤4000 µg/plate	Yes	*Salmonella typhimurium* strain TA97	Mutagenicity at the histidine operon	↔ with and without metabolic activation
Teo et al. *(26)*	*d,l,* and *d,l*/≤5000 µg/plate	Yes	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537	Mutagenicity at the histidine operon	↔ with and without metabolic activation
Teo et al. *(26)*	*d,l,* and *d,l*/≤5000 µg/plate	Yes	*Escherichia coli* strain WP2 *uvrA*	Mutagenicity at the tryptophan operon	↔ with and without metabolic activation
Teo et al. *(26)*	*d*/≤500 µg/mL; *l*/≤800 µg/mL; *d,l*/≤600 µg/mL	Yes	*L5178Y/TK*$^{+/-}$ mouse lymphoma cells	Mutagenicity	↔ with and without metabolic activation
NTP *(8)*	*d,l*/≤5000 µg/mL	Yes	Chinese hamster ovary cells	Chromosomal aberration	Equivocal, weakly positive to positive results obtained in some trials with ≥1750 µg/mL without metabolic activation and ≥1000 µg/mL with metabolic activation; results in other trials were negative

Reference	Enantiomers tested/concentration	Testing with metabolic activation	Species or cell type/strain	Endpoint	Results
In vitro tests					
NTP *(8)*	*d,l*,≤2000 µg/mL	Yes	Chinese hamster ovary cells	Sister chromatid exchange	↑ at ≥702 µg/mL without metabolic activation; equivocal with metabolic activation (trials in 2 labs produced negative or weakly positive results at ≥1600 µg/mL
Walker and Dumars *(63)* (abstract)	NS (assumed to be *d,l*)/ "therapeutic levels"	NS	Human pediatric lymphocytes	Sister chromatid exchange	Small but significant ↑ in lymphocytes from 2 of 4 subjects
Matthews et al. *(64)*	NS (assumed to be *d,l*)/2.09–8.36 mM **[488–1950 µg/mL]**	No	A-31-1-13 BALB/c-3T3 cells	Transformation	↔
In vivo test					
Teo et al. *(26)*	25–250 mg/kg bw *d*-methylphenidate, 125–500 mg/kg bw *l*-methylphenidate, or 50–250 mg/kg bw *d,l*-methylphenidate	not applicable	CD-1 mice (male and female)	Bone marrow micronucleus formation	↔

↔ no change; ↑statistically significant increase

2.4 Carcinogenicity

2.4.1 Human

Review of pharmacy and medical records from 1969 to 1973 for a cohort of 143,574 patients in a medical care program indicated that the number of cancers was lower than expected in 529 patients taking methylphenidate *(65)*. Whereas 32.7 cases of cancer were expected, only 15 cases were observed ($P < 0.002$). Study authors urged caution in the interpretation of the finding because the small sample size limited the power to detect modest increases in cancer, and the study covered a relatively short time period (< 20 years).

2.4.2 Experimental animal

Drug manufacturers reported no evidence of carcinogenicity in male or female p53+/– transgenic mice exposed to up to 60–74 mg/kg bw/day racemic methylphenidate through feed for 24 weeks *(2, 5, 7)*; the transgenic mouse strain is reportedly sensitive to genotoxic carcinogens. CERHR was not able to locate the original study report.

The NTP *(8, 66)* examined the carcinogenicity of *d,l*-methylphenidate in F344/N rats and B6C3F$_1$ mice in studies conducted according to FDA GLP. The studies used pharmacopoeia grade *d,l*-methylphenidate hydrochloride, which has a purity of >99%. The drug was mixed in feed, and stability, homogeneity, and target concentrations were verified. Animals were 6 weeks old at the start of the study and 70 animals/sex/group were randomly assigned to dose groups. Rats were fed diets containing 0, 100, 500, or 1000 ppm methylphenidate hydrochloride, and mice were fed diets containing 0, 50, 250, or 500 ppm methylphenidate hydrochloride. Males were exposed for 104 weeks and females for 105 weeks. Male rats received estimated methylphenidate doses of 4, 20, and 42 mg/kg bw/day, and females received estimated doses of 0, 4, 22, and 47 mg/kg bw/day. Doses estimated in mice were 0, 5, 28, or 56 mg/kg bw/day in males and 0, 7, 34, or 66 mg/kg bw/day in females. Dose selection was based on results of the 13-week study described in Section 2.2.2. According to study authors, doses in this study were 40–60 times higher than therapeutic human doses. Animals were examined daily and weighed before, during, and after treatment. Interim killings were conducted in 10 animals/sex/group at 9 and 15 months to examine hematology, clinical chemistry, and organ weights. At terminal kill, rats were necropsied. Organs from major systems were collected from all animals and fixed in 10% neutral buffered formalin for histopathologic evaluation. Among the organs examined were clitoral gland (rat only), mammary gland, ovary, prostate gland, testis, epididymis, seminal vesicle, and uterus. Statistical analyses included the Cox method and Tarone life table test for survival, Fisher exact test and Cochran-Armitage trend test for lesion incidence, and the Dunnett, Williams, Dunn, or Shirley test for continuous variables.

In rats, survival of treated groups was similar to controls. Starting at week 30 of the study, mean body weights of rats in the 500 and 1000 ppm groups were lower than controls. Body weights of female rats were significantly lower than controls at 9 and 15 months. Final body weights in the 100, 500, and 1000 ppm groups were 102, 95, and 90% of control values in males and 96, 89, and 78% of control values in females. Feed intake of treated animals was similar to controls. The only clinical sign was increased fighting in males of the 1000 ppm group. At the 9-month kill, leukocyte and lymphocyte numbers were generally increased in males and females. **[The results section reports that statistical significance for leukocyte and lymphocyte increases was obtained at the 1000 ppm dose. While tables in the NTP report support the statement for statistical significance in lymphocytes, the tables indicate that statistical significance for leukocytes was obtained at most dose levels in males and at ≥500 ppm in females.]** No differences in white blood cell numbers were observed at 15 months. Clinical chemistry findings reported in the results section include decreased serum alanine aminotransferase activity in males

from the 500 and 1000 ppm groups at 9 months and in males from all treatment groups at 15 months. **[Other significant effects listed in NTP tables included reduced aspartate aminotransferase levels in the 1000 ppm males at 9 months, increased creatinine levels in 1000 ppm females at 9 months, and increased blood urea nitrogen levels in females at 15 months.]** In the results section it was reported that absolute and relative brain weights were increased in females exposed to 1000 ppm, and relative brain weights were significantly increased in females exposed to ≥500 ppm. **[According to Tables F3 and F4 in the report, statistically significant organ weight changes at the 9-month kill included increased relative kidney weight (≥500 ppm males), relative liver weight (1000 ppm males), testis weight (1000 ppm), absolute brain weight (1000 ppm females), and relative brain weight (≥100 ppm females), and decreased absolute liver weight (≥500 ppm females). Statistically significant organ weight changes at the 15-month kill included increased relative kidney weight (1000 ppm males), relative liver weight (≥500 ppm males and females), and relative brain weight (≥500 ppm females) and decreased absolute kidney weight (1000 ppm females) and absolute liver weight (≥500 ppm females).]** There were no increases in the incidence of neoplastic or non-neoplastic lesions in males or females. Negative trends were reported for neoplastic lesions in male adrenal gland and female mammary gland. Incidence of benign pheochromocytomas was significantly reduced in males of all dose groups, but the effect was not dose related. Incidence of mammary gland fibroadenomas was significantly reduced in the 500- and 1000-ppm groups. In females, there were also dose-related reductions in incidence of galactoceles and lactation.

In the mouse study, methylphenidate did not affect survival. Mean body weights of treated groups were 3–11% lower than controls throughout the study. Final body weights of the respective low- to high-dose treatment groups were 97, 89, and 93% of control values in males and 98, 93, and 97% of control values in females. Although some significant but minor effects were observed for hematologic and clinical chemistry parameters at 9 and 15 months, the study authors stated the differences were not biologically significant. According to NTP tables, significant organ weight changes at 9 months included increased relative liver weight (≥50 ppm females, 500 ppm males), relative brain weights (≥250 ppm males), and relative kidney and testis weight (500 ppm males). **[The results section of the NTP report only describes weight effects in liver.]** At 15 months, relative liver weight was significantly increased in males and females from all dose groups. In males and females of the 500 ppm group, the incidences of eosinophilic foci and all foci were increased in liver. Hepatic neoplastic findings are summarized in Table 18. Treatment with 500 ppm methylphenidate resulted in significantly increased incidences of hepatocellular adenoma and carcinoma in males and females of the 500 ppm group. The incidence of hepatoblastoma, a rare neoplasm, was increased in males of the 500 ppm group. According to study authors, progression of hepatic foci from cellular alteration to adenoma to carcinoma may represent a spectrum of proliferative liver lesions. Because methylphenidate is not mutagenic in *Salmonella* tests, the study authors postulated that liver tumorigenesis may have been due to a nongenotoxic mechanism, such as increased cell proliferation. According to study authors, a decreased trend for alveolar/bronchial adenomas in males and increased trend in females was apparently due to variances in control animals and incidences in treated groups were within historical control values; therefore, the authors did not consider the effects to be treatment related.

The study authors concluded that under the conditions of this study, there was *no evidence of carcinogenic activity* in F344/N rats and *some evidence of carcinogenic activity* of methylphenidate hydrochloride in male and female B6C3F_1 mice, based on hepatocellular neoplasms.

Table 18. Incidence of Liver Lesions or Tumors in Mice Treated with *d,l*-Methylphenidate in the Diet

Tumor types and parameters	Dose (ppm)			
	0	50	250	500
Females: Values presented as incidence/number examined (%) or [%][a]				
Eosinophilic foci	3/49 [6.1%]	3/48 [6.3%]	8/49 [16.3%]	25/50** [50%]
All foci	5/49 [10%]	8/48 [17%]	11/49 [22%]	26/50** [52%]
Hepatocellular adenoma (multiple)	2/49 [4.1%]	0/48	3/49 [6.1%]	15/50** [30%]
Hepatocellular adenoma (single or multiple)				
Overall rate[b]	6/49 (12%)	10/48 (21%)	10/49 (20%)	28/50 (56%)***
Adjusted rate[c]	16.2%	26.6%	26.1%	62.2%***
Terminal rate[d]	6/37 (16%)	8/35 (23%)	9/37 (24%)	27/44 (61%)***
Hepatocellular carcinoma				
Overall rate[b]	5/49 (10%)	3/48 (6%)	2/49 (4%)	6/50 (12%)
Adjusted rate[c]	13.5%	8.3%	5.4%	13.2%
Terminal rate[d]	5/37 (14%)	2/35 (6%)	2/37 (5%)	5/44 (11%)
Hepatocellular carcinoma or adenoma				
Overall rate[b]	9/49 (18%)	11/48 (23%)	11/49 (22%)	30/50 (60%)***
Adjusted rate[c]	24.3%	28.7%	28.7%	65.2%**
Terminal rate[d]	9/37 (24%)	8/35 (23%)	10/37 (27%)	28/44 (64%)***
Males: Values presented as incidence/number examined (%) or [%][a]				
Eosinophilic foci	6/50 [12%]	8/50 [16%]	9/50 [18%]	14/50* [28%]
All foci	9/50 [18%]	12/50 [24%]	14/50 [28%]	18/50* [36%]
Hepatocellular adenoma (multiple)	5/50 [10%]	10/50 [20%]	6/50 [12%]	14/50* [28%]
Hepatocellular adenoma (single or multiple)				
Overall rate[b]	18/50 (36%)	18/50 (36%)	16/50 (32%)	29/50 (58%)†
Adjusted rate[c]	39.1%	39.1%	35.5%	64.2%†
Terminal rate[d]	17/45 (38%)	17/45 (38%)	15/44 (34%)	25/41 (61%)†
Hepatocellular carcinoma				
Overall rate[b]	10/50 (20%)	9/50 (18%)	17/50 (34%)	11/50 (22%)
Adjusted rate[c]	20.7%	19.5%	34.7%	23.4%
Terminal rate[d]	7/45 (16%)	8/45 (18%)	12/44 (27%)	6/41 (15%)
Hepatoblastoma				
Overall rate[b]	0/50	1/50 (2%)	1/50 (2%)	5/50 (10%)††
Adjusted rate[c]	0%	2.2%	2.3%	12.2%††
Terminal rate[d]	0/45	1/45 (2%)	1/44 (2%)	5/41 (12%)††
Hepatocellular adenoma, carcinoma, or hepatoblastoma				
Overall rate[b]	24/50 (48%)	23/50 (46%)	26/50 (52%)	34/50 (68%)†††
Adjusted rate[c]	49.9%	48.9%	53.0%	70.7%
Terminal rate[d]	21/45 (47%)	21/45 (47%)	21/44 (48%)	27/41 (66%)†††

From *(8, 66)*.

*$P < 0.05$; ** $P < 0.01$; ***$P < 0.001$; †$P = 0.02$; ††$P = 0.026$; †††$P = 0.037$.

[a]( ) = study author calculations, [ ] = CERHR calculations; [b]Total number; [c]Kaplan-Meier estimated incidence adjusted for intercurrent mortality; [d]Observed incidence at terminal kill.

2.5 Potentially sensitive subpopulations

2.5.1 Pharmacogenetics
Information on ethnic variation is not available *(30)*.

No data were located on variations associated with esterase polymorphisms. Identification of the specific esterase(s) responsible for the metabolism of methylphenidate is needed because hydrolysis by esterases is the predominant metabolic pathway in humans, several esterases present a typical ontogenetic profile, and genetic polymorphisms exist for several esterases.

2.5.2 Sex-related differences
An FDA review of Focalin reported no difference in pharmacokinetics of *d*-methylphenidate in boys and girls following single or repeat dosing in a small sample (n = 4–5/sex) *(30)*. Table 19 lists results for the single dose exposure. Similar effects were observed following repeat dosing.

Table 19. Pharmacokinetic Parameters in Boys and Girls Administered a Single 10 mg Dose of *d*-Methylphenidate, FDA

Parameter[a]	Girls (n = 4)	Boys (n = 5)
Age (years)	9.5±2.1	10.4±2.9
Height (cm)	138.3±9.8	146.6±19.4
Weight (kg)	32.8±6.5	40.6±13.8
C_{max} (ng/mL)	22.7±7.8	20.4±5.6
T_{max} (hours)	1.0±0.4	1.3±0.4
$AUC_{0–12h}$ (ng-hour/mL)	85.2±25.5	80.1±18.6
$AUC_{0–\infty}$ (ng-hour/mL)	89.1±26.6	88.1±17.0
Half-life (hours)	2.0±0.3	2.5±0.4

[a]Results presented as mean±SD. From *(30)*.

The FDA review of Focalin reported that *d*-methylphenidate C_{max} was 20–35% higher and AUC was 26–37% higher in adult female (n = 6) compared to male (n = 9) volunteers when adjusted for body weight, possibly indicating higher bioavailability in females *(30)*. The FDA noted that the clinical significance of the finding is not clear. T_{max} and half-life did not differ between males and females. The study is summarized in Table 20.

An FDA review of Ritalin LA reported higher weight-adjusted volume of distribution and clearance in women compared to men, but similar plasma level profiles *(29)*. The FDA stated that there appears to be a gender-related but clinically insignificant effect.

No difference in mean dose-adjusted $AUC_{0–\infty}$ values for Concerta was reported in healthy adult men (36.7 ng-hour/mL) and women (37.1 ng-hour/mL) *(7)*.

Table 20. Pharmacokinetic Parameters in Men and Women Administered a Single 20 mg Dose of *d*-Methylphenidate under Fasting or Fed Conditions

Parameter[a]	Fasting		Fed	
	Females (n = 6)	Males (n = 9)	Females (n = 6)	Males (n = 9)
Body weight (kg)	60.4±4.7	79.2±12.4	See fasting	See fasting
Dose/kg	0.33±0.03	0.26±0.04	See fasting	See fasting
C_{max} (ng/mL)	32.0±9.4 (+76%)	18.2±5.6	28.1±4.8 (+55%)	18.1±4.9
C_{max} /(dose/kg)	96.0±28.3 (+35%)	71.8±19.3	84.4±12.5 (+20%)	70.6±15.9
T_{max} (hours)	1.4±0.4	1.7±0.6	2.6±0.7	3.1±0.9
$AUC_{0–12h}$ (ng-hour/mL)	159.7±55.9	88.1±31.0	167.4±45.3	101.4±30.4
$AUC_{0–\infty}$ (ng-hour/mL)	164.3±56.3 (+79%)	91.9±31.9	172.0±45.9 (+64%)	105.2±31.7
$AUC_{0–\infty}$/(dose/kg)	488.2±148.8 (+37%)	355.2±100.9	511.6±106.3(+26%)	407.0±98.1
Half-life (hours)	2.7±0.3	2.7±0.3	2.8±0.5	2.8±0.2

[a]Results presented as mean±SD. The percentage figures in parentheses are the changes in females compared to the comparable parameter in males. From *(30)*.

2.5.3 Children and Juvenile Mice

Pharmacokinetic parameters in children and adults orally administered 0.30 mg/kg bw methylphenidate are listed in Table 21 *(33)*. The study authors concluded that results were similar in adults and children.

Table 21. Comparison of Pharmacokinetics in Children and Adults Orally Administered 0.30 mg/kg bw Methylphenidate

Subjects	T_{max} (hours)	C_{max} (ng/mL)	Clearance (L-hr/kg)	Half-life (hours)
Adults (n = 10)	2.1 ± 0.3	7.8 ± 0.8	10.5 ± 1.7	2.14
Children (n = 6)[a]	1.5 ± 0.2	10.8 ± 1.9	10.2 ± 2.2	2.43

Results presented as mean±SEM. [a]One child was given 2 mg/kg bw methylphenidate; although not explicitly stated, it does not appear that that the child was included in the analysis.
From *(33)*.

Dosing with 20 mg methylphenidate resulted in about twice the plasma level of methylphenidate in children aged 7–12 years compared to adults aged 18–35 years *(10)*. Because apparent clearance normalized to body weight was found to be independent of age, higher blood levels in children are thought to be almost exclusively due to lower body weights and volumes of distribution *(10)*. In an FDA review for Ritalin LA, a slightly shorter half-life was reported for children versus adults (~2.6 versus 3.4 hours) *(29)*.

In a study summarized in an FDA review for Focalin, C_{max} and AUC were compared in adults and children administered similar doses of *d*-methylphenidate on a mg/kg bw basis *(30)*. *d*-Methylphenidate C_{max} values were similar but AUC values were slightly lower in adults (Table 22). **[CERHR notes that the conclusion was based on data from two separate studies.]**

Table 22. Comparison of C_{max} and AUC Values for *d*-Methylphenidate in Adults and Children

Age group	Number	Dose (mg/kg bw)[c]	C_{max} (ng/mL)[c]	AUC (ng-hour/mL)[c]
Children (< 12 years)[a]	7	0.31±0.09	26.04±10.79	94.51±26.0
Adults	15	0.29±0.05	23.72±9.91	120.9±55.3

[a]Children were dosed with 10 mg *d*-methylphenidate twice daily. [b]Adults were dosed with 2 × 10 mg *d*-methylphenidate as a single dose. [c]Errors were not specified. Based on other data in this report, the values are most likely mean±SD.
From *(30)*. **[Data were obtained from two separate studies.]**

Fukui et al. *(67)* conducted an in vitro study to investigate methylphenidate effects on dopamine signaling in neostriatal slices from young (14–15- or 21–22-day old) or adult (6–8-week-old) male C57BL/6 mice. The slices were incubated in 100 µM methylphenidate **[23.3 µg/mL, assuming that values were provided for the free base]** for 2 or 5 minutes, and an immunoblotting technique was used to measure dopamine and cAMP-regulated phosphoprotein M_r 32 kDa (DARPP-32) phosphorylation at the Thr34 and Thr5 sites. In adult animals, methylphenidate increased Thr34- DARPP-32 phosphorylation, but decreased Thr75-DARPP-32 phosphorylation at both time periods. In the two younger groups, there was no increased in Thr34-DARPP-32 phosphorylation and a reduction in Thr75-DARPP-32 phosphorylation only occurred in slices from the 21–22-day-old animals at 5 minutes. Similar results were seen with cocaine, but methamphetamine regulation of DARPP-32 phosphorylation was similar in adult and young animals. Incubation of neostriatal slices with SKF81297, a dopamine D1 receptor agonist, increased Thr34-DARPP-32 and decreased Thr75-DARPP-32 phosphorylation in both young and mature animals at a similar level. According to study authors, "These results suggest that the dopamine D1-type receptor signaling pathway in neostriatal medium spiny neurons is fully functional in young mice, but that the machinery for dopamine release and/or reuptake, or its regulation at presynaptic dopaminergic terminals is immature in young mice."

2.6. Summary of General Toxicology and Biologic Effects

2.6.1 Pharmacodynamics and pharmacokinetics

Stimulatory effects of methylphenidate presumably occur through activation of the brain stem arousal system and cortex *(11, 12)*. The mode of action for therapeutic treatment of ADHD is not known. It is thought that methylphenidate blocks reuptake of norepinephrine and dopamine by the presynaptic neuron, thus increasing levels of these monoamine neurotransmitters in the extraneuronal space *(5, 7, 10, 12)*. A limited inhibition of monoamine oxidase activity may also occur (reviewed in *(27)*). Dosing of rats with methylphenidate metabolites (ritalinic acid, *p*-hydroxymethylphenidate, and 6-oxomethylphenidate) resulted in no pharmacologic activity, thus indicating that the parent compound is most likely the pharmacologically active species (reviewed in *(8)*). Numerous studies in rats demonstrated that the *d*-enantiomer is the pharmacologically active component (reviewed by Teo et al. *(44)*).

Methylphenidate is available in immediate-release, long-acting, and intermediate-acting formulations. In humans, immediate-release formulations reach peak blood levels within 1–3 hours following oral ingestion (See Sections 2.1.1.2 and 2.1.1.6). Extended-release (long-acting) formulations usually result in a sharp initial slope to peak level during the first 1–3 hours after ingestion followed by a more gradual peak 3–4 hours later. Intermediate-acting formulations were reported to have the same bioavailability as immediate-acting formulations but are absorbed more

slowly. Maximum blood levels of methylphenidate in children given therapeutic doses of the drug in the racemic or *d*-enantiomer form were within a similar range when presented as total or *d*-enantiomer; that range was ~5–20 ng/mL (see Sections 2.1.1.2 and 2.1.1.6).

Consistent with humans, rapid absorption of methylphenidate was demonstrated in rats, mice, and monkeys (reviewed in NTP *(8)*). Studies in rats and rabbits demonstrated T_{max} values of ~0.25–2 hours following dosing with up to 75 mg/kg bw/day *d,l*-methylphenidate or up to 100 mg/kg bw/day *d*-methylphenidate *(44, 46, 48)*. T_{max} was reported at 0.5–5 hours in dogs dosed with 10 mg/kg bw/day *d,l*-methylphenidate or up to 5 mg/kg bw/day *d*-methylphenidate *(49)*. In those same studies, maximum blood levels of *d*-methylphenidate were dependent on dose and ranged from ~3 to 946 ng/mL in rats, ~2 to 565 ng/mL in rabbits, and 2 to 333 ng/mL in dogs.

Apparent volumes of distribution for methylphenidate in humans have been reported at 6 L/kg following iv exposure *(10, 38)*, at 7–33.2 L/kg in 4 children given 10–15 mg methylphenidate orally *(36)*, and at ~40 L/kg in children given ~0.9 mg/kg bw (~28 mg) orally *(37)*. Binding of methylphenidate to plasma protein is low (10–33%) (*(28)*; reviewed in *(1, 10)*). Methylphenidate disposition is stereospecific, resulting in higher plasma levels of the *d*- versus the *l*-enantiomer in humans (reviewed in *(1)*). Peak plasma levels of the *d*-enantiomer were 5–8 times higher than the *l*-enantiomer in children dosed with 10–20 mg methylphenidate *(32, 35, 43)*. Two studies in pregnant rats also demonstrated higher blood levels of the *d*-enantiomer (~2 times higher) at doses of 7–75 mg/kg bw/day *(46, 48)*. In pregnant rabbits, the *l*-enantiomer was ~1.5–6 times higher than the *d*-enantiomer at doses of 20–60 mg/kg bw/day, while the *d*-enantiomer was ~3–9 times higher than the *l*-enantiomer at 200 mg/kg bw/day *(46, 48)*. Higher levels of the *l*-enantiomer (~1.3–2 times higher than the *d*-enantiomer) were observed in non-pregnant dogs dosed with 10 mg/kg bw/day methylphenidate.

The FDA *(30)* reported proportionality of pharmacokinetic parameters to administered dose in children given 2.5–10 mg *d*-methylphenidate or 5–20 mg *d,l*-methylphenidate *(30)*. One manufacturer reported that C_{max} and AUC values increased proportionally to dose in children given once-daily oral doses of 20 or 40 mg for 1 week or adults given single oral doses of 10–60 mg *(5)*. However, a study in 4 healthy individuals and 1 narcolepsy patient reported disproportionate increases in AUC (corrected to a 10-mg dose) between 20 and 40 mg and dose-related decreases in oral clearance, most likely due to saturated presystemic metabolism, at doses between 10 and 60 mg methylphenidate *(39)*. **[The Panel notes that author conclusions are reasonable but with so few humans involved, firm conclusion cannot be made.]** The FDA *(29)* reported the possibility of "nonlinearity" at a dose of 60 mg. Modi et al. *(40)* postulated that linearity may be affected by drug formulation due to higher blood concentrations obtained with immediate- versus sustained-release formulations. In an experimental animal study, disproportionate increases in AUC for both enantiomers in pregnant rats dosed with 7–75 mg/kg bw/day and for the *d*-enantiomer in rabbits dosed with 20–200 mg/kg bw/day led study authors to suggest saturation of metabolic processes *(48)*.

In the predominant human metabolic pathway for methylphenidate, nonmicrosomal hydrolytic esterases found throughout the body rapidly biotransform methylphenidate to α-phenyl-piperidine acetic acid (commonly called ritalinic acid) *(10)*, a metabolite believed to have little to no pharmacologic activity *(8)*. The low absolute oral bioavailability of methylphenidate in children (~30%, range: ~10–52%) implies extensive presystemic biotransformation *(10, 31)*. There appears to be no substantial interconversion between the *d*- and *l*- enantiomers *(30)*. Less than 2% of methylphenidate is metabolized in minor pathways involving aromatic hydroxylation to *p*-hydroxy compounds, microsomal oxidation to oxo- compounds, and conjugation; the minor metabolites are not believed to be pharmacologically active (reviewed in *(1, 8)*). Though no

metabolism by or inhibition of CYP isoenzymes has been observed in in vitro studies *(2, 5*), a review of drug interaction reports concluded that methylphenidate is involved in pharmacokinetic interactions suggesting inhibition of one or more hepatic CYP enzymes *(42*).

In contrast to humans who metabolize the majority of methylphenidate to ritalinic acid, less than half (~23–40%) of a methylphenidate dose is esterified to form ritalinic acid following oral or parenteral exposure of rats and dogs (reviewed by *(8*)). More than 50% of metabolites in rats and dogs are derived from microsomal oxidation or aromatic hydroxylation reactions. Many of the metabolites undergo further conjugation and de-esterification reactions. Less than 1% of methylphenidate is excreted unchanged in all species. It was reported that one dog study demonstrated evidence of CYP inhibition by methylphenidate (reviewed in *(42*)).

Methylphenidate half-lives of ~2–8 hours were reported for oral administration of immediate- or extended-release *d*- or *d,l*-formulations at doses up to 20 mg in adults and children *(2, 5, 7, 10, 12, 30*). Half-lives for extended-release products are expected to be longer than immediate-release formulations due to slower absorption as the rate limiting process *(5*). Mean total body clearance in children administered 10–15 mg methylphenidate by iv infusion was reported at 2.52 L/kg-hour, a value exceeding average blood flow to the liver (1.4 L/kg-hour) and suggesting extrahepatic metabolism (reviewed in *(38*)). Mean clearance rates of ~9–10 L/kg-hour were reported in children orally exposed to methylphenidate at up to 0.41 mg/kg bw *(33, 35*) and 0.9 mg/kg bw *(37*). Oral dosing with radiolabeled methylphenidate results in recovery of 80–97% of the radioactivity in human urine *(7, 10, 12*) and 1–3% in feces *(10*). Ritalinic acid is the main urinary metabolite and represents about 60–86% of the dose in humans *(7, 10*). Less than 1% of the methylphenidate dose is excreted unchanged in urine *(10*).

Methylphenidate elimination half-lives were reported at ~1–4 hours in rats, rabbits, and dogs dosed with up to 75 mg/kg bw/day *d,l*-methylphenidate *(44, 46, 48, 49*) and ~0.2–4 hours in rats, rabbits, and dogs dosed with up to 100 mg/kg bw/day *d*-methylphenidate *(44, 46, 49*). Consistent with humans, urinary excretion is the major elimination route in mice, dogs, and rats (reviewed in *(8*)). Studies in rats, mice, and dogs demonstrated 50–80% of methylphenidate doses excreted in urine over 24–48 hours *(8*). In rats dosed with 10–20 mg/kg bw methylphenidate orally or by ip injection, 30–40% of elimination occurred through feces and a significant amount of the dose was also excreted in bile (reviewed in *(8*)).

2.6.2 General toxicity

2.6.2.1 Humans

Common side effects associated with methylphenidate treatment have been reported as nervousness, insomnia, reduced appetite, abdominal pain, weight loss, and tachycardia, jitteriness, social withdrawal, irritability, anxiety, and proneness to crying. The effects may be transient or persistent. Following overdose with methylphenidate, symptoms result primarily from overstimulation of the CNS and include vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions possibly followed by coma, euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and/or dry mucous membranes. Chronic methylphenidate abuse can lead to tolerance and symptoms similar to those observed with amphetamine toxicity including psychic dependence, abnormal behavior, psychotic episodes, paranoid delusions, or hallucinations *(11, 13*).

2.6.2.2 Experimental Animal

LD_{50} values for various species are summarized in Table 16. Death following exposure to high dose levels of methylphenidate is most probably due to excessive adrenergic stimulation *(8)*. The most common signs of toxicity observed in methylphenidate repeat-dose studies in rats, mice, and dogs were weight loss, reduced feed intake, and clinical signs such as hyperactivity. In a review by the FDA *(30)*, maximum tolerated doses for *d*-methylphenidate were identified as 100 mg/kg bw/day in rats, based upon hyperactivity, hypersensitivity, and self-mutilation, and 10 mg/kg bw/day in dogs, based upon hyperactivity, salivation, and elevated body temperature. NOELs for *d*-methylphenidate were identified at <20 mg/kg bw/day in rats and 1 mg/kg bw/day in dogs. NOELs for *d,l*-methylphenidate were <40 mg/kg bw/day for rats and 2 mg/kg bw/day for dogs. Subchronic studies available for Expert Panel review suggested *d*-methylphenidate LOAELs of 50 mg/kg bw/day in rats *(44)* and 10 mg/kg bw/day in dogs *(49)* based upon reduced body weight gain. In addition, those studies in rats and dogs found similar toxicity of *d*- and *d-,l*-methylphenidate at equimolar concentrations of the *d*-enantiomer and found that effects reversed or improved following a recovery period. Though not consistently observed, some repeat dose studies reported liver lesions in rats and mice *(8)* and clinical chemistry or hematological changes in rats or dogs *(44, 49)*; in most cases the effects occurred at or above doses causing weight changes or clinical signs of toxicity.

2.6.3 Genetic toxicology

As noted in Section 2.3, negative results were obtained in most methylphenidate genetic toxicity tests including in vitro mutagenicity tests in *S. typhimurium*, *E. coli*, and mouse lymphoma cells, a transformation assay in A-31-1-13 BALB/c-3T3 cells, and an in vivo micronucleus study in mice. However, equivocal or positive results were obtained in other in vitro tests including a chromosomal aberration assay in Chinese hamster ovary cells and sister chromatid exchange assays in Chinese hamster ovary cells or human pediatric lymphocytes. Based on results of their mutagenicity studies in *S. typhimurium* and chromosomal aberration and sister chromatid exchange tests in Chinese hamster ovary cells (Table 17), the NTP *(8)* concluded that methylphenidate ". . . is not a gene mutagen in bacteria or mammalian cells, but . . . might have some potential for inducing clastogenic damage in mammalian cells." However, it was noted that increases in sister chromatid exchange occurred at doses causing severe toxicity and increases in chromosomal aberrations did not correlate well with dose.

2.6.4 Carcinogenicity

One study of 529 patients exposed to methylphenidate that included a < 20 year follow-up reviewed pharmacy and medical records from 1969 to 1973 for a cohort of 143,574 patients in a medical care program and reported that the number of cancers in patients exposed to methylphenidate was lower than expected, 15 versus an expected 32.7 cases *(65)*.

Labels from drug manufacturers reported no evidence of carcinogenicity in male or female p53+/– transgenic mice exposed to up to 60–74 mg/kg bw/day racemic methylphenidate through feed for 24 weeks. In a 2-year GLP dietary carcinogenicity study, there was no evidence of neoplasia at *d,l*-methylphenidate doses up to 47 mg/kg bw/day in rats *(8, 66)*. However, significant increases in hepatic neoplasms (adenomas or adenomas and carcinomas) were observed in mice receiving 500 ppm *d,l*-methylphenidate (56–66 mg/kg bw/day). With the exception of an increase in hepatic foci, there were no other treatment-related increases in non-neoplastic lesions, including in reproductive organs. The study authors concluded that under the conditions of this study, there was no evidence of carcinogenic activity in F344/N rats and based on hepatocellular neoplasms, some evidence of carcinogenic activity of methylphenidate hydrochloride in male and female $B6C3F_1$ mice.

2.6.5 Potentially sensitive subpopulations

There is no information on genetic or ontological differences that could affect metabolism or disposition of methylphenidate. In FDA reviews of methylphenidate drug studies, slight differences in some pharmacokinetic parameters were noted between men and women and between adults and children (Table 19, Table 20, Table 22). The Expert Panel believes these differences have not been shown to be clinically important. No data were located on variations associated with esterase polymorphisms. There is a need to identify the specific esterase(s) responsible for the metabolism of methylphenidate. This need is most relevant given that 1) hydrolysis by esterases is the predominant metabolic pathway in humans; 2) several esterases present a typical ontogenetic profile; and 3) genetic polymorphisms exist for several esterases.

A study in mouse neostriatal medium spiny neurons slices demonstrated that young mice (14–22 days old) have an intact dopamine D1-type receptor signaling pathway but that the regulation of the pathway following in vitro exposure to methylphenidate is different in young versus adult mice *(67*).

3.0 DEVELOPMENTAL TOXICITY DATA

3.1 Human Data

3.1.1 Methylphenidate Exposure During Pregnancy

Debooy et al. *(68)*, support not indicated, reported on 39 infants (1 set of twins) born to 38 women in a 2-year period in Manitoba for whom there was evidence in the maternal record of iv use of pentazocine (an opioid) and methylphenidate. **[The authors indicate that biochemical drug testing was not performed, so the evidence is presumably based on maternal report.]** All the mothers smoked cigarettes and 10 women (26%) abused other drugs. Eight of the infants (21%) were born prior to 37 gestational weeks and 12 infants (31%) had a birth weight lower than the 10th percentile for gestational age. Eleven infants (28%) were diagnosed with withdrawal **[criteria not specified]**. There were 4 infants (10%) with malformations: 1 with a ventricular septal defect, 1 with polydactyly, and 2 (the twins) with fetal alcohol syndrome. One infant died of extreme prematurity. Follow-up information was available on 30 children. Twelve of the children were readmitted to the hospital, 11 were diagnosed with behavioral problems, and 5 had failure to thrive. Child abuse and neglect was suspected in eight children.

Strengths/Weaknesses: The strength of this paper is the evaluation of the pentazocine-methylphenidate combination, which is of clinical importance. The evaluation of a mixed exposure, however, is a weakness in attempting to understand the toxicity of methylphenidate itself. While, the iv exposure route reflects abuse scenarios, therapeutic methylphenidate exposure occurs through the oral route. Other weaknesses include the many other potential harmful exposures such as sexually transmitted diseases, cigarettes, ethanol, and child abuse. Much of the information was obtained from medical records, and there appeared to be no controls.

Utility (Adequacy) for CERHR Evaluation Process: This study is not useful in the evaluation process.

The National Collaborative Perinatal Project *(69)* reported on 50,282 mother-child pairs in which pregnancy had lasted at least 5 lunar months. Information on medication exposure during pregnancy was collected at the time of the first prenatal visit and recorded prospectively thereafter. Outcome information was based on physical examination of the child up to the age of 1 year in 91% of the sample and for up to 4 years of age in an unspecified proportion of the sample. There were 11 pregnancy exposures (first 4 lunar months) to methylphenidate, which were analyzed as part of 96 pregnancies exposed to "other sympathomimetics," which included 16 other agents. Relative risks were calculated using the entire sample as a reference group. There were 7 malformations in the other sympathomimetic group, giving a crude relative risk of 1.13 **[95% CI not provided]**.

Strengths/Weaknesses: The National Collaborative Perinatal Project was a good study that was properly analyzed; however, this study contains only 11 methylphenidate exposures.

Utility (Adequacy) for CERHR Evaluation Process: This study is not useful in the evaluation process.

3.1.2. Adverse Effects of Methylphenidate Therapy in Children

There are several issues to take into account when reviewing studies on side effects in children. These issues may account for the inconsistent and sometimes contradictory results of different reports. Studying side effects is especially problematic because of the subjective nature of the outcome measure. Specific considerations are as follows:

- Side Effect Check Lists deal with subjective qualities such as headache and dizziness.
- Parents and teachers may observe different side effects in the home versus school environment; some studies include one assessment, others include both.
- Parent reports may be biased because parents want to see their children feel better and may over report symptoms at the beginning of a study.
- Children may not accurately report on many of the effects (i.e., headache, dizziness, anorexia) and may not understand some of them because of their cognitive age.
- Different durations of drug treatment may give rise to different side effects.
- Different drug doses may give rise to different side effects.
- Drug compliance is not documented in these studies.
- Many of these studies lack control groups or have inadequate control groups. When placebo controls are available, it is noteworthy how commonly side effects occur on placebo.

Side effects of methylphenidate reported to the FDA were listed in Table 13 in Section 2.2.1.1. In the Concerta product label, treatment-emergent events in a 4-week placebo-controlled trial in children included headache in 15/106 children on methylphenidate and 10/99 on placebo **[P = 0.40, Fisher exact test]**. Abdominal pain occurred in 7/106 children on methylphenidate and 1/99 on placebo **[P = 0.07, Fisher exact test]**, and anorexia occurred in 4/106 children on methylphenidate and 0/99 on placebo **[P = 0.12, Fisher exact test]**. There were smaller differences between methylphenidate and placebo for other adverse effects.

3.1.2.1 Controlled Side Effect Evaluations

Published studies were identified in which methylphenidate was compared with placebo with regard to adverse effects *(70-76*). Some controlled study data on side effects were summarized in Table 14 in Section 2.2.1.1. Additional details are presented here.

Rapoport et al. *(70*) performed a randomized controlled trial, supported by NIMH, using 76 children age 6–12 years (mean = 9 years) referred for persistent distractibility or motor restlessness and impulsivity. Subjects were randomized in a blinded manner to treatment with methylphenidate 10 mg in the morning (n = 29), imipramine 25 mg morning and evening (n = 29), or placebo (n = 18). The focus of the study was effectiveness **[not discussed here]**, but side effect data were also reported **[method of obtaining side effect information not specified; the Expert Panel assumes that side effects were recorded at the end of the study at 6 weeks]**. The authors concluded that compared to placebo, children on methylphenidate were more likely to have stomachache (7 of 29 on methylphenidate compared to 0 of 18 on placebo **[*P* = 0.034, Fisher exact test by CERHR]**), drowsiness (5 of 29 on methylphenidate compared to 0 of 18 on placebo **[*P* = 0.141, Fisher exact test by CERHR]**, and increased blood pressure (> 10 mm Hg increase in diastolic pressure in 8 of 29 on methylphenidate and 0 of 18 on placebo **[*P* = 0.017, Fisher exact test by CERHR]**). There were no differences between the methylphenidate and placebo groups in the incidence of appetite change or sleep disturbance.

Strengths/Weaknesses: Weaknesses in this study include inadequate delineation of the method of assessing side effects and the possibility of a multiple comparison problem leading to a greater chance of Type I error.

Utility (Adequacy) for CERHR Evaluation Process: This study has marginal utility for the evaluation process; because of the missing methodologic information, confidence in the study is low.

Conners and Taylor *(71)*, supported by NIMH and Abbott Laboratories, randomized 60 children (3 girls, 57 boys) with "hyperkinesis due to minimal brain dysfunction" to pemoline (n = 19), methylphenidate (n = 20), or placebo (n = 21). The children ranged from 6 to 11 years old (mean age = 7 years, 11 months). Medication or placebo capsules were given twice daily, permitting the blind to be maintained while dosing pemoline once daily and methylphenidate twice daily. Medication doses were increased each week as necessary for clinical response. The mean final doses were pemoline 2.25 mg/kg bw/day and methylphenidate 0.82 mg/kg bw/day. Side effect information was recorded by a physician on a standard 49-item form at baseline and 4 and 8 weeks after initiation of therapy **[efficacy endpoints were also evaluated, but are not presented here]**. The most common side effect of methylphenidate was difficulty sleeping, occurring in 13/20 children on medication and 5/21 on placebo **[*P* = 0.01, Fisher exact test]**. Appetite problems occurred in 8/20 children on methylphenidate and 5/21 on placebo **[*P* = 0.33, Fisher exact test]**. Increased crying was noted in 10/20 children on methylphenidate and 5/19 children on placebo **[*P* = 0.11, Fisher exact test]**. Headache occurred in 5/20 children on methylphenidate and 2/21 children on placebo **[*P* = 0.24, Fisher exact test]**. The remainder of the side effects occurred in 0, 1, or 2 children on methylphenidate.

Strengths/Weaknesses: Strengths include the blinded placebo control and the ratings prior to and during therapy. The use of parent as well as physician ratings is a strength. A weakness is the absence of efficacy endpoints.

Utility (Adequacy) for CERHR Evaluation Process: This study is useful for the evaluation process.

Barkley et al. *(72)*, support not indicated, gave 83 children, 5–13 years old, a 7–10 day trial of twice-daily placebo, methylphenidate 0.3 mg/kg bw/dose, or methylphenidate 0.5 mg/kg bw/dose. Each child was crossed over to each treatment in random order. Evaluations, performed on 80 children who completed the study, included effectiveness endpoints **[not discussed here]** and side effects, derived from a behavior questionnaire completed by parents at the end of each treatment period. A list of 17 common side effects was presented on the questionnaire with a scale for the evaluation of severity ranging from 0 (not present) to 9 (severe). Side effects were evaluated with regard to whether they were present or absent at each evaluation, whether they were "severe" (rank of 7 or higher), and with regard to mean severity rank. The frequency of the most common side effects on each treatment is given in Table 23. The authors concluded that decreased appetite and sleep problems were the most common symptoms of stimulant therapy. They noted, however, that most children in whom these side effects occurred rated them as mild (a severity rank of $\leqslant$ 3).

Table 23. Frequency of Side Effects on Placebo or Methylphenidate

	Number of affected children (of 80)		
		Methylphenidate	
Symptom	Placebo	0.3 mg/kg bw/dose	0.5 mg/kg bw/dose
Decreased appetite	12	42	45
Severe	1	6	10
Insomnia	32	50	54
Severe	6	14	14
Stomachache	14	31	28
Severe	0	1	5
Headache	9	21	17
Severe	0	1	3
Prone to crying	39	47	43
Severe	8	13	8

From *(72)*.

Strengths/Weaknesses: The use of a triple-blind placebo controlled design is a strength as is completion of rating scales by parents and teachers. The short duration of treatment (10 days) is a weakness.

Utility (Adequacy) for CERHR Evaluation Process: This study is useful in the evaluation process.

Handen et al. *(73)*, supported by NICHD, the Edith L. Trees Foundation, and Children's Hospital of Pittsburgh, enrolled 27 children with a diagnosis of ADHD and an IQ of 48–74 (mean 64). The children were observed without stimulant medication for 2 weeks (some of them had previously been on medication), followed by three 1-week periods on placebo, methylphenidate 0.3 mg/kg bw/dose, and methylphenidate 0.6 mg/kg bw/dose. The treatments were given twice daily. The presence of side effects was evaluated by teachers using a 13-item questionnaire based on the side effects reported in the methylphenidate product label. For 14 of the children, a scale was used to rank side effect severity. Two children were discontinued from the study due to social withdrawal on methylphenidate 0.3 mg/kg bw/dose and were not evaluated at the 0.6 mg/kg bw/dose level. None of the 13 side effects were reported in a significantly larger proportion of children on methylphenidate than placebo. Three side effects were more common on placebo than on at least one of the methylphenidate regimens: irritability, anxiety, and high activity. **[The statistical methods given in the paper include ANOVA, which is not appropriate for proportions.]** The authors concluded that many of the side effects attributed to methylphenidate may be symptoms of ADHD. They noted, for example, that appetite problems appear to be common in children with ADHD and were not increased with the use of methylphenidate in their study.

Strengths/Weaknesses: It is difficult to assess somatic complaints in mentally retarded children, whose responses can be influenced by whoever questions them. This study does not provide assurance that the assessment of side effects was reliable. In addition, the statistical handling of the data was unclear and/or inappropriate.

Utility (Adequacy) for CERHR Evaluation Process: Confidence in the findings of this report is low.

Ahmann et al. *(75)* treated 206 children aged 5–15 with methylphenidate 0 or 0.3 mg/kg bw/dose 3 times daily for 7 days (week 1) followed by 7 days of the opposite treatment (0.3 or 0 mg/kg bw/dose methylphenidate, week 2). Subjects were then either randomized to methylphenidate 0 or 0.5 mg/kg bw/dose 3 times/day (n = 46) or were given placebo in week 3 if the week 2 treatment was methylphenidate 0.3 mg/kg bw/dose and methylphenidate 0.5 mg/kg bw/dose if the week 2 treatment was placebo. The week 4 regimen was the opposite of week 3 (methylphenidate 0.5 or 0 mg/kg bw/day). Thus, all children received 2 weeks of placebo (methylphenidate 0 mg/kg bw/dose), and 1 week each of methylphenidate 0.3 and 0.5 mg/kg bw/dose, with the higher dose regimen always later in time than the lower dose regimen. **[The Expert Panel notes that the change in randomization scheme after the first 46 patients was to avoid the possibility of 2 successive weeks of methylphenidate.]** The children were evaluated by their parents using an 18-item side effect inventory. Four children did not complete the study due to side effects on methylphenidate. A comparison of the presence of side effects on methylphenidate or on placebo was expressed as an odds ratio with 95% CI. Weeks 1 and 2 were analyzed separately from weeks 3 and 4; that is, each methylphenidate dose condition had its own placebo period for comparison. Of the 18 side effects, 5 were more prevalent on methylphenidate, 4 were more prevalent on placebo, and 9 did not significantly differ by treatment condition. The 5 side effects and odds ratios (95% CI) that increased on methylphenidate were insomnia 3.13 (1.80–5.42), appetite disturbance 19.00 (9.18–39.31), stomachache 7.00 (3.29–14.89), headache 5.29 (2.51–11.15), and dizziness 7.50 (1.93–29.13). The 4 side effects and odds ratios that were less prevalent on methylphenidate were staring and daydreaming 0.47 (0.27–0.84), irritability 0.33 (0.18–0.61), anxiety 0.42 (0.23–0.76), and nail biting 0.19 (0.07–0.53). The authors found that the prevalence of appetite disturbance was dose-related. Separate analyses did not show age or sex to be significantly associated with medication side effects. The authors concluded that many of the symptoms attributed to methylphenidate therapy in anecdotal reports may be ADHD symptoms, some of which improve on stimulant therapy. Insomnia, decreased appetite, stomachache, headache, and dizziness, which were increased in this study, were also increased in other studies and may have been medication effects, according to the authors.

Strengths/Weaknesses: Strengths include the large sample size and the randomized, double-blinded, placebo-controlled design. Weaknesses include evaluation by parents only. The dosing schedule (3 times/day, 7 days/week) may limit comparability to other studies. It is of interest that the number of patients reporting side effects was greater at baseline than on the placebo treatment.

Utility (Adequacy) for CERHR Evaluation Process: This study is useful in the evaluation process.

Fine and Johnston *(74)*, supported by CIBA-Geigy Canada, randomized 12 children with ADHD to received methylphenidate 0, 0.3, or 0.6 mg/kg bw/dose twice/daily, randomized across days for 3 weeks. **[The Expert Panel is uncertain whether treatment changed from one day to the next.]** Parents evaluated side effects using a 16-item questionnaire on which each symptom was scored using a 0–9 ranking scale. The results were presented and analyzed as means of the severity ranks; the authors concluded that trouble sleeping, decreased appetite, and nail biting occurred "significantly more frequently" on active drug than placebo based on higher mean ranks for these three symptoms.

Strengths/Weaknesses: Use of a placebo arm is a strength. Weaknesses include the small sample size limited number of days of assessment, and lack of clarity concerning treatment assignments.

Utility (Adequacy) for CERHR Evaluation Process: This study is not useful for the evaluation process.

Kent et al. ***(77)*** evaluated the effect of a third daily dose of methylphenidate at 4 PM on sleep, noting that typical therapy involves only morning and midday dosing in order to avoid sleep disturbance. Twelve children with ADHD, aged 5.5–11.25 years (mean ± SD 9.0 ± 2 years) were studied in an inpatient setting. Methylphenidate dosing was begun using 5 mg at 7 AM and noon, with these doses titrated up to 15 or 20 mg/dose twice/day based on clinical response. The titration phase was completed within 14 days, following which children were given an additional dose at 4:00 PM of 0, 10, or 15 mg methylphenidate. Each child received each of the 3 dose regimens for a 4-day trial, in random order. Sleep latency was evaluated by checking the subject every 10 minutes at bedtime until sleep was identified. Sleep adequacy was evaluated by subjective report and by staff evaluation of the child's appearance during the daytime. There were no differences between treatments in sleep latency. The proportion of children who were evaluated as being tired or who said they were tired during the day was not different by treatment. The authors concluded that there was no evidence of sleep disturbance with an afternoon dose of methylphenidate, although they acknowledged that the structured inpatient setting may not be generalizable to home environments.

Strengths/Weaknesses: The structured setting is a strength, but also a weakness in that the inpatient situation may not represent the typical outpatient treatment setting. The comorbidity for oppositional-defiant disorder or conduct disorder is a weakness, as is the subjective nature of the reports of sleepiness from the children and the lack of a control group. The very long sleep latencies (50 minutes) raise the possibility that the environment or the ADHD may have interfered with sleep.

Utility (Adequacy) for CERHR Evaluation Process: This study is marginally useful in the evaluation process.

Schachar et al. ***(76)***, supported by the Medical Research Council of Canada, randomized 91 children (mean age 8.3–8.4 years, range 6–12) with ADHD to methylphenidate or placebo for a planned 6-month treatment period. Side effects were evaluated at 4 months in 66 subjects who had remained on their initially assigned therapy, including 37 children on methylphenidate and 29 children on placebo. During a 3- or 4-week titration period, methylphenidate doses were increased by 10 mg/day each week to reach a target dose of 0.7 mg/kg bw/dose given twice daily. Medication dose could be increased or decreased based on therapeutic response and side effects at the discretion of a study physician. Non-medication therapies were also used. Side effects were evaluated by parents and teachers using a telephone interview at baseline, at the end of titration, and at 4 months. The telephone interview consisted of a list of 14 side effects to be rated on a 10-point ranking scale. Four side effect domains were constructed: physiological (insomnia, dizziness, anorexia, headache, daytime drowsiness), affective (irritability, social withdrawal, sadness, crying), tics (motor or vocal), and over-focusing (staring, preoccupation). Ranks within each domain were summed to create a score. Side effect scores were considered clinically significant if they increased more than 1 standard deviation from the baseline scores for the sample or if any side effect increased from "absent or mild" to "moderate or severe" **[ranks corresponding to these adjectives were not given in the report]**. The side effect data were presented as means and standard deviations of the four domain scores and evaluated using ANOVA. The authors stated that anorexia, stomachache, withdrawal, sadness, and crying were the most common side effects to increase with methylphenidate. Ten percent of children assigned to methylphenidate discontinued the medication due to side effects. The authors suggested that

the higher rate of discontinuation for side effects in their study compared to other placebo-controlled studies may reflect the longer duration of treatment in their study.

Strengths/Weaknesses: The large sample size and extended treatment period are strengths of this study, as are the evaluation by parents and teachers and the inclusion of nonpharmacologic interventions. The inclusion of children with comorbid oppositional-defiant disorder or conduct disorder is a weakness. Only children remaining on the assigned treatment were evaluated for side effects, even though children discontinuing the treatments may have had more prominent side effects. This strategy resulted in the exclusion of a nonrandom quarter of the study population. It is also a weakness that medications were given on weekends and holidays at the parents' discretion. The summing of rank scores was not well-justified.

Utility (Adequacy) for CERHR Evaluation Process: This report is not adequate for the evaluation process.

Efron et al. ***(78)***, supported by a hospital research fund, randomized 114 boys and 11 girls with ADHD to a 2-week trial of *d*-amphetamine or methylphenidate, followed by a 24-hour wash-out period, followed by a 2-week trial of the other stimulant. The mean age (range) of the subjects was 104.8 months (60–179 months).The *d*-amphetamine dose was 0.15 mg/kg bw/dose and the methylphenidate dose was 0.30 mg/kg bw/dose, both given twice/day, rounded to the nearest tablet size. Investigators, subjects, teachers, and family members were blinded to the identity of the medication. Evaluations included effectiveness endpoints **[not discussed here]** and side effects, derived from a behavior questionnaire completed by parents at the end of each 2-week treatment period. A list of 17 common side effects was presented on the questionnaire with a scale for the evaluation of severity ranging from 0 (not present) to 9 (severe). Side effects were evaluated with regard to whether they were present or absent at baseline and on treatment and with regard to mean severity score. Poor appetite occurred in a larger proportion of subjects on methylphenidate (56%) than at baseline (34%)**.** Anxiousness, headaches, and nightmares occurred more often at baseline than on methylphenidate therapy (anxiousness: 77% at baseline, 61% on methylphenidate; headache: 41% at baseline, 24% on methylphenidate; and nightmares: 39% at baseline, 21% on methylphenidate). The remaining symptoms were identified as present in similar proportions of children at baseline and on methylphenidate. The authors concluded that many side effects identified on stimulant medication may be side effects associated with the underlying disorder rather than due to the medication therapy.

Strengths/Weaknesses: The double-blind cross-over design is a strength of this study. The limitation of drug therapy to 2 weeks is a weakness.

Utility (Adequacy) for CERHR Evaluation Process: This study is useful in the evaluation process.

Connor ***(79)***, support not indicated, published a review of side effects reported in 2 studies with similar designs, one conducted in preschool-age children (mean age 4.1 years, n = 32) and another in school age children (mean age 8.2 years, n = 83). The types of side effects that were significantly increased compared to controls differed in each age group. Side effects reported in preschool-age children were sadness, nightmares, appetite suppression, drowsiness, less talking, and lack of interest. Reported side effects in school-age children were appetite suppression, insomnia, stomachache, and headache. There appeared to be a slight increase in side effects reported as severe in preschool (10%) versus school age (3.6%) children. Connor *(79)* stated that more studies are needed before firm conclusions can be made about safety and efficacy during different developmental stages.

Strengths/Weaknesses: This review does not add new information.

Utility (Adequacy) for CERHR Evaluation Process: This review is not useful in the evaluation process.

3.1.2.2 Clinical laboratory findings

Satterfield et al. *(80)*, supported by NIMH, performed clinical blood chemistry determinations at baseline on an initial cohort of 115 boys aged 6–12 years who were being started on stimulant therapy. Blood testing was repeated every 6 months for up to 48 months. Of the initial cohort, 70 boys were sampled at 12 months, 44 boys at 24 months, 15 boys at 36 months, and 7 boys at 48 months. Testing included red and white blood cell counts, hemoglobin, hematocrit, eosinophils, protein-bound iodine (an estimate of thyroid hormone status), glucose, lactate dehydrogenase, alkaline phosphatase, bilirubin, calcium, phosphorus, protein, albumin, transaminase **[not otherwise specified],** urea nitrogen, uric acid, and cholesterol. Small significant changes were noted over time in some measures, attributed by the authors to normal maturational changes **[normative data not given or referenced]**. The authors concluded that there were no adverse effects of methylphenidate therapy on these clinical laboratory parameters.

Strengths/Weaknesses: It is a weakness that normative data were not given or referenced.

Utility (Adequacy) for CERHR Evaluation Process: This study can be used in the evaluation process.

Aarskog et al. *(81)* and **Shaywitz et al. *(34)*** examined the acute effects of oral methylphenidate treatment on growth hormone or prolactin levels in children. Treatment of 10 children with 20 mg methylphenidate resulted in an increase from a mean baseline serum growth hormone level of 3.8 ng/mL to a mean peak level of 10.6 ng/mL at 60 minutes *(81)*. Mean plasma levels of growth hormone rose from a baseline level of 4.40 ng/mL to a peak level of 10.5 ng/mL at 2 hours in 11 children who received 0.34 mg/kg bw methylphenidate *(34)*. Following the peak, growth hormone levels returned to baseline values in both studies. One study demonstrated that adults treated with methylphenidate also experience an acute increase in serum growth hormone levels *(82)*. In the study by Shaywitz et al. *(34)*, mean plasma prolactin levels in children decreased from a baseline value of 9.50 ng/mL to 3.80 ng/mL within 1.5 hours of dosing with 0.34 mg/kg bw methylphenidate.

Recognizing that *d*-amphetamine and methylphenidate are as effective as *l*-dopa in releasing growth hormone, Aarskog et al. *(81)* compared serum growth hormone levels at baseline and following acute administration of *l*-dopa/carbidopa and *d*-amphetamine in 7 children (ages 6–13 years), before and after 6–8 months therapy with 5–35 mg/day methylphenidate **[purity not specified]**. Growth hormone levels were determined using a radioimmunosorbent method. Prior to methylphenidate therapy, mean ± SEM baseline levels of serum growth hormone were 2.3±0.6 ng/mL in the *l*-dopa/carbidopa study and 3.1±0.9 ng/mL in the *d*-amphetamine study. After methylphenidate therapy, baseline levels of growth hormone were 4.5±1.6 in the *l*-dopa/carbidopa and 8.6±1.5 ng/mL in the *d*-amphetamine groups. The increase in baseline levels of growth hormone following methylphenidate therapy in the *d*-amphetamine study were statistically significant, but there was no significant difference after the baseline values for the *l*-dopa/carbidopa and *d*-amphetamine studies were combined. Extended therapy with methylphenidate changed individual responses to acute *d*-amphetamine treatment. In most children, standard growth hormone provocation curves were obtained with acute *d*-amphetamine treatment prior to methylphenidate therapy. Subsequent to methylphenidate therapy, acute *d*-

amphetamine treatment resulted in "tendencies" for delayed response and an initial fall in growth hormone concentration, with or without a subsequent rise **[the term "tendency" was not defined and statistical analyses were not presented]**. The study authors concluded that extended methylphenidate treatment may have effects on growth hormone homeostasis, but urged caution in the interpretation of results because occasional high levels of growth hormone were due to factors such as stress.

Strengths/Weaknesses: These studies appeared to have been appropriately performed and yield data with interesting implications. It is a weakness of the study by Aarskog et al. *(81)* that statistical methods were not presented.

Utility (Adequacy) for CERHR Evaluation Process: These studies can be used as supplemental information in the evaluation process.

Schultz et al. *(83)*, in a study funded in part by NIH grants, compared diurnal concentrations of growth hormone and prolactin in children during periods with and without methylphenidate exposure. The 9 children (mean age 11.1±1.7 [SD] years) examined in the study were on methylphenidate therapy (20–120 mg/day) for 3 months to 4 years. During a 24-hour period, blood was collected continually for measurement of serum growth hormone and prolactin concentrations by RIA. **[It was not stated if children took methylphenidate on the day of analysis.]** Following the 24-hour analysis period, growth hormone response to insulin-arginine stimulation was examined. About half the subjects took their morning methylphenidate dose prior to the insulin-arginine tolerance test, while the other half waited until the test was completed before taking methylphenidate. The study was repeated after methylphenidate therapy was discontinued for 11 days to 10 weeks, and values during treatment and the abstinence period were compared. Patterns of diurnal growth hormone and prolactin levels were similar during periods with and without methylphenidate treatment. There were normal fluctuations in levels throughout the day and peak hormone release occurred during sleep. Mean integrated concentrations of growth hormone and prolactin and fasting levels of somatomedin are listed in Table 24. There were no significant differences in values during the time periods of treatment and following the abstinence period. No significant differences in growth hormone levels were observed when subjects were stratified according to doses >0.90 mg/kg bw/day (n = 4) or <0.90 mg/kg bw/day (n = 5). A significantly higher peak level of growth hormone following insulin-arginine administration in subjects during the methylphenidate treatment period appeared to be related to the acute administration of methylphenidate prior to the insulin-arginine test in about half the subjects. The study authors concluded that these data suggest growth deficits in methylphenidate-treated children are not related to alterations in the hypothalamic-pituitary somatomedin axis.

Table 24. Comparison of Growth Hormone, Prolactin, and Somatomedin Levels in Children During and Following Abstinence from Methylphenidate Therapy

Measurement	Serum concentration (ng/mL except somatomedin)	
	Before methylphenidate	During methylphenidate
Integrated 24-hour growth hormone	3.82±0.39	4.38±0.35
Integrated growth hormone during sleep	5.5±0.49	6.4±0.6
Integrated 24-hour prolactin	13.0±1.7	13.7±1.9
Integrated prolactin during waking hours	7.7±1.4	9.2±1.7
Integrated prolactin during sleep	13.0±1.7	24.3±3.2
Fasting somatomedin (units/mL)	0.76±0.03	0.88±0.03

Data expressed as mean ± SEM, n=9. From Schultz et al. *(83)*.

Strengths/Weaknesses: Strengths include the evaluation of children on long-term therapy and the use of continual measurements over 24 hours. A weakness is the small number of subjects.

Utility (Adequacy) for the CERHR Evaluation Process: This report is useful in the evaluation process, although confidence in the conclusions is limited by the small sample.

Hunt et al. ***(84)***, in a study funded by the McArthur foundation and focusing on neurochemical mechanisms of ADHD, measured growth hormone levels in response to a clonidine challenge before, during, and 1 day after methylphenidate treatment of 8 boys (mean age 11 years) for at least 3 months with ≥0.3 mg/kg bw/day methylphenidate. **[The dose was stated to be 0.5 mg/kg bw/day in the results section. The duration of methylphenidate treatment prior to conducting the clonidine challenge during the treatment period was not specified.]** For analyses conducted during treatment, methylphenidate was given at 8:00–8:30 AM, 1 hour prior to the challenge with 3 μg/mL clonidine, an alpha adrenergic agent. In the time periods before and after methylphenidate treatment, clonidine was administered at 9–9:30 AM. Blood was collected before clonidine administration and throughout a 4-hour period following clonidine dosing. Plasma growth hormone levels were determined in 4 or 5 subjects/time period by RIA. **[There was no discussion about methods used for statistical analyses.]** Results of growth hormone analyses are listed in Table 25, which shows an attenuation of growth hormone increase in response to clonidine challenge during and after methylphenidate treatment (the augmentation in growth hormone response to clonidine was decreased by 53% and then rebounded to 66% of control levels). The clonidine inhibition of 3-methoxy-4-hydroxyphenelethylene release tended to be more pronounced during the methylphenidate treatment period. Methylphenidate treatment resulted in no significant or consistent effects on norepinephrine and epinephrine release following clonidine challenge.

Table 25. Growth Hormone Response to a Clonidine Challenge in Boys Before, During, and After Methylphenidate Treatment

	Plasma growth hormone		
	Peak (ng/mL)		AUC (ng-min/mL)
Methylphenidate status	Baseline	Following clonidine	Following clonidine
Before treatment	4.3±1.4	31.3±4.6	3010±823
During treatment	~7[a]	14.8±3.2*	1620±353*
One day after treatment	~3[a]	20.8±3.9*	2325±623

Data expressed as mean ± SEM, n=8.
*Statistically significant compared to methylphenidate pre-treatment levels.
[a]Value estimated from a graph. From *(84)*.

Strengths/Weaknesses: It is a strength that effects on growth hormone were evaluated after relatively long-term treatment (3 months), but a weakness that subjects were in different pubertal stages. The small number of subjects is also a weakness.

Utility (Adequacy) for CERHR Evaluation: This report can be used in the evaluation process.

3.1.2.3 Cardiovascular function

Several factors must be taken into account when reviewing the studies on the effects of methylphenidate on cardiovascular function in children. Not all of these factors were taken into account in every study reviewed. Because there are so many variables and many studies do not control for them appropriately, the results are inconsistent and contradictory.

- There is large intra-individual variability in heart rate and blood pressure. There are normal hour-to-hour and day-to-day fluctuations in heart rate and blood pressure; thus, one-time measurement does not necessarily reflect a "normal" measurement.
- There are normal ranges for both heart rate and blood pressure for different age groups of children.
- Conditions under which the children had their heart rate and blood pressure measured may affect the results—quiet environment, period of rest before measurement, etc.
- Measurement tools differ and include blood pressure machines versus sphygmomanometer measurements, and apical/radial pulse measurement versus pulse measurement by machine.
- Reliability of measurement may be questionable if different people do the measurements.
- Proper technique of blood pressure measurement is not always used. Sources of error include supine versus seated measurements and the appropriateness of cuff size.
- The anxiety effect of monitoring that has been previously documented in adults (called "white coat syndrome") could also occur in children.
- Varying durations of methylphenidate treatment might influence study results.
- Some children were drug naïve while others were not, which could affect results if there were up- or down-regulation of receptors involved in cardiovascular modulation.
- In some studies, children's doses were titrated up to a maximum dose before results were obtained, while others were given a set dose. There may be physiological differences between these two circumstances.
- Differences in heart rate and blood pressure that are statistically significant may not be clinically significant.
- None of the studies examined the long-term effects of methylphenidate treatment.
- The studies were conducted before the establishment of current published norms *(85*).

Knights and Hinton *(86*), supported by CIBA Co. Ltd. and the Ontario Mental Health Foundation, randomized 40 children with "minimal brain dysfunction" to methylphenidate (n = 20) or placebo (n = 20). The children ranged from ages 8 to 15 with a mean age of 10.5 years. The initial methylphenidate dose was 20 mg once a day with an increase over 4 days to 20 mg twice a day. Children were examined prior to starting medication and at the end of a 6-week period. Examinations included blood pressure and heart rate. Differences between pretreatment and on-treatment values were compared by *t* test (methylphenidate compared to placebo). The change in systolic blood pressure did not differ between the two treatment groups. Children on methylphenidate for 6 weeks had a mean 1.9 mm Hg increase in diastolic blood pressure while children on placebo for 6 weeks had a mean 2.7 mm Hg decrease in diastolic blood pressure. Heart rate increased 15.6 beats/minute on methylphenidate and 0.9 beats/minute on placebo. The difference between treatment arms was significant at $P < 0.1$ for diastolic blood pressure and heart rate **[variances were not given]**.

Strengths/Weaknesses: Strengths of this study include the randomized, placebo-controlled, double-blind design. Weaknesses include the lack of information on how heart rate and blood pressure were measured, and the reporting of mean blood pressure (in mm) and heart rate (in beats/minute) to one decimal place, which is clinically meaningless. The blood pressure changes in this study were not clinically significant.

Utility (Adequacy) for CERHR Evaluation Process: This report can be used in the evaluation process, although confidence in the results is only moderate.

Greenberg and Yellin *(87)*, supported by NIMH, randomized 47 hyperactive children (7 girls, 40 boys; 6–13 years old) to either imipramine-placebo or methylphenidate-placebo. All subjects crossed over between their assigned medication and placebo. Children previously on methylphenidate were weaned off and had a 7-day drug-free period prior to starting study medication. The study medication was increased over a 1-week period and maintained at full dosage (100 mg imipramine, 40 mg methylphenidate) for a 1-week period. Methylphenidate did not produce a significant increase in systolic pressure, diastolic pressure, or pulse compared to placebo.

Strengths/Weaknesses: The use of a placebo arm is a strength. It is unclear, however, how blood pressure and heart rate measurements were taken. Subjects were studied after only 1 week on medication.

Utility (Adequacy) for CERHR Evaluation Process: This report can be used in the evaluation process, although confidence in the results is only moderate.

Aman and Werry *(88)*, supported by the Medical Research Council of New Zealand, CIBA (UK), and NIMH, performed a double-blind, placebo-controlled, crossover study with 10 boys diagnosed as hyperkinetic or subject to "unsocialized aggressive reactions." The children ranged from 84 months to 116 months of age (mean 104 months) with weights ranging from 22 kg to 38 kg (mean 30.4 kg). Each subject received methylphenidate and placebo in random order with methylphenidate given at a dose of 0.5 mg/kg bw **[the discussion and summary indicate 0.3 mg/kg bw]**. The drugs were administered by parents 90 minutes before the subjects were to arrive at the laboratory. Each subject was tested a total of three times (no medication, placebo or methylphenidate, methylphenidate or placebo). **[It is not indicated whether subjects were tested after a single dose of medication or while being on medication for some number of days, nor is it stated how many subjects were on other medications, except for the statement, "The study was run during school vacation when most were not receiving any medication."]** Heart rate and respiratory rate were measured for 1 minute at rest, at the end of successive 4-minute sessions of light, moderate, and heavy bicycle exercise, and after 4 minutes of post-exercise rest. Eight of the 10 subjects had their heart rates decrease from the first session (no drug) to the placebo session. The response of heart and respiratory rates to level of exercise and medication was evaluated by ANOVA. Methylphenidate produced an increase in basal and exercise-associated heart rate (a mean 3–9 beat/minute difference compared to placebo). Respiratory rate was not significantly altered by methylphenidate. The authors concluded that methylphenidate causes small but significant increases in heart rate during rest and exertion, with no increase in respiratory rate, and they postulated a vasoconstriction-associated decrease in oxygen expenditure during exercise.

Strengths/Weaknesses: The double-blind, placebo-controlled design is a strength. It is not known, however, whether subjects were tested after a single dose of methylphenidate or whether they had been on methylphenidate for some period of time. The decrease in heart rate from the pre-drug to the placebo session in 8/10 subjects indicates the variability of heart rate.

Utility (Adequacy) for CERHR Evaluation Process: This report can be used in the evaluation process, although confidence in the results is only moderate.

Ballard et al. *(89)*, support not indicated, examined cardiovascular responses in 27 hyperactive children (24 boys, 3 girls) being treated with methylphenidate. The children had a mean age of 10.41 years and a mean weight of 37.09 kg. Subjects were tested after a dose of methylphenidate and after a dose of placebo, in random order with 1 month separating the test sessions. For the

children who were tested on methylphenidate first, placebo was given for 30 days before the second test. Medication was given once daily at doses that had been optimized based on clinical response; these doses ranged from 0.13 mg/kg bw to 0.89 mg/kg bw (mean 0.48 mg/kg bw; 5–30 mg/day). One and a half hours after taking methylphenidate or placebo, a 12-lead EKG was recorded after the subject rested in bed 5 minutes and before, immediately after, and 10 minutes following a 5-minute treadmill exercise period. Heart rate was monitored with a telemetry system. Blood pressure was measured during each minute of the testing procedure using a sphygmomanometer. Oxygen consumption was measured using an open-circuit method **[citing methods in a 1968 publication]**. Data were analyzed using ANOVA. Methylphenidate significantly increased heart rate, systolic blood pressure, and mean arterial blood pressure compared to placebo during rest, exercise, and recovery. The mean increase in heart rate was 8.1 beats/minute, the mean increase in systolic blood pressure was 6.2 mm Hg, and the mean increase in mean arterial blood pressure was 4.4 mm Hg. The increases in heart rate, systolic blood pressure, and diastolic blood pressure were correlated with weight-adjusted methylphenidate dose. There were large differences among children in response to methylphenidate compared to placebo. The largest increase in heart rate during the pre-exercise rest period was 40 beats/minute, and the smallest was a 17 beat/minute decrease in heart rate on methylphenidate compared to placebo. The largest change in blood pressure (systolic/diastolic) was a 22/12 mm Hg increase, whereas other subjects had decreases of up to 7 mm Hg in blood pressure on methylphenidate compared to placebo. There was no difference in oxygen consumption on methylphenidate compared to placebo. All EKGs were reportedly normal. The authors expressed concern that some of the cardiovascular changes were large and that accommodation to the cardiovascular effects of methylphenidate had not been demonstrated. Some of the children in this study had been on medication for more than a year, and there was no difference in cardiovascular response between these children and those who had been on placebo for 30 days prior to testing, which the authors interpreted as demonstration that tolerance does not develop to the cardiovascular effects of methylphenidate. The authors also noted that increased blood pressure did not result in a slowing of heart rate, leading them to conclude that methylphenidate blocks the baroreceptor reflex.

Strengths/Weaknesses: This was a well designed placebo-controlled study, although the children were not drug-naïve. The difference between placebo-treated subjects and normal controls suggests that ADHD children may have distinctive physiologic characteristics. This study does not address long-term consequences of the cardiorespiratory changes that were noted.

Utility (Adequacy) for CERHR Evaluation Process: This report can be used in the evaluation process.

Conners and Taylor *(71)*, supported by NIMH and Abbott Laboratories, randomized 60 children (3 girls, 57 boys) with "hyperkinesis due to minimal brain dysfunction" to pemoline (n = 19), methylphenidate (n = 20), or placebo (n = 21). The children ranged from 6 to 11 years old (mean 7 years, 11 months). Medication or placebo capsules were given twice daily permitting the blind to be maintained while dosing pemoline once daily and methylphenidate twice daily. Medication doses were increased each week as necessary for clinical response. The mean final doses were pemoline 2.25 mg/kg bw/day and methylphenidate 0.82 mg/kg bw/day. Measurement of pulse and blood pressure were recorded at weeks 0, 4, and 8. There was a greater increase in pulse rate at week 4 in the placebo group than in the stimulant groups, but by week 8 there was no difference in pulse rate between groups. There were no differences between groups in systolic blood pressure. Diastolic blood pressure decreased in the placebo and pemoline groups at week 4 and 8, but increased in the methylphenidate group by a mean of 2.4 mm Hg at week 4 **[data not shown, statistical analysis not indicated]**.

Strengths/Weaknesses: The lack of data is an important weakness of this report.

Utility (Adequacy) for CERHR Evaluation Process: This report is not useful in the evaluation process.

Satterfield et al. *(80)*, supported by NIMH, evaluated blood pressure and pulse rate annually in boys aged 6–12 years who were on methylphenidate therapy (mean dose 0.47 mg/kg bw/day at 1 year and 0.52 mg/kg bw/day at 2 years). There were 74 boys at 0 and 12 months, 44 boys at 24 months, and 36 boys at 36 months. Comparisons to baseline were made by *t* test. Systolic and diastolic blood pressure was significantly higher than baseline at 2 and 3 years, and pulse rate was higher than baseline at 1 year and lower than baseline at 3 years. The mean increase in systolic blood pressure from baseline to year 3 was 7.9 mm Hg, and for diastolic blood pressure the mean increase was 4.6 mm Hg. The authors interpreted these changes as consistent with normal maturation.

Strengths/Weaknesses: Weaknesses include the withholding of medication on the day the measurements were performed, the lack of description of how measurements were made, and the yearly interval for the measurements. The conclusion that changes are consistent with normal maturation is inappropriate given the many other variables that were not controlled.

Utility (Adequacy) for CERHR Evaluation Process: This study is not useful in the evaluation process.

Brown et al. *(90)*, supported by NIMH and NIH, evaluated 11 boys with attention deficit disorder on methylphenidate and placebo in a randomized, blinded, cross-over design. The children were all males whose ages ranged from 9 years 1 month to 12 years 1 month (mean 10 years 5 months). The methylphenidate dose was 0.3 mg/kg bw administered twice/day. At the end of each 2-week dosage period the subjects were assessed with attention tasks 1.5 hours after being given medication. During the same clinic visit, heart rate and blood pressure were measured. Analysis using multivariate ANOVA showed no difference between in heart rate or blood pressure between methylphenidate and placebo.

Strengths/Weaknesses: Strengths include the randomized, blinded, placebo-controlled design and the clear definition of how measurements were made. Weaknesses include the evaluation of short-term effects (2 weeks) and the recording of heart rate for only 1 minute, with large variability among subjects.

Utility (Adequacy) for CERHR Evaluation Process: This report can be used in the evaluation process.

Brown and Sexson *(91)*, supported by the NIH and Emory University, evaluated 11 boys with ADHD on placebo and 3 dose levels of methylphenidate (0.15, 0.3, and 0.5 mg/kg bw given twice daily). Each boy was tested after 2 weeks on each of the medication regimens in random order. The children were all black males ranging from age 12 years 10 months to age 14 years 10 months (mean 13 years 7 months). Heart rate and blood pressure were assessed at least 1 hour after the medication dose. The relationship between dose and cardiovascular parameters was assessed using ANOVA followed by pair-wise testing of blood pressure measurements at each methylphenidate dose compared to placebo. The authors found significant effects for systolic and diastolic blood pressure, significant on pair-wise testing only for diastolic blood pressure, which increased from a placebo mean of 69.0 mm Hg to a mean of 83.0 mm Hg with a methylphenidate

dose of 0.5 mg/kg bw twice daily. The authors reported no significant effect of methylphenidate on heart rate. **[The graph representing heart rate as a function of dose shows an increase parallel to that of diastolic blood pressure.]**

Strengths/Weaknesses: The use of drug-naïve subjects is a strength. Measurements were taken 1 hour after medication was given, and it is a weakness that the duration of the effects was not evaluated.

Utility (Adequacy) for CERHR Evaluation Process: This study can be used in the evaluation process, although its application to chronic medication use is not straightforward.

Kelly et al. *(92)*, support not indicated, investigated the response of pulse to methylphenidate in 47 drug-naive children (3 females, 44 males) with ADHD. The children ranged from 6 to 12 years old (mean 8.3 years). Each week, subjects received a single dose of methylphenidate, following which pulse was measured using a fingertip photocell. Each subject was evaluated after 5 different methylphenidate dose regimens (0, 5, 10, 15, and 20 mg) in random order; thus, the data consisted of 5 weekly measurements for each child, each weekly measurement being a response to a different methylphenidate dose. Resting pulse rate was assessed prior to and after the administration of the medication during several 5-minute measuring periods. Data were analyzed using ANOVA with post hoc Tukey test. There was a significantly higher post-medication heart rate at 120 minutes after 15 and 20 mg of methylphenidate. Pulse rate was also increased 180 minutes after 10, 15, and 20 mg of methylphenidate. The mean response to placebo was a decrease of 4–7 beats/minute over 180 minutes, whereas the mean response to 20 mg methylphenidate was an increase of 2–6 beats/minute over the same interval.

Strengths/Weaknesses: The measurement protocol was rigorous with several measurements averaged over 5-minute periods in drug-naïve subjects. Measurements were made before and after medication administration, which is a strength.

Utility (Adequacy) for CERHR Evaluation Process: This study is well designed and useful for the evaluation process.

3.1.2.4. Seizures

Knights and Hinton *(86)*, supported by CIBA Co. Ltd. and the Ontario Mental Health Foundation, randomized 40 children with "minimal brain dysfunction" to methylphenidate (n = 20) or placebo (n = 20). The children ranged from ages 8 to 15 years with a mean age of 10.5 years. The initial methylphenidate dose was 20 mg once a day with an increase over 4 days to 20 mg twice a day. Children were examined prior to starting medication and at the end of a 6-week period. There were 33 children who had electroencephalograms (EEG) before and on therapy. Eleven of the children had abnormal EEGs before therapy; there was no methylphenidate-associated increase in EEG abnormalities.

Strengths/Weaknesses: This report is limited by the small number of children who were evaluated.

Utility (Adequacy) for CERHR Evaluation Process: This report is useful, with the sample size limitations noted.

Gross-Tsur et al. *(93)*, supported by the Israel Ministry of Health, studied 30 children with epilepsy and ADHD. The mean age of the children was 9.8 years (range 6.4–16.4 years). Children

had baseline evaluations of seizure frequency, antiepileptic drug levels, and EEGs. They were randomized to receive 8 weeks of placebo or 8 weeks of methylphenidate 0.3 mg/kg bw given once in the morning. After 8 weeks, testing was repeated and each subject crossed over to the opposite therapy. After 8 weeks on the second therapy, testing was repeated. Each child's usual antiepileptic medication was continued throughout the study. Seizure frequency on therapy was monitored with weekly calls to the parents and monthly clinic visits. There were 25 children who were seizure-free at baseline; none of these children had seizures on methylphenidate. Of the 5 children who had seizures at baseline (1 or 2 seizures/week), 4 had seizures while on methylphenidate, and 3 of the 4 had an increase in seizure frequency on methylphenidate **[the seizure frequency on placebo was not reported]**. Abnormal EEGs were identified in 23 children prior to methylphenidate. On methylphenidate, 19 of these children had abnormal EEGs; 4 had become normal. There were three children in whom the abnormality on EEG was different on methylphenidate than it was off methylphenidate. **[Changes, if any, on placebo were not mentioned.]** Antiepileptic drug levels changed on methylphenidate and on placebo in some children. The direction of the change was not uniform with either treatment and there was no significant net effect of methylphenidate on antiepileptic drug levels. The authors concluded that methylphenidate could be used in children with a history of epilepsy, but that children who were still having seizures might experience an increase in seizure frequency while on drug therapy.

Strengths/Weaknesses: The strength of this study is the documentation of compliance with antiepileptic treatment. Weaknesses include lack of reporting of seizure frequency or EEG changes on placebo. It is also not clear if the children with abnormal brain imaging were those who had seizures.

Utility (Adequacy) for CERHR Evaluation Process: This paper is not useful for the evaluation process.

Hemmer et al. *(94)*, supported by the Crown Family, performed EEGs on 179 males (3–20 years old) and 55 females (3–19 years old) with ADHD. The mean age of the subjects was 9–10 years. Epileptiform EEGs were obtained in 36 subjects prior to stimulant therapy or up to 8 weeks after the initiation of therapy. The decision to accept stimulant therapy was made by parents and did not appear to be influenced by the EEG results. There were 175 subjects treated with stimulants of whom 30 (17%) had had an epileptiform EEG. Of the 29 subjects who declined stimulant therapy, 6 (21%) had had an epileptiform EEG. Seizures occurred in four subjects **[follow-up period not specified]**. All of the subjects with seizures were in the stimulant group, although one child had a seizure after being off stimulant medication for 2 months. Three of the four children had prior epileptiform EEGs. The authors concluded that a normal EEG prior to stimulant therapy was reassuring that seizures would not occur on therapy. They were not convinced that the stimulant therapy caused the seizures that occurred based on the timing of the seizures with respect to the start of stimulant therapy, and based on the low overall incidence of seizures (2%) in the stimulant-using population. **[The specific stimulants were not named except in the four cases of seizure. The stimulants used in these cases were methylphenidate and *d*-amphetamine.]**

Strengths/Weaknesses: The incidence of epileptiform EEGs in this study (15.4%) is much higher than the estimated incidence of EEG abnormalities in an unselected population of children (2%), suggesting that these children may have had underlying neurologic disorders other than ADHD. The statement that children with normal EEGs are at a low risk of seizure is stating the obvious.

Utility (Adequacy) for CERHR Evaluation Process: This report does not add useful information for the evaluation process.

3.1.2.5 Psychotic symptoms

Psychotic symptoms developing on methylphenidate, described in case reports, include hallucinations *(95, 96*), delusions *(97*), and mania *(98*). Some of the case report authors have suggested that methylphenidate and other stimulants may unmask incipient psychiatric disorders in susceptible individuals *(97, 98*).

Cherland and Fitzpatrick *(99*), support not indicated, performed a chart review at the Royal University Hospital in Saskatoon. Of 98 children treated with stimulant medication, 9 developed psychotic-like symptoms (7 on methylphenidate and 2 on pemoline **[it is not clear whether the children who may have become psychotic on pemoline also became psychotic on methylphenidate]**). Two of the children who developed psychotic symptoms on methylphenidate were subsequently diagnosed with bipolar disorder, and one was diagnosed with a pervasive developmental disorder not otherwise specified. The authors point out that inasmuch as their study was retrospective, assessments were not fully standardized, and follow-up was not consistent.

Strengths/Weaknesses: In addition to the weaknesses identified by the authors, weaknesses also include the small number of children, lack of a control group, and difficulty determining which reactions were associated with which medications, and which were associated also with underlying illnesses.

Utility (Adequacy) for CERHR Evaluation Process: This report is of moderate utility in the evaluation process.

3.1.2.6 Onset or Worsening of Tics on Methylphenidate

Tourette disorder is a chronic neurologic disorder characterized by repeated and involuntary body movements (tics) and uncontrollable vocal sounds. Tics can include eye blinking, repeated throat clearing or sniffing, coughing, arm thrusting, kicking movements, shoulder shrugging, or jumping. A large proportion of children with Tourette disorder have comorbid ADHD (reviewed by Leckman *(100*)). In 1974, a case report was published describing a 9-year-old boy treated with methylphenidate for hyperactivity who developed Tourette disorder on therapy *(101*); since that report, additional papers have described tics or Tourette disorder in association with stimulant therapy (Table 26). In spite of the impression expressed by some authors that stimulant therapy can be associated with the de novo appearance of tics or the worsening of pre-existing tic disorders, only one of the controlled studies *(72*) concluded that there was an increased incidence of tic appearance or worsening compared with that on placebo or at baseline *(72, 75, 78, 102, 103*).

[The Expert Panel noted some general limitations with most tic studies. A consideration in the evaluation of tic studies is whether the subjects in placebo or stimulant treatment groups had prior drug exposure, which might in itself account for development of tics, but this issue was only addressed by the Tourette Syndrome study group *(103*). Methods for rating the presence of tics need to be known. None of the studies controlled for substance abuse.]

Table 26. Reports of Tics in Children Treated with Stimulant Medication

Medication	Stimulant dose (mg/day except where indicated)	Characteristics of the children	Outcome	Comments[a]	Reference
Methylphenidate	10	9-year-old boy	Tics developed	Tics did not resolve after medication stopped, and haloperidol was required, suggesting that the tics/Tourette disorder may have been spontaneous.	*(101)*
Methylphenidate	10–60	20 children, mean age 10 years, range 7–14. 18 boys, 2 girls	20/1520 (1.3%) children on methylphenidate either developed (14) or had worsening of pre-existing tics (6). Tics resolved in most with discontinuation or reduction in dose, and recurred spontaneously in 1 subject.	Strength: Large number of charts reviewed. Weaknesses: Combined anecdotal recollections of several authors, without controls or statistical analysis.	*(104)*
Methylphenidate, *d*-amphetamine, methamphetamine	Not reported	32 Tourette disorder patients who had been exposed to stimulants (unspecified ages)	17/32 experienced worsened symptoms when on stimulants	This report is descriptive, with no doses or ages given. Other medications in the mix were not considered. Omitted from consideration were 39 of 45 subjects with preexisting Tourette disorder that did not worsen.	*(105)*
Methylphenidate, imipramine	5–40	Boys aged 7, 8, and 11.5 years	Worsening of Tourette disorder	These three case reports do not provide useful information.	*(106)*
Methylphenidate	Mean 29.3, Range 7.5–70	134 with Tourette disorder, 21 treated with stimulants	Increased tics in 4/21	This paper provides evidence that Tourette disorder is not an absolute contraindication to methylphenidate use; however, a variety of stimulants were used both before and after the diagnosis of Tourette disorder.	*(107)*
d-Amphetamine, methylphenidate	Not reported	4 boys, 8–11 years old	Tourette disorder developed and continued	This paper indicates the independence of Tourette disorder from medication, but	*(108)*

Medication	Stimulant dose (mg/day except where indicated)	Characteristics of the children	Outcome	Comments[a]	Reference
d-amphetamine/ pemoline methylphenidate/ pemoline			after medication	includes only 4 children who used 3 medications alone and in combination with no indication of dose.	
Methylphenidate, *d*-amphetamine, pemoline	Not reported	200 children, 48 with Tourette disorder	8/48 tics worsened	Strengths: Inclusion of a fairly homogeneous population of 48 children with pre-existing Tourette disorder. Weaknesses: Retrospective review, dose range not given; there was no independent diagnosis; follow-up duration was variable.	*(109)*
Methylphenidate, pemoline, *d*-amphetamine	Not reported	170 twins and individuals	50% with worsening of tics, some developed tics	Strength: Twin study (in 6 monozygotic twins, discordant for medications; other twin developed Tourette disorder suggesting genetic basis). Weaknesses: Doses were not given; Tourette disorder was pre-existing; the relationship of tic worsening to therapy was vague.	*(110)*
Methylphenidate	10–30	4 boys, 8–11 years old	Tics not worsened	Strength: Single-blind. Weakness: Only 4 subjects; all had Tourette disorder and ADHD.	*(111)*
Methylphenidate, *d*-amphetamine	Up to 90 mg/day methylphenidate; up to 45 mg/day *d*-amphetamine	45 hyperactive boys age 6–12 years	10/45 had increase in tics or development of tics only on methylphenidate; 6/45 only on *d*-amphetamine, and 11 on both.	Strengths: Compared methylphenidate and *d*-amphetamine; high doses used. Weakness: Tics were not clearly distinguished from other behavioral changes and disorders (e.g., obsessive-compulsive disorder) that developed over the course of the study.	*(112)*
Methylphenidate	0, 0.3, or 0.5 mg/kg bw twice/day	82 children age 5–13 years crossed over to each dose for 7–10 days	Tics occurred in 18% of subjects on placebo and on low dose and 28% of subjects on high dose; $P < 0.05$ according to authors.	Strengths: Double-blinded, placebo controlled cross-over design; ratings by parents and teachers. Weaknesses: No measures to actively exclude new cases of Tourette disorder (there may not have been any). Rating scale used the broad term "tics/nervous movements" which may explain high rates in	*(72)*

Medication	Stimulant dose (mg/day except where indicated)	Characteristics of the children	Outcome	Comments[a]	Reference
				both placebo and active drug groups. Also, no notation of whether subjects were "drug naïve." Time-course of exposure to drug unclear: 7–10 days on drug, followed by placebo OR 2 active drug phases back to back. Duration of exposure may influence frequency of tics.	
Methylphenidate	0, 0.3, 0.5 mg/kg bw 3 times/day	206 children age 5–15 years crossed over to each dose for 1 week (2 placebo weeks were included in random order)	No increase in tics on either dose of methylphenidate	Strengths: Used the dose scheme of *(72)*; children with Tourette disorder were excluded. Weakness: The randomization scheme was changed after the first 46 children were enrolled. Used parent ratings only. Rating scale used the broad term "tics/nervous movements" which may explain high rates in both placebo and active drug groups. Also, no notation of whether subjects were "drug naïve." Not clear if the study design was the same as *(72)*. Here it is 1 week on and 1 week off. Short-term exposures to drug do not necessarily reflect risks in long-term use.	*(75)*
Methylphenidate, *d*-amphetamine, pemoline	Methylphenidate dose (mean ± SD): 21.1 ± 11.7 with tics, 24.4 ± 17.2 without tics; *d*-amphetamine dose (mean ± SD): 14.2 ± 5.2 with tics, 15.8 ± 6.8 without tics	122 children with ADHD age 3.6–15.8 years	Tic/dyskinesias occurred in 8.2% of children treated with medication	Strengths: Large study with standarized diagnosis of ADHD (DSM-IIIR). Weaknesses include retrospective design, unknown weight-adjusted doses, and reliance on chart review for parental assessments of unusual tic-like movements such as "eye bugging." Prior medication history not detailed.	*(113)*
Methylphenidate	0.1, 0.3, 0.5 mg/kg bw twice	34 children with ADHD	Small increase in frequency of tics (motor	Strengths: The observation of three in-school settings, including lunch-room and	*(114, 115)*

Medication	Stimulant dose (mg/day except where indicated)	Characteristics of the children	Outcome	Comments[a]	Reference
	daily	aged 6.1–11.9 years	tics increased, verbal tics decreased). The increase occurred only on the low dose (mean 4.4 mg **[likely subtherapeutic]**).	playground, is interesting (with physician, teacher, and parent ratings) in *(114)*. Weaknesses: The sample size is small and the observation period was only 6 weeks. The tics were clinically unimportant (e.g., the teachers did not notice them).	
Methylphenidate, *d*-amphetamine	Methylphenidate 35–90; *d*-amphetamine 10–45	20 children, mean age ± SD 9.4 ± 2.0 years	Reversible increase in tics, particularly with *d*-amphetamine. Methylphenidate-associated tics returned to placebo baseline with continued methylphenidate treatment.	Strengths: Two drugs were compared; wide range of doses; double blind. Weakness: Small sample size.	*(116)*
Methylphenidate, *d*-amphetamine	Methylphenidate 0.6 mg/kg bw/day, *d*-amphetamine 0.3 mg/kg bw/day	125 children with ADHD, mean age ± SD 104.8 ± 27.6 months; range 60–179 months (5–15 years)	Tics present in 35% of subjects at baseline and 26–28% of subjects after 2 weeks on either drug.	Strengths: Moderately high doses of two drugs were evaluated. Used Barkley scale as in the Ahmann study *(75)*. Weaknesses: Lack of placebo control; the item scored was "tics or nervous movements," (in this case the rating scale may overestimate prevalence of tics at baseline, confounding analysis); the duration of the study was only 2 weeks on each drug; no notation of whether subjects were "drug naïve."	*(78)*
Methylphenidate	0.5 mg/kg bw/day mean dose	72 children with ADHD	10/51 developed tics, 7/21 tics worsened; incidence of new and worsened tics similar with placebo. 40% of tics developed 4–12 months after medication started.	Strengths: Placebo-controlled; identifies differences in parent and teacher evaluations; 80% of sample took their medication for 8–12 months; demonstrates waxing and waning of tics regardless of origin (but doses were adjusted if tics emerged or worsened until the tics improved somewhat). Subjects had no history of exposure to meds for ADHD or tics.	*(102)*

Medication	Stimulant dose (mg/day except where indicated)	Characteristics of the children	Outcome	Comments[a]	Reference
				Age range is small: methylphenidate group: 8.4 years (SD 1.6) and placebo group: 8.3 (1.5). Naturalistic design useful for clinical practice compared to fixed dose. Weaknesses: Excluded severe tics and Tourette disorder; scoring performed by research assistants based on parents' narratives; prior to medication, 30% had motor or vocal tics; parents could initiate cross-over if child's behavior worsened. Did not note whether they had prior exposure to any other psychotropic medications such as neuroleptics. Utility: Study adequate for evaluation process.	
Methylphenidate	0.1, 0.3, 0.5 mg/kg bw 3 times daily	34 children with ADHD and tics	Transient increase in tics; long-term methylphenidate use did not cause tics to develop or worsen.	Strength: 2-year prospective study. Weakness: Not blinded to treatment.	*(117)*
Methylphenidate, *d*-amphetamine, pemoline	Not reported	374 children on methylphenidate, 126 children on *d*-amphetamine, 13 on pemoline	Tics present in 7.8% of children; not more frequent in any medication category	Strength: Comparison of three medications. Weakness: Retrospective chart review.	*(118)*
Methylphenidate, clonidine	5–60	104 children age 7–14 years	Proportion of subjects with worsening tics was similar with methylphenidate (20%: includes 8 subjects treated with methylphenidate alone	Strengths: A wide range of doses was studied; followed up to 9 active treatment weeks. Excluded subjects with secondary tic disorders such as tardive tics (which can occur with use and with discontinuation of neuroleptics) and subjects with several other major psychiatric disorders.	*(103)*

Medication	Stimulant dose (mg/day except where indicated)	Characteristics of the children	Outcome	Comments[a]	Reference
			and 6 treated with methylphenidate + clonidine), clonidine alone (26%), and placebo (22%). The greatest reduction in tic severity and ADHD severity occurred in the methylphenidate + clonidine group.	Weaknesses: Because all subjects had comorbid ADHD and DSM-IV Tourette disorder, or chronic motor or vocal tic disorder, cannot necessarily generalize findings to children without baseline tic disorders. Table 1 of study, "Subject Characteristics at Baseline," does list some subjects as having major depressive disorder, which appears to contradict enrollment criteria. Some subjects were on clonidine for ADHD; clonidine may suppress tics. For methylphenidate, the development of tics was dose-limiting. Severity rating scales were evaluated with *t* tests. Utility: This important and well designed study is adequate for the evaluation process.	

[a]None of the studies screened for substance abuse.

Strengths/Weaknesses: The strength of the overall data set on tics in children treated with stimulant medication is the demonstration that the use of controls and blinded evaluators results in the disappearance of the association between stimulant medication and tics that was suggested by older, anecdotal reports. Weaknesses of the studies generally include small numbers of subjects and short observation periods. Worsening of tics can be due to the natural waxing phase of spontaneous tics and Tourette disorder, which has a high incidence in the ADHD population. Many studies do not discriminate between different observers (e.g., parents, teachers, records), much less evaluate inter-rater reliability.

Utility (Adequacy) for CERHR Evaluation Process: The data set is generally useful in the evaluation process.

3.1.2.7 Substance Use Disorders

Studies examining associations between pharmacotherapy for ADHD and substance use disorders were reviewed. The studies are presented below in order of evaluations conducted during childhood, adolescence, and adulthood.

Chilcoat and Breslau *(119)*, supported by NIDA and NIMH, included a limited assessment of stimulant treatment for ADHD and risk of childhood drug use. In the longitudinal study focusing on ADHD effects on illicit drug use, 717 children were assessed at ages 6 and 11 years. The children were born between 1983 and 1985. African American children represented 46.2% of the subjects; 57.4% of all subjects had been low birth weight infants (< 2500 g). **[Subject sex was not specified.]** At ages 6 and 11 years, the children were asked about drug use and psychiatric evaluations were conducted on both the children and their mothers. A total of 146 of the children had been diagnosed with ADHD at age 6 years and 100 of those children had been low birth weight infants. At age 11, 30 of the children (20.2%) with ADHD were being treated with medication. It was stated that nearly all were receiving methylphenidate, but no information was provided about other medications used. **[Duration of treatment was not specified.]** The children were considered drug users if they had ever used tobacco, alcohol, marijuana, or inhalants. Rates of drug use were 31.0% in children receiving medication for ADHD compared to 28.2% in children not receiving pharmacotherapy for ADHD. In a group of 24 children who were not diagnosed with ADHD at age 6 but were receiving medication for treatment of ADHD at age 11, the rate of drug use (16.6%) was the same as the incidence of drug use in a group of children not receiving medication. **[The number of children not receiving medication was not specified.]** The authors stated that models were used to control for severity of ADHD. The study authors concluded that use of stimulant medications had no effect on drug use in children. Associations were found between drug use and level of externalizing problems (e.g., aggressiveness, acting out, and disruptive behavior), ADHD in combination with moderate externalization of problems, low level of parental monitoring, and drug use by peers.

Strengths/Weaknesses: A strength is that this was the only study that looked at very young children (6 and 11 years). Several weaknesses were noted. A paucity of information was provided for statistical procedures. Children were asked if drugs were “ever used,” which is not very useful in establishing “substance use disorder.” The study noted that over half the children were of low birth weight; this observation needs to be statistically controlled because it may underlie some of the associations noted with ADHD and externalizing behavior. Important parameters (e.g., duration of treatment) were not described.

Utility (Adequacy) for CERHR Evaluation Process: The study is not useful for the evaluation process.

Beck et al. *(120)*, in a study supported in part by the CIBA Corporation, examined the effects of methylphenidate treatment on substance abuse. The treatment group consisted of 30 adolescents (23 males and 7 females; 14–19 years old) with minimal brain dysfunction who had been treated with methylphenidate for ≥6 months during childhood but were not currently receiving methylphenidate treatment. The control group consisted of 30 adolescents who were comparable in age, sex, and socioeconomic background and had no chronic disabilities or previous psychiatric history. Subjects were interviewed to obtain information about use of marijuana, heroin, hashish, mescaline, glue, and a category of "other" substances at the time of interview and more than 6 months prior to the interview. In the treatment group, 1 subject reported habitual heroin use >6 months prior to interview and 2 subjects reported occasional use of marijuana during both time periods. Two control subjects reported habitual use of heroin, 1 reported habitual use of marijuana, 1 reported habitual glue sniffing >6 months prior to interview, and 3 reported habitual use of marijuana at the time of interview. Occasional or unspecified drug use was reported by 5–7 control subjects during each time period. **[No statistical analyses were conducted.]** The study authors concluded that methylphenidate treatment during childhood does not contribute to later substance abuse. Effects on growth were also examined and are reported in Section 3.1.2.8.

Strengths/Weaknesses: A strength is that this study is one of few examining methylphenidate treatment in children who may not have ADHD (i.e., subjects in treatment group defined as having minimal brain dysfunction). A weakness of the study is that the comparison group neither received stimulant treatment nor had minimal brain dysfunction. Only 2 (6%) of 30 treatment subjects reported occasional use of marijuana. This percentage appears to be very low since Monitoring the Future data suggest that in 1975, 40% of 12th graders used marijuana in the previous year *(21)*. Thus, the reliability of the collected information is suspect.

Utility (Adequacy) for CERHR Evaluation Process: The study is not useful for the evaluation process.

Biederman et al. *(121)*, in a study supported by the NIMH and NIDA, evaluated the risk of substance use disorders associated with psychotropic medication for treatment of ADHD. Data were obtained and reanalyzed from an ADHD longitudinal genetics study conducted in 260 families. Females were not evaluated because most medicated subjects were male; subjects younger than 15 were excluded due to the significantly younger age of medicated versus non-medicated subjects. Subject groups consisted of Caucasian males who were ≥15 years old and had previously received medication for ADHD (n = 56), had ADHD but were not medicated (n = 19), or did not have ADHD (n = 137). The average duration of treatment was 4.4 years. **[The types of medications used were not specified.]** Multiple logistic regression was used to correct confounding by age, socioeconomic status, lifetime risk of conduct disorder, and substance use disorders in parents. Substance use disorders were examined for alcohol, marijuana, hallucinogen, cocaine/stimulant, and tobacco. ADHD subjects who had been medicated had a significantly reduced risk of any substance use disorder compared to unmedicated subjects with ADHD (OR 0.15, 95% CI 0.04–0.6). Unmedicated subjects with ADHD had a significantly increased risk of any substance use disorder compared to controls without ADHD (OR 6.3, 95% CI 1.8–21.4). With the exception of tobacco use, the medicated group had reduced risk of all other individual substance use disorders compared to the unmedicated ADHD group, but the sample size was too small to evaluate statistical significance for individual substances. The study authors concluded that pharmacotherapy is associated with an 85% reduction in risk for substance use disorders in youths with ADHD.

Strengths/Weaknesses: Strengths of this study include well-articulated competing hypotheses and longitudinal design, as well as masked assessment and careful definition of the sample restricted to Caucasian males older than 15 years of age. Authors pay considerable attention to quality control and structured DSM-IIIR interviews were used to establish the diagnosis of substance use disorders (because of small numbers, abuse and dependence were analyzed as a single category as substance use disorder). Important variables, including comparisons of treated and untreated ADHD children, were considered in analyses. The study addresses implicitly the issue of self-medication by determining that treated groups had a diminished odds ratio for substance abuse. Other strengths include control of parental substance use disorder and presentation of outcomes as an aggregate of any substance use disorder and disaggregated by substance. Limitations include use of an exclusively tertiary referred Caucasian sample, so findings may not apply to less privileged or lower income risk groups. Other weaknesses include lack of specification of the drugs that the treated members of the cohort received. The authors correctly identified lack of power as diminishing confidence in null findings. Other weaknesses are that the age ranges of subjects and the time period they had been off medication were not specified.

Utility (Adequacy) for CERHR Evaluation Process: The study is useful for the evaluation process.

Barkley et al. *(122)* (also reported in **Fischer and Barkley *(123)***), in a study supported by the NIMH, examined possible associations between stimulant medication therapy during childhood or adolescence and substance use during adolescence and young adulthood. During each evaluation period, subjects or their parents were asked about stimulant therapy, behavior, mental health, illicit drug use, and education history; psychological tests were conducted and subjects were rated according to scales. Groups consisted of 91% males and 9% females. Racial distribution was 94% white, 5% black, and 1% Hispanic. Subject ages were 12–20 years during the adolescent evaluation and 19–25 years during the adult evaluation. During the adolescent evaluation, 119 subjects diagnosed as hyperactive were available for interview and parents were questioned about stimulant therapy during childhood. Ninety-eight were treated with stimulants during childhood, while 21 were not. Percentages treated with each type of stimulant during childhood were 80% methylphenidate, 3% *d*-amphetamine, and 20% pemoline. Some subjects received more than 1 type of stimulant; *d*-amphetamine was given to 2% and pemoline to 22% of the children in the methylphenidate group. All children in the pemoline group had also received *d*-amphetamine. Mean durations of treatment during childhood were 44.8 months for methylphenidate, 32.8 months for amphetamine, 13.3 months for pemoline, and 40.2 months for stimulants in general. During the adult evaluation, 147 hyperactive subjects were questioned about stimulant treatment during high school, but were not asked to identify the specific stimulant medication taken. Thirty-two subjects were treated with stimulants and 115 were not treated with stimulants during high school. Mean duration of stimulant treatment during high school was 26.6 months. Seven of the subjects were receiving stimulant treatment at the time of the interview. **[Severity of ADHD symptoms and conduct disorders were the only potentially confounding factors considered.]**

At the adolescent evaluation, subjects were asked if they had ever tried cigarettes, alcohol, marijuana, hashish, cocaine, heroin, hallucinogens, unprescribed stimulants, sedatives, or tranquilizers. **[Information about frequency of use was not obtained and substance abuse/dependency was not considered.]** The proportion of hyperactive subjects who had ever tried any of the substances was similar in the stimulant-treated and untreated groups by chi-square analysis. No significant differences were found when all stimulants (cocaine, amphetamines) were combined or when duration of stimulant therapy was considered.

When evaluated in adulthood, subjects were questioned about their use of alcohol, marijuana, cocaine, amphetamines/speed, any stimulant, hallucinogens, narcotics, sedatives, or other drugs. Frequencies of substance use were log transformed due to high standard deviations and compared by ANOVA. Stimulant treatment in childhood did not significantly increase the frequency of any type of substance use in early adulthood. The frequency of cocaine use was significantly higher ($P = 0.043$) in subjects who were treated with stimulant medications in high school, but the results were no longer significant when corrected for severity of ADHD and conduct disorder. **[Table 3 of the study, which presents effects of high school stimulant treatment, lists group numbers for childhood treatment (n = 21 untreated, 98 treated) instead of high school treatment (n = 115 treated, 32 untreated).]** The proportion of subjects who ever used each of the substances was analyzed by chi-square. If statistically significant findings were observed, a binary logistic analysis was conducted to adjust for severity of ADHD symptoms and conduct disorders. A greater percentage of adults who were treated with stimulants in childhood and in high school used cocaine at least once (5% untreated compared to 26% treated in childhood, $P = 0.037$ and 20% untreated compared to 40% treated in high school, $P = 0.016$). Due to increased cocaine use, the use of any stimulant was also increased in adults treated during high school (25% in untreated compared to 47% in treated, $P = 0.018$). Additional analyses indicated that risk of cocaine use was primarily mediated by severity of conduct disorder and not by use of stimulant medication. Increased duration of stimulant treatment was not found to affect adversely the risk of substance use. No significant differences in adult substance abuse/dependence rates (diagnosed by DSM-III-R criteria) were noted in hyperactive subjects who were or were not treated with stimulants in childhood or during high school. **[There were no statistical analyses for abuse/dependency in adults.]** The study authors concluded that there is no compelling evidence that stimulant treatment of children or adolescents with ADHD leads to increased risk of substance experimentation, use, dependence, or abuse by adulthood.

Strengths/Weaknesses: A strength of this study is that substance abuse was defined by DSM-III-R criteria. This study considered not only substance use, but also examined frequency/quantity and distinguished experimentation from problem use. Initiation and experimentation did not differ by stimulant medication exposure status. Another strength is consideration of duration of treatment, with considerable detail provided on the length of time subjects received different medications. Two time frames of stimulant medication use and drug use were examined; uniquely, illicit drug use was examined while a few subjects were still receiving medication. An important study finding was that cocaine use was related to adolescent treatment but this relationship was lost when severity of ADHD was statistically controlled; this finding emphasizes the need for such control in other studies. In addition to the paucity of control variables (including family history), a major weakness noted by authors on page 100 of the *Pediatrics* article is that the assessor was not masked to stimulant exposure history. It is both a strength and a weakness that the authors specify the medications to which the children were exposed, but because of small cell sizes and a predominance of methylphenidate, stimulants were only evaluated as a single generic exposure. However, the authors did use standard instruments. Weaknesses include the fact that tobacco use was not adequately evaluated. The authors were correct in noting that it is difficult to ascertain whether the weak association between high school stimulant treatment and cocaine use was an artifact of multiple comparisons. However, another conceptual weakness they did not consider is that perhaps children who are more deviant and, therefore, with or without treatment, more prone to substance use disorders, are more likely to continue to be treated into high school. Though important, it was not stated whether subjects treated in high school received stimulants at both ages, especially as findings were mediated by severity of ADHD. The authors themselves point out that their study design did not permit them to identify the temporal

sequences of conduct disorder and substance use disorder, leading to difficulties in interpretation of the worrisome finding of a possible connection between stimulant treatment and cocaine use.

Utility (Adequacy) for CERHR Evaluation Process: This study is useful for the CERHR process.

Lambert and Hartsough *(124)* and Lambert *(125)*, in studies supported by the Tobacco-Related Disease Research Program, examined the effects of ADHD and stimulant treatment on tobacco use and substance dependency in a longitudinal sample of 492 adults. According to information provided in the Lambert study *(125)*, subjects were born in the San Francisco area between 1962 and 1968. About 22% of the subjects were female and 23% represented ethnic minority groups. The authors reported that among subjects using stimulant medications, 69% used only methylphenidate, 16% used combinations of methylphenidate and other stimulants, and 15% used other CNS stimulants (amphetamines, pemoline). At various stages throughout their lives, the subjects were questioned about their use of tobacco, alcohol, marijuana, stimulants, and cocaine. A total of 399 subjects were said to be available for interview. **[These studies appear to have numerous discrepancies or mathematical errors in text compared to tables or in different parts of tables. In adding numbers presented in some study tables, it appears that either mathematical errors were made or more than 399 subjects were evaluated for some endpoints (i.e., Table 3 in Lambert and Hartsough *(124)*). In other cases, fewer than 399 subjects were included in analyses and it is not clear if or why some subjects were excluded (Table 5 in Lambert and Hartsough *(124)*).]**

In the Lambert and Hartsough study *(124)*, subjects were placed into hyperactive or control groups. According to information presented in Lambert *(125)*, there were 217 hyperactive subjects (136 with primary hyperactivity with no causal explanation, 31 with secondary hyperactivity possibly due to organic factors, and 50 with untreated hyperactivity). There were 182 controls (141 age controls and 41 with non-ADHD behavioral problems). Information in Lambert *(125)* indicates that only 80% of the primary hyperactive group and 66% of the secondary hyperactive group received stimulant treatment. **[It is not clear why untreated subjects in the primary and secondary hyperactive group were not put into the untreated hyperactive control group.]** It appears that about 3% of controls received stimulant treatment. Subgroups of individuals were grouped together based on similarity of health, familial, educational, and social background factors. **[There was no discussion of adjustment for additional confounding factors such as severity of ADHD.]** The rate of smoking in adults who had ADHD as children and who never used stimulant medication (n = 47) was 37.0%; for adults who had used stimulant medication for up to a year (n = 28), the rate of smoking was 22.0%; and for adults who had used stimulant medication for ≥1 year (n = 52), the rate of smoking was 40.9% ($P < 0.03$ for never used compared to use ≥ 1 year, by chi-square). The Mantel-Haenszel test for linear trend was also significant for duration of stimulant use ($P < 0.01$). Significant linear trends ($P < 0.03$) were noted for rates of tobacco dependency in adults who had ADHD as children and who never used stimulant medication (n = 81; 32.1% rate) or had used stimulant medication for up to 1 year (n = 9; 38.5% rate) or ≥1 year (n = 84; 48.8% rate). Significant linear trends ($P < 0.05$) were also noted for rates of cocaine dependency in adults who had ADHD as children and who never used stimulant medication (15.0%) or had used stimulant medication for up to 1 year (17.9%) or ≥1 year (27.4%). **[The text states that statistical significance by chi-square was obtained for cocaine dependency, but the legend of Table 7 in the study indicates that results of chi-square analyses were not significant for either tobacco or cocaine dependency. It is not clear how the numbers of subjects were selected for each analysis and why the numbers were so different for each analysis. The number using stimulant medication for up to 1 year is listed as 9, but this figure cannot be correct based on the percentages given in**

the table. Assuming the correct number is 52 (based on 1 version of the total number of subjects in the report), Fisher exact test by CERHR shows a significant difference for tobacco prevalence between subjects with ≥1 year use of stimulant medication and subjects without use of stimulant medication, *P* = 0.039; none of the other comparisons for tobacco or cocaine use were statistically significant. The Expert Panel has little faith in these conclusions, however, given the confusion in the paper concerning the number of subjects in various comparison groups.] A comparison of subjects who had ADHD as children with subjects who did not have ADHD as children showed that subjects with ADHD began smoking regularly at a younger age and had a higher rate of smoking and cocaine dependency as adults. The study authors concluded that there is a possible link between stimulant medication and rates of smoking and tobacco and cocaine dependency in adulthood.

In the Lambert study *(125*), subjects were divided into groups of 268 who received no CNS stimulant treatment and a group of 131 who received stimulant treatment. **[According to Table 18.2 in the paper, the group with no stimulant treatment was comprised of 162 subjects without ADHD and 106 with ADHD (41 severe, 25 moderate, and 40 mild). The stimulant treatment group was comprised of 10 subjects without ADHD and 121 subjects with ADHD (62 severe, 48 moderate, and 11 mild).]** The percentage of subjects who had not yet become regular smokers was significantly higher ($P \leq 0.05$ by Lee Desu statistic) in the untreated group (~60%) compared to the treated group (45%). The same subjects were evaluated according to the age when stimulant treatment was ended: age 10, age 11–13, or after age 14. Stimulant treatment appeared to protect against smoking during childhood. However, in adulthood, smoking rates were significantly higher ($P < 0.001$ by chi-square) in treated groups (41%) compared to the untreated group (19%). Adjusted odds ratios were calculated. **[The confounding factors considered in the analyses are not clearly identified, but it appears that childhood conduct disorders were considered in addition to socioeconomic status, cognitive ability, and ethnicity. It is not clear how many subjects were included and how the subjects were classified in calculating the odds ratios. It is assumed that as in previous analyses, subjects with and without ADHD were collapsed into the same groups based on stimulant exposure.]** In the group treated with stimulants for more than 1 year, odds ratios were described as significant for daily smoking (2.817) and cocaine dependency (2.251) in adulthood. In subjects exposed <1 year, a significant odds ratio (3.951) was obtained for daily smoking in adulthood **[95% CIs were not listed]**. ADHD severity was found to be significantly related to tobacco, cocaine, and stimulant dependency in adulthood.

Strengths/Weaknesses: A strength of these studies is the emphasis on cigarette consumption, which possibly indicated self-medication, as higher rates of smoking were found in untreated ADHD subjects. However, the inconsistencies in sample sizes and inaccuracies in study tables are serious and make conclusions very tenuous. Other weaknesses include the inadequate description of sample in terms of ethnicity, social class, parental substance use, severity of ADHD, and many other potential confounders. In addition, the authors tended to make sweeping conclusions on the basis of univariate analyses. All of these weaknesses make interpretation of reported findings problematic.

Utility (Adequacy) for CERHR Evaluation Process: These studies are not useful for the evaluation process.

Paternite *(126*) and Loney *(127*) (from the same group) examined the effects of stimulant medication in childhood on substance use in adulthood. One of the studies *(126*) was partially supported by NIMH. Subjects were selected from 219 **[listed as 285 in 1 study, but this figure appears to be an error]** boys (98% white) who were referred to the University of Iowa child

psychiatric clinic at 4–12 years of age. Boys were diagnosed as having hyperkinetic reaction (70%) or minimal brain dysfunction (30%). By more current standards, ~70% of the boys would have been diagnosed with ADHD and the term ADHD is used in the later paper for convenience. Aggressiveness was noted in 7% of the boys, who would have likely received a diagnosis of oppositional defiant disorder according to more recent terminology. Based on treatment preferences of 3 different physicians, 182 of the boys received stimulant medication and 37 were not given medication. At follow-up during adulthood (21–23 years old), 97 of 121 subjects medicated with methylphenidate in childhood were available for evaluation. **[It appears that the 121 medicated subjects were selected from the group of 182 medicated subjects. The number of untreated subjects available for evaluation in adulthood was not specified.]** The medicated subjects were treated between 1967 and 1972 at a mean age of 8.8 years. Mean methylphenidate dose was 32 mg/day (8–80 mg/day range) and mean duration of treatment was ~30 months **[reported as 30.4 and 36 months in the 2 papers]** with a range of 1–76 months. **[It was not stated how many untreated subjects were included in analyses.]**

In the Paternite et al. study *(126)*, regression analyses were conducted to determine associations between methylphenidate dose, response, or treatment duration and alcoholism, drug abuse disorder, psychiatric conditions, and measurements of social function and IQ. Child age, symptom dimensions, and the two other medication variables were held constant in each analysis. Neither alcoholism nor drug abuse disorders were significantly associated with methylphenidate treatment, although there was a trend between increased dosage and fewer diagnoses of alcoholism ($r = –0.2$, $P < 0.10$). **[Most data were not shown since only values approaching or reaching statistical significance were listed in tables.]** The only adverse finding related to methylphenidate treatment was an association between better response to treatment and reduced likelihood of high school graduation ($r = –0.34$, $P < 0.01$). Additional findings included associations between increased dosage and reduced suicide attempts; better medication response with improved psychiatric outcomes and social functioning; and longer treatment duration with improved psychiatric outcomes, higher IQ, and better reading scores. Significant associations or trends were noted between inattention-overactivity and unemployment and adverse outcomes on some psychiatric or behavioral measures. Associations or trends noted for aggression were drug abuse disorder, antisocial personality disorder, and adverse outcomes on some psychiatric or behavioral measurements. **[The Expert Panel notes that a number of unique positive associations with medication were observed (e.g., reduced suicide attempts). Only one adverse significant association with medication was reported and it is surprising: "better response to treatment and reduced likelihood of high school graduation."]**

In the study by Loney et al. *(127)*, rates of involvement (experimentation, continuation, or escalation of use) with alcohol, tobacco, barbiturates, tranquilizers, stimulants, marijuana, glue, cocaine, LSD, and opioids were compared between ADHD subjects who either were or were not treated with methylphenidate. The analyses controlled for year of birth and inattention, overactivity, or aggressive defiance symptoms. In unmedicated compared to medicated subjects, adult involvement was significantly increased ($P < 0.05$) for tobacco, stimulants, glue, and opioids. **[The unit on the Y axis of involvement graphs (Figures 17.1 and 17.2 of the study) is not specified and it is not clear what kind of analysis was conducted.]** According to the study authors' interpretation of the data, medicated subjects progressed less far along the path from experimentation to continued use. Significantly fewer ($P < 0.05$) medicated versus unmedicated subjects (respective percentages) had experimented with glue (~22 vs. 38%), stimulants (38 vs. 58%), LSD (~30 vs. 49%), and opioids (~23 vs. 42%). Medicated versus unmedicated subjects (respective percentages) had significantly lower rates of alcoholism (27 vs. 56%, $P = 0.002$) and antisocial personality disorder (24 vs. 44%, $P = 0.004$). Drug abuse rates were similar between the 2 groups (17 vs. 19%). Loney et al. *(127)* concluded that their studies did not indicate a

negative effect of childhood methylphenidate treatment on future drug use, but suggested that further research is needed. **[The Expert Panel notes evidence of self-medication, as non-treated subjects were more likely to be 'involved' with tobacco and stimulants.]**

Strengths/Weaknesses: Strengths include a relatively lucid exposition of the technical problems in this field and an ethnically homogenous sample that consisted of all pre-adolescent subjects at the time of intake. Other strengths were that both treated and untreated subjects had ADHD and that inattention/hyperactivity and aggression were explored separately. In the Paternite et al. study *(126*), regression analyses were applied to consider many putative associations, including some that were unique (e.g., social function). Weaknesses include the need to reclassify now outdated clinical measures to fit modern criteria and the use of other outdated measures for outcomes, as well as lack of consideration of family risk factors, both genetic and environmental. The small size of the unmedicated subgroup (n=37) would tend to bias the evaluation against finding a negative effect in the unmedicated group. It is not clear how the follow-up medicated subjects were selected or how many untreated subjects were followed to adulthood. For example, the authors failed to describe clearly in these 2 articles how an initial sample of 182 treated subjects became 121 and then 97.

Some weaknesses in the interpretation of the Loney et al. *(127*) study were noted. The main finding was that medicated subjects were less likely to go from "experimentation to continued use" (terms not defined). Drug abuse (not defined) was reported to be similar among treated and untreated groups, but medicated subjects were less likely to "experiment" with most drugs. Therefore, the conclusion that drug abuse rates are not impacted by medication is problematic. Because fewer medicated subjects experimented, it appears that the proportion of medicated subjects who experimented and went on to continuous drug use was higher than the proportion of unmedicated subjects. A statistical control is needed for this finding.

Utility (Adequacy) for CERHR Evaluation Process: The Paternite et al. *(126*) study is of limited utility; the Loney et al. study *(127*) is not useful for the evaluation process.

Mannuzza et al. *(128*), in a study supported by the NIMH and NIDA, examined substance abuse in Caucasian adults who as children were randomly treated with methylphenidate or placebo in studies to examine the effects of methylphenidate on reading disorders. The probands in this study had reading disorders, but no other psychiatric problems. They received methylphenidate or placebo at 7–12 years of age over a period of 12–18 weeks. Average methylphenidate doses of treated subjects were 43.9–48.8 mg/day. Sixteen years later (average age 26 years), the probands were interviewed about use of substances such as alcohol; marijuana; cocaine, crack, or other stimulants; barbiturates/tranquilizers; psychedelics/hallucinogens; heroin and other opioids; and other substances such as inhalants. The numbers of probands interviewed were 39 (79% male) in the methylphenidate group and 63 (70% male) in the placebo group. Results in the proband groups were compared to each other and to a comparison group of 129 Caucasian individuals (74% male) who had no behavior problems prior to 13 years of age. Dichotomous data were analyzed using logistic regression analysis and continuous data were analyzed using ANCOVA, with age and social class co-varied. Other factors such as gender, parent marital status, number of siblings, school grade, reading grade equivalent, and family stability were stated to be similar between groups. There were no significant differences in rates of substance abuse disorder. Rates of substance abuse disorder were 41% in the methylphenidate group, 37% in the placebo group, and 40% in the comparison group. For substances abusers, there were no significant group differences in age of onset, duration, number of abuse episodes, or dependence. Significantly more subjects in the comparison group reported ever using marijuana/hashish and stimulants. Rates of stimulant use were 46% in the methylphenidate group, 41% in the placebo group, and

60% in the comparison group. The study authors concluded that results of this study failed to support the theory that treatment with stimulants during childhood increases risk for substance abuse later in life.

Strengths/Weaknesses: A strength of this study is that the sample of children with reading disorders was randomly assigned to methylphenidate or placebo groups. The study was well controlled for possible moderators or mediators of effect and masked interviewers were used. There was a detailed examination of abuse using a number of parameters. It is a strength in refuting the sensitization hypothesis that the sample, ethnically homogeneous Caucasian, had developmental reading disabilities not ADHD or comorbid conditions and were treated for a fixed period dictated by study design rather than clinical condition. However, these strengths also weaken the relevance to "real life" situations where methylphenidate is most often used for long duration in children already at behavioral risk. The authors document a number of potential background characteristics, although not parental history of substance use. The article would be strengthened by calculations of power to detect an effect if one did exist. A weakness of this study is that the very short treatment period (12–18 weeks) limits generalizability to populations more commonly using stimulants.

Utility (Adequacy) for CERHR Evaluation Process: This study is useful for the evaluation process.

Wilens et al. *(129)* conducted a meta-analysis of studies examining possible associations between long-term medication for treatment of ADHD and substance use disorders. The studies reviewed in the analysis are listed in Table 27 and include published reports identified in a PubMed search, data presented at scientific meetings, and unpublished findings. **[Published studies are reviewed in detail above.]** Included in the analysis were prospective studies examining subjects during adolescence *(121, 129*) and young adulthood *(124, 126, 127*). One retrospective study examined subjects during adulthood (Huss 1999 abstract cited in *(129*)). A total of 674 medicated and 360 unmedicated subjects with ADHD were included in the meta-analysis. The analysis did not examine nicotine use. ORs for drug and alcohol substance abuse disorders are listed in Table 27. An OR >1 indicates a protective effect of medication, while an OR <1 indicates an adverse effect of medication. **[According to ORs and CIs listed in Table 27, none of the studies demonstrated a significant adverse effect of medication.]** The pooled OR of 1.9 (95% CI 1.1–3.6) suggests a nearly 2-fold reduction in risk of substance abuse disorders in youths medicated versus unmedicated for treatment of ADHD. Additional analyses indicated that no single study heavily influenced outcome. Studies that controlled for baseline severity of ADHD were found to have larger ORs **[statement not consistently supported by drug data in Table 27]**. A greater protective effect of medication was found in studies examining adolescent (OR 5.8) verus adult subjects (OR 1.4) **[95% CIs were not presented]**. The study authors concluded that results suggested an association between stimulant treatment in childhood and reduced risk of subsequent drug and alcohol disorders.

Strengths/Weaknesses: This paper reviewed numerous studies, some of which were not published. Strengths of this study include statistical analyses (albeit of data of heterogeneous quality and composition) and care in checking that no single study heavily influenced the combined estimates, as well as attention to publication bias. Other strengths were largely conceptual. The authors raised an important issue about baseline severity of ADHD in moderating impact of stimulant treatment; unfortunately, part of that analysis was based on unpublished observations (Barkley et al.). Another interesting point is that children from families with a history of substance use may be more resistant to stimulant treatment. On the other hand, children with more severe oppositional and aggressive disorders (and thus at greater risk of later substance

use disorder whether treated or untreated) are more likely to receive stimulant treatment than children at lower baseline risk. It can be regarded as either a strength or a weakness that samples were heterogeneous in the age of follow-up with two studies looking at adolescents who were presumably quite early in the substance use disorder trajectory and the remainder looking at adults. Another weakness is that the reviewed studies used differing measures of varying validity to document substance use disorder. Problems also include conflation of prospective and retrospective studies and exclusion of cigarette/tobacco use as an outcome when it was a primary outcome of a limited study that found an adverse effect of childhood stimulant treatment *(124*).

Utility (Adequacy) for CERHR Evaluation Process: This report is of marginal utility for the evaluation process.

Table 27. Meta-Analyses for Studies Examining Substance Abuse in Subjects Who Were or Were Not Medicated for ADHD

Reference	Similar baseline severity?	Number of ADHD subjects		ORs (95% CI)	
		Medicated	Unmedicated	Drugs	Alcohol
Lambert and Hartsough, 1998 *(124*)	No	93	81	0.47 (0.22–1.0)	0.6 (0.32–1.1)
Biederman et al., 1999. *(121*)	Yes	145[b]	45[b]	3.9 (1.8–8.1)	8.1 (3.9–17.2)
Huss, 1999 abstract cited in *(129*)	No	98	21	2.2 (0.99–5.1)	No data
Loney et al. *(127*)	Yes	182	37	1.1 (0.46–2.8)	3.6 (1.7–7.4)
Molina and Pelham, 1999 abstract cited in *(129*)	Yes	53	73	4.6 (1.5–14.5)	6.6 (1.4–30.2)
Barkley unpublished data cited in *(129*)[a]	Yes	Not specified	Not specified	0.83 (0.29–2.3)	0.98 (0.36–2.7)

[a]This study may have been published later as *(122*).
[b]According to CERHR review of this study, there were 56 medicated and 19 unmedicated subjects with ADHD. From *(129*)

As noted above, some studies examining the effects of ADHD medications also found associations between ADHD and/or conduct disorders and substance use *(119, 124, 126*). Numerous studies examined possible associations between ADHD, independent of treatment, and substance abuse **[not considered here]**. In a review article, Wilens *(130*) concluded, "There is a robust literature supporting a relationship between ADHD and SUD **[substance use disorders]**. Noncomorbid ADHD appears to confer an intermediate risk factor for SUD, although conduct and bipolar disorder appear to heighten the risk of early onset of SUD. Both family-genetic and self medication influences appear to be operational in the development and continuation of SUD in ADHD subjects."

[The Expert Panel noted that in general, the studies examining substance use disorders are complicated by the well known association in pedigrees of substance use disorders, ADHD, and other psychiatric disorders and by the studies' varying sophistication in measuring true

substance use disorder compared to simple experimentation or initiation. A weakness of all the studies is the use of self-report only to measure substance use without confirmation by biologic markers such as urine or hair, which might enhance accurate identification of users.]

3.1.2.8 Effects on height and weight

A number of studies on the effects of methylphenidate therapy on height and weight of in children are summarized in Table 28. The 1992 Multimodal Treatment Study of ADHD, which included height and weight data, is summarized following the table.

There are several variables considered by the Expert Panel in reviewing these studies. Differences in study design and comparison groups may account for the inconsistent and contradictory results observed across the entire data set. The following observations were made about the data set in general:

- In some studies, control groups were absent or inadequate.
- Various medication dosages were used.
- The use of drug-naïve subjects is highly desirable.
- Duration of drug treatment, which may affect pharmacokinetics, was inadequate in some studies.
- The presence or absence of drug holidays may have affected the results of some studies.
- A wide age range, including prepubertal and pubertal children, may have affected results.
- Intervals of measurements, whether monthly, yearly, or some other interval, could influence results.
- Inexact methods to measure growth and height were used in some studies.
- Long term follow-up and consideration of normal growth and weight gain were variable among studies.
- Height does not vary linearly with age; thus, the wider age range of the sample, the more vulnerable are direct comparisons of averaged height measurements.
- Methods for assessing growth deficits varied; for example, studies included absolute differences, growth percentiles from old/outdated growth charts, or other metrics.
- Some studies used growth percentiles from standardized growth charts; averages of percentiles overemphasize small differences near the mean at the expense of similar difference at the extremes.
- Many studies failed to consider parental height or body-mass index (BMI) (i.e., genetic influences).

Table 28. Methylphenidate Growth Studies

<table>
<tr><th>Parameters</th><th>Results and author conclusions</th><th>Comments</th><th>Reference</th></tr>
<tr><td>n = 29 (sex unspecified)
Control: Unmedicated ADHD controls (n = 7); Anthropometric scale
Age: Elementary school-aged
Duration: Group 1 ≥ 9 months; Group 2 ≥ 2 years
Dose: 20, 30, or 40 mg/day</td><td><u>Methylphenidate and d-amphetamine combined results</u>
-The group that discontinued medication after 9 months (n = 13) gained twice as much weight in the summer as the group staying on medication (n = 7). Weight rebound was not sufficient to compensate for the initial weight suppression.
-Over 2 years, medicated group (n = 9) had a percentile weight change of –20.38, compared to +6.79 in the control group (n = 7). For height, the medicated group percentile change was –13.45 compared to +1.29 in controls.
-Tolerance did not develop for weight gain suppression in the 2-year group; these children had a mean weight gain of 1.8 kg, compared to the expected 3.1 kg.
-Percentile height decrease correlated with percentile weight decrease, but was not significant compared to baseline
<u>Methylphenidate results:</u>
-Difference in weight gain between group discontinuing medication in the summer (0.41 kg/mo) and group continuing medication (0.29 kg/mo) was not significant.
-20 mg/day did not inhibit weight gain.
-30 or 40 mg/day had a suppressive effect on weight gain.</td><td>Strength: Control group.
Weakness (First data set): Most were in special classes for learning and behavior problems; measurements only 3 times in 9 months; 13/20 taken off medication during summer, making exposures non-uniform. (Second data set): Data obtained retrospectively from school nurse records; medication information obtained from parent or nurse reports; different medication doses for children; small number for subjects (9) and controls (7); use of percentiles.
It is difficult to draw conclusions from these data.</td><td>(131)</td></tr>
<tr><td>n = 20 (sex unspecified for methylphenidate group, however 44 of 49 in study were male)
Control: 14 unmedicated ADHD males
Age (years): 7.4
Duration: mean = 3.0 years
Dose: unspecified</td><td><table><tr><th></th><th>N</th><th colspan="2">Percentile change in growth
Weight</th><th>Height</th></tr><tr><td>All doses</td><td>20</td><td>–6.35</td><td>–5.20</td></tr><tr><td>High dose (> 20 mg/day)</td><td>10</td><td>–10.00</td><td>–9.40</td></tr><tr><td>Low dose (≤20 mg/day)</td><td>10</td><td>–2.70</td><td>–1.00</td></tr><tr><td>Control</td><td>14</td><td>+6.79</td><td>+1.29</td></tr></table>-Low-dose group did not statistically differ from controls; high-dose group exhibited suppression of both height and weight.
-Summer continuance did not significantly influence weight suppression. However, summer continuance was statistically related to an increased</td><td>Strength: Use of a control group.
Weakness: Evaluation performed once/year.
Growth was evaluated by total change in the normative percentiles for weight and height.</td><td>(132)</td></tr>
</table>

Parameters	Results and author conclusions	Comments	Reference
	percentile height loss (n = 17, $P = 0.05$), thus indicating a recovery effect.		
n = 30 (23 male) Control: 30 normal controls Age (years): 14–19 (Mean: boys 16.4, girls 17.8) Duration ≥ 6 months during childhood	<table><tr><th></th><th colspan="3">Height, mean inches (range)</th></tr><tr><th></th><th>N</th><th>Boys</th><th>Girls</th></tr><tr><td>Methylphenidate</td><td>30</td><td>69.2 (64–73)</td><td>64 (64–67)[a]</td></tr><tr><td>Control</td><td>30</td><td>68.7 (64–72)</td><td>64.2 (61–65)</td></tr></table> No statistically significant effect on height. [a]As in the original; however, the lower value of the range is unlikely to also be the mean.	Strength: Use of a control group. Weakness: Retrospective data. General comments: Low socioeconomic class; treatment duration ⩾ 6 months; little can be concluded from this study.	*(120)*
n = 32 (sex unspecified; 4:1 male:female ratio for study as a whole) Control: Anthropometric scale (historical control) Age (years):10.3 (range 8–13) Duration ≥ 3 years Dose: 27 (10–60) mg/day	<table><tr><th></th><th></th><th colspan="2">Weight (kg/month)</th><th colspan="2">Height (cm/month)</th></tr><tr><th></th><th>N</th><th>School Year</th><th>Summer</th><th>School Year</th><th>Summer</th></tr><tr><td>Continued</td><td>8</td><td>0.24 ± 0.20</td><td>0.21 ± 0.22</td><td>0.42 ± 0.12</td><td>0.48 ± 0.35</td></tr><tr><td>Discontinued</td><td>2 4</td><td>0.21 ± 0.20</td><td>0.47 ± 0.38</td><td>0.37 ± 0.21</td><td>0.60 ± 0.52</td></tr><tr><td>Expected</td><td></td><td colspan="2">0.28</td><td colspan="2">0.52</td></tr></table>mean ± SD -Growth rate differences between school year and summer in discontinued group were statistically significant, indicating rebound for both height and weight. -Increased dose correlated with increased growth suppression, but did not affect the degree of rebound.	Strength: 3-year study period Weaknesses: Measurements twice/year; measurement with a yardstick is unlikely to be sensitive to 0.01 cm, as the data are expressed; potential inclusion of puberty in age group; use of historical control. General comment: Results suggest growth rebound.	*(133)*
n = 23 (all male) Control: treatment drop out group of boys on medication ≤ 4 months (n = 12) Age (years): 8.91 ± 1.61 Duration: 12 months (continuous) Dose: 20.62 ± 8.56 mg/day [± not defined]	<table><tr><th></th><th colspan="3">Percentile Scores</th></tr><tr><th></th><th>N</th><th>Weight</th><th>Height</th></tr><tr><td>All doses</td><td>23</td><td>-8.81</td><td>+3.19</td></tr><tr><td>> 20 mg/day</td><td>5</td><td>-15.40</td><td>-3.00</td></tr><tr><td>≤ 20 mg/day</td><td>18</td><td>-6.88</td><td>+5.12</td></tr><tr><td>Treatment dropout group</td><td>12</td><td>+1.61</td><td>-1.46</td></tr></table> -Statistically significant decrease in weight but not in height. -Compared methylphenidate to imipramine and found similar results of decreased weight but not height in both treatment groups.	Weaknesses: Methylphenidate compared only to imipramine; 1-year measurements only; confusing pretreatment regimen, which included placebo period. General comment: Difficult to interpret conclusion.	*(134)*

Parameters	Results and author conclusions	Comments	Reference
n = 60 (52 male) Control: Iowa Growth Tables Age (years): 9.0 (3–13.9) Duration: 5.1 (2.0–9.7) years Dose: 34 (10–120) mg/day	Mean change in percentile[a] Time after onset / Weight / Height / Mean Dose, mg/day[b] 1 year / -5.2 ($P < .05$) / -0.1 (P = NS) / 24.4 All 60 on medication Final follow-up 30 on medication, 30 off / +11.4 ($P < .001$) / +12.8 ($P < .001$) / 43.8 [a] For all patients [b] For patients still on medication -Some weight loss in the first 3 years compared to expected norms (statistically significant only in the first year), which recovered in later years. -Both height and weight exhibited a statistically significant percentile increase at final follow-up. -Patients who had discontinued medication at final follow-up showed a "larger" (not statistically significant) weight and height rebound than those still on medication.	Strength: Longer treatment period (at least 2 years). Weaknesses: Data partly retrospective; measurements converted to percentiles for comparison. Comments: The utility of this study is in showing that height and weight deficits are compensated in long-term treatment.	*(135)*
n = 20 (17 male) Control: 6 males off medication; 23 (20 male) age-matched controls Duration: 12 months Dose: 0.60 (0.24–1.35) mg/kg bw/day	Children in study had been treated with methylphenidate for an average of 30.3 months (range 9–47); all were treated for at least 8 of the 12 months in the study. -Compared to controls, hyperactive children had slightly more lean body mass, a higher percent body fat, and larger muscle girths. -Hyperactive children increased less in lean body mass, but more of their weight gain was in body fat. -Unmedicated hyperactive children did not differ significantly from medicated children. -Methylphenidate-treated children experienced the same amount of growth as normal children, but body composition differed.	Strengths: Control group of children without ADHD; use of other measures such as body fat composition and lean body mass.	*(136)*
n = 28 (24 boys) for 1 year; 13 (11 boys) for 2 years	-At 1 year of growth, no significant difference in height, weight, lean body mass, % body fat, or body girth. -Skeletal width of medicated hyperactive children was significantly	Strengths: Age- and sex-matched controls; 12 and 24-month follow-up.	*(137)*

Parameters	Results and author conclusions	Comments	Reference
Control: 24 (21 male) unmedicated hyperactive children for 1 year, 10 (9 male) unmedicated hyperactive children for 2 years; plus age- and sex-matched normal controls Age: Group means were 9.7–10.7 years Duration: 12 or 24 months Dose: 1-year group: 24.1 mg/day (10–40); 2-year group 21.9 mg/day (12–40)	increased compared to controls; however, age was significantly different as well and accounted for the increase. -No difference between medicated and unmedicated hyperactive children. -Over a 12-month period, hyperactive children had significantly slower rate of body girth increase. -Over a 24-month period, hyperactive children added more fat weight than controls. -Methylphenidate use over 1 or 2 years did not produce growth suppression.	Weakness: Excessive variation within groups, for example, in drug duration. General comments: The differences in skeletal widths are probably not important because age differences could account for the skeletal differences. The results appear to be counterintuitive.	
n = 36 (sex unspecified) Duration: 16 months Dose: 10–20 mg/day	Letter to the editor. Full study results below in *(138)* -No significant difference in height and weight percentile distribution before and after treatment. -Annual growth was above the norm in 23 patients. -Possible growth stimulant effect in 6 patients between 5 and 8 years of age.	The conclusions may not be reliable based on the letter format and the use of percentiles for comparisons.	*(139)*
n = 36 (all male) Control: pretreatment measurements; normal children (historical control) Age (years): 5-10 Duration: 16 (6–26) months (interrupted on weekends and vacations) Dose: 10–20 mg/day	-Rates of annual growth were above normal for 23 patients, below for 13. Only 2 had a significantly decreased rate, whereas 6 patients (aged 5–8 years old) had a significantly increased growth rate. -Percentile distribution for height and weight was not significantly different from controls. -64% of patients had above normal rates of annual growth. -Concluded that relatively low doses given in divided doses are well tolerated and do not suppress growth in children with minimal brain dysfunction.	Strengths: Prospective study; included growth rates, not just percentiles. Weakness: Drug therapy was interrupted on weekends and holidays; used historical controls consisting of white North American children from 1962; used varying intervals for measurements.	*(138)*

Parameters	Results and author conclusions	Comments	Reference
n = 72 (all male) Age (years): 6–12 Duration: 1 or 2 years Mean Dose Year N mg/kg bw/day 1 72 0.47 2 48 0.59	Results for Year 1: Summer medication group (n = 31): significant height and weight deficit prior to summer; significant height increase in summer. No summer medication group (n = 41): significant weight deficit prior to summer; significant height decrease after summer. Total: Significant mean weight decrease of 0.88 kg and mean height decrease of 1.03 cm from expected. Results for Year 2: -The second year of treatment showed no significant height or weight difference from expected values. However, the 2-year cumulative weight deficit was significant. -Patients on medication for 2 years experienced a height deficit in the first year that was compensated by a height gain in the second year Conclusions: -Growth deficits decreased with length of treatment, suggesting development of tolerance. -Summer drug holidays had no significant effect on height but did have a minimally significant effect on weight. However, average daily dosage for patients treated in the summers was significantly higher throughout the year than patients who did not take summer medication (as much as twice the dose), which may also account for increased weight deficits. -The temporary height reduction of less than 1% is not clinically significant.	Strengths: Prospective study; monthly measurements; medication compliance documented by urinalysis. Weakness: Included boys who were theoretically in the pubertal age group, although it is difficult to predict the adolescent growth spurt. General comments: Used predicted height and weight velocities based on Iowa norms; the decrease in growth deficits with length of treatment could represent development of tolerance or temporary developmental deviations not related to complications of stimulant treatment.	*(140)*
n = 85 (all male) Control: 8 nondrug growth predicting factors Age (years): 9.2 at referral, 14.5 (12–18) at follow-up Duration: mean = 36 months Dose: 33.1 (5–80) mg	-Retrospective analysis. -Longer duration of treatment resulted in increased growth suppression; drug holidays decreased suppressant effects. -Findings suggested that the presence of early side effects such as nausea, vomiting, and appetite suppression a major predictor of growth deficit. Also found that maintenance dose was not a major predictor of growth suppression.	Strengths: Large sample size; controlled for parental heights and weights; controlled for nondrug growth-predicting variables; first study to use multiple regression analysis. Weaknesses: Included adolescents in pubertal age; growth measured only once, at 3 years; large range of drug doses (5–80 mg).	*(141)*

<table>
<tr><th>Parameters</th><th>Results and author conclusions</th><th>Comments</th><th>Reference</th></tr>
<tr><td>n = 26 (25 male)
Control: 8 (all male) unmedicated ADHD; 25 (24 male) normal
Age (years): 5–13
Duration: 1–3 years
Dose ≤ 0.8 mg/kg bw/day</td><td>-No significant effect on growth in the first, second, or third years of treatment.
-Data indicate no effect on growth of male children younger than 13 years of age with doses up to 0.8 mg/kg bw/day for 1 or 2 years or 0.6 mg/kg bw/day for 3 years.
-Authors note that children in the study had not yet reached the adolescent growth spurt.</td><td>Strengths: Used unmedicated ADHD group and non-ADHD group for comparison; rigorous measurements; took parental stature into account.</td><td>(142)</td></tr>
<tr><td>n = 86 (sex unspecified)
Control: National Centre for Health Statistics; pretreatment percentiles
Age (years): 8
Duration: up to 4 years with varying drug holidays
Mean Dose: 40 mg/day</td><td><table><tr><th></th><th>Treatment period, years (n)</th><th></th><th></th><th></th></tr><tr><th></th><th>< 1 (86)</th><th>1–2 (81)</th><th>2–3 (54)</th><th>3–4 (42)</th></tr><tr><td>Mean duration (range), weeks</td><td>20.7 (1–47)</td><td>59.4 (26–85)</td><td>99.1 (43–142)</td><td>130.0 (51–190)</td></tr><tr><td>Daily dose (range), mg</td><td>39.9 (10.0–58.0)</td><td>41.3 (12.4–59.4)</td><td>41.0 (22.4–59.4)</td><td>41.4 (16.2–62.6)</td></tr><tr><td>Cumulative dose (range), g</td><td>5.9 (0.2–18.5)</td><td>17.2 (5.6–34.9)</td><td>28.5 (10.5–48.0)</td><td>37.9 (9.5–68.1)</td></tr></table><table><tr><th></th><th>Treatment year</th><th></th><th></th><th></th></tr><tr><th></th><th>1</th><th>2</th><th>3</th><th>4</th></tr><tr><td>Height percentile decrement</td><td>1.4 (n = 51; P = NS)</td><td>8.1 (n = 56; P < .001)</td><td>13.4 (n = 37; P < .001)</td><td>18.1 (n = 19; P < .001)</td></tr><tr><td>Weight percentile decrement</td><td>9.7 (n = 69; P < .001)</td><td>15.9 (n = 69; P < .001)</td><td>18.6 (n = 44; P < .001)</td><td>20.8 (n = 26; P < .001)</td></tr></table>-Significant weight deficit all 4 years of treatment and significant height deficit after the first year.
-Dose and duration were significantly related to growth suppression.
-Children who were initially larger showed greater growth deficits.
-Weight suppression appeared to plateau with time.
-Onset of weight suppression occurred earlier than that of height suppression.
-Authors note that all children were pre-pubertal.</td><td>General comments: This study included a very large range of treatment durations and medication doses (daily and cumulative). The height percentile decrements are of concern, but the absolute height decrement was 3.3 cm over the 4 years of follow-up, demonstrating the limitations of using percentiles. It is important that all children were pre-pubertal.</td><td>(143)</td></tr>
</table>

Parameters	Results and author conclusions	Comments	Reference
n = 8 (all male) Control: Pre-treatment measurements Age (years): 8.5 (6–9.5) Duration: 1 year Dose: 1.3 mg/kg bw/day; 39 (10–60) mg/day	-Weight decreased 9.5 ± 3.3 percentage points ($P < 0.001$); weight velocity was 3.0 kg/year lower than expected ($P < 0.005$). -Height decreased 2.4 ± 1.5 percentage points (P = NS); height velocity 0.5 cm/year lower than expected (P = NS). -Significant suppression of both weight and weight velocity. Authors speculate that lack of significant height suppression could be due to the short half-life of methylphenidate.	Strength: Measured height velocity. Weaknesses: Small sample size (8); lack of control group. General comment: The main objective was to look at prolactin and growth hormone.	*(144)*
n = 61 (all male) Control: 99 normal males Age (years): 6–12 Duration: 2.24 years (range 6 months to 5.2 years); follow-up occurred between the ages of 16 and 23 (mean = 9 years after diagnosis) Dose: 44.9 mg/day	-Even when there was a suppressive effect on height during treatment, growth rebound after discontinuation of therapy compensated so that there was no final adverse effect on height. -Complicated by multiple pharmacologic use; 82% of children received other medications at intervals during treatment: 11% *d*-amphetamine; 25% imipramine hydrochloride; 62% thioridazine hydrochloride. However, there were no significant differences at follow-up between methylphenidate-only patients and those who had taken other drugs.	Strengths: Long-term follow-up; non-ADHD controls. Weaknesses: Children received concomitant medications; incomplete histories; controls were a full year older than probands; self-reported heights in 40% of subjects, although these heights did not differ significantly from the heights that were directly measured.	*(145)*
n = 58 (53 male) Age (years): 9.2 (6–12) Duration: Two groups on medication for 2 years; the ON group continued during the summers and the OFF group had summer drug holidays	-After the first summer, the OFF group (n = 32) weighed significantly more (0.9 kg) than the ON group (n = 26) ($P < 0.005$), but there was no significant difference in height. -After 2 summers, the OFF group (n = 14) was significantly taller (1.5 cm) than the ON group (n = 14) ($P < 0.02$), but there was no significant difference in weight. -Results suggest a reduction in growth velocity while on methylphenidate. However study did not address long term effects of treatment.	Weaknesses: Treatment received before study began; summer period not defined; used absolute height and weight measurements.	*(146)*
n = 29 (sex unspecified) Control: 30 random unmedicated healthy Age (years): 7.8 ± 2.4 Duration: mean = 14 months	-Significant height and weight deficits compared with controls. -Children with higher initial weight percentiles experienced greater weight loss. -Authors analyzed differences between methylphenidate- and desipramine-treated children and found growth suppression less pronounced with desipramine.	Strength: Control group of unmedicated healthy children; used various assessments of growth (simple growth deficits, percent deficits, frequency percentiles, growth velocity).	*(147)*

Parameters	Results and author conclusions	Comments	Reference
Dose: 31.4 ± 17.6 mg/day (1.0 ± 0.5 mg/kg bw/day) [±SD]		General comment: Primary focus was desipramine, although one group received methylphenidate.	
n = 23 (all male) Control: 23 unmedicated ADHD males Age (years): 9.0 (7–12) Duration: 21 months Dose: 23 mg/day (0.55 mg/kg bw/day)	-No statistically significant effect on weight, height, heart rate, diastolic or systolic blood pressure. -No significant weight deficit at high doses at the end of treatment period (mean 2.2 kg difference). -Authors note that the relationship between dose and decreased weight could become clinically significant if treatment with high doses is extended past 2 years.	Strengths: Untreated ADHD controls; treatment duration of almost 2 years. Comments: In the multiple regression analysis, baseline weight and height explained 88% of the variance in final weight and height.	*(148)*
n = 32 (29 male) Age (years): 7.5 (3.6–15.5) Duration ≥ 5 months; mean duration of follow-up = 11.2 months Dose: 25.5 mg/day (1.0 mg/kg bw/day)	-All height and weight measurements are represented as *z* scores. -Initial weight 0.7; initial height 0.6. -Weight change at follow-up –0.4. -Height change at follow-up –0.1. -Children were divided into 2 groups to analyze effects of pre-treatment weight; 75% of the heavy group (n = 16) experienced decreased BMI from expected compared to 50% of the thinner group (n = 16). BMI slope analysis showed significant difference in growth deficit between heavy and thin groups. -Major predictor of decreased BMI was pre-treatment weight. No significant effect of dose, duration of follow-up, or age on degree of weight loss. -Retrospective study; did not account for drug holidays.	Strengths: No prior drug treatment; used weight-for-height curves (BMI). Weaknesses: Retrospective study; data on weekend treatment only partially available; BMI curves were from a Caucasian sample and not generalizable to non-white children.	*(149)*
n = 124 (all male) Control: 109 normal male controls Age (years): 14.5 (6-17) Dose: methylphenidate equivalent dose (twice the *d*-amphetamine and half the pemoline dose) = 38	-Of the 124 ADHD children, 110 were medicated at some time in their lives with either methylphenidate, *d*-amphetamine, or pemoline. At the time of the study, 53 had been treated in the preceding 2 years with a mean methylphenidate equivalent dose of 38 mg/day. -ADHD children were 4 kg lighter and 3 cm shorter than controls; neither difference was statistically significant. There was a statistically significant height deficit ($P = 0.03$) when height was converted to a *z* score. Significantly more ADHD children were at least 2 standard	Strengths: Normal controls; used *z* scores; corrected for parental heights; performed pubertal assessments. Weaknesses: Measurements only at 4-year follow-up; missing data.	*(150)*

Parameters	Results and author conclusions	Comments	Reference
(5–120) mg/day	deviations shorter than the mean ($P = 0.02$) when corrected for age and parental heights. -No significant difference was found for height or weight between unmedicated and stimulant-treated children with ADHD. -Modest height deficits were unrelated to weight deficits or stimulant treatment, and only evident in ADHD children in early adolescence. This result indicates that ADHD children may experience delayed growth, rather than permanent stunting of growth. -No evidence of weight suppression or delayed pubertal development. -No association between height and drug treatment, drug class, duration of treatment, or dose regimen was identified.		
n = 301 (260 male) Control: Non-ADHD controls with idiopathic growth hormone deficiency or idiopathic short stature (n = 3596, 2656 male) Age (years): 3–20 Duration: ~3 ± 2 (SD) years on growth hormone therapy (stimulant treatment duration unspecified) Dose: Not specified	-Children with either idiopathic growth hormone deficiency (IGHD) or idiopathic short stature (ISS) on methylphenidate or pemoline for ADHD (results not separated by medication). -All children on growth hormone therapy and below fifth percentile for height at start of treatment. -No effect of stimulant medication on growth of children treated with growth hormone for ISS. -Small negative effect of stimulant medication on growth of children treated with growth hormone for IGHD.	Weakness: Stimulant treatment duration not specified. General comment: Caution is needed in interpreting negative results, but follow-up is indicated and study results are interesting.	*(151)*
n = 9 (all male) Control: 9 normal males Age (years): 3–10 Duration: 1–2 years; mean 13 ± 4 months **[error not specified]** Dose: 10.0 (7.5–12.5) mg/day; 0.5 mg/kg bw/day	-No child changed height percentile during treatment. -No significant differences in bone mineral density, serum bone-specific alkaline phosphatase, or urinary deoxypyridinoline. -No effect of methylphenidate on bone mineral density turnover in children treated for 1–2 years.	Weaknesses: Sample size too small to anticipate seeing a difference in these bone parameters. A cohort of vulnerable children might have been preferable.	*(152)*

Parameters	Results and author conclusions	Comments	Reference
Review of height and weight studies	-Eight of 11 studies reviewing weight reported significant decreases in expected versus actual weight gain of children treated with methylphenidate. Four of 10 studies found height reductions; however, in 2 of these studies there was a subsequent significant height rebound. -Studies suggest that there is an association between methylphenidate treatment and decreased weight gain in some children, and this effect may be dose-dependant. Effects appear to be transient and are diminished by drug holidays, dosage adjustment, and parent education of administration timing. -Height effects appear dose-related and are diminished in some children by summer drug holidays. However, height decreases are not significant in follow-up studies after 4 years.	General comment: The studies reviewed are included in this table.	*(153)*
n = 23 (all male) Control: Norwegian population sample Age (years): 3–13 Duration: 1–5 years Dose: Range 7.5–70.0 mg/day Year N Dose (mg/day) 0–1 23 23.9 1–2 22 27.4 2–3 17 30.8 3–4 11 33.3 4–5 9 27.8	-Compared 23 boys on methylphenidate to 68 boys on a racemic mixture of *l*- and *d*-amphetamine. -No statistically significant difference between methylphenidate and amphetamine-treated children in height or weight except for a lower weight gain in amphetamine-treated children during the first year ($P < 0.05$). -Twenty-one boys (31%) on amphetamine and 4 (17%) on methylphenidate either lost or did not gain weight during the first year; weight loss ranged from 0 to 9.5 kg. There was no significant dose difference between those who lost weight in the first year and those who did not. All boys who had lost weight in the first year experienced subsequent sufficient weight gains. -Children above the 50th percentile in weight prior to treatment had significantly increased weight loss compared to those below the 50th percentile ($P < 0.05$), suggesting a slimming effect. -No effect on height was observed. -No effect of cumulative dose or age was observed. -Concluded that methylphenidate and amphetamine do not have adverse growth effects for most children. -Retrospective study; some missing data; broad age range; measurement reliability uncertainty.	Strengths: Large number of subjects followed for an extended time period; results and conclusions are consistent with previous studies. Weaknesses: Large age range of subjects; inclusion of pubertal subjects; once-yearly height and weight data, collected retrospectively; included developmentally delayed children without reference to whether they had a growth-retarding syndrome. General comments: Standard Norwegian population sample comparison. Multiple regression showed that neither cumulative dose nor age had a significant effect on growth when initial weight and height were controlled.	*(154)*

Parameters	Results and author conclusions	Comments	Reference
n = 84 (68 male) Control: 87 (71 male) normal healthy siblings Age (years): 8.7 (5–17) Duration ≥ 2 years Dose: 18.0 (10–45) mg/day for girls; 22.5 (5–85) mg/day for boys	-Height velocity decreased compared to age-matched sibling controls. After 1 year of treatment, 60% had a change in SD scores **[probably a *z*-score]** <0. After 3 years, 90% of girls and 76% of boys had SD score change <0. -After 3 years, heights were 3–4 cm less than age- or time-matched sibling controls (0.5 SD for boys and 0.6 SD for girls). -Growth rates declined at both high and low doses. In boys, the change in growth velocity was inversely proportional to dose. In girls, growth rates decreased at all doses but no dose correlation was observed (possibly due to a smaller dose variance). -ADHD children's growth rates prior to methylphenidate treatment were not statistically different from non-ADHD siblings, indicating that the growth deficit was due to medication rather than problems intrinsic to ADHD. -Retrospective study; limited dose variance in girls; no long term follow-up.	Strengths: Height and weight obtained every 3–6 months; evaluated height velocities and *z*-scores. Weaknesses: Retrospective study; no untreated ADHD controls. General comments: Community-based study in pediatricians' offices; sibling controls (to control for genetic influence) do not appear to have added anything.	*(155)*
n = 51 (44 male) Control: National Centre for Health Statistics Age (years): 7.2 (3.1–11.4) Duration: 6–32 months Dose: 1.0 ± 0.24 mg/kg bw/day; 27.5 (10–40) mg/day	-After 6 months, weight was 1.7 kg less than expected; 76% lost weight. After 30 months there was a 3.0-kg deficit. -During the first 2 years, the height deficit was approximately 1 cm/year; the average height deficit after 42 months was 2.4 cm. -In the first 6 months, 86% had a decreased height velocity. However, after 30 months, the deficit attenuated and most children had normal height velocity. -Thirty-one percent experienced weight deficit even without reported appetite suppression. -Average weight deficit was 2.4 times the height deficit after 30 months. -Significant decrease in height and weight after 6 and 18 months ($P < 0.001$) and after 30 months ($P < 0.01$). -Retrospective study; results do not separate methylphenidate (n = 19) from dexamphetamine (n = 32) treatment; 10 patients were also on clonidine; did not account for drug holidays.	Strengths: Rigorous measurements, obtained every 6 months; height, weight, and height velocity corrected for age and sex using SD scores. Weaknesses: Retrospective study; no control group; no long-term follow-up. General comments: Height velocity was lowest during the first 6 months, but in most cases normalized after 3 years; results consistent with other findings.	*(156)*

The Multimodal Treatment Study of ADHD (MTA) *(157)*, was organized in 1992 by the National Institute of Mental Health and the Department of Education. This study compared 4 different treatment strategies for ADHD in children aged 7–9.9 years. Assignment was random but not blinded. The treatment strategies were an intensive medication strategy, a behavioral therapy, a combination of medication and behavioral therapy, and community care. The medication-including arms initially used methylphenidate, although other medications could be used if methylphenidate failed to be effective. Nearly all of the children assigned to the medication arm and the combined arm were on methylphenidate for the 14 months of the study *(157)*. Children in the behavioral group were not prescribed medication. Children assigned to community care were managed by their own health care providers without study-imposed restrictions. Two-thirds of these children were prescribed stimulant medication and 87% of the stimulant prescriptions in this group were for methylphenidate. **[The Expert Panel notes the opportunity for confusion in the authors' names for their groups. Children in three groups could have received medication (the medication group, the behavioral therapy group, and the community care group), yet the authors use the term medication group to refer to a specific "carefully-crafted" regimen developed by algorithm and involving 3-times/day dosing.]**

Following 14 months of treatment in their randomly assigned groups, children were followed for an additional 10 months without study-prescribed interventions. Subjects and their parents were free to choose any therapy available in their communities. Assessment 24 months after randomization included changes in height and weight from baseline and from the 14-month time point *(158)*. Analysis of height and weight change from 0 to 14 months was by intention-to-treat. Analysis from baseline to 24 months and from 14 to 24 months was by medication exposure status, based on whether any medication was reported to have been used in the interval, regardless of group assignment. There were 4 medication status groups, reflecting medication exposure during months 0–14 and months 14–24: Med-Med, No Med-No Med, Med-No Med, and No Med-Med.

During months 0–14, children assigned to received medication (either the medication group or the combined therapy group) had smaller increases in height and weight than children assigned to behavioral therapy or to community care. The reported values are given in Table 29. The authors observed that the contrast between the medication group and the behavior group may have been the most meaningful because children in the medication group were most likely to have received intensive therapy with stimulants and children in the behavioral therapy were likely to have not been exposed to stimulants during the course of the treatment period. The changes in height and weight for the treatment period (months 0–14) and the post-treatment period (months 14–24) are shown in Table 30, organized by self-identified exposure to medication. **[The Expert Panel notes that some children assigned to the medication treatment group did not receive medication, and some children assigned to the behavioral therapy group did receive medication.]** There appeared to be an association between self-reported exposure to medication and a decrease in height increase and weight gain. The authors indicated that self-selection regarding medication status may have influenced growth outcomes, particularly because the Med-Med group started the study shorter (by 1.69 cm) and lighter (by 0.96 kg) than the No Med-No Med group. Over time, these differences by medication exposure status became larger**.** Age and sex of the child was not significantly related to the growth effects of stimulant exposure.

Table 29. Height and Weight Change in Children in the Multimodal Treatment Study During the 14-Month Treatment Phase

Treatment group (n)	Height increase (cm)	Weight increase (kg)
Medication (120)	4.25	1.64
Behavioral therapy (135)	6.19	4.53
Combined (135)	4.85	2.52
Community care (131)	5.68	3.13

[Numbers are assumed to represent means. SD and SEM not given; statistical analysis not provided.] Data from *(158)*.

Table 30. Height and Weight Change in Children in the Multimodal Treatment Study According to Self-Identified Medication Exposure

Exposure group (n), expressed as months 0–14/ months 14–24	Height increase (cm), mean ± SD		Weight increase (kg), mean ± SD	
	months 0–14	months 14–24	months 0–14	months 14–24
Med-Med (222)	5.88±1.80[ac]	4.53±1.61[a]	2.36±3.00[a]	3.81±2.84[a]
No Med-No Med (106)	6.93±2.21[b]	5.40±2.18[b]	5.14±3.53[b]	4.83±3.10[b]
Med-No Med (63)	5.94±1.84[cd]	4.94±2.06[ab]	3.54±3.84[c]	4.73±3.42[ab]
No Med-Med (42)	6.64±1.49[bd]	4.79±1.62[ab]	4.21±3.43[bc]	3.37±2.87[a]

Within columns, groups with different superscripts are different by ANOVA with post hoc Newman-Keuls Multiple Comparison Test [performed by CERHR]. Data from *(158)*.

Strengths/Weaknesses: Strengths include the large sample size, the well-defined pre-pubertal age group, the use of z-scores as a secondary analysis, and consideration of the issue of regression towards the mean. Weaknesses included the lack of blinding; lack of true randomization (choice to switch off medication may have reflected family concern about growth); failure to consider mid-parental height, bone age, or normal seasonality of growth; the use of other medications if methylphenidate failed; the lack of a standard protocol in the community group of children who could get other medication; the failure of some children in the medication group to receive medication; and the pre-study shorter and lighter status of children in the Med-Med group.

Utility (Adequacy) for CERHR Evaluation Process: This study is of moderate utility in the evaluation of height and weight effects and should be considered along with the other studies in Table 28.

Overall Assessment of Height and Weight Data: While the observations in this area are consistent with most clinical experience, the quality of data in the older papers is suboptimal. These articles have variable but generally marginal-to-moderate utility with incomplete documentation of compliance or actual dosing regimens and with failure to consider (in most cases) basic factors that are usually assessed in growth studies, such as mid-parent height and parent BMI; family history of timing of puberty onset; the child's actual physical or

endocrinologic level of puberty at start of treatment (some of the youngsters were as old as 15 when the studies were conducted); and measurement of skeletal maturity (bone age), which particularly in school-aged children is considered a useful indication of expected growth potential. The seasonal differences in expected growth (in the northern hemisphere, children grow faster in summer) are not accounted for by designs that compare children whose families chose to leave them on stimulants through the summer and children whose families did not leave them on medication during the summer. Thus, it cannot be ruled out that those who remained on the medicines also had other conditions or behavioral patterns that motivated their parents to continue the medication and might also (like fetal alcohol effects) decrease growth.

In addition, assessments of growth do not appear to be masked to stimulant exposure history. For example, in the reports of Safer et al. *(131-133*), the nurse who obtained the measurements was not masked to the children's drug histories and in fact in many cases actually administered the drugs herself. The studies did not control for potential confounders such as intrauterine exposure to tobacco, ethanol, and illicit drugs, or parental mental health.

Findings overall seem to suggest that appetite and growth suppression are less with methylphenidate than with amphetamines, but these findings are not conclusive. There are interesting and clinically relevant issues of mechanism that have not been fully elucidated. It is unclear whether the growth alterations that are noted are primarily related to appetite suppression (as might be expected given the widespread use of amphetamines by dieters) or by endocrine alterations as well. If the issue is only appetite suppression, it is possible to test a number of useful clinical interventions, such as feeding the child a high-calorie supplement before the first daily dose and monitoring whether this intervention alters the patterns of growth. The possible role of stimulant-associated endocrine changes cannot be addressed with the current data set because the endocrinologic data are outdated and use comparison drugs that increase the release of prolactin, creating a possible artifact of lower hormone levels with stimulants.

3.2 Experimental Animal Data

3.2.1 Prenatal toxicity endpoints

Teo et al. *(46)*, from Celgene Corporation, performed a developmental toxicity study in Sprague-Dawley rats and New Zealand White rabbits using *d*-methylphenidate (98–102% purity) and *d,l*-methylphenidate (chiral purity 50:50). Treatment was by gavage twice/day with equal doses 6 hours apart. A range-finding study in rats appeared identical to the range-finding study reported in Teo et al. *(47*), discussed in Section 3.2.2. The range-finding study in rabbits used 5 pregnant animals/group given *d*-methylphenidate at 0, 4, 50, or 300 mg/kg bw/day or *d,l*-methylphenidate at 8, 100, or 600 mg/kg bw/day **[days of treatment not specified, but GD 6–18 in the main study]**. Cesarean sections were performed on GD 29. Clinical signs, body weight losses, and maternal deaths occurred in the groups given 300 mg/kg bw/day *d*-methylphenidate and 600 mg/kg bw/day *d,l*-methylphenidate. Absolute and relative feed consumption were decreased in these dose groups and in the group given 50 mg/kg bw/day *d*-methylphenidate. There were no resorbed conceptuses or dead fetuses. Decreased fetal body weight occurred in pregnancies exposed to *d,l*-methylphenidate 600 mg/kg bw/day and a single fetus in the *d*-methylphenidate 300 mg/kg bw/day group had external malformations (missing digits). **[There was insufficient detail in the reporting of the dose range-finding study to evaluate other outcome parameters or to determine LOAEL, NOAEL, or benchmark dose.]**

In the main rat study, 25 pregnant animals/group were treated with 2 equal daily gavage doses 6 hours apart of *d*-methylphenidate or *d,l*-methylphenidate on GD 7–17 **(**plug day = GD 0**)**. Total doses were 0, 2, 6, or 20 mg/kg bw/day *d*-methylphenidate or 40 mg/kg bw/day *d,l*-

methylphenidate. Dams were killed on GD 20 and all fetuses were given external examinations. Half the litters were microdissected for soft tissue examinations and half were prepared for skeletal evaluation. Data were analyzed using ANOVA with post hoc Dunnett test or Kruskal-Wallis with Dunnett test, depending on homogeneity of variance. Clinical signs occurred in the 6 and 20 mg/kg bw/day *d*-methylphenidate groups and in the 40 mg/kg bw/day *d,l*-methylphenidate group. Some of these signs occurred more often in the 40 mg/kg bw/day *d,l*-methylphenidate group than in the 20 mg/kg bw/day *d*-methylphenidate group in spite of the 2 groups being treated with identical amounts of the active enantiomer (*d*-methylphenidate). Absolute and relative feed consumption and body weight gain during the dosing period were decreased in the 6 and 20 mg/kg bw/day *d*-methylphenidate groups and in the 40 mg/kg bw/day *d,l*-methylphenidate group. There were no treatment-related changes in corpora lutea or implantations per dam or in litter values for live or dead fetuses, resorptions, sex ratio, fetal body weight, or fetal alterations. A decrease in fetal weight in the 2 mg/kg bw/day group was discounted by the study authors because it did not appear in the higher-dose groups. When analyzed on a per fetus basis, there was an increase in total fetal alterations in the 6 and 20 mg/kg bw/day *d*-methylphenidate groups. The authors state that the incidence of fetal alterations was within the historical control range. No separate delineation of malformations appeared in the paper. **[Benchmark dose[1] modeling by CERHR using the *d*-methylphenidate data gave BMD_{10} values for the various ossification delay endpoints in the 31–36 mg/kg bw/day range and BMDL values in the 23–24 mg/kg bw/day range. The Expert Panel notes, however, that this analysis was based on per fetus data and that there were no treatment-related alterations in litter parameters.]** The authors concluded that the decreases in maternal feed intake and weight gain were likely due to the anorectic effect of methylphenidate and that there were no developmental effects at *d*-methylphenidate doses up to 20 mg/kg bw/day, 40 times the human dose. The authors calculated, based on pharmacologic data (discussed in Section 2), that this dose was 5.6 times the human exposure (AUC basis). Similarly, *d,l*-methylphenidate was tested at 11.7 times the AUC obtained with the maximum therapeutic doses in humans.

In the main rabbit study, 20 pregnant animals/group were treated with *d*-methylphenidate or *d,l*-methylphenidate using 2 equal gavage doses 6 hours apart. Total daily doses were 0, 4, 20, or 100 mg/kg bw/day *d*-methylphenidate or 200 mg/kg bw/day *d,l*-methylphenidate. Treatment was given from GD 6–18. Does were killed on GD 29 and fetuses removed by cesarean section. All fetuses were examined externally, microdissected to evaluate soft tissues, and evaluated for skeletal malformations. Statistical analysis was similar to that used in the rat study. There were clinical signs in does in the *d*-methylphenidate 100 mg/kg bw/day group and the *d,l*-methylphenidate 200 mg/kg bw/day group. There was a higher incidence of clinical signs in the 200 mg/kg bw/day *d,l*-methylphenidate group than in the 100 mg/kg bw/day *d*-methylphenidate group in spite of the 2 groups being treated with identical amounts of the active enantiomer (*d*-methylphenidate). The authors state there were no adverse effects of any treatment on mean number of corpora lutea, implantations, live or dead fetuses/litter, placental morphology, resorptions, sex ratio, fetal body weights, or fetal alterations; the data table shows a decrease in fetal alterations in the 200 mg/kg bw/day *d,l*-methylphenidate group. The authors concluded that there were no reproductive effects of *d*-methylphenidate in rabbits at maternal doses up to 100

[1] The BMD_{10} is the benchmark dose associated with a 10% effect, estimated from a curve fit to the experimental data. The BMDL represents the dose associated with the lower 95% confidence interval around this estimate. Benchmark doses are used commonly in a regulatory setting; however, they are used in this report when the underlying data permit their calculation, and are only supplied to provide one kind of description of the dose-response relationship in the underlying study. Calculation of a benchmark dose in this report does not mean that regulation based on the underlying data is recommended, or even that the underlying data are suitable for regulatory decision-making.

mg/kg bw/day, which is 200 times the human dose. The authors calculated based on pharmacologic data (discussed in Section 2) that this dose was 1.7 times the human exposure (AUC basis). Similarly, *d,l*-methylphenidate was tested at 3.79 times the AUC obtained with the maximum therapeutic doses in humans.

Strengths/Weaknesses: These are standard developmental toxicity studies in CD rats and New Zealand White rabbits conducted for product safety assessment. The studies appear to have been conducted according to standard Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) GLP guidelines. A strength is standardized experimental parameters that produce data sets comparable to other agents. These studies used oral gavage dosing twice/day with doses 6 hours apart, a dosing scenario consistent with therapeutic exposures. The studies have sufficient group sizes, appropriate controls, and appropriate statistical analyses. The investigators controlled for litter effects. Chemical purity and stability were verified. The developmental toxicity studies included external, visceral, and skeletal examinations of term fetuses. A weakness of this study is lack of hypothesis testing related to the specific agents under study. It is not clear why the authors chose to present gestational body weight data as opposed to body weight gain data. Gestational body weights were not affected at any dose of *d*-methylphenidate, but gestational body weight gains were significantly decreased in the 6 and 20 mg/kg bw/day *d*-methylphenidate groups over the entire dosing period (GD 7–18). There appears to be an error in Table 3 of the study. "Dams with viable fetuses" is listed as 100% in the *d,l*-methylphenidate group, although the authors list 22 of 23 litters here. Aside from clinical observations, there were no other signs of maternal toxicity seen in the rabbit developmental toxicity study. The authors selected the *d*-methylphenidate high-dose (100 mg/kg bw/day) based on a probe study that found no effects at 50 mg/kg bw/day and excessive toxicity at 300 mg/kg bw/day. Higher doses in the rabbit study could have increased the exposure margin between the rabbit study and maximum therapeutic human dose AUC, which is currently 1.7.

Utility (Adequacy) for CERHR Evaluation Process: The studies are adequate for the CERHR process. Gavage dosing is comparable to human oral dosing. The comparison to human doses based on AUC is valuable.

3.2.2 Postnatal development and behavior

Pizzi et al. ***(159)***, support not indicated, evaluated growth in hooded rat pups **[strain not otherwise indicated]** after treatment with methylphenidate 35 mg/kg bw sc twice/day on PND 5–24. Control littermates received injections of saline. Litters were standardized on PND 1 to 8 pups with a preference for males. In the first experiment, 12 males from each treatment group were killed on PND 25. Body weight and length, femur length, and weights of thyroid, pituitary, testes, adrenals, and brain were significantly reduced in the group that had been treated with methylphenidate. Body weight in the methylphenidate-treated animals was 78% that of the controls, and organ weights in the methylphenidate-treated animals ranged from 59 to 93% of corresponding control organ weights. At least 16 control animals and at least 14 animals from the methylphenidate group were killed or died between PND 458 and 537 **[the text does not say exactly how many animals were involved and implies that a different number contributed data to each of the measurements]**. Body weight, femur length, and organ weights did not differ between the two groups of adults. In a second experiment, treatments were the same as in the first experiment. Animals (14–16/group) were killed at 25 or 35 days of age, and body weight, femur length, and weights of brain and pituitary were measured. The 25-day-old animals had similar degrees of methylphenidate-associated growth impairment as in the first experiment. At 35 days, there were no differences between the groups. The authors concluded that catch-up growth after high-dose methylphenidate treatment in juvenile animals is rapid and complete.

Pizzi et al. *(160)* further examined the effects of methylphenidate on growth of hooded rats **[strain not otherwise indicated]** in a series of studies funded by a grant from the Northeastern Illinois University Committee on Organized Research. The first study attempted to replicate the findings of the Pizzi et al. *(159)* study addressed above. Female rats were sc injected with saline or 35 mg/kg bw/day methylphenidate (half the dose of the previous study) on PND 5–24 and evaluated for growth on PND 25 and 55 (n = 12–15/group/time period). As was noted in the previous study in male rats, methylphenidate treatment significantly reduced body weight, femur length, and pituitary weight in PND 25-females. In contrast to the findings in male rats, brain weight was not affected. In methylphenidate-treated animals, body weight was 90.5% and femur length was 95% of control values. A rebound in growth occurred following treatment, as no significant differences in femur length or body, pituitary, or brain weight were observed in PND 55-females. In the second experiment, neonatal male rats received saline or methylphenidate 100 mg/kg bw twice daily sc for 10 days beginning on PND 5. Dosing was stopped at that time due to a 67% mortality rate in treated animals. During evaluation at PND 529–537 (n = 14–16/group), it was found that methylphenidate had no effect on femur length or weights of thyroid, pituitary, testes, adrenals, or brain. In the third experiment, peri-adolescent males and females were sc injected on PND 35–54 with methylphenidate 35 mg/kg bw/day, a dose that induced stereotypy. Twelve animals/sex/group were evaluated on PND 55. Body weight was said to be reduced in males **[90% of control values]** but not females. Methylphenidate treatment did not significantly affect femur length or weights of pituitary, cerebrum, or cerebellum in either sex on PND 55, demonstrating a growth rebound in males. Body weights were again measured in 12–17 animals/sex/group on PND 85 and found to not be affected by methylphenidate treatment. The study authors concluded that reversible growth impairment occurs with methylphenidate treatment of neonatal rats, but that no growth impairment occurs with treatment of peri-adolescent rats. **[Reduced body weight in peri-adolescent males is not considered in the conclusion made about growth in peri-adolescents. However, the Expert Panel notes that linear growth is a better index of growth than BMI.]**

Strengths/Weaknesses: Strengths included examination of the appropriate developmental period for childhood therapeutic use and availability of multiple measures of growth. The group sizes are adequate, although the numbers of animals used for some measures is unclear. Weaknesses included no identification of enantiomer and no reporting of feed intake or maturational indices. In addition, simple organ weights were used as endpoints. The lack of dose-response information is a weakness.

Utility (Adequacy) for CERHR Evaluation Process: The studies can be used for understanding potential growth effects of childhood therapeutic use. The lack of dose-response data together with growth retardation and some lethality limits the utility of these studies, although the work generally supports the idea that there is recovery later in life from early-life effects of treatment.

Greeley and Kizer *(161)*, in a series of six experiments supported by the NIMH, examined the effects of methylphenidate HCL **[chirality not specified but assumed to be *d,l*-]** on growth and endocrine function in developing Sprague-Dawley rats. Detailed descriptions of the protocols and results for each experiment are summarized in Table 31, while major findings and author conclusions are discussed in this paragraph. Repeated dosing with high levels of methylphenidate (≥35 mg/kg bw twice daily) was found to inhibit body weight gain and skeletal growth in neonatal (5–7-day-old) and weanling (18–21-day-old) rats, but the effect did not persist 12 months after treatment ended. Data obtained in pair-fed weanling control rats suggested that the inhibition in growth was due to decreased feed consumption at 35 mg/kg bw, whereas this explanation did not entirely account for decreased naso-anal length seen at 100 mg/kg. The study authors concluded that inhibition of growth was not likely related to effects on growth hormone

since repeated dosing with methylphenidate reduced growth hormone levels only in female rats **[not dose-related]**, whereas inhibited growth was observed in both sexes. The acute dosing data demonstrating reductions in growth hormone levels in males were discounted by study authors because they did not reflect temporal fluctuations. Repeated dosing with ≥35 mg/kg bw methylphenidate twice daily resulted in reduced basal serum insulin levels, enhanced response to a glucose load 20 minutes following challenge, and then return to baseline insulin levels, which remained lower than control levels. Serum prolactin levels were consistently decreased in males and females treated with ≥3 mg/kg bw twice daily **[no dose-response relationship was evident]**. Twice daily treatment of neonates with ≥ 35 mg/kg bw delayed vaginal opening **[body weights not shown for females]** and reduced the number of estrous cycles following treatment. Mean ± SEM day of vaginal opening (38.2 ± 2.3) was similar when methylphenidate treatment was started at 21 days of age as when methylphenidate was started at 5–7 days of age, but there was no longer a significant difference from the control value and the numbers of estrous cycles were reduced only during treatment. Because effects on gonadotropin levels were inconsistent, the study authors concluded that they were not likely related to effects on puberty and estrous cycling. Estrous cycle effects are also discussed in Section 4.2.

Strengths/Weaknesses: Strengths include use of multiple doses and appropriate age dosing for comparison with human childhood therapeutic use. The study provides data on estrous cycling in addition to vaginal patency. The availability of extensive dose-response data is a strength. A weakness is that body weights were not reported at vaginal opening. Because variability indices were not reported, it is not clear if the study had sufficient power to detect hormone changes. Some group sizes were small (5 or 6) or not specified, and it is not known whether sample sizes represent multiple samples per litter, which can inflate the Type I error rate. It is difficult to discern whether methylphenidate has direct effects on vaginal opening and hormone levels or if effects are secondary to delayed development and altered growth rates.

Utility (Adequacy) for CERHR Evaluation Process: The study is useful for assessing whether delayed puberty occurs, although it cannot be used to determine whether effects are direct or secondary to growth retardation. The use of the extensive hormone data is hampered by a lack of dose-related effects. Confidence in the data is reduced due to small sample sizes and the inability to link sample sizes to number of litters.

Table 31. Postnatal Methylphenidate Treatment Studies in Rats

Methylphenidate administration	Parameters examined	Results
0, 1, 3, 10, 35, or 100 mg/kg bw, sc, twice daily for 21 days in 5–7-day-old males and females (n not specified). Blood was collected for serum hormone measurements 24 hours following the last treatment (n = 5–16).	Body weight during treatment **[data only shown for males]**	↓ at ≥35 mg/kg bw
	Body weight 1 year after treatment	↔ **[Data not shown]**
	Naso-anal length during treatment **[data only shown for males]**	↓ at ≥35 mg/kg bw
	Naso-anal length 1 year after treatment	↔ **[Data not shown]**
	LH	↓ at ≥1 mg/kg bw (M) and at 3 and 10 mg/kg bw (F)
	FSH	↓ at ≥10 mg/kg bw (M)
	Prolactin	↓ at ≥3 mg/kg bw (M and F)
	Growth hormone	↑ at 1 mg/kg bw (F) and ↓ at 3, 10, and 100 mg/kg bw (F)
0, 0 (pair-fed), 35, or 100 mg/kg bw, sc, twice daily for 18 days in 18–21-day-old males (n not specified).	Body weight during treatment	↓ at ≥35 mg/kg bw similar to pair-fed controls
	Naso-anal length during treatment	↓ at ≥35 mg/kg bw similar to pair-fed controls ↓ at 100 mg/kg bw compared to both controls
0, 35, or 100 mg/kg bw, sc twice daily for 21 days in 5–7-day-old females (n = 5–11/group).	Age at vaginal patency	↑ by 3.6 days at 35 mg/kg bw and 4.7 days at 100 mg/kg bw
	Number of estrous cycles per 30 days after treatment ended	↓ by 2 cycles at 35 mg/kg bw and 4.4 cycles at 100 mg/kg bw
0 or 35 mg/kg bw, sc, twice daily for 30 days in 21–23-day-old females (n = 9/group).	Age at vaginal patency	↔ **[Although the mean day of vaginal opening was similar to the value obtained with treatment initiation at 5–7 days.]**
	Number of estrous cycles during treatment	↓ by 3.1 cycles
	Number of estrous cycles after treatment ended	↔
0, 1, 3, 10, 35, or 100 mg/kg bw, sc, twice daily for 21 days to 5–7 day-old males. LH-RH (20 ng) challenge given by iv 24 hours later and blood collected for serum LH measurement (n = 6/group).	LH	↑ at 100 mg/kg bw
Single dose of 0, 35, or 100 mg/kg bw, ip, to 25–27-day-old males. Blood collected for serum hormone measurements over period of 10 minutes to 7 days (n not specified).	LH	↓ at 35 mg/kg bw (10 min) and 100 m/kg bw (10 min and 1 hr)
	FSH	↓ at ≥35 mg/kg bw (10 min)
	Growth hormone	↓ at ≥35 mg/kg bw (most time points) but ↑ at 16–18 hours
0, 1, 3, 35, and 100 mg/kg bw, sc, twice daily for 21 days to 5–7-day old rats of unspecified sex. Rats fasted for 24 hours after last treatment, and were killed before (0 min.) or after (10–60 minutes) receiving an ip glucose load, for measurement of serum insulin (n = 5–12/group/time period).	Insulin	↓ at ≥35 mg/kg bw (before and 10 and 60 minutes after glucose load) ↑ at 3 and 100 mg/kg bw (20 minutes after glucose load)

↑ = statistically significant increase, ↓ = statistically significant decrease, ↔ = no effect, M = males, F = females. From Greeley and Kizer *(161)*.

Teo et al. *(47)*, from Celgene Corporation, treated pregnant Sprague-Dawley rats with *d*-methylphenidate (purity 98–102%) or *d,l*-methylphenidate (chiral purity 50:50) given orally in 2 daily doses 6 hours apart. **[The route (oral) is indicated only in the Discussion section; another paper by these authors *(46)* used gavage treatment and the Expert Panel assumes gavage treatment for this study as well.]** In a dose range-finding study, doses of *d*-methylphenidate were 2, 20, and 100 mg/kg bw/day and doses of *d,l*-methylphenidate were 4, 40, and 200 mg/kg bw/day. A control group was treated with the sterile water vehicle. There were 8 rats in each dose group, half of which were treated on GD 7–17 (plug = GD 0) and scheduled for cesarean section on GD 20 and half of which were treated on GD 7–PND 6, permitted to litter, and followed during the lactation period. The highest two doses of each methylphenidate preparation produced clinical signs of toxicity in the dams that continued into the lactation period. There were reductions in body weight gain in all groups except the control and the 2 mg/kg bw/day *d*-methylphenidate groups. Adverse affects on pup body weight were identified at 100 mg/kg bw/day *d*-methylphenidate in the litters delivered by cesarean section, and at 100 mg/kg bw/day *d*-methylphenidate and 40 mg/kg bw/day *d,l*-methylphenidate in the litters delivered naturally. **[There was insufficient detail in the reporting of the dose range-finding study to evaluate other outcome parameters or to determine LOAEL, NOAEL, or benchmark dose.]**

In the main study, 25 pregnant rats/dose group were given *d*-methylphenidate at 0, 2, 6, or 20 mg/kg bw/day or *d,l*-methylphenidate 40 mg/kg bw/day. Animals were given these doses in 2 equal treatments **[presumed gavage]** separated by 6 hours on GD 7–PND 20 (plug = GD 0, birth = PND 1). Pups were weaned on PND 21 and 25 male and female offspring per dose group were followed as the F_1 generation, using at least 1 pup/sex/litter where possible. The rest of the offspring were killed and necropsied. The F_1 animals were evaluated using a passive-avoidance test (beginning on PND 23) and a water-filled M-maze (on PND 70). Females were evaluated for vaginal patency beginning on PND 28 and males were evaluated for preputial separation beginning on PND 39. At approximately 90 days of age, one F_1 male and female/litter were cohabited for 21 days after which males were killed and necropsied. Females were killed and necropsied on GD 20. Data were analyzed using ANOVA with post hoc Dunnett test or Kruskal-Wallis with Dunn test, depending on homogeneity of variance.

Clinical signs (hyperactivity and aggression) were noted in the F_0 dams given 6 mg/kg bw/day *d*-methylphenidate. Additional clinical signs were noted at 20 mg/kg bw/day *d*-methylphenidate and at 40 mg/kg bw/day *d,l*-methylphenidate. **[Clinical signs were evaluated by CERHR using the benchmark dose[2] approach. The most sensitive sign in presumed pregnant rats was hyperactivity with a BMD_{10} of 3.9 mg/kg bw/day and a BMDL of 3.6 mg/kg bw/day. In lactating rats, the most sensitive sign was repetitive sniffing with a BMD_{10} of 3.4 mg/kg bw/day and a BMDL of 3.2 mg/kg bw/day.**] There was a higher incidence of clinical signs at 40 mg/kg bw/day *d,l*-methylphenidate than 20 mg/kg bw/day *d*-methylphenidate, although the amount of the active enantiomer (*d*-methylphenidate) was identical in both treatments. Maternal body weight gain and feed consumption (absolute and relative) were reduced to a similar degree by 20 mg/kg bw/day *d*-methylphenidate and 40 mg/kg bw/day *d,l*-methylphenidate, with no significant effect by pair-wise comparison at 2 or 6 mg/kg bw/day *d*-methylphenidate.

[2] The BMD_{10} is the benchmark dose associated with a 10% effect, estimated from a curve fit to the experimental data. The BMDL represents the dose associated with the lower 95% confidence interval around this estimate. Benchmark doses are used commonly in a regulatory setting; however, they are used in this report when the underlying data permit their calculation, and are only supplied to provide one kind of description of the dose-response relationship in the underlying study. Calculation of a benchmark dose in this report does not mean that regulation based on the underlying data is recommended, or even that the underlying data are suitable for regulatory decision-making.

[Evaluation by CERHR of the decrease in feed consumption from GD 7–20 using the benchmark dose approach gave a BMD_{10} of 23 mg/kg bw/day and a BMDL of 19 mg/kg bw/day. The F_0 weight data were not provided in a form suitable for benchmark dose calculation.]

Duration of gestation was significantly prolonged by about 0.5 days in the groups given *d*-methylphenidate 20 mg/kg bw/day and *d,l*-methylphenidate 40 mg/kg bw/day. There were no treatment-related effects on number of live or stillborn pups, pup survival during the lactation period, or pup weight at birth or during the lactation period. There were no notable findings in pups necropsied on PND 21. Body weight and feed consumption in the F_1 males in the *d,l*-methylphenidate 40 mg/kg bw/day group were decreased for several individual weeks and overall in the PND 1–71 time period. There was no effect on body weight or feed consumption for any of the doses of *d*-methylphenidate and female F_1 body weight was not affected by any of the treatments during PND 1–71. There were no treatment-related effects on day of preputial separation or vaginal patency, and no effects on passive-avoidance test or water-filled M-maze performance **[data not shown]**. Terminal body weights were decreased in F_1 males in the *d*-methylphenidate 20 mg/kg bw/day and *d,l*-methylphenidate 40 mg/kg bw/day groups. Relative weight of the testis was increased in the *d,l*-methylphenidate 40 mg/kg bw/day group, but not in any of the *d*-methylphenidate groups. Mating of the F_1 animals showed no treatment-related effects on number of pregnant animals, corpora lutea, or implantations, and no alterations in live or dead fetuses/litter, resorptions, sex ratio, or fetal weight.

The authors estimated from AUC values that the top dose of *d*-methylphenidate used in this study was 5.6 times the human therapeutic dose. The decrease in weight in F_1 males was evaluated as consistent with the decrease in feed consumption, although no explanation could be given for the lack of effect in females. *d*-Methylphenidate at this dose was considered not to have adverse effects on reproductive parameters after exposure during pregnancy and lactation.

Strengths/Weaknesses: A strength of this study was that it was conducted according to the FIFRA style. Sample sizes were adequate in both the dose-range finding study and the main study. The oral route is a strength because it is consistent with human therapeutic exposure, although it limits comparison to other studies. A weakness is that it is unclear if individual data were available and if GLP quality assurance was used. No data were shown for behavioral assessments, puberty measures, estrous cycles, or sperm. More detail is needed on the F_1 mating protocols to be sure they were of sufficient sensitivity to detect adverse effects. Very few neurological examinations were conducted and for those examinations performed (passive-avoidance, water maze), no data were provided.

Utility (Adequacy) for CERHR Evaluation Process: This study is valuable for assessing fertility after developmental exposure.

McDougall et al. *(162)*, in a study partially supported by an ASI research grant, examined behavioral sensitization associated with methylphenidate treatment in developing rats. A series of studies was conducted in which Sprague-Dawley rats were ip injected with methylphenidate **[purity not specified]** or saline during pretreatment periods on PND 16–20 or PND 10–14. During the pretreatment period, the frequency of line crosses (a measure of horizontal locomotor activity) and stereotyped sniffing was assessed for 40 minutes, 5 minutes after the rats were injected. Following 1 or 7 abstinence days, sensitization of locomotor activity and stereotyped sniffing was assessed in rats receiving a challenge dose of methylphenidate or saline. Five minutes after receiving the challenge dose, rats were observed for 40 minutes. An increase in line crosses or sniffing in rats pretreated and challenged with methylphenidate compared to rats

pretreated with saline and challenged with methylphenidate was considered to be a sensitization response. Data were analyzed by ANOVA and Student *t*-test or Tukey test. A summary of pre-treatment and challenge doses, days of treatment, and sensitization results for the three main experiments is listed in
Table 32. Treatment groups consisted of 7–8 rats from different litters, with approximately equal numbers of males and females.

During pretreatment periods, it was found that methylphenidate caused dose-dependent increases in line crosses and stereotyped sniffing. During the pretreatment period, potency of doses for inducing line crossing was 5 > 10 > 20 > 2.5 mg/kg bw/day, with statistical significance obtained at 5 and 10 mg/kg bw/day. Potency of doses for inducing stereotyped sniffing during the pretreatment period was 20 > 10 > 5 > 2 mg/kg bw/day, with statistical significance obtained at the two highest doses. The study authors stated that locomotor response was sensitized in rats pretreated with 2.5–20 mg/kg bw/day methylphenidate and challenged with 2.5 mg/kg bw methylphenidate. Numerous pretreatment and challenge doses induced sensitization of stereotyped sniffing in both age groups following a 1-day abstinence period. Following a 7-day abstinence, the authors stated that sensitization remained only in rats pretreated with the 20 mg/kg bw/day dose. **[However, it appears that sensitization also occurred in rats pretreated with 10 mg/kg bw/day and challenged with 2.5 mg/kg bw methylphenidate (see Table** 32**).]** The study authors concluded that methylphenidate treatment produces sensitization in young rats, but that the sensitization decreases over time, by contrast with adult rats in which sensitization may persist for months. The authors interpreted this lack of long-term sensitization in young rats as a prediction that methylphenidate in children will not increase the likelihood of stimulant abuse.

Table 32. Sensitization Responses in Rats Treated with Methylphenidate

Pretreatment		Challenge		Sensitization response[a]	
Dose (mg/kg bw/day)	PND	Dose (mg/kg bw)	Test day (PND)	Line crosses	Stereotyped sniffing
2.5	16–20	2.5	22	↑	↔
5.0		5.0		↔	↑
10.0		10		↓	↑
20.0		20		↓	↑
2.5		2.5	28	↔	↔
5.0		5.0		↔	↔
10.0		10		↔	↔
20.0		20		↓	↑
2.5	16–20	2.5	22	↔	↔
5.0				↑	↔
10.0				↑	↑
20.0				↑	↑
2.5			28	↔	↔
5.0				↔	↔
10.0				↔	↑
20.0				↔	↑
20.0	10–14	2.5	16	↔	↑
		20		↔	↑
		2.5	22	↔	↔
		20		↔	↑

[a]Change following challenge in methylphenidate pretreatment group compared to corresponding saline pretreatment group. ↑, ↓ ,↔ statistically significant increase, decrease, no effect. From *(162)*.

Strengths/Weaknesses: A strength of this study is the multiple-dose and litter-based design. Group sizes were adequate, with internal replication between experiments. Testing for sensitization using challenge doses is a strength. A weakness is that conclusions regarding age-dependent effects (adult vs. juvenile) may not be valid, as no adult data were presented. Conclusions regarding addiction potential also need supporting data. It is unclear if treated animals were growth retarded and maturation was delayed, an important consideration because immature rats have distinct developmental activity profiles. It is a weakness that the statistical design collapsed males and females without correction for repeated samples from a litter, and that there was no mention of masking of the subjective behavioral assessment to treatment status. The very short neonatal exposure period limits the applicability of the data.

Utility (Adequacy) for CERHR Evaluation Process: The study has adequate design and reporting, but interpretation for use in the evaluation process is not straightforward.

Brandon et al. *(163)*, in a study supported by NIDA, evaluated the adult effects of the treatment of adolescent Sprague-Dawley rats with methylphenidate. Five-week-old animals (12 per treatment group **[sex not specified]**) were treated with methylphenidate HCl **[purity not specified]** 10 mg/kg bw/day or saline ip for 7 days. The animals were challenged as 8-week-old adults with cocaine 7.5 mg/kg bw ip following which they were evaluated for activity (ambulation and rearing) in a rodent cage fitted with photocells. The experiment was repeated using a 5 mg/kg bw/day dose of methylphenidate HCl and a 15-mg/kg bw cocaine challenge, and using a 2 mg/kg bw/day dose of methylphenidate HCl and a range of cocaine challenges (3.75–30 mg/kg bw). Adolescent treatment with 5 or 10 mg/kg bw/day methylphenidate caused a significant increase in locomotor activity in response to cocaine; however, 2 mg/kg bw/day

methylphenidate treatment during adolescence was not different from saline in sensitizing the animals to the subsequent cocaine challenge as adults. The 2 mg/kg bw/day adolescent treatment, however, sensitized the animals as adults trained to poke their noses in a hole to receive a 75 µg/kg bw infusion of cocaine. Adult animals pretreated as adolescents with methylphenidate demonstrated a larger number of nose-pokes and self-administered a larger amount of cocaine than did adult animals pretreated as adolescents with saline. Based on a cited study, the authors stated that the 2 mg/kg bw/day methylphenidate dose approximated therapeutic exposures in children based on plasma concentration. The sensitization in adolescence to the self-administration of low doses of cocaine in adult life was interpreted as consistent with "alterations in brain substances mediating the increased incentive value of low reinforcers…our results also suggest that adolescent exposure to [methylphenidate] may potentially increase future vulnerability to low doses of cocaine." A long-lasting reduction in synthesis of the dopamine transporter in the prefrontal cortex and nucleus accumbens was postulated as a mechanism of this sensitization effect.

Strengths/Weaknesses: Strengths of this study include use of multiple doses and appropriate ages at dosing. Weaknesses include no reporting of gender or growth and maturation endpoints. It is unclear if baseline activity (prior to challenges) was evaluated. It is also unclear if a litter-based design was used, which is important even if the dam was not treated. The short dosing duration and the ip dosing limit the applicability of the data.

Utility (Adequacy) for CERHR Evaluation Process: The study is potentially useful in addressing addiction potential. However, the incomplete data reporting, the short dosing duration, and the late onset of dosing detract from the utility of this study in the evaluation process.

Bolaños et al. ***(164)***, supported by NIDA and NIMH, treated male Sprague-Dawley rats with methylphenidate in saline at 0 or 2.0 mg/kg bw/dose ip at 9 AM and 1 PM daily from PND 19 through 35. Animals were weaned on PND 23 and same-sex littermates were housed 4-to-a-cage until PND 50 and then 2-to-a-cage. Behavioral testing was performed beginning on PND 40 for play behavior (n=30), and beginning 6 weeks after the last injection for other assessments, which included sucrose preference (solutions ranging from 0.125 to 1%; n=30), locomotor activity in a novel environment (n=42), elevated plus-maze (with self-grooming behavior) (n=30), social interaction in an adverse environment (n=30), sexual behavior (n=30), and forced swimming (n=30). There was at least a 2-week period between tests **[test order not specified, except that forced swim was tested last]**. Different animals (8/treatment group) were evaluated for plasma corticosterone response to a 20-minute restraint stress. Samples were obtained from the tail vein at 0 minutes (onset of restraint), and 15 minutes (during restraint), and at 40 and 90 minutes, when restraint was reapplied briefly for the collection of samples. Corticosterone was measured by competitive enzyme immunoassay. Statistical analysis was performed using ANOVA with post hoc Scheffé test as well as Student *t*, chi-square, and *F* tests. There were no treatment effects on rat weight (which was assessed daily), fluid intake (per cage), play behavior, or social interaction in an adverse environment. Methylphenidate treatment decreased sucrose preference except at the 1% concentration, and spontaneous ambulatory activity in a novel environment was decreased by methylphenidate treatment. Methylphenidate-exposed animals spent less time in the open arms of the elevated plus-maze and more time self-grooming. Sexual behavior was decreased by methylphenidate treatment, with a smaller proportion of exposed animals showing intromission and ejaculation compared to the controls. During the forced swim test, methylphenidate-exposed animals took less time to become immobile. Corticosterone concentrations in plasma were numerically higher at all time points after the initiation of restraint, with the difference from control being statistically significance at 15 minutes. The authors concluded that methylphenidate treatment during the juvenile period resulted in adults that were

less sensitive to reward (sucrose), less responsive with respect to motor activity in a novel environment, and less sexually responsive. By contrast, juvenile treatment resulted in greater sensitivity to aversive stimuli including swim stress and anxiogenic situations (the elevated plus-maze). The authors hypothesized that changes in the transcription factor cAMP response element-binding protein in the mesolimbic dopamine system may have been responsible for these findings.

Strengths/Weaknesses: The multiple different assessments are a strength. The ip route of administration and the use of a single dose level are weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: The study can be used in assessing the potential for lasting effects of juvenile treatment; however, the single dose level precludes quantitative evaluation.

Carlezon et al. *(165)*, supported by NIDA, NIMH, and the Tourette's Syndrome Association, treated male Sprague-Dawley rats ip from PND 20–35 with methylphenidate 2 mg/kg bw/dose, cocaine 15 mg/kg bw/dose, or vehicle at 9 AM and 1 PM. Rats were weaned on PND 25 and housed with same-sex littermates. Beginning on PND 60, rats underwent behavioral testing. Tests included place-conditioning studies in which cocaine injection (at 3 difference dose levels) was conditioned to be associated with 1 compartment of a 3-compartment apparatus and rats were evaluated for compartment preference after 2 days of conditioning (n=106 rats **[group allocations not given]**), forced swim test (n=32 rats **[group allocations not given, only vehicle and methylphenidate treatments were evaluated]**), and locomotor activity during 30-minute test sessions on each of 3 consecutive days (n=13 methylphenidate-treated and 10 vehicle-treated animals). Statistical analysis was performed using ANOVA with *F* tests. In the place conditioning study, juvenile treatment with vehicle resulted in an increase in time spent in the cocaine-associated compartment when the highest dose of cocaine (20 mg/kg bw ip) was used for conditioning. When the juvenile treatment was either methylphenidate or cocaine, less time was spent in the cocaine-associated compartment when cocaine 10 mg/kg bw was used for the conditioning; this apparent aversion to cocaine disappeared when cocaine 20 mg/kg bw was used for conditioning. In the forced swim test, juvenile treatment with methylphenidate was associated with a small but statistically significant increase in immobility and a decrease in swimming or climbing behavior. Locomotor activity was not different by juvenile treatment on the first day of testing but was higher in methylphenidate-exposed than control animals on the second and third day. The authors concluded that juvenile treatment with methylphenidate may have made cocaine less rewarding and more aversive in adulthood, which would correspond to a decreased susceptibility to substance abuse in children treated with methylphenidate. Results of the forced swim test were interpreted as a possible liability to depression, and the locomotor activity results suggested a decrease in habituation to new environments.

Strengths/Weaknesses: The ip route of methylphenidate administration and the use of a single dose level are weaknesses.

Utility (Adequacy) for CERHR Evaluation Process: The study can be used in assessing the potential for lasting effects of juvenile treatment; however, the single dose level precludes quantitative evaluation.

3.2.3 Postnatal neurochemical effects

Wagner et al. *(166)*, supported by US Public Health Service (PHS), treated neonatal Sprague-Dawley rats with two daily sc doses of methamphetamine hydrochloride, *d*-amphetamine sulfate, or methylphenidate. The total dose of each stimulant was 12.5, 25, or 50 mg/kg bw/day. A control

group was given injections of the saline vehicle. Neonates were treated on PND 10–40, and were raised in litters of 10 that were constructed from pooled and redistributed PND 3 pups (without regard to sex). At least two litters were used per treatment group. Pups were killed 2 weeks after the last treatment and brains were dissected to provide samples of caudate, midbrain, hypothalamus, pons-medulla, and telencephalon. Dopamine concentration was determined in caudate samples using HPLC, and norepinephrine concentrations were determined in other regions using alumina adsorptions with spectrofluorometric analysis. Statistical comparisons were made using one-way ANOVA. Caudate dopamine was reduced by *d*-amphetamine 50 mg/kg bw/day and by methamphetamine 25 and 50 mg/kg bw/day. There were no alterations associated with methylphenidate treatment. The authors concluded that the lack of alteration in catecholamine levels was consistent with findings in the brains of adult rats and monkeys after methylphenidate treatment.

Strengths/Weaknesses: Strengths of this study include appropriate ages of animals at treatment and avoidance of a split-litter design. The randomized postnatal pup distribution minimized genetic litter effects. Weaknesses are that no growth or maturation parameters were stated, methods for measuring norepinephrine may not have been sensitive, and no information was provided on dopamine or norepinephrine turnover. The hypothesis being tested was unclear. There were only 2 litters per treatment and an unknown number of samples per litter (the reported degrees-of-freedom (3,24) suggest up to 4 samples per litter). The failure to specify the statistical design is a weakness. The number of significant changes is 3 of 66, which is less than predicted by a Type I error probability of 0.05.

Utility (Adequacy) for CERHR Evaluation Process: The statistical problems of this study limit its utility for the evaluation process.

Brandon et al. *(167)*, in a study supported by NIDA, examined midbrain dopamine neuron activity in adolescent rats treated with methylphenidate. Five-week-old male Sprague-Dawley rats were randomly assigned to groups that received saline or 2.0 mg/kg bw/day methylphenidate **[purity not specified]** by ip injection for 7 days. **[The number of rats treated was not specified.]** Extracellular single-unit recordings were taken in anesthetized rats 1–3 days or 14–21 days following dosing to evaluate activity of dopamine neurons in the ventral tegmental area. Statistical significance of results was analyzed by Student *t*-test. Methylphenidate treatment resulted in a significantly increased dopamine neuronal firing rate, an increased trend for percent spikes emitted as bursts, and significant increases in burst frequency and spikes per burst during the 1–3 day withdrawal period. During the 14–21-day withdrawal period, methylphenidate-treated rats displayed attenuated dopamine neuronal activity, as indicated by reduced firing rate and increased interspike interval. Autoreceptor-mediated inhibition of firing, as measured by response to the dopamine receptor agonist quinpirole, was equivalent in saline- and methylphenidate-treated rats during both time periods. The study authors concluded "Adolescent exposure to methylphenidate induces neuronal changes associated with increased addiction liability in rats."

Strengths/Weaknesses: Strengths include the large sample size and an adequate experimental design for the hypothesis being tested; however, the basis for dose selection is unclear. More detail on methodology would have been helpful. The use of the ip route and cumulative dosing in naïve rats make comparison to human exposures difficult.

Utility (Adequacy) for CERHR Evaluation Process: The unique experimental methods and short-duration exposure limit the utility of these data for the evaluation process.

Kuczenski and Segal *(168)*, supported by PHS, the Veterans Administration, and the University of California, administered methylphenidate to adolescent male Sprague-Dawley rats by gavage. Animals were obtained at 28 days of age and habituated to the laboratory environment for 10 days. They began gavage treatment with saline at 38 days of age and treatment with methylphenidate at 41 days of age. Animals had guide cannulas placed stereotactically in the dorsal hippocampus and nucleus accumbens. One day before experimentation, dialysis probes were placed through the cannulas to permit acclimation. **[Animals were used for assessments of locomotor activity as well as brain neurochemistry and it is not possible to tell whether the same animals were used for both endpoints, or the ages at which guide cannulas were placed and neurochemistry experiments performed.]** Acute doses of 1.0, 2.5, or 5.0 mg/kg bw methylphenidate were given by gavage. The 1.0 and 2.5 mg/kg bw doses were selected to produce blood levels similar to those obtained clinically, and the 5.0 mg/kg bw dose was estimated to produce blood levels higher than those achieved clinically. **[Blood levels were not measured, but were estimated based on previous work in rats. Clinical blood levels were considered to be 8–40 ng/mL.]** There were 6–10 animals/treatment group, tested during the dark phase of a reverse dark-light cycle. Hippocampus norepinephrine concentration was increased by all doses of methylphenidate, peaking 40 minutes after the treatment (samples were collected every 20 minutes). Peak hippocampus norepinephrine concentration after the 5.0 mg/kg bw dose was about 20 nM compared to a baseline concentration of about 5 nM **[estimated from a graph]**. Nucleus accumbens dopamine was increased only after the 5.0 mg/kg bw dose, peaking 60 minutes after treatment at about 22 nM compared to a baseline value of about 16 nM **[estimated from a graph]**. Total activity (estimated from videotaping of animals over 9 hours) decreased when methylphenidate was given at 0.75, 1.0, 2.5, or 3.0 mg/kg bw/dose every 3 hours for 3 doses. The authors concluded that there was an association between the increase in hippocampal norepinephrine and decrease in locomotor activity, based on these endpoints occurring in the same dose range, but that a role for dopamine in the nucleus accumbens could not be documented.

Strengths/Weaknesses: A strength of this study is use of multiple doses and experimental procedures that were adequate for the hypotheses being tested. Group sizes were adequate and there was statistical control for multiple comparisons. The dose regimen was chosen with consideration of species differences in pharmacokinetics. A weakness is that dosing was late for evaluation of adolescence. Gender was not stated and growth was not evaluated. It is unclear if the association between neurotransmittters and behavior was evaluated statistically.

Utility (Adequacy) for CERHR Evaluation Process: This study is adequate for the evaluation process; however, the lack of dose-related effects of methylphenidate alone on behavior coupled with the use of either acute or repeated exposure to young adult rats limits the usefulness of these data.

3.2.4 Unpublished studies

Information for additional studies that were apparently not published was presented in drug labels for methylphenidate. Although the lack of study reports does not allow review by the Expert Panel, the information is presented below for completeness.

Dosing of rats with 45 mg/kg bw/day methylphenidate (4 times the maximum recommended human dose based on surface area) throughout pregnancy and lactation resulted in reduced offspring body weight gain, but no other postnatal developmental effects; the no effect level for pre- and postnatal development was identified as 15 mg/kg bw/day, a value equal to the maximum recommended human dose on a mg/m^2 basis *(10)*.

Increased fetal skeletal variations were observed, but there was no evidence of specific teratogenic activity following oral dosing of rats with 75 mg/kg bw/day methylphenidate during organogenesis; maternal toxicity was observed at that dose, which is 7 times the maximum recommended human dose on a mg/m^2 basis *(10)*. The no effect level for embryo-fetal development was identified as 25 mg/kg bw/day, 2 times the maximum recommended human dose on a mg/m^2 basis.

Decreased postnatal pup weight gain and survival and maternal toxicity were observed in a reproductive study where rats were orally dosed with 58 mg/kg bw/day methylphenidate throughout gestation and lactation; the dose was 30 times and 6 times the maximum recommended human dose on a mg/kg bw and mg/m^2 basis, respectively *(5)*.

In a study where 7-day-old rats were orally administered methylphenidate for 9 weeks, neurobehavioral assessment during adulthood revealed decreased spontaneous locomotor activity in males and females of the 50 mg/kg bw/day group (6 times the maximum recommended human dose based on mg/m^2) and deficient acquisition of a learning task in females of the 100 mg/kg bw/day group (12 times the maximum recommended human dose on a mg/m^2 basis) *(10)*. The no effect level for juvenile neurobehavioral development was identified at 5 mg/kg bw/day, half the maximum recommended human dose on a mg/m^2 basis.

Spina bifida incidence was increased in fetuses of rabbits orally dosed during organogenesis with 200 mg/kg bw/day racemic methylphenidate, 40 and 100 times the maximum recommended human dose on a mg/m^2 and mg/kg bw basis, respectively *(7, 10)*. The no effect level for embryo-fetal development was identified at 60 mg/kg bw/day, 11 times the maximum recommended human dose based on surface area.

[The Expert Panel notes that descriptions in secondary sources such as product labels do not contain sufficient detail to contribute to the evaluation process.]

3.3 Utility of Developmental Toxicity Data

Human data are not sufficient to evaluate developmental toxicity following prenatal exposure to methylphenidate. There are human studies on childhood exposure to methylphenidate evaluating effects on heart rate, blood pressure, tics, growth, and risks of developing substance abuse disorders. There are insufficient data to determine the effects of childhood methylphenidate exposure on seizures and psychotic symptoms.

The database includes studies on prenatal methylphenidate exposure in rats and rabbits. A rat and rabbit study by Teo et al. *(46)* included an assessment of prenatal mortality and external, visceral, and skeletal malformations. There are data on postnatal growth and survival following prenatal and lactational exposure of rats to methylphenidate *(47)*. There was one multiple-dose study examining growth in immature animals exposed to methylphenidate by sc injection *(161)*. There are insufficient data for evaluating developmental neurotoxicity in animals.

3.4 Summary of Developmental Toxicity Data

3.4.1 Human Data

No conclusions could be drawn from two human studies of methylphenidate exposure during pregnancy *(68, 69)* due to study design limitations such as lack of a comparison group, no control of confounding factors, multiple exposures to other drugs, and/or inadequate analyses that grouped methylphenidate data with data for other drugs.

Nine controlled studies examining side effects in children were identified *(70-78*). Side effects observed more often in the methylphenidate group compared to the placebo group in at least 3 of the studies (number of studies reporting effects) included appetite problems (6), stomachache (4), insomnia (4), crying (3), and headache (3). Side effects that were reported in only 1 of the studies included drowsiness, increased blood pressure (discussed below), irritability, anxiety, high activity, dizziness, nail biting, and withdrawal. Some authors noted that certain side effects may actually be related to ADHD. One study that evaluated clinical chemistry and hematology parameters in methylphenidate-treated children for up to 48 months reported no adverse effects *(80*).

Controlled studies conducted before the establishment of current published norms *(85*) evaluated cardiovascular effects in children treated with methylphenidate or placebo over a period of 1 week or more. Some of these studies did not use standardized measurement techniques. The time period between dosing and testing was not clear in many studies. Four studies reported increased heart rate (3–16 beats per minute) *(86, 88, 89, 91*), while no increases in heart rate were reported in two other studies *(87, 90*). Three studies reported blood pressure effects including an increase in systolic (6.2 mm Hg) and mean arterial blood pressure (4.4 mm Hg) *(89*) and an increase in diastolic blood pressure (1.9–14 mm Hg) *(86, 91*); no increases in blood pressure were reported in 3 other studies *(87, 91*). A dose-response comparison of these studies is not possible because units of dosing (e.g., mg/day vs. mg/kg bw/day) were not consistent between studies. However, two studies provided some information on possible dose-response relationships. In the Ballard et al. study *(89*), increases in heart rate and blood pressure were correlated with weight-adjusted dose, which ranged from 0.13–0.89 mg/kg bw. Children in the Brown and Sexson study *(91*) received twice daily doses of 0.15, 0.3, or 0.5 mg/kg bw; blood pressure increased at 0.5 mg/kg bw. There are no long-term studies examining the effects of methylphenidate on heart rate and blood pressure.

Possible effects of stimulant medications on seizures were evaluated in three studies. In a study where 40 children with "minimal brain dysfunction" received placebo or 20–40 mg/day methylphenidate for 6 weeks, 11 children had abnormal EEGs prior to drug treatment and methylphenidate therapy did not increase the frequency of abnormal EEGs *(86*).

Case reports have described the development of psychotic symptoms (e.g., hallucinations, delusions, mania) in children treated with methylphenidate. A retrospective chart review study reported that 9 of 98 children treated with stimulant medications (7 on methylphenidate and 2 on pemoline) developed psychotic symptoms and 2 were later diagnosed with bipolar disorder *(99*). The Expert Panel is not aware of controlled studies examining relationships between stimulant treatment and psychosis in children.

Since the appearance of a 1974 case report describing development of Tourette disorder in a 9-year-old boy treated with methylphenidate *(101*), a number of papers describing tics or Tourette disorder in association with stimulant therapy were published (Table 26). However, of five controlled studies *(72, 75, 78, 102, 103*) with methylphenidate doses up to 0.6 mg/kg bw or 60 mg/day, four *(75, 78, 102, 103*) did not demonstrate increased incidence of tic onset or worsening of symptoms compared to placebo or baseline levels. It has been reported that a large proportion of children with Tourette disorder have comorbid ADHD (reviewed by Leckman *(100*)), thus complicating the interpretation of studies on methylphenidate therapy and tics.

Concerns have been raised that stimulant treatment in childhood can increase the risk for developing substance abuse disorders later in life. Numerous studies examining possible associations between ADHD, independent of treatment, and substance abuse were not considered

by the Expert Panel. The Panel notes a review by Wilens *(130*) that concluded, "There is a robust literature supporting a relationship between ADHD and SUD **[substance use disorders]**. Noncomorbid ADHD appears to confer an intermediate risk factor for SUD, although conduct and bipolar disorder appear to heighten the risk of early onset of SUD. . ." In studies found to be useful or to have limited usefulness for evaluating risks of substance abuse, the type of stimulant treatment was not specified in 1 study *(121*) and stimulant therapies in the other studies included methylphenidate in 80 *(122*) or 100% *(126*) of subjects. None of the studies found evidence that prolonged treatment of ADHD with stimulants in childhood increased the risk of tobacco or cigarette use in adolescence *(121, 122*) or alcohol or substance abuse in adolescence *(121, 122*) or adulthood *(122, 126*). One study *(121*) reported a reduction in substance abuse in treated individuals compared to untreated individuals with ADHD. A study in which children with reading disorders were treated with methylphenidate for 12–18 weeks, a time period much shorter than typical treatment periods for ADHD, also found no increased risk of substance use disorder in adulthood *(128*).

The effects of methylphenidate on growth of children were evaluated in 27 studies summarized in Table 28 and in the 1992 Multimodal Treatment Study of ADHD *(157*). Studies reported variable results. However, the weight of evidence suggests that methylphenidate treatment is associated with an initial decrease in height and weight gain in children. It is not known whether final adult height and weight are affected by current treatment regimens, which frequently include continuous use and use beyond childhood. The quality of data in the older papers is suboptimal. These articles have variable but generally marginal-to-moderate utility with lack of masked assessments, incomplete documentation of compliance, or actual dosing regimens. The studies fail to consider (in most cases) basic factors that are usually assessed in growth studies, such as mid-parent height and parent BMI; family history of timing of puberty onset; the child's actual physical or endocrinologic level of puberty at start of treatment (some of the youngsters were as old as 15 when the studies were conducted); and measurement of skeletal maturity (bone age), which particularly in school-aged children is considered a useful indication of expected growth potential. The seasonal differences in expected growth (in the northern hemisphere, children grow faster in summer) are not accounted for by designs that compare children whose families chose to leave them on stimulants through the summer and children whose families did not leave them on medication during the summer. Thus, it cannot be ruled out that those who remained on the medicines also had other conditions or behavioral patterns that motivated their parents to continue the medication and might also (like fetal alcohol effects) decrease growth.

Findings overall seem to suggest that appetite and growth suppression are less with methylphenidate than with amphetamines, but these findings are not conclusive. Growth studies have not included control for potential confounders such as intrauterine exposure to tobacco, ethanol, and illicit drugs, or parental mental health.

It is unclear whether there is an endocrinologic contribution to the growth effects of methylphenidate. Studies examining the acute effects of therapeutic methylphenidate doses on growth hormone levels reported increases in growth hormone levels that returned to baseline levels following dosing *(34, 81*), an effect that also occurs in adults *(82*). An acute decrease in prolactin was also reported following methylphenidate dosing *(34*). Diurnal concentrations of growth hormone and prolactin were measured in subjects receiving methylphenidate therapy (20–120 mg/day) for 3 months to 4 years, while they were on therapy, and during an 11-day to 10-week abstinence period *(83*). During periods with and without methylphenidate treatment, patterns of diurnal growth hormone and prolactin release were similar with normal fluctuations throughout the day and peak hormone release during sleep. One study demonstrated standard growth hormone provocation curves in children treated with *d*-amphetamine prior to

methylphenidate treatment *(81*). However, after 6–8 months of therapy with 5–35 mg/day methylphenidate, there were "tendencies" for delayed growth hormone response to acute *d*-amphetamine treatment consisting of an initial fall in concentration, with or without a subsequent rise. In a study comparing growth hormone responses to a clonidine challenge in children before and after a minimum of 3 months treatment with ≥0.3 mg/kg bw/day methylphenidate, methylphenidate treatment was found to inhibit clonidine-induced increase in growth hormone levels *(84*).

3.4.2 Experimental Animal Data

Key studies on methylphenidate experimental animal developmental toxicity are summarized in Table 33. The most useful study for evaluating prenatal endpoints was conducted in rats and rabbits by Teo et al. *(46*). These investigators gavage dosed 25 rats/group with 0, 2, 6, or 20 mg/kg bw/day d-methylphenidate or 40 mg/kg bw/day *d,l*-methylphenidate administered in 2 divided doses on GD 7–17. Dams were killed on GD 20 for microdissection of half the litters and skeletal evaluation of the other half. Clinical signs were observed in dams dosed with 6 and 20 mg/kg bw/day *d*-methylphenidate and 40 mg/kg bw/day *d,l*-methylphenidate group, with some signs occurring more often in the 40 mg/kg bw/day *d,l*-methylphenidate group than in the 20 mg/kg bw/day *d*-methylphenidate group. Also noted in the ≥ 6 mg/kg bw/day *d*-methylphenidate and 40 mg/kg bw/day *d,l*-methylphenidate groups were reductions in feed intake and body weight gain during treatment. There were no treatment-related changes in corpora lutea or implantations per dam or in litter values for live or dead fetuses, resorptions, sex ratio, fetal body weight, or fetal alterations. The percent of fetuses with alterations was increased in the 6 and 20 mg/kg bw/day *d*-methylphenidate groups when analyzed on a per fetus, but not per litter basis. Fetal incidence rates were within the laboratory historical control range. No separate delineation of malformations appeared in the paper **[CERHR Benchmark dose modeling of d-methylphenidate resulted in BMD_{10} values in the 31–36 mg/kg bw/day range and BMDL values in the 23–24 mg/kg bw/day range for the various fetal ossification delays.]**

Teo et al. *(46*) gavage dosed 20 rabbits/group with 0, 4, 20, or 100 mg/kg bw/day *d*-methylphenidate or 200 mg/kg bw/day *d,l*-methylphenidate administered in 2 divided doses on GD 6–18. Does were killed on GD 29 for microdissection and evaluation of fetuses for skeletal malformations. Clinical signs were observed in does dosed with 100 mg/kg bw/day *d*-methylphenidate and 200 mg/kg bw/day *d,l*-methylphenidate, with some clinical signs occurring more often in the 200 mg/kg bw/day *d,l*-methylphenidate group. There were no adverse effects on mean number of corpora lutea, implantations, live or dead fetuses/litter, resorptions, sex ratio, or fetal alterations at any dose level.

The most useful study for evaluating posnatal endpoints was conducted by Teo et al. *(47*). These investigators dosed 25 pregnant rats/dose group with *d*-methylphenidate 0, 2, 6, or 20 mg/kg bw/day or *d,l*-methylphenidate 40 mg/kg bw/day, given in 2 divided treatments **[presumed gavage]** on GD 7–PND 20 (plug = GD 0, birth = PND 1). Pups were weaned on PND 21 and 25 male and female offspring per dose group were followed as the F_1 generation, using at least 1 pup/sex/litter where possible. The rest of the offspring were killed and necropsied. Clinical signs (hyperactivity and aggression) were noted in the F_0 dams given 6 mg/kg bw/day *d*-methylphenidate. Additional clinical signs were noted at 20 mg/kg bw/day *d*-methylphenidate and at 40 mg/kg bw/day *d,l*-methylphenidate, with a higher incidence of clinical signs at 40 mg/kg bw/day *d,l*-methylphenidate. Maternal body weight gain and feed consumption (absolute and relative) were reduced to a similar degree by 20 mg/kg bw/day *d*-methylphenidate and 40 mg/kg bw/day *d,l*-methylphenidate. **[CERHR benchmark dose modeling for decreased feed consumption from GD 7–20 resulted in a BMD_{10} of 23 mg/kg bw/day and a BMDL of 19 mg/kg bw/day. Body weight data were not provided in a form suitable for benchmark dose**

calculation.] Duration of gestation was prolonged by about 0.5 days with 20 mg/kg bw/day *d*-methylphenidate and 40 mg/kg bw/day *d,l*-methylphenidate. There were no treatment-related effects on number of live or stillborn pups, pup birth weight, and pup weight or survival during the lactation period. There were no notable findings in pups necropsied on PND 21. Treatment-related reductions in body weight gain and feed consumption occurred in F_1 males of the 40 mg/kg bw/day *d,l*-methylphenidate group during the PND 1–71 time period. Terminal body weights were decreased in F_1 males dosed with 20 mg/kg bw/day *d*-methylphenidate and 40 mg/kg bw/day *d,l*-methylphenidate. The authors stated that there were no treatment-related effects on day of preputial separation or vaginal patency, and no effects on passive-avoidance test or water-filled M-maze performance **[data not shown]**. Mating of the F_1 animals showed no treatment-related effects on number of pregnant animals, corpora lutea, or implantations, and no alterations in live or dead fetuses/litter, resorptions, sex ratio, or fetal weight. The authors estimated from AUC values that the high dose of *d*-methylphenidate used in this study was 5.6 times the human therapeutic dose. The decrease in weight in F_1 males was evaluated as consistent with the decrease in feed consumption, although no explanation could be given for the lack of effect in females. *d*-Methylphenidate at this dose was considered not to have adverse reproductive effects. **[Results of the F_1 mating study are repeated in Section 4.2 for comparison to other studies with reproductive endpoints; because exposure of the F_1 animals was through treatment of their dams during pregnancy and lactation, this study is a developmental study, albeit one with reproductive endpoints.]**

A series of experiments by Greeley and Kizer *(161)* provided some useful information, although the studies were conducted with high doses administered through the sc route; humans typically are exposed by oral or iv routes. The studies involved twice daily sc administration of 1 or more dose levels between 2 and 200 mg/kg bw/day methylphenidate delivered as two divided doses to Sprague-Dawley rats during ~PND 5–26. Growth (body weight and naso-anal length) was reduced in rats treated with ≥70 mg/kg bw/day methylphenidate on ~PND 5–26, but there was no effect on naso-anal length 1 year following treatment. Inhibited growth appeared to result from anorexigenic properties of methylphenidate at 70 mg/kg bw/day, but additional factors were apparently involved at 200 mg/kg bw/day. It did not appear that growth was inhibited due to reduction in growth hormone because decreases were noted only in female rats, while growth was restricted in both sexes. Other effects of methylphenidate treatment included reduced prolactin at ≥6 mg/kg bw/day **[no dose-response effect noted]** and decreased basal insulin and enhanced response to glucose challenge at 70 mg/kg bw/day. Dosing of females with 70 or 200 mg/kg bw/day methylphenidate on ~PND 5–26 resulted in delayed vaginal opening. Although not statistically significant, a delay in vaginal opening in rats given 70 mg/kg bw/day methylphenidate on ~PND 21–51 was similar to the value observed in the younger rats. It is difficult to discern whether these effects were secondary to the effects of methylphenidate on growth. Effects of methylphenidate on estrous cycling are summarized in Section 4.2.

Single dose level sc injection studies in immature rats by Pizzi et al. *(159, 160)* also demonstrated reversible inhibition of body weight gain with ≥35 mg/kg bw/day methylphenidate and brain growth with 70 mg/kg bw/day methylphenidate.

Effects of behavioral sensitization following methylphenidate exposure in immature rats were examined by McDougall et al. *(162)* and Brandon et al. *(163)*. McDougall reported sensitized locomotor and stereotypy responses following a methylphenidate challenge in PND 22 rats pretreated ip with methylphenidate ≥2.5 mg/kg bw/day (locomotor) and ≥5.0 mg/kg bw/day (stereotypy) on PND 16–20; by PND 28, there was no evidence of locomotor sensitization and stereotypic sensitization was observed only in rats pretreated with ≥10 mg/kg bw/day. Pretreatment of PND 10–14-rats with 20 mg/kg bw/day methylphenidate resulted only in

sensitization of stereotypic responses following methylphenidate challenge. In studies using a cocaine challenge, Brandon et al. *(163*) reported that ip pretreatment of 5-week-old rats with ≥5 mg/kg bw/day methylphenidate for 7 days resulted in increased locomotor response following the challenge. Pretreatment of 5-week-old animals with 2 mg/kg bw/day methylphenidate resulted in greater self administration of cocaine. While McDougall et al. *(162*) concluded that their study did not suggest a greater likelihood of substance abuse following methylphenidate treatment, Brandon et al. *(163*) concluded that their study suggested a greater vulnerability to low doses of cocaine following adolescent exposure to methylphenidate.

In two studies *(164, 165*), male Sprague-Dawley rats treated during peri-adolescence (PND 19 or 20 through PND 35) with ip methylphenidate 2 mg/kg bw twice daily showed effects on adult behavior in the absence of generalized toxicity. Alterations in behavior included decreased sucrose preference, decreased spontaneous ambulatory activity in a novel environment, increased anxiety, decreased sexual behavior, and a decrease in escape behavior on forced swim testing. There was also a decrease in the reinforcing effects of cocaine in adult rats treated during the peri-adolescent period with methylphenidate. Posnatal neurochemical effects of methylphenidate were evaluated in a small number of studies. One study limited by statistical procedures found no effects on brain dopamine levels in rats 2 weeks after dosing with up to 50 mg/kg bw/day methylphenidate sc on PND 10–40 *(166*). Acute gavage dosing of 41-day-old rats with methylphenidate resulted in increases in hippocampus norepinephrine level at ≥1 mg/kg bw and increase in nucleus accumbens dopamine level at 5.0 mg/kg bw; an association was found between decreased norepinephrine and reduced activity following administration of ≥0.75 mg/kg bw methylphenidate every 3 hours for a total of 3 doses*(168*). Alterations in activity of dopamine neurons in the ventral tegmental area were demonstrated for up to 21 days following treatment of 5-week-old rats with 2 mg/kg bw/day methylphenidate for 7 days *(167*).

Expert Panel Conclusions

Human data are insufficient for an evaluation of the developmental toxicity of methylphenidate following prenatal exposure.

Data are insufficient for an evaluation of methylphenidate effects on growth in children and adolescents. Growth studies in these children demonstrate an association of reduced growth and methylphenidate treatment; however, a causal association with the medication is not possible due to a lack of control of potential confounding factors. These potential confounders could be causing the observed growth effects.

Data are insufficient to evaluate methylphenidate effects on heart rate and blood pressure. Some studies demonstrated short-term elevations of heart rate and blood pressure. The clinical importance of these findings is unclear. It is not known whether sustained or clinically-important effects occur.

Data are insufficient to evaluate whether methylphenidate therapy alters the risk of tobacco use, problematic alcohol consumption, and illicit substance abuse in adolescents and adults, although limited data suggest that there is a reduction in illicit substance abuse in medication-treated versus untreated children and adolescents with ADHD.

Data are sufficient to conclude that methylphenidate treatment of children at standard therapeutic doses does not increase the incidence of tics or movement disorders.

Data are insufficient for a full evaluation of developmental toxicity of methylphenidate in rats and rabbits after exposure during gestation. The one published paper that presents rat and rabbit data does not present adequate detail on the results for the Expert Panel to reach a conclusion.

Data are sufficient to conclude that postnatal sc administration in rats at 35 mg/kg bw/day and higher produces reversible growth restriction. These data are assumed relevant to human clinical use, but additional pharmacokinetic data are needed to interpret fully the results.

Data are insufficient for the evaluation of developmental neurotoxicity in experimental animals.

Data on methylphenidate-associated sensitization to other stimulants are insufficient for evaluation.

Note: The definitions of the term sufficient and the terms assumed relevant, relevant, and not relevant are in the CERHR guidelines at http://cerhr.niehs.nih.gov/news/guidelines.html.

Table 33. Summary of Animal Developmental Toxicity Studies

Species/ strain	Enantiomer/ exposures	Maternal effect level	Critical developmental effects	Developmental effect level	Reference
Sprague-Dawley rats	*d*-methylphenidate / gavage 0, 2, 6, 20 mg/kg bw/day[a] on GD 7–17	LOAEL = 6 mg/kg bw/day (decreased body weight gain) NOAEL = 2 mg/kg bw/day.	Total fetal alterations (on a per fetus, but not per litter basis)	LOAEL = 6 mg/kg bw/day (maternal blood level = 463 ng/mL) **[BMD_{10} = 31–36 mg/kg bw/day; BMDL = 23–24 mg/kg bw/day]**	Teo et al. *(46)*
Sprague-Dawley rats	*d*-methylphenidate / presumed gavage 0, 2, 6, or 20 mg/kg bw/day[a] on GD7–PND 20	LOAEL = 20 mg/kg bw/day (decreased feed intake and weight gain) NOAEL = 6 mg/kg bw/day **[BMD_{10} = 23 mg/kg bw/day; BMDL = 19 mg/kg bw/day (for feed intake, the only endpoint with acceptable data for modeling)]**	Decreased terminal body weight in adult male offspring	LOAEL = 20 mg/kg bw/day NOAEL = 6 mg/kg bw/day	Teo et al. *(47)*
Sprague-Dawley rats	Enantiomer not specified. sc 0, 2, 6, 20, 70, or 200 mg/kg bw[a] on ~PND 5–26	N/A	Decreased body weight and naso-anal length during treatment	LOAEL = 70 mg/kg bw/day	Greeley and Kizer *(161)*
			Decreased prolactin	LOAEL = 6 mg/kg bw/day	
			Decreased growth hormone in females only	LOAEL = 6 mg/kg bw/day	
			Decreased basal insulin but enhanced response to glucose load	LOAEL = 70 mg/kg bw/day	
Sprague-Dawley rats	Enantiomer not specified. sc 0, 70, or 200 mg/kg bw[a] on ~PND 5–26	N/A	Delayed vaginal opening and decreased number of estrous cycles following treatment	LOAEL = 70 mg/kg bw/day	Greeley and Kizer *(161)*

Species/ strain	Enantiomer/ exposures	Maternal effect level	Critical developmental effects	Developmental effect level	Reference
New Zealand White rabbits	*d*-methylphenidate / gavage 0, 4, 20, or 100 mg/kg bw/day[a] on GD 6–18	LOAEL = 100 mg/kg bw/day (clinical signs) NOAEL = 20 mg/kg bw/day	No adverse developmental effects	NOAEL = 100 mg/kg bw/day (maternal blood level = 39 ng/mL)	Teo et al. *(46)*

[a]Doses were given in two divided doses and the values are presented as total daily dose.
[b]The BMD_{10} is the benchmark dose associated with a 10% effect, estimated from a curve fit to the experimental data. The BMDL represents the dose associated with the lower 95% confidence interval around this estimate. Benchmark doses are used commonly in a regulatory setting; however, they are used in this report when the underlying data permit their calculation, and are only supplied to provide one kind of description of the dose-response relationship in the underlying study. Calculation of a benchmark dose in this report does not mean that regulation based on the underlying data is recommended, or even that the underlying data are suitable for regulatory decision-making.
N/A = non-applicable

4.0 REPRODUCTIVE TOXICITY DATA

4.1 Human Data

No studies on human reproductive effects of methylphenidate were located.

4.2 Experimental Animal Data

Morrissey et al. *(62)* reviewed results of reproductive organ weight findings and sperm morphology and vaginal cytology examinations (SMVCE) conducted at the end of 50 NTP 13-week toxicity studies in rats and mice. The purpose of the review was to evaluate SMVCE as a screen for reproductive toxicants. Methylphenidate HCl was one of the chemicals reviewed, and the 13-week dietary methylphenidate study in rats and mice is discussed in detail in Section 2.2.2. Results of the SMVCE analysis appear to also be discussed in an introduction of an NTP reproductive toxicity study on methylphenidate *(169*). According to Morrissey et al. *(62*), the only reproductive effects reported in male rats were an increase in relative epididymis weight and percent abnormal sperm at doses of 125, 500, and/or 2000 ppm **[the specific doses at which each effect was observed was not specified]**. A subsequent examination of the SMVCE raw data from an Environmental Health Research and Testing report *(170*) indicated that a 0.18% increase in abnormal sperm was seen at 2000 ppm. Environmental Health Research and Testing and the NTP *(169*) reported no sperm effects in male rats. Sperm motility was not affected in male rats. Raw data in the Environmental Health Research and Testing report indicated disrupted estrous cycles, consisting of predominantly diestrus stage, in 7/10 rats exposed to 2000 ppm. Effects reported in mice were decreases in absolute cauda epididymis, epididymis, and testis weights and increased relative testis weight at doses of 125, 500, and/or 2000 ppm. Although not identified in Morrissey et al. (64), sperm motility was significantly reduced in male mice at all dose levels of methylphenidate (68.7% motility in treated group versus 57.5, 60.1, and 60.7% in each respective treatment group per the Environmental Health Research and Testing report). Percent normal sperm was not affected in mice and there was no effect on sperm density in either rats or mice. There were inconsistencies in the reporting of effects of methylphenidate treatment on estrous cycles of mice. Environmental Health Research and Testing reported that treatment altered the relative frequency of various estrous stages in mice but Morrissey et al. did not report any effects on estrous cycles of mice treated with methylphenidate. **[Based on a review of raw estrous cycle data presented in the Environmental Health Research and Testing report, the Expert Panel noted that there were no obvious effects on estrous cycles of mice.]**

The positive results in mice were not reproducible in the subsequent NTP continuous breeding study in mice (see below *(169*)). Differences in these results are discussed further below.

Strengths/Weaknesses: A strength of this study is that SMVCE assessments were conducted by a single designated laboratory. Samples were coded and a sufficient number of sperm were examined in each sample (~500). The study was conducted under standardized protocols and GLP. A weakness is that dosing was not well-timed relative to reproductive maturation. Data were not presented in the Morrissey et al. report; therefore, supplemental SMVCE data from the Environmental Health Research and Testing report were needed to interpret the results. The increase in abnormal sperm in the 13-week rat methylphenidate study was small (0.18% at the high dose) and not biologically significant. This small increase in abnormal sperm was not identified as a treatment-related effect in either the Environmental Health Research and Testing report or subsequent NTP *(169*) report, and likely reflects a difference in the statistical database-level analyses used in Morrissey et al. (64). Female rat body weights were not given, making it difficult to interpret estrous cycle data. Furthermore, there were significant decreases in murine male body weights in the 13-week study, which may have confounded reproductive parameters (terminal body weights were decreased by 7, 14, and 18% at 125, 500, and 2000 ppm, respectively). The Environmental Health Research and Testing report attributed the decreases in sperm motility to decreased male body weights. Decreases in male reproductive organ weights were observed in CD-1 mice in the presence of body weight changes by Chapin et al. *(171*), although motility was not affected in the Chapin et al. study. Regression analysis conducted by the Expert Panel did not find an association between body weight and sperm motility or cauda weight and

sperm motility. As shown in the Environmental Health Research and Testing report, the sperm motility data do not exhibit a clear dose-response relationship.

Utility (Adequacy) for CERHR Evaluation Process: With supplemental data from the Environmental Health Research and Testing report, this study is useful for the CERHR process.

Greeley and Kizer *(161)* examined vaginal opening and estrous cycling in Sprague-Dawley rats sc injected twice daily with saline or methylphenidate at 35 or 100 mg/kg bw for 21 days at 5–7 days of age (n = 5–11/group) or 35 mg/kg bw for 30 days at 21–23 days of age (n = 9/group). The study is described in detail in Section 3.2.2 and Table 31. In the 5–7-day-old rats, methylphenidate significantly delayed vaginal opening from 34.4±0.5 (SEM) days of age in controls to 38±0.7 days in the 35 mg/kg bw group and 39.1±1.1 days in the 100 mg/kg bw group. The numbers of estrous cycles in the 30-day period following treatment were significantly reduced from 5.2±0.5 in the control group to 3.2±0.2 in the 35 mg/kg bw group and 0.8±0.3 in the 100 mg/kg bw group. Methylphenidate treatment started at 21–23 days of age did not significantly delay vaginal opening. **[However, the mean ± SEM day of vaginal opening was within the same range as the younger age group. The values were: 35.1±0.6 days of age in control vs. 38.2±2.3 days of age in the 35 mg/kg bw group.]** In the older group, the numbers of estrous cycles per 30 days were reduced during treatment (5.4±0.3 in control versus 2.3±0.2 in treated), but there was no effect on estrous cycling following treatment. Measurement of LH and FSH levels did not result in a clear pattern of effect, leading study authors to conclude that effects on those gonadotropins were not a likely cause of estrous cycle changes. Doses that delayed vaginal opening and estrous cycling were also found to inhibit growth.

Strengths/Weaknesses: A strength is that this study is one of the few to directly dose neonatal pups with methylphenidate. This study is valuable in that it probes two sensitive periods for sexual differentiation in the rat. A weakness is that there is no information describing how pups were assigned to treatment groups and whether the authors controlled for litter effects. Litter effects could be a large confounder in this study. Although the group size is small, it appears adequate for detecting relevant effects. Methylphenidate was administered to rat pups by sc injection, while humans typically are exposed by oral or iv routes. The 100 mg/kg dose clearly exceeded the maximum tolerated dose, as rat pups (5–7 days of age) given methylphenidate for 21 days weighed ~40% less than controls. Pups given 35 mg/kg methylphenidate weighed ~15% less than controls. It is difficult to discern whether methylphenidate has direct effects on vaginal opening and hormone levels or effects are secondary to delayed development and altered growth rates at high doses of methylphenidate. For graphed data, sample sizes were not given. Rat pups were given a single dose of methylphenidate and killed at various times thereafter for the determination of growth hormone, FSH, LH, and prolactin levels. The dose-response relationships for these hormones were mostly poor or nonexistent in the neonatal rat pups given 0, 1, 3, 10, 35, or 100 mg/kg bw/day methylphenidate. Concentrations of LH, FSH, and growth hormone were highly variable in the juvenile animals given bolus doses of 35 or 100 mg/kg bw methylphenidate. Hormone concentrations may vary due to diurnal variation, variations in growth/maturation rate, or inappropriate sampling of hormones, particularly hormones that are episodically released. It is difficult to determine if the FSH/LH assays were sensitive to treatment due to missing information in the protocols and results. Insulin levels were decreased by methylphenidate at rest and 10 and 60 minutes after glucose administration, whereas serum insulin was markedly increased 20 minutes after glucose treatment. The mechanism for this effect is not understood. It would be useful to replicate this result because sample sizes at 20 minutes were 5 or 6 compared with samples of 9–12 for most other time points examined.

Utility (Adequacy) for CERHR Evaluation Process: The study is useful for assessing whether delayed puberty occurs, although it cannot be used to determine whether effects are direct or secondary to growth retardation.

The NTP *(169)* conducted a continuous breeding study (Reproductive Assessment by Continuous Breeding, RACB) to examine the reproductive toxicity of methylphenidate in mice. In the GLP study,

male and female Swiss CD-1 mice were fed diets containing 0, 0.012, 0.05, or 0.1% methylphenidate hydrochloride. Authors estimated respective methylphenidate doses of 0, 18.2, 75.7, and 160.2 mg/kg bw/day in males and 0, 17.7, 76.0, and 150 mg/kg bw/day in females. Doses were selected based on effects reported in the literature and the goal was to minimize possible confounding due to hepatic toxicity or body weight effects. Purity of methylphenidate hydrochloride was >99%. **[Though not specified, it is assumed that the racemic form of the drug was administered.]** Stability and levels of methylphenidate in feed were verified. The control group contained 40 mating pairs and each treatment group contained 20 mating pairs each. Animals were exposed to methylphenidate during a 7-day pre-cohabitation period, a 98-day cohabitation period, and during the 21-day nursing period for the last litter produced. **[Though not clearly explained in the protocol, CERHR is aware that this type of study involves removing all but the last litter produced so that the animals can continue mating.]** After the last litter was weaned, the animals from the high-dose group were given diets containing the same levels of methylphenidate hydrochloride as their parents (0.1% or 151.7 mg/kg bw/day in males and 171.4 mg/kg bw/day in females). Upon reaching sexual maturity, male and female F_1 control and high-dose animals (~20/group/sex) were mated within respective treatment groups for 7 days in order to evaluate fertility. Statistical analyses include Cochran-Armitage and Fisher exact test to evaluate fertility; Kruskal-Wallis, Jonckheere, and Wilcox-Mann-Whitney U tests to evaluate numbers of litters, live pups, and organ weights; F-test and *t*-test to evaluate pup weight (co-varied with litter size); and Jonckeere, Shirley, and Dunn test to evaluate body weight and food intake.

Due to deaths of mice in each dose group, reproductive parameters were examined in 30–37 pairs of F_0 controls and 15–19 F_0 pairs/treatment group. Methylphenidate treatment of F_0 mice did not significantly affect fertility, cumulative days to litter, number of litters/pair, litter size, live pups, or live pup sex or weight. Methylphenidate did not affect food intake in male or female F_0 mice. F_0 female body weight was not affected, but body weights of males in the 0.1% group were significantly lower at weeks 6, 10, and 14. SMVCE and necropsies were conducted in 10 F_0 mice/sex from the control and 0.1% dose groups **[presumably after weaning of the F_1 litters]**. Vaginal smears conducted for 12 days prior to necropsy revealed no effect of 0.1% methylphenidate on estrous cycle length or frequency of stages. Absolute and adjusted (to body weight) liver weights were increased in F_0 females from the 0.1% groups. Treatment with 0.1% methylphenidate had no effect on epididymal sperm motility or density; percentage of abnormal sperm was reduced in the 0.1% group. Body weight was significantly reduced in males treated with 0.1% methylphenidate. There was no effect on absolute weight of seminal vesicles, right epididymis, right testis, cauda epididymus, or prostate gland. Absolute and relative liver weight were increased in males of the 0.1% group. No histopathological evaluations were conducted in F_0 mice.

There were no significant effects on postnatal survival, weight gain, or food intake in F_1 pups. In the reproductive assessment of F_1 mice, 17/20 control pairs and 18/19 pairs in the 0.1% methylphenidate group were fertile. Treatment of F_1 mice with 0.1% methylphenidate had no significant effects on mating, fertility, live pups/litter, or pup sex or weight. All surviving F_1 animals underwent an SMVCE analysis and were necropsied at the end of the study **[presumably following birth of the F_2 litters]**. Monitoring of estrous cycles for 12 days prior to necropsy revealed no effect of 0.1% methylphenidate on length of estrous cycle or frequency of estrous phases. Terminal body weight of F_1 females in the 0.1% group was not affected. Absolute and relative liver and ovary weights and absolute kidney weights were increased in F_1 females of the 0.1% group. In F_1 males of the 0.1% group, there was no adverse effect on epididymal sperm motility, density, or morphology and testicular sperm count. Terminal body weights of males in the 0.1% group were not affected. Organ weight changes in F_1 males of the 0.1% group included an increase in absolute and relative liver weight, and decrease in absolute and relative seminal vesicle weight. No histopathological evaluations were conducted in F_1 mice.

[The Expert Panel notes that contrary to the Morrissey et al. *(62)* results in rats, the NTP study *(169)* demonstrated that epididymal sperm abnormalities were significantly decreased relative to

concurrent controls. It is possible that the apparent discrepancy is due to the use by Morrissey et al. of a trend test (Jonkheere) and the use by NTP of pair-wise comparisons to the control group. These pair-wise comparisons may have been statistically significant in the absences of a significant trend. The NTP authors concluded that there were no changes in murine reproductive endpoints at <1000 ppm in the diet.]

The report of the subcontractor, Environmental Health Research and Testing Inc., for the sperm/estrous cycle evaluations from both the subchronic (13 week) toxicity studies in rats and mice *(170*), which included evaluation of reproductive organs, estrous cycle data, and sperm parameters and the RACB study in mice *(169*), which included fertility measures as well as reproductive organ, estrous cycle, and sperm data, has been provided to the Expert Panel. These reports are an important source of information for evaluating the male reproductive toxicity of methylphenidate.

A significant reduction in sperm motility was found in the subchronic study; however, this effect was not seen in the RACB study. The two studies were compared to determine the basis for this discrepancy.

Table 34 compares design parameters and
Table 35 compares outcome measures.

Table 34. Comparison of Two NTP Studies Evaluating Effects of Methylphenidate on Sperm Parameters in Mice

	Study design	
Parameter	Subchronic *(8*)	RACB (F_0 generation) *(169*)
Strain of mice	$B6C3F_1$	CD-1 Swiss
Age at initiation of dosing	6 weeks	11 weeks
Duration of dosing	13 weeks	20 weeks
Doses	0, 500, 2000 ppm	0, 1000 ppm
Group size	10	10–20 (depending on endpoint)
Route	Feed	Feed
Mating experience	No	Yes

Table 35. Comparison of Reproductive Organ and Sperm Parameters from Two NTP Studies Evaluating Methylphenidate

	Subchronic *(8*)			RACB F_0 *(169*)	
Parameter	Control	500 ppm	2000 ppm	Control	1000 ppm
Body weight	36±0.5	31±1*	29±6*	43±1[1]	39±1*
Testes weight (g)	130±3	116±2*	115±2*	144±4	145±10
Cauda weight (g)	17±1	14±0.5*	13±0.4*	18±1	17±1
Motility (% motile)	69±3	60±1*	61±2*	91±1	93±1
Sperm head morphology (% abnormal)	1.8±0.2	1.7±0.2	2.0±0.2	5.7±1.0	3.1±0.3*
Sperm density (10^6/g cauda)	801±83	888±74	869±78	1442±117	1512±130
Total sperm (10^6)	14±4	13±4	11±3	27±3	25±2

Data expressed as mean ± SEM. *Statistical difference from respective control group, *t* test.

Mice in the control group of the subchronic study were smaller, had smaller testes, lower sperm density, lower motility, and fewer sperm with morphological abnormalities than mice in the control group of the RACB study. These differences may be related to strain differences or to differences in age. The Expert Panel was not able to find studies directly comparing methylphenidate effects in CD-1 and B6C3F_1 miceThe Panel noted that mice were in different stages of development upon commencement of dosing. B6C3F1 were exposed in the prepubertal stage. F_0 CD-1 Swiss mice were dosed in adulthood. F_1 CD-1 Swiss mice were exposed indirectly during gestation and lactation and directly beginning at weaning.

The B6C3F_1 mice in the subchronic study also demonstrated an effect of methylphenidate on body and reproductive organ weights. It is possible that the sperm motility effects were secondary to growth retardation. However, regression analysis conducted on the individual data did not reveal an association between testis or cauda epididymis weight and sperm motility.

The contractor's report from the subchronic study also included the detailed analysis of the rat sperm. Although a significant group difference in sperm motility was not found in the sample (n=10/group), the *P* value for the mean comparison was 0.07.

Strengths/Weaknesses: Strengths include verification of test material purity, dietary concentrations, homogeneity, and stability of methylphenidate in the diet. Sample sizes were sufficient and statistical analyses were appropriate. With respect to study weaknesses, it would have been useful if the researchers had included histopathology on the F_1 seminal vesicles and ovaries to confirm that weight changes in these organs did not correlate with histological changes.

Utility (Adequacy) for CERHR Evaluation Process: This study is very useful in the evaluation process.

Teo et al. *(47)*, from Celgene Corporation, treated pregnant Sprague-Dawley rats with *d*-methylphenidate (purity 98–102%) or *d,l*-methylphenidate (chiral purity 50:50) given orally in 2 daily doses 6 hours apart. **[The route (oral) is indicated only in the Discussion section; another paper by these authors *(46)* used gavage treatment and the Expert Panel assumes gavage treatment for this study as well.]** In the main study, discussed in Section 3.2.2, 25 pregnant rats/dose group were given *d*-methylphenidate at 0, 2, 6, or 20 mg/kg bw/day or *d,l*-methylphenidate 40 mg/kg bw/day. Animals were given these doses in 2 equal treatments **[presumed gavage]** separated by 6 hours on GD 7–PND 20 (plug = GD 0, birth = PND 1). Pups were weaned on PND 21 and 25 male and female offspring per dose group were followed as the F_1 generation, using at least 1 pup/sex/litter where possible. Females were evaluated for vaginal patency beginning on PND 28 and males were evaluated for preputial separation beginning on PND 39. At approximately 90 days of age, 1 F_1 male and 1 F_1 female/litter were cohabited for 21 days, after which males were killed and necropsied. Females were killed and necropsied on GD 20. Data were analyzed using ANOVA with post hoc Dunnett test or Kruskal-Wallis with Dunn test, depending on homogeneity of variance.

Clinical signs (hyperactivity and aggression) were noted in the F_0 dams given 6 mg/kg bw/day *d*-methylphenidate. Additional clinical signs were noted at 20 mg/kg bw/day *d*-methylphenidate and at 40 mg/kg bw/day *d,l*-methylphenidate. There was a higher incidence of clinical signs at 40 mg/kg bw/day *d,l*-methylphenidate than at 20 mg/kg bw/day *d*-methylphenidate, although the amount of the active enantiomer (*d*-methylphenidate) was identical in both treatments. Duration of gestation was prolonged by about 0.5 days in the groups given *d*-methylphenidate 20 mg/kg bw/day and *d,l*-methylphenidate 40 mg/kg bw/day. There were no treatment-related effects on number of live or stillborn pups, pup survival during the lactation period, or pup weight at birth or during the lactation period. There were no notable findings in pups necropsied on PND 21. Body weight gain and feed consumption in the F_1

males in the *d,l*-methylphenidate 40 mg/kg bw/day group were decreased for several individual weeks and overall in the PND 1–71 time period. There was no effect on body weight or feed consumption for any of the doses of *d*-methylphenidate, and female F_1 body weight was not affected by any of the treatments during PND 1–71. There were no treatment-related effects on day of preputial separation or vaginal patency. Terminal body weights were decreased in F_1 males in the *d*-methylphenidate 20 mg/kg bw/day and *d,l*-methylphenidate 40 mg/kg bw/day groups. Relative weight of the testis was increased in the *d,l*-methylphenidate 40 mg/kg bw/day group, but not in any of the *d*-methylphenidate groups. Mating of the F_1 animals showed no treatment-related effects on number of pregnant animals, corpora lutea, or implantations, and no alterations in live or dead fetuses/litter, resorptions, sex ratio, or fetal weight. Doses of *d*- and *d,l*-methylphenidate were 40 and 27 times the maximum daily human therapeutic dose, respectively. The authors estimated from AUC values that the top doses of *d*-methylphenidate and *d,l*-methylphenidate used in this study were 5.6 and 11.9 times the human therapeutic dose. The decrease in weight in F_1 males was evaluated as consistent with the decrease in feed consumption, although no explanation could be given for the lack of effect in females. *d*-Methylphenidate at this dose was considered not to have adverse reproductive effects. **[The Expert Panel notes that dosing of the F_1 animals in the study of Teo et al. *(47)* occurred only through treatment of their dams during pregnancy and lactation. This study is, then, a developmental toxicity study. The study is presented here, however, because many of the endpoints were reproductive in nature. The study is presented in this section for comparison with the available reproductive toxicity studies, but the conclusions derived from this study are presented in Section 3. The Expert Panel notes that aside from decreased gestational body weight gains, minimal clinical signs (dilated pupils and increased vocalization in *d,l*-methylphenidate dams only) and effects on F_1 male body weight gains and terminal body weights at 20 and 40 mg/kg bw/day *d*- or *d,l*-methylphenidate, respectively, neither compound produced significant adverse effects in F_0 or F_1 rats.]**

Strengths/Weaknesses: This study had sufficient group sizes, appropriate controls, and appropriate statistical analyses. The investigators controlled for litter effects. Chemical purity and stability were verified. A weakness is that there were no toxicokinetic measurements taken during lactation. Pups were only exposed to methylphenidate through maternal milk on PND 1–20. This feature, coupled with interspecies differences in developmental stage at birth, makes it difficult to extrapolate this dose regimen to children who are given methylphenidate directly. Also, there was some confusion in the study text describing *d,l*-methylphenidate-associated maternal body weights (Section 3.2.2.). The passage begins by describing a decrease in maternal body weight gains at 40 mg/kg bw/day *d,l*-methylphenidate during the dosing and gestation periods. Later, the text states, “Weights were significantly greater for the 40 mg/kg bw/day *d,l*-methylphenidate groups on GD 12–15,” which is inconsistent with Figure 2 of the study. The study text also states, “No differences were seen in body weight gains between the 40 mg/kg bw/day *d,l*-methylphenidate and vehicle control groups.” The study interval for this statement is not identified (e.g., lactation body weight gains?). Aside from the passages describing maternal body weight effects, the text was clearly presented.

Utility (Adequacy) for CERHR Evaluation Process: This study is useful for the evaluation process, although limited based on the weaknesses identified above.

4.3 Utility of Reproductive Toxicity Data

There are no data for evaluating possible reproductive toxicity in humans. There is an NTP *(169)* study examining fertility in two generations of mice exposed to methylphenidate through diet and an NTP study examining estrous cyclicity, reproductive organ weights, and sperm parameters in mouse and rat subchronic studies *(170)*. A study conducted in rats *(47)* provided some information about reproductive toxicity in F_1 offspring following in utero and lactational exposure to methylphenidate, but was not

sufficient for examining reproductive toxicity in rats because there was no exposure of F_0 males and females prior to mating.

4.4 Summary of Reproductive Toxicity Data

4.4.1 Human Data
No human data were located.

4.4.2 Experimental Animal Data
In an NTP continuous breeding study *(169)*, male and female Swiss CD-1 mice were fed diets containing 0, 0.012, 0.05, or 0.1% methylphenidate hydrochloride **[presumably *d,l*-enantiomers]**. Authors estimated methylphenidate doses of 0, 18.2, 75.7, and 160.2 mg/kg bw/day in males and 0, 17.7, 76.0, and 150 mg/kg bw/day in females. The control group contained 40 mating pairs and the treatment groups 20 mating pairs each. Animals were exposed to methylphenidate during a 7-day pre-cohabitation period, a 98-day cohabitation period, and during the 21-day nursing period for the last litter produced. After the last litter was weaned, the offspring from the high-dose group were given diets containing the same levels of methylphenidate hydrochloride as their parents (0.1% or 151.7 mg/kg bw/day in males and 171.4 mg/kg bw/day in females). Upon reaching sexual maturity, male and female F_1 control and high-dose animals (~20/group/sex) were mated within respective treatment groups for 7 days in order to evaluate fertility. Estrous cycles and sperm parameters were examined in F_0 and F_1 mice of the 0.1% methylphenidate group. Methylphenidate treatment had no effect on fertility, live pups/litter, pup sex or weight, estrous cycles, or sperm motility, density, or morphology in F_0 and F_1 mice; cumulative days to litter and number of litters/pair in F_0 mice; or mating of F_1 mice.

In contrast to negative findings in the continuous breeding study, $B6C3F_1$ mice fed diets containing 0.0125, 0.05, and 0.2% methylphenidate for 13 weeks experienced slight reductions in sperm motility (69% motility in control versus 57–61% motility in treated groups) and decreased testis and cauda weight, which are likely related to reductions in body weight *(170)*. The Expert Panel noted several differences between the two studies, including different strains of mice, different ages at initiation of treatment, and different exposure durations. Estrous cycles were altered in rats fed diets containing 0.2% methylphenidate.

Teo et al. *(47)* treated Sprague-Dawley rats with 0, 2, 6, or 20 mg/kg bw/day *d*-methylphenidate (purity 98–102%) or 40 mg/kg bw/day *d,l*-methylphenidate given orally **[presumed gavage]** in 2 daily doses 6 hours apart from GD 7–PND 20. Pups were weaned on PND 21 and 25 male and female offspring per dose group were followed as the F_1 generation, using at least 1 pup/sex/litter where possible. Maternal and typical developmental toxicity findings are reported in Section 3.2 **[The Expert Panel notes that because exposure of the F_1 animals was entirely through treatment of their dams, all the findings in the study can be considered developmental. The study is presented in this section for comparison with the available reproductive toxicity studies, but the conclusions derived from this study are presented in Section 3.]** Duration of gestation was prolonged by about 0.5 days in the F_0 dams given *d*-methylphenidate 20 mg/kg bw/day and *d,l*-methylphenidate 40 mg/kg bw/day. There were no treatment-related effects on day of preputial separation or vaginal patency in F_1 rats. Mating of the F_1 animals showed no treatment-related effects on number of pregnant animals, corpora lutea, or implantations, and no alterations in live or dead fetuses/litter, resorptions, sex ratio, or fetal weight.

One study provided information on vaginal opening and estrous cycling in rats sc dosed with 0, 70, or 200 mg/kg bw methylphenidate given in 2 divided doses on ~PND 5–26. While the animals were dosed through the sc route, the panel notes that humans typically are exposed through oral or iv routes *(161)*. Methylphenidate significantly delayed vaginal opening from 34.4 ± 0.5 (SEM) days of age in controls to 38 ± 0.7 (70 mg/kg bw) and 39.1 ± 1.1 (200 mg/kg bw) days of age in the treatment groups. The

numbers of estrous cycles in the 30-day period following treatment were significantly reduced from 5.2 ± 0.5 in the control group to 3.2 ± 0.2 (70 mg/kg bw) and 0.8 ± 0.3 (200 mg/kg bw) in the treatment groups. A second group of rats was treated with 70 mg/kg bw methylphenidate for 30 days beginning at 21–23 days of age. Though not significant, vaginal opening was delayed, and occurred at the same approximate time period as the younger group (38.2 ± 2.3 days); numbers of estrous cycles were reduced only during treatment. The Expert Panel notes that it is difficult to discern whether methylphenidate has direct effects on vaginal opening and hormone levels or effects are secondary to delayed development and altered growth rates at high doses of methylphenidate.

Expert Panel Conclusion

There are no human data on possible reproductive effects of methylphenidate.

There are insufficient data to evaluate the effects of methylphenidate on reproductive toxicity in experimental animals. There is 1 study demonstrating reduced sperm motility in mice fed diets containing ≥0.0125% methylphenidate (15 mg/kg bw/day*) and altered estrous cycle profile in rats fed diets containing 0.2% methylphenidate (150 mg/kg bw/day*); however, a second study in a different mouse strain using a different design did not identify effects on sperm motility or estrous cyclicity at doses up to 0.1% methylphenidate in diet (~ 150–160 mg/kg bw/day*).

*See Section 2 for mg/kg bw/day values estimated by study authors

Note: The definitions of the term sufficient and the terms assumed relevant, relevant, and not relevant are in the CERHR guidelines at http://cerhr.niehs.nih.gov/news/guidelines.html.

5.0 SUMMARIES, CONCLUSIONS, AND CRITICAL DATA NEEDS

Section 5.1 Developmental Toxicity

The Expert Panel concluded that within a number of spheres there was insufficient evidence to evaluate the developmental toxicity in humans of methylphenidate treatment. This deficiency was noted in the consideration of prenatal exposure due to a combination of design limitations and paucity of studies. With respect to growth in children and adolescents, an association of reduced growth and methylphenidate treatment was noted; however, determination of a causal association with the medication was not possible due to a lack of control of potential confounding factors that could be causing the observed growth effects. Data were also insufficient on the effects of methylphenidate on heart rate and blood pressure. Although some studies demonstrated short-term elevations of heart rate and blood pressure, the clinical importance of these findings is unclear, and it is not known whether sustained or clinically important effects occur. The evaluation of a possible relationship between methylphenidate therapy and altered risk of tobacco use, problematic alcohol use, and illicit substance use in adolescents and adults was also considered inconclusive, although limited data suggested that there was a reduction in illicit substance abuse in medication-treated versus untreated children and adolescents with ADHD.

With respect to the experimental animal data, the Expert Panel concluded that available data were insufficient for a full evaluation of developmental toxicity of methylphenidate in rats and rabbits after gestational exposure. The one published paper that presented these data did not present adequate detail on the results for the Expert Panel to reach a conclusion. With regard to postnatal exposure there was limited but sufficient evidence to evaluate effects on growth; in 2 studies sc administration of methylphenidate to rats at doses of 35 mg/kg bw/day or higher produced reversible growth restriction.

The Expert Panel also felt that data were insufficient for the evaluation of developmental neurotoxicity in experimental animals because of inadequate experimental designs, single dose level studies, and routes of administration that do not reflect human therapeutic or abuse scenarios. In a similar fashion, the question of methylphenidate-associated sensitization to other stimulants could not be fully evaluated.

5.2 Reproductive Toxicity

There are no data examining the effects of methylphenidate on human reproductive endpoints.

The Expert Panel concluded that the experimental animal data are insufficient to evaluate the effects of methylphenidate on reproductive toxicity. Two mouse studies, including a subchronic study with limited assessment of reproductive endpoints and a continuous breeding study, had divergent outcomes in reproductive organ weights and sperm motility. These differences in outcome, which complicated interpretation, may be related to species/strain used, age at initiation of exposure, and/or other study design differences. The continuous breeding study reported no differences in fertility in two generations of mice, including the F_1 generation that was exposed during development. Two rat studies designed to examine reproductive effects of methylphenidate after exposure during the perinatal period also yielded different results with respect to delayed markers of puberty onset.

5.3 Human Exposure Data

Methlyphenidate is a medication marketed for the treatment of ADHD and narcolepsy in children 6 years and older and in adults. It is available as a 50/50 mixture of the *d*-threo and *l*-threo-enantiomers (1) or only the *d*-threo-enantiomer (2). Between 2000 and 2002, there was a 64% increase in the

production of methylphenidate in the US. Treatment of ADHD in teenagers and adults is increasing and is an emerging area of study. More people of reproductive age may be taking methylphenidate. There is no information on the numbers of pregnant or lactating women prescribed the drug. Human exposures are primarily through therapeutic medication use and to a lesser extent, drug abuse (oral, nasal, iv). No information was identified on possible environmental or occupational exposure.

Recommended oral doses are 10–60 mg/day for children older than 6 years and for adults. Methylphenidate is available in short-acting, intermediate-acting, and extended-release formulations, and is administered 1–3 times daily, depending on the required dose and the form of medication. Dose schedules can be individualized according to patient needs. The Expert Panel is aware of off-label uses of methylphenidate to treat depression, primarily as an adjunct to antidepressant medication, and to treat patients with post-stroke cognitive impairment. The Expert Panel is also aware of off-label use of methylphenidate in children younger than 6 years of age.

5.4 Overall Conclusions

There is a substantial published database of studies designed to investigate the potential adverse reproductive and developmental effects of methylphenidate exposure in both humans and laboratory animals. However, thorough review of these numerous studies led the Expert Panel to judge that the data were generally insufficient to reach valid scientific conclusions with regard to possible reproductive or developmental effects.

Specifically, the Expert Panel found data were available but **insufficient** to evaluate

- Developmental toxicity in humans exposed prenatally;
- Reproductive toxicity in humans (no data available);
- Effects on growth in exposed children and adolescents;
- Effects on heart rate and blood pressure in exposed children;
- Altered risks of tobacco use, problematic alcohol consumption, or illicit substance abuse in adolescents or adults;
- Developmental toxicity, including neurotoxicity, in laboratory animals;
- Sensitization to other stimulants in laboratory animals; and
- Reproductive toxicity in laboratory animals.

The Expert Panel judged the data **sufficient** to conclude that

- Postnatal subcutaneous administration of ≥35 mg/kg bw/day methylphenidate to rats produces reversible growth restriction; and
- Methylphenidate treatment of children at standard therapeutic doses does not increase the incidence of tics or movement disorders.

Thus, the only conclusions the Expert Panel was able to reach with regard to potential adverse effects in humans following therapeutic exposures were (1) negligible concern for methylphenidate-induced tics and movement disorders predicated on human data and (2) minimal concern for methylphenidate-induced growth restriction predicated on data derived from rat studies using high doses and sc route of administration.

The Expert Panel was impressed with the paucity of interpretable toxicity data relevant to human therapeutic use.

The decision to use the medication must be made by the responsible health care provider, the patient, and the family if the patient is a minor.

5.5 Critical Data Needs

Critical data needs are defined as research or studies that would provide information to substantially reduce uncertainty and increase confidence in assessment of human reproductive and developmental risks. Although numerous studies documenting effects of childhood exposures were available, the Expert Panel found the studies were generally limited due to inadequate design or use of outdated methods or standards. Therefore, the Expert Panel concluded that better quality studies are required to effectively evaluate toxicity concerns associated with methylphenidate. There are a number of considerations that should be applied in the design of quality human studies for methylphenidate. The studies need to use current techniques and age-standardized norms. Confounding factors such as prenatal and/or postnatal exposure to tobacco, alcohol, and illicit drugs, parental psychiatric disorders, and care-giving environment need to be noted and adequately controlled. Subpopulations that are susceptible to development of ADHD (e.g., children born prematurely) need to be considered in study design and interpretation. The studies need to consider currently under-represented populations such as children born prematurely, non-White individuals, and females. Current trends in treatment such as infrequent use of drug holidays and durations of exposure that often extend through adolescence and into adulthood need to be considered. The studies should compare endpoints in individuals within the same developmental stage (e.g., childhood versus adolescence) and use appropriate controls.

5.5.1 Developmental and Reproductive Toxicology Data Needs

Human Studies:

- Studies are needed on pre- and postnatal development effects following in utero exposure to methylphenidate, stratified by trimester of exposure.
- Pharmacokinetics data relating to gestation and lactation are needed.
- Data on possible reproductive effects of methylphenidate in humans are needed.
- Studies are needed to characterize the effects of methylphenidate on short-term growth velocity (height and weight), with appropriate controls for confounders.
- Studies are needed to characterize the effects of methylphenidate treatment on final height and weight.
- Due to off-label use of methylphenidate in children <6 years old, studies are needed to identify possible developmental issues that can affect variations in drug efficacy and toxicity.
- Studies are needed to identify age-related variations that affect efficacy and toxicity because of the increasingly wide age range of exposure.
- Studies are needed to evaluate possible effects of methylphenidate on pubertal progression.
- Studies are needed to evaluate possible effects of methylphenidate treatment on tobacco use, problematic use of alcohol, and illicit substance use in children, adolescents, and adults.
- Toxicity data are needed for under-represented populations of children and adolescents including girls, non-Caucasians, children with dysmorphic and genetic syndromes and global mental retardation, and children born prematurely.

Experimental Animal Studies:

- Data are needed on developmental neurotoxicity in animals. The studies should include routes of exposure consistent with human exposure scenarios and multiple dose levels.
- Studies on rat and rabbit developmental and reproductive toxicity, and pharmacokinetics related to gestation and lactation need to be obtained from the FDA, other agencies, or industry. These data are either not available or available only as summaries, thus precluding independent scientific review by the Expert Panel.

- Studies are needed to evaluate possible effects of methylphenidate on pubertal timing and quality.
- Studies are needed to model data obtained by non-oral routes of administration so these data can be more useful in evaluating human oral exposures.
- Valid animal models of ADHD need to be used in studies of methylphenidate toxicity in order to evaluate toxicity in a system that more closely approximates the human patient population.
- Nonhuman primate or guinea pig studies would be useful to evaluate effects of gestational methylphenidate use in the second and third trimesters.

5.5.2 Endpoints Other than Reproductive and Developmental Toxicity

- Data are needed to determine the numbers of methylphenidate prescriptions for teenagers and adults, children <6 years old, and pregnant and lactating women.
- Studies are needed to characterize the long-term effects of methylphenidate treatment on heart rate and blood pressure. The studies need to consider ethnic variation in subpopulations, such as African Americans, who are especially susceptible to cardiovascular disease.

5.5.3 Non-Critical Data Needs

Although the following data needs are not critical for a risk evaluation, they would be generally informative:

- Data are needed on methylphenidate-associated sensitization to other stimulants.
- Studies are needed to identify the specific esterase(s) that metabolize methylphenidate.
- Information is needed on the effects of ontogeny and polymorphisms on esterase activity and other factors (e.g., receptor activity) that may affect efficacy and toxicity of methylphenidate.

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