DEVELOPMENT OF A REFERENCE DOSE (RfD) FOR METHAMPHETAMINE

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Introduction

The clandestine synthesis of methamphetamine is a growing public health and environmental concern. It is estimated that for every pound of methamphetamine synthesized there are six or more pounds of hazardous materials or chemicals produced. These are often left on the premises, dumped down local septic systems or illegally dumped in backyards, open spaces, in ditches along roadways or down municipal sewer systems. In addition to concerns over the health and well being of peace officers and public health officials, there is increasing concern about potential health impacts on the public and unknowing inhabitants, including children and the elderly, who subsequently occupy dwellings where illegal drug labs have been located.

Under the provisions of Senate Bill 536 (Bowen, Chapter 587, Statutes of 2005), the Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidance for risk-based target remediation standards for methamphetamine, methyl iodide, phenyl-2-propanone and phosphine to ensure protection of the health of all persons who subsequently occupy a former clandestine methamphetamine lab. The Department of Toxic Substances Control (DTSC) will use this guidance to develop the standards. Senate Bill 536 requires that guidance be developed first for methamphetamine.

Strategy for Developing a Risk-Based Remediation Standard for Methamphetamine

To develop a risk-based remediation standard, the toxicity of a chemical – its adverse health effects and the doses that are required to elicit them – must be well characterized. In addition, the pathways of exposure to the chemical must be identified, algorithms to quantitatively estimate the magnitude of exposure via each pathway must be developed, and appropriate parameters for each of the exposure algorithms must be researched and justified.

This report describes the toxicity of methamphetamine and provides justification for a sub-chronic *reference dose (RfD)* for the drug.[1] RfDs are concentrations or doses at or below which adverse health effects are not likely to occur. A central assumption is that a population threshold exists below which adverse effects will not occur in a population; however, such a threshold is not observable and can only be estimated. Areas of uncertainty in estimating effects among a diverse human population are addressed using extrapolation and uncertainty factors. Therefore, an RfD for methamphetamine is an estimate of its toxicity threshold in humans.

To develop an RfD for methamphetamine, the critical effect(s) of the drug must be identified. According to the United States Environmental Protection Agency (U.S. EPA), *critical effect* is

[1] The model that was adopted to estimate the magnitude of exposure to methamphetamine in a former clandestine lab is described in a separate document.

the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases. Therefore, if an exposure standard (i.e., a cleanup level) for a chemical is set low enough to prevent the occurrence of its critical effect, then the standard will prevent the occurrence of any other toxic effect as well.

For methamphetamine, we have taken a health-protective position that *any* effect induced by the drug is an adverse effect and, potentially, a critical effect. Characteristic signs and symptoms of methamphetamine toxicity in humans include general sympathomimetic effects such as stimulation of the central nervous system (CNS), dyspnea (shortness of breath or labored breathing), mydriasis (dilation of the pupils), hyperpyrexia (exceptionally high fever), diaphoresis (profuse perspiration) and anorexia (loss of appetite), and cardiovascular effects such as tachycardia (rapid heart rate), palpitations (irregular and/or forceful heart beats), and hypertension. Higher doses and/or repeated exposure can lead to cardiomyopathy, myocardial infarction, rhabdomyolysis (destruction of skeletal muscle cells), intracerebral bleeding and stroke, seizure and coma. In a report of 18 cases of methamphetamine poisoning in pediatric patients (Kolecki, 1998), the most common presenting symptom was agitation, and the most common presenting signs were tachycardia, inconsolable irritability and crying, and protracted vomiting. Less commonly observed were hyperthermia, ataxia (loss of muscle coordination), nystagmus (roving eye movements), and seizure. Based on this brief summary of adverse effects, candidates for the critical effect of methamphetamine include CNS stimulation, mydriasis, anorexia, tachycardia and hypertension. More severe effects such as seizure and myocardial infarction would be expected to occur at higher doses and therefore would not be regarded as critical effects.

Scope of the Literature Review: Emphasis on Research in Human Subjects

Approximately 160 published research reports were critically reviewed to characterize the toxicity of methamphetamine. In general, the literature review was limited to studies of the effects of methamphetamine in humans. Human studies were preferred for the following reasons:

- Since the late 1930s, more than 100 peer-reviewed reports characterizing the effects of methamphetamine in humans under controlled conditions have been published.
- Toxic effects have been described following multiple routes of exposure, including intravenous injection, subcutaneous injection, intramuscular injection, ingestion, and inhalation.
- Several studies have been conducted characterizing adverse effects in potentially sensitive sub-populations, including children, pregnant women and the elderly.
- Studies have been conducted characterizing adverse effects in normal, drug-naïve individuals; persons with limited “recreational” experience with methamphetamine, persons with pre-existing health problems (e.g., narcolepsy), and persons with pre-existing psychiatric illness (e.g., depression).
- Multiple doses of methamphetamine have been evaluated.

- Studies characterizing the effects of acute, sub-acute and sub-chronic daily exposure to methamphetamine have been conducted. Exposure durations as long as 20 weeks have been evaluated.
- Several studies have been conducted under placebo-controlled, double blind conditions.
- Studies examining the effects of sustained-release formulations of methamphetamine have been conducted. This mode of dosing more closely mimics the long-term, low level exposure that is anticipated to occur in humans residing in a former clandestine methamphetamine lab.

Conversely, there were several reasons why an intensive review of the animal toxicity literature was not conducted. Foremost among these is the large species-dependent disparity in sensitivity to the drug, with laboratory animals (particularly rats and mice) generally being much less sensitive to methamphetamine than humans. For example, in characterizing the cognitive effects of postnatal exposure to methamphetamine in mice, Acevedo et al. (2007) utilized a daily dose of 5 mg/kg. In an adult human, this would be equivalent to a total dose of 300-350 mg, which would be potentially life-threatening. In addition, the pharmacokinetics of methamphetamine in laboratory animals and humans differ substantially. As Cho et al. (2003) point out, the elimination half life of methamphetamine is 70 minutes in rats; in humans, the half-life is 12 hours.

Given the wealth of studies examining the effects of methamphetamine in humans and the uncertain relevance of data derived from laboratory animal studies, the literature review presented in this report focuses almost exclusively on human toxicity data.

Primary Support Studies Cited to Identify Methamphetamine's Critical Effects

The primary study used for development of an RfD for methamphetamine was a sub-chronic study of the drug's efficacy in reducing weight gain during pregnancy (Chapman, 1961). The study involved a total of 84 women who were administered a sustained-release formulation of d-methamphetamine (Desoxyn® Gradumet®). Three doses of methamphetamine were tested, and the study was conducted under placebo-controlled, double blind conditions. The duration of treatment was 15-16 weeks. Sub-chronic dosing with methamphetamine produced a dose-related decrease in weight gain over the course of pregnancy. This effect was highly statistically significant. Based on the results of this study, the critical effects of methamphetamine were identified as appetite suppression and consequent reduction in body weight gain, and the lowest observed adverse effect level (LOAEL) for methamphetamine was 0.08 mg/kg-day. The results of the Chapman study were corroborated in a smaller but similar study conducted by Bayly (1960). A detailed summary of the Chapman study and statistical analysis of the data are provided in the next section of this report.

A large study of the efficacy of methamphetamine as an aid in the treatment of enuresis (bed wetting) in children (Young and Turner, 1965; summarized on pages 51-53) was also evaluated as a potential basis for development of the RfD. This study involved 299 children 4-15 years of

age.[2] Most of the children in one treatment group of 110 children were given 5 mg of Methedrine (d-methamphetamine) each day just before bedtime. There were 105 children in the control (non-drug) group. Sleep disturbance was experienced in eight of the 110 children who received Methedrine. This effect disappeared when the dose of the drug was reduced to 2.5 mg. These results confirm the frequently reported observation that a critical effect of methamphetamine is disturbance of sleep. They suggest that the LOAEL for methamphetamine in children was 5 mg (0.2 mg/kg-day), and that the no observed adverse effect level (NOAEL) was 2.5 mg (0.1 mg/kg-day). However, the conclusion that 0.1 mg/kg-day represents a childhood NOEAL must be tempered by the fact that it is based on observations from just eight children.

The LOAELs reported by Chapman (1961) and Young and Turner (1965) were 0.08 mg/kg-day and 0.2 mg/kg-day, respectively, suggesting that adults may be more sensitive to methamphetamine than children.[3] The fact that the critical effects were weight loss in the adult study and sleep disturbance in the childhood study may account in part for this disparity.[4] Another significant difference between the two studies was the drug formulation: a slow release formulation which produces more constant blood levels over a longer duration was used in the adult study but not in the childhood study.

Young and Turner also identified a NOAEL, 0.1 mg/kg-day. The lack of an experimentally identified NOAEL in the Chapman study has a significant impact on the derivation of the RfD for methamphetamine. For the purpose of estimating an RfD, an experimentally identified NOAEL is generally incorporated into the calculation without an additional uncertainty factor. In contrast, if a LOAEL is used as a basis for the RfD, it is usually divided by a 10-fold uncertainty factor to estimate a NOAEL. Therefore, a NOAEL estimated from the data of Chapman (1961) is 0.008 mg/kg. Comparing the *experimentally determined* NOAEL from the Young and Turner study (0.1 mg/kg-day) with the *estimated* NOAEL from the Chapman study (0.008 mg/kg-day), it is clear that the choice of Chapman (1961) as the primary basis for development of a methamphetamine RfD effectively adds an additional 12.5-fold safety factor to the RfD.

The decision to adopt the results of Chapman (1961) as a basis for derivation of the RfD for methamphetamine was based on the following considerations:

(1) Chapman utilized the Gradumet® (sustained release) formulation of methamphetamine, which reduces the rate of drug absorption and produces more constant blood levels over a longer duration. This more closely mimics the long-term, low level exposure that is anticipated to occur as a result of living in a remediated methamphetamine lab.
(2) The NOAEL reported by Young and Turner was based on interviews with the parents of the children who participated in the study, not on direct observation by the researchers

[2] The average age of the children who received Methedrine was 7.1 years. For the purpose of calculating doses on a mg/kg body weight basis, the average body weight of a 7 year-old child is 25.1 kg (U.S. EPA, 1997).
[3] In assessing the relative sensitivities of adults and children with ADHD to stimulants, Dulcan (1997) suggested that adults are indeed more sensitive to both the therapeutic and side effects of these drugs.
[4] It should be noted that Chapman (1961) also identified women who experienced insomnia, and no significant differences across treatment groups were observed. [See Table 3, page 13]

themselves. This endpoint is not quantitative and was observed in just eight of the 110 treated children.

(3) As noted in several authoritative reviews (discussed in the following section), children may develop tolerance to the common side effects of stimulants. Therefore, the children in the Young and Turner study who initially experienced disturbance of sleep may have simply developed tolerance to this effect. If this were the case, sleep disturbance may have disappeared even if the dose of methamphetamine had not been reduced by half.

Comprehensive Reviews of the Adverse Effects of Stimulants in Children with ADHD

A primary source of uncertainty in the RfD calculation is the potential adverse effects of methamphetamine on the psychological, social, and cognitive development of children. To address this uncertainty, three recent comprehensive reviews of the effects of stimulants in children with Attention Deficit/Hyperactivity Disorder (ADHD) were consulted. While they do not specifically address the adverse effects of methamphetamine, these reviews provide detailed, authoritative summaries on the effects of drugs whose pharmacodynamics are similar to those of methamphetamine (e.g., methylphenidate) or whose pharmacodynamics and chemical structure are similar to that of methamphetamine (e.g., amphetamine).

In 1997, the American Medical Association's Council on Scientific Affairs published a report on the diagnosis and treatment of ADHD in children and adolescents (Goldman et al., 1997). The report was based on a comprehensive literature review using a National Library of Medicine database search of reports published between 1975 and March 1997. A significant portion of this report addressed the efficacy and adverse effects of stimulants commonly used to treat ADHD, and concluded the following:

- More than 170 studies have been conducted examining the effect of stimulants in children with ADHD. A total of over 6000 school-age children were involved in these studies.
- In treating ADHD, the response rate for any single stimulant drug is over 70 percent, and up to 90 percent of children will respond to at least one stimulant without significant adverse events if the dose is carefully titrated.
- Stimulants have been "unequivocally shown (i.e., by double-blind, placebo-controlled studies) to reduce core symptoms of hyperactivity, impulsivity and inattentiveness." Contrary to popular wisdom, the effect of stimulants in children with ADHD is not "paradoxical" because the direction of behavioral changes in children with psychological conditions other than ADHD (e.g., learning disabilities or depression) and normal controls is the same.
- Stimulants may produce adverse effects, but these are usually mild, of short duration, and controllable with adjustments in dose or the timing of dosing. The most common adverse effects are insomnia, decreased appetite, stomachache, headache, and jitteriness.
- A small percentage [not specified] of children administered a stimulant may experience cognitive impairment that requires a reduction in the dose or cessation of treatment. Rare cases of psychosis have also been reported.

A 1998 National Institutes of Health (NIH) Consensus Statement on the diagnosis and treatment of ADHD was prepared by a 13-member panel representing the fields of psychology, psychiatry, neurology, pediatrics, epidemiology, biostatistics and education. The panel developed its conclusions based on open forum presentations from 31 experts in the same fields and extensive review of the scientific literature. Two of the predefined questions the panel was tasked with addressing were, "What are the effective treatments for ADHD?" and "What are the risks of the use of stimulant medication and other treatments?" Regarding these questions, the panel concluded the following:

- In terms of short-term efficacy, few if any differences have been found among the major stimulants that are used to treat ADHD.
- Stimulants may not "normalize" the entire range of behaviors associated with ADHD, and children who are being treated with stimulants may continue to display certain behavior problems more frequently than normal children.
- While little information is available on the effects of long-term stimulant treatment, "…there is no conclusive evidence that careful therapeutic use is harmful."
- Adverse drug effects are usually related to dose. Moderate doses are most often associated with decreased appetite and insomnia, both of which occur early in treatment and may decrease with continued dosing.
- Very high doses of stimulants, particularly amphetamines, may cause central nervous system and cardiovascular damage as well as hypertension. A "rare percentage" [not specified] of children and adults treated with high doses may experience hallucinations. High doses are also associated with compulsive behaviors and movement disorders.
- There is a clear need for studies on the effects (risks and benefits) of long-term treatment with stimulants, alone and in combination with various behavioral treatments.

In 2001, the American Academy of Pediatrics (AAP) issued a clinical practice guideline for treatment of children between 6 and 12 years of age with ADHD.[5] The guideline was authored by a subcommittee composed of primary care and developmental-behavioral pediatricians, as well as experts in the fields of neurology, psychology, child psychiatry, education, family practice and epidemiology. The subcommittee's recommendations for treatment of children with ADHD were based on a systematic review of the published literature on this topic. A primary focus of this effort was an investigation of the efficacy and safety of stimulants[6] in treating the core symptoms of ADHD. Regarding the use of stimulants, the subcommittee reached the following conclusions:

- Three formal meta-analyses and one review of reviews support the short-term efficacy of stimulants in reducing the core symptoms of ADHD.

[5] A more recent AAP report (Brown et al., 2005) reviews additional information on specific treatments for ADHD, summarizing the empirical literature which provided the basis for the practice guideline's recommendations for pharmacologic and/or behavioral intervention.

[6] "First-line" stimulants evaluated were Methylphenidate [short-acting (e.g., Ritalin®), intermediate-acting (e.g., Ritalin SR®) and extended release (e.g., Concerta®)] and d-Amphetamine [short-acting (e.g., Dexedrine®), intermediate-acting (e.g., Adderall®), and extended release (e.g., Adderall-XR®)]. Both Adderall formulations are composed to mixed amphetamine salts (75 percent *d*-amphetamine and 25 percent *l*-amphetamine). Methamphetamine was not included in this evaluation, presumably because there were no published studies that met the subcommittee's criteria for inclusion.

- Most studies of stimulants have been short-term, demonstrating efficacy over several days or weeks. One study involving 579 children[7] demonstrated efficacy for as long as 14 months.
- No significant differences were found in the efficacy of methylphenidate and amphetamine and the different forms of these drugs; both improved core symptoms equally. Further, the results of numerous crossover trials indicate the efficacy of different stimulants in the same child.
- Stimulant dosages usually are not weight dependent, and marked individual variability in the dose-response relationship exists. Therefore, clinicians should begin with a low dose and titrate upward.
- Stimulants are generally considered safe. Side effects occur early in treatment and tend to be mild and short-lived.
- The most common side effects of stimulants are decreased appetite, stomachache, headache, delayed sleep onset, jitteriness and social withdrawal. Rarely, with high doses, some children experience psychotic reactions, mood disturbances or hallucinations. Most of these side effects can be managed by adjusting the dose or the dosing schedule.
- In a review of seven studies that compared stimulants with placebo or other medications, there was no evidence of an increase in the frequency of motor tics in children treated with stimulants.
- Behavioral rebound, motor tics and growth delay have been reported clinically, but these effects have not been observed consistently in controlled studies.

In summary, all three reviews concluded pharmacological doses of methylphenidate and amphetamine provide an effective means of reducing the core symptoms of ADHD in children. However, as noted in the NIH review, the social, psychological and cognitive difficulties experienced by children with ADHD are not uniformly ameliorated by stimulant treatment; some behavior problems appear to be unaffected by these drugs. Moreover, there was clear consensus on the primary adverse effects of stimulants in children, with appetite suppression and insomnia being most commonly observed. Side effects generally occur early in treatment, and tend to be mild and short-lived. In rare cases, however, children treated with higher doses may experience cognitive impairment, psychosis, mood disturbances and hallucinations, all of which would require reduction in the dose or cessation of treatment. Treatment durations as long as 14 weeks have been evaluated, but data on the effects of long-term treatment or potential adverse neurodevelopmental consequences are lacking.

Relevance of Studies on the Effects of Stimulants in Children with ADHD

While comprehensive and authoritative, the reviews cited above have limited relevance to the identification of the potential adverse health effects of low doses of methamphetamine in young children. In part, this is attributable to the fact that they primarily address the two most widely prescribed stimulants for treatment of ADHD, methylphenidate (e.g., Ritalin®) and amphetamine (e.g., Dexedrine®). While methamphetamine is occasionally prescribed to treat ADHD (Bhandary et al., 1997), controlled investigations of its use in children or adults with

[7] This study is commonly referred to as the MTA, or multimodal treatment study of children with ADHD.

ADHD have not been published in peer-reviewed scientific journals. However, all three reviews concluded that, at prescribed pharmacological doses, different stimulants appear to equally efficacious and produce similar side effects. Nevertheless, in comparison with methylphenidate and amphetamine, methamphetamine is generally regarded to be a more potent central nervous system stimulant. Since the primary low-dose side effects of methylphenidate and amphetamine – appetite suppression and insomnia – are centrally mediated, it is likely that methamphetamine will elicit these effects at lower doses than the stimulants commonly prescribed for ADHD. Therefore, while qualitative conclusions regarding the potential adverse effects of methylphenidate and amphetamine are likely applicable to methamphetamine as well, it is reasonable to conclude that methamphetamine will produce these effects at lower doses.

It may be argued that the relevance of these studies is limited because they involve children with ADHD, not "normal" children. However, the prevalence of ADHD in school-age children is estimated to be in the general range of 4-12 percent (AAP, 2001), and estimates as high as 16 percent have been reported (Goldman et al., 1998). Therefore, children with ADHD represent a small but significant sub-population of children. Furthermore, as Goldman et al. (1998) have noted, several placebo-controlled studies have noted stimulants appear to produce similar behavioral changes in children with ADHD, children with various other psychological difficulties, and normal children. For this reason, the effects of stimulants in children with ADHD probably reflect the response of normal children to these drugs as well.

A third limitation of the studies cited in these reviews is their relatively short duration and narrow focus. For the most part, these studies examined the efficacy of short-term (approximately three months) stimulant treatment on improvement in symptoms of ADHD. As noted in the NIH consensus statement, little information exists concerning the longer-term effects of pharmacological doses of stimulants.

Additional Sources of Uncertainty

Uncertainty factors are used to derive an RfD from experimental data. As summarized by U.S. EPA, uncertainty factors are used to account for

- Variation in susceptibility among the members of the human population
- Uncertainty in extrapolating animal data to humans
- Uncertainty in extrapolating from the results of a short-term study to long-term exposure
- Uncertainty in extrapolating from a LOAEL to a NOAEL
- Uncertainty associated with extrapolation when the database is incomplete

The exposure assessment (presented in a separate report) presumes that methamphetamine residues will not persist in an indoor environment where people are living for longer than a few months. Over time, surface residue concentrations will be depleted by mechanisms such as transfer to uncontaminated surfaces and periodic cleaning. Since the RfD was derived from the results of a study in which subjects were exposed continuously to methamphetamine for a period of four months, an uncertainty factor that accounts for short-term to long-term exposure is not required. Similarly, since this study involved human subjects, an uncertainty factor that accounts

for animal to human extrapolation is not needed. Standard 10-fold uncertainty factors were used to account for inter-individual variability in the human population and extrapolation from a LOAEL to a NOAEL. Uncertainties concerning the adequacy of the toxicity database include

- The possibility that early life exposure to methamphetamine will adversely affect neurological and psychosocial development later in life
- The possibility that early life exposure to methamphetamine will predispose children to substance abuse disorders later in life
- The possibility that very young children (1-2 years old) are more sensitive to the adverse effects of methamphetamine than older children (6-12 years old), who are typically evaluated in studies of the effects of stimulants in children with ADHD[8]

These concerns are discussed in more detail in the following section as justification for adoption of an additional 3-fold uncertainty factor.

Organization of the Report

This report was prepared to provide scientific justification for a reference dose for methamphetamine. The next section of the report provides a detailed analysis of the Chapman (1961) study, the primary study that was used to derive theRfD. This is followed by summaries of approximately thirty-five studies that characterize the range of effects of methamphetamine in humans. The summaries are grouped according to the end-points that were investigated, such as appetite suppression and weight loss, endocrine effects, sympathomimetic effects, subjective effects and pharmacokinetics. Despite wide variations in experimental objectives, test doses, route of exposure and duration of exposure, these studies generally support the conclusion that the lowest experimentally-derived adverse effect level for methamphetamine in humans (adults and children) is 0.1 – 0.2 mg/kg-day. Using the results of the Chapman (1961) study and incorporating appropriate uncertainty factors, the sub-chronic RfD for methamphetamine is $2.7x10^{-4}$ mg/kg-day.

[8] A limited number of studies have been conducted on the effects of stimulants in pre-school children. Of the 34 methylphenidate studies that were reviewed by the American Academy of Pediatrics, six were conducted in preschoolers (Brown et al., 2005). However, only the findings from studies in school-age children were included in AAP's technical report (2001).

Summary of Principal Study for Identification of the Critical Effect and Determination of an RfD for Methamphetamine

Principal Study: Control of Weight Gain in Pregnancy, Utilizing Methamphetamine (Chapman, 1961)

Study Objective: evaluate the efficacy and safety of a sustained-release form of methamphetamine (Desoxyn® Gradumet®, Abbott Laboratories) for controlling weight gain in obstetric patients.

Study Design: placebo control, double blind
Patients were *not* randomly assigned to a treatment group; each patient's dose was adjusted according to her body weight (BW) at the beginning of the study.[9]

Table 1: Treatment Groups

	n[10]	Initial BW (kg)	Initial Dose (mg/kg BW)	Start of Dosing (gestation week)	Dosing Duration (weeks)
Placebo	23	67.2 ± 10.4	0	23.4 ± 3.9	16.4 ± 4.0
5 mg	10	61.2 ± 6.3	0.08	24.9 ± 4.6	14.7 ± 4.9
10 mg	35	67.5 ± 7.6	0.15	24.2 ± 3.3	15.3 ± 3.2
15 mg	16	87.7 ± 8.8	0.17	22.6 ± 3.8	16.5 ± 3.9

Values shown are mean ± standard deviation (SD).

Patients were selected for participation in the study because they were overweight or experienced excessive weight gain in the course of their pregnancy. Women in the first trimester were excluded from the study. All patients were given a standard vitamin and mineral supplement during the course of treatment. Diet was not controlled, although consumption of protein and fresh vegetables was stressed. A "six-meal-a-day" plan (not described) was "advised repeatedly."

Methamphetamine was administered orally in a sustained release formulation (Desoxyn® Gradumet®, Abbott Laboratories) that prolongs the duration of action and reduces the peak blood levels of the drug.

Patients were seen routinely every two weeks, at which time an evaluation of blood pressure, heart rate, body weight, urinanalysis, fetal size and uterine size was conducted. Blood counts were evaluated each trimester, and blood chemistry was tested at term.

[9] However, the data indicate that there was considerable overlap in the initial body weights of women in the placebo, 5 mg and 10 mg groups. Since women in the 15 mg group weighed more, their dose on a mg/kg body weight basis was only slightly higher than the women in the 10 mg group.
[10] Data from twelve women who withdrew from the study (designated "intolerant" by the study's author) and nine women who were administered a diuretic to treat edema are not included in summary statistics.

Randomly selected patients (approximately half the total) had electrocardiograms taken before and during the study, and were followed in labor with evaluation of total protein, albumin:globulin ratio, and electrolytes.

Nine patients, whose weight gain was judged to be excessive and edema was evident, were treated with a "suitable" (unspecified) diuretic. No patients in the placebo group were treated with a diuretic. Since diuretics usually cause weight loss, data from patients who were treated with a diuretic were not included in summary statistics presented in Tables 1 and 2.

Table 2: Summary of Results

	Weight Gain			Final Weight	Final Dose
	(kg)	(kg/week)	(kg/week/kg BW)	(kg)	(mg/kg)
Placebo	6.88 ± 3.27	0.43 ± 0.19	0.0064 ± 0.0027	74.1 ± 11.5	0
5 mg	1.27 ± 2.55	0.12 ± 0.20	0.0020 ± 0.0033	62.5 ± 6.4	0.08
10 mg	2.90 ± 3.44	0.18 ± 0.21	0.0027 ± 0.0032	70.4 ± 8.5	0.14
15 mg	-0.57 ± 3.03	-0.005 ± 0.021	-0.00005 ± 0.0022	87.1 ± 8.2	0.17

According to the study's author, "The normal weight curves of Thompson were utilized as standard for excessive weight gain, and in the last half of pregnancy a normal weight gain was considered to be 0.8 pound [0.36 kg] per week." Average weight gain in the placebo group was only slightly higher than this target rate.

Of the 61 women treated with methamphetamine, 23 lost weight over the course of treatment. According to the author, "The babies born to these mothers appeared normal and healthy." None of the women in the placebo group lost weight.

The original publication did not provide statistical analysis of the data. Therefore, the weight change data were analyzed using analysis of variance (ANOVA) based on general linear modeling (SAS 9.1, SAS Institute, Cary, NC). This analysis confirmed the significant group effect [$F(3,80) = 18.83$, $p < .0001$] and significant difference from control for the 5, 10 and 15 mg/kg groups (Bonferroni post hoc test, $p < .05$), as well as a difference between the 10 and 15 mg/kg groups ($p < .05$). An additional test for homogeneity of variance across groups (Levene test) did not support the null hypothesis of no difference in variance between groups [$F(3, 80) = 3.77$, $p = .01$]. Although ANOVA is robust to violation of the homogeneity assumption, a second analysis (Welch's ANOVA) which does not assume homogeneity of variance confirmed the group effect [$F(3, 27) = 49.98$, $p < .0001$].

All electrocardiogram and laboratory results for all patients evaluated were within normal ranges.

Reported side effects are shown in Table 3. No consistent dose-related effects are apparent.

Table 3: Summary of Side Effects

		Side Effects [# of patients (percent)]						
	n	**Edema**	**Nervousness**	**Insomnia**	**↑ BP[11]**	**Depression**	**Intolerance**	**Σ**
Placebo	25	0	3 (15 percent)	1 (4 percent)	0	1 (4 percent)	2 (8 percent)	7 (28 percent)
5 mg	17	2 (12 percent)	0	0	0	0	5 (29 percent)	7 (41 percent)
10 mg	43	4 (9 percent)	5 (12 percent)	0	2 (5 percent)	0	4 (9 percent)	15 (35 percent)
15 mg	20	4 (20 percent)	2 (10 percent)	1 (5 percent)	0	0	1 (5 percent)	8 (40 percent)

Comments

1. Group sizes: Subjects in each group *at the beginning of the study* are shown.

2. Placebo group: One patient reportedly experienced increased hunger.

3. 5 mg group: Five patients "showed some degree of intolerance manifested as nervousness or insomnia" yet no patients were specifically indicated as having experienced these symptoms (in contrast to the other three treatment groups).

4. 15 mg group: Two patients who complained of nervousness, although one experienced this symptom only occasionally. The single patient who complained of insomnia also experienced this symptom only occasionally

5. Diuretics: All but one of the patients experiencing edema was treated with a "suitable diuretic." The patient with untreated edema was in the 15 mg group. In discussing the results for the 5 mg group, the report's author stated, "Two patients in the controlled weight group required diuretics to maintain the weight within acceptable limits," suggesting that, for some patients, a diuretic was used in combination with methamphetamine to control weight gain. However, of the nine patients who were treated with a diuretic, six gained no weight or actually lost weight. None of the patients in the placebo group was treated with a diuretic even though this group gained more weight than any of the three treated groups.

6. Summation of side effects: In the final column, patients experiencing any side effect were combined with patients described as "intolerant" to determine whether there was a dose-related increase in total adverse effects. No such increase is apparent.

[11] BP: blood pressure

7. Intolerance to drug treatment: Symptoms of "intolerance" were "nervousness, gastrointestinal complaints of a bizarre nature, tachycardia, and insomnia." The author noted that "….when intolerance was found…the dosage was diminished and the symptom pattern was found to be the same." However, four patients were switched to the placebo instead of receiving a lower dose, but they continued to experience symptoms of "intolerance."

Reference Dose Determination

The RfD determination is based on the LOAEL estimation of 0.08 mg/kg from the previous discussion and combining it with an aggregate uncertainty factors (UF). UFs are based on the uncertainties and variabilities in the estimation of the LOAEL in the Chapman (1961) study as well as the scientific literature on the effects of methamphetamine. The components of the aggregate uncertainty factor are discussed below.

Uncertainty Factors

- **LOAEL-to-NOEL extrapolation**
  - A no observed adverse effect level (NOAEL) was not observed in this study.
  - Of the ten women who received 5 mg methamphetamine, four lost weight and six (60 percent) experienced "normal" weight gain (identified by the author as no more than 0.36 kg/week). None of the 23 women receiving the placebo lost weight, and seven (30 percent) experienced "normal" weight gain.
  - Appetite suppression and consequent weight loss are widely recognized indicators of the effects of low doses of methamphetamine on the central nervous system.[12]
  - In a 1960 investigation conducted by Bayly, pregnant women who were given 10 mg/day of Desoxyn® Gradumet® for 15-16 weeks gained significantly less weight than placebo controls.[13] These results provide independent verification of the results obtained by Chapman (1961).
  - Given that methamphetamine produces CNS stimulation at relatively low doses, it is unclear whether any clinical study of methamphetamine can truly be regarded as "double blind." As Modell (1960) noted,

    … the ability to distinguish medication from placebo by any effect other than the one under examination (in this case weight loss) makes it exceedingly difficult to prevent bias and psychological factors from shaping the apparent effects of the drug. This tends to reduce the sensitivity of methods of clinical evaluation of these drugs as well as to make it especially difficult to design a study in which these factors do not bias results.

    Conclusion: apply a 10-fold uncertainty factor to estimate a NOAEL from a study where the lowest dose produced an adverse effect.

- **Inter-individual variation in population response**
  - Variation in human sensitivity to stimulants is well-characterized. Reports on the use of stimulants (amphetamine and methylphenidate) in children and adults with ADHD emphasize the need to individually titrate the dose of the drug.

[12] Several studies evaluating the dose-response relationships of these effects are summarized on pages 21-31in the section, *Supporting Studies for a Methamphetamine RfD*.
[13] A detailed summary of the Bayly (1960) report is provided on pages 21-22 in the section, *Supporting Studies for a Methamphetamine RfD.*

- Clinical studies of the use of stimulants for treatment of ADHD indicate that children are *not* more sensitive than adults to this class of medications and may in fact be less sensitive to them. According to Dulcan (1997), "Adults are more sensitive than children to both the therapeutic and side effects of stimulants. As a result, similar absolute doses are commonly used [for treatment of ADHD]." Furthermore, in a comprehensive review of the use of stimulants in children with ADHD, Greenhill et al. (1999) stated, "When dose is weight-adjusted, there do not appear to be age effects on dose." Therefore, even though the Chapman study examined the effects of methamphetamine on adult women, the doses used in the study (on a mg/kg body weight basis) are probably reasonably indicative of the sensitivity of children to the drug. The fact that LOAELs in the Chapman (1961) study and the Young and Turner (1965) study[14] are similar (see discussion on page 4) also indicates that children and adults have similar sensitivities to methamphetamine.
- The range of variation in children's sensitivity to low doses of methamphetamine is indicated by the results of the Young & Turner (1965) study, where children were dosed sub-chronically with methamphetamine. Most of the 110 treated children received a dose of 5 mg/day, but 8 required a dose of 2.5 mg/day because they experienced adverse effects (insomnia) at 5 mg/day. Conversely, one child was dosed with 10 mg/day and three were dosed with 7.5 mg/day without experiencing adverse effects. These results suggest at least four-fold range in children's sensitivity to the drug.
- The dose-response relationship for the CNS stimulating effects of methamphetamine appears to be relatively sharp (that is, a small increment in dose produces a pronounced increase in CNS stimulation). In a dose range-finding study conducted by Perez-Reyes et al. (1991b), doses of 20, 25, 30 and 40 mg were administered by inhalation to subjects familiar with the subjective effects of methamphetamine. Doses of 20 and 25 mg produced minimal subjective effects, while 30 mg produced more distinct and sustained effects. The highest dose, 40 mg, produced extreme subjective effects.[15]
- Some individuals are much *less* sensitive to methamphetamine than the general population. For example, a study examining the effectiveness of the drug in the treatment of narcolepsy utilized oral doses as high as 40-60 mg/day (Mitler et al. 1993).

Conclusion: apply a 10-fold uncertainty factor to account for variation in individual sensitivity to methamphetamine.

- **Completeness of the database**
  - Significant adverse effects on neurodevelopment have been reported in animal studies. For example, prenatal methamphetamine exposure in mice results in long-term hippocampus-dependent cognitive deficits (Acevedo et al., 2007). However, the doses used in laboratory animal studies are typically 10 to 100 times greater than the

[14] A detailed summary of the Young and Turner (1965) report is provided on pages 52-54 in the section, *Supporting Studies for a Methamphetamine RfD*.
[15] A detailed summary of the Perez-Reyes (1991b) report is provided on pages 43-44 in the section, *Supporting Studies for a Methamphetamine RfD*.

doses employed in the Chapman study. [16] Furthermore, pronounced differences in the pharmacokinetics of methamphetamine in humans and rats have been reported [Cho et al. (2001)].[17] Also, Greenhill et al. (1999) have noted that the toxic effects of stimulants reported in animal studies have not been observed in humans receiving therapeutic doses. Consequently, quantitative methamphetamine toxicity data generated using rats as an animal model must be carefully evaluated because its relevance to human health may be limited.

- Research reports examining the safety and efficacy of stimulants in children with ADHD were evaluated by Greenhill et al. (1999), who noted

> *Stimulant-related adverse events occur early in treatment for children with ADHD and appear to be mild, short-lived and responsive to dose or timing adjustments…Delay of sleep onset, reduced appetite, stomachache, headache and jitteriness are the most frequently cited…Twenty-three controlled studies found no differences for these adverse events among the stimulants, with only abdominal discomfort, sleep delay, and headache being reported more often in those treated with stimulants than those receiving placebo in 2 or more of the 23 controlled trials.*

The same report also noted,

> *Rarely, children [receiving stimulants] have been reported to display cognitive impairments or perseverative behaviors, but these usually respond to a decrease in dose. Very rarely children receiving high doses of stimulants have shown psychotic reactions, hallucinosis, or mood disturbances.*

- The risk-based cleanup standard for methamphetamine is based on an exposure scenario involving 1-2 year olds as the most exposed population. Children in the 1-2 year age bracket are also widely regarded as being more sensitive to the adverse effects of neurotoxins. However, there is no research on the effects of methamphetamine in 1-2 year olds. Three studies of the use of methamphetamine to treat enuresis in children are reviewed elsewhere in this document,[18] but none of these studies involved children younger than 5 years of age. For example, in an investigation conducted by Young & Turner (1965), children whose average age was 7 years were administered methamphetamine for an average duration of 2 months.
- Concerns that exposure to stimulants during childhood may enhance the likelihood of stimulant abuse later in life are not supported by currently available data. In a 16-year follow-up study of children who were given methylphenidate (Ritalin®) for 12-18 weeks[19], Mannuzza et al. (2003) reported no significant difference between children treated with Ritalin® (n=43) and a matching placebo group (n=66) in the

[16] The methamphetamine dose used in the mouse studies conducted by Acevedo et al. was 5 mg/kg, which is 62.5-fold greater than the lowest dose (0.08 mg/kg) in the Chapman study.
[17] For example, the elimination half-life for methamphetamine is 11-12 hours in humans and 70 minutes in rats.
[18] See pages 52-55 under the heading, *Supporting Studies for a Methamphetamine RfD.*
[19] Children with ADHD have been found to be at increased risk of substance abuse disorder (SUD) in adolescence and adulthood. Children evaluated in the Mannuzza et al. study had developmental reading disorders but no other psychiatric diagnoses.

prevalence of substance abuse disorder (abuse or dependence) for any of the seven drug categories evaluated. In addition, a meta analysis of six studies – two with follow-up in adolescence and four in young adulthood[20] – indicated a 1.9-fold *reduction* in risk for substance use disorder in youths who were administered stimulants compared with children who did not receive pharmacotherapy for treatment of ADHD (Wilens et al., 2003). On the other hand, stimulants differ in their capacity to induce euphoria, which in turn appears to be related to their abuse potential. Since methamphetamine's euphoria-inducing effect is a significant aspect of its pharmacodynamic action, and stimulants used for the treatment of ADHD are less potent in this regard,[21] these studies may not reflect the potential for substance abuse problems to develop in individuals exposed to methamphetamine early in life.

- Hundreds of studies examining adverse effects of methamphetamine in humans have been published. Unfortunately, many of these studies are marginally useful or largely irrelevant because
  - They characterized adverse effects in meth-dependent addicts.
  - They characterized adverse effects in persons who recently used or concurrently use methamphetamine or another psychoactive drug for recreational purposes.
  - The drug was administered by intravenous injection or inhalation, causing extremely rapid absorption and higher peak blood levels than would be achieved by dermal absorption and ingestion, exposure routes that are most relevant for a 1-2 year old child in a residence previously used as a clandestine methamphetamine manufacturing lab.
  - The effects of just a single dose of the drug were characterized. Multiple dose studies of methamphetamine's effects in humans are unusual.
- Human studies have a very significant advantage over animal studies insofar as the subjects can report any subjective effects they experience. These effects may or may not result in measurable biochemical response and are even less likely to result in discernable pathology.

Conclusion: add a 3-fold uncertainty factor for incompleteness of the database.

- **Duration of treatment vs. anticipated exposure scenario duration**
  - In this study, the average duration of treatment was four months.
  - The risk-based cleanup standard for methamphetamine is based in part on a post-cleanup exposure scenario, with all surfaces remediated to a target cleanup level. Re-contamination of surfaces will not occur because a primary contaminant source ("reservoir") does not exist. Repeated contact and other activities as well as periodic cleaning will cause contaminant levels to decline over time. Therefore, the post-cleanup scenario will produce sub-chronic exposure to meth lab contaminants.

[20] Pooled data comprised 674 stimulant-treated subjects and 360 untreated subjects who were followed at least four years.

[21] For example, data published by Volkow et al. (1998) suggest that methylphenidate's uptake into the brain is too slow to produce rapid blockade of dopamine transporters, which is thought to be the biochemical mechanism responsible for induction of euphoria.

Conclusion: no additional uncertainty factor to account for longer-term exposure is required.

RfD Calculation

The sub-chronic RfD is calculated as

$$\frac{LOAEL}{UF} = RfD = \frac{0.08\ mg/kg-day}{(10 \times 10 \times 3)} = 2.7 \times 10^{-4}\ mg/kg-day = 0.3\ \mu g/kg-day$$

Where

0.08 mg/kg-day	=	the experimentally observed LOAEL
10	=	uncertainty factor used to estimate a NOAEL from a LOAEL
10	=	uncertainty factor used to account for inter-individual variation in sensitivity
3	=	uncertainty factor used to account for deficiencies in the toxicity database

List of Supporting Studies for a Methamphetamine RfD

1. Other Studies Evaluating Methamphetamine for Treatment of Obesity:
    Bayly (1960)
    Shutter and Garell (1966)
    Simkin and Wallace (1960)
    Matthews (1970) (note description of side effects)
    Hughes (1960)
    Kolecki (1998)

2. Effects of Methamphetamine on Appetite and Caloric Intake:
    Johnson et al. (1999a)
    Martin et al. (1971)
    Comer et al. (2001)
    Ong et al. (1983)

3. Effects of Methamphetamine on Fatty Acid Metabolism:
    Pinter and Pattee (1968)
    Pinter and Pattee (1970)

4. Endocrine Effects of Methamphetamine: p. 37
    Besser et al. (1969)
    Rees et al. (1970)

5. Cardiovascular and Sympathomimetic Effects of Methamphetamine:
    Johnson et a. (2000)
    Martin et al. (1971)
    Mitler et al. (1993)

6. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Amphetamine-Naïve Subjects:
    Schepers et al. (2003)
    Shappell et al. (1996)

7. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Recreational Amphetamine Users:
    Perez-Reyes et al. (1991a)
        Cook et al. (1992)
        Cook et al. (1993)
    Perez-Reyes et al. (1991b)
        Cook et al. (1993)

8. Assessment of Euphoric and Dysphoric Subjective Effects of Methamphetamine:
    Johnson et al. (1999b)

Wachtel et al. (2002)
Soderpalm et al. (2003)

9. Effects of Methamphetamine on Psychomotor Performance, Resistance to Fatigue, Decision Making and Memory:
Shappell et al. (1992)
Stanny et al. (1993)
Wiegmann et al. (1996)
Mewaldt and Ghonheim (1979)

10. Utilization of MRI to Identify Brain Regions Affected by Methamphetamine: Correlation with Subjective Effects:
Vollm et al. (2004)

11. Studies Evaluating the Use of Methamphetamine to Treat Children for Enuresis:
Young and Turner (1965)
Kapoor & Saksena (1969)
Kennedy & Sloop (1965)

12. Case Studies of Children treated with Methamphetamine:
Zike (1972)
Bussing and Levin (1993)

13. Potential Developmental Toxicity of Methamphetamine:
Sussmann (1963)
Smith et al. (2001)
Chang et al. (2004)
Smith et al. (2003)
Smith et al. (2008)

Supporting Studies for a Methamphetamine RfD

1. Other Studies Evaluating Methamphetamine for Treatment of Obesity

A number of studies have evaluated the effectiveness of methamphetamine for the treatment of obesity. A study conducted by Bayly (1960) provides the strongest support for the results obtained by Chapman (1961). In this study, pregnant women were administered daily doses of 10 mg Desoxyn® Gradumet®, the same sustained-release methamphetamine formulation used in the Chapman investigation, for a similar period of time (15-16 weeks). Women administered methamphetamine gained approximately 60 percent as much weight as women in the placebo group. No significant side effects were reported. Although this study was conducted under double blind conditions, the 1961 Chapman study is more robust scientifically for the following reasons:

1) The Chapman study evaluated three doses of methamphetamine (5, 10 and 15 mg) while the Bayly study examined just one dose (10 mg).

2) In both studies, a number of women were administered diuretics to control weight gain as an adjunct to methamphetamine therapy. Since the Chapman report provided data on individual women, those who received a diuretic could easily be identified and eliminated from the data set and the effects of methamphetamine treatment alone could be evaluated. The Bayly report simply provided the number of women in each group who received a diuretic, so the effects of methamphetamine treatment alone could not be examined.

There are several other published investigations of methamphetamine's anorectic effect, but the design of these studies renders them less suitable for development of an RfD. For example, studies conducted by Shutter and Garell (1966) and Simkin and Wallace (1960) evaluated the effectiveness of 16-20 weeks' treatment with Ambar Extentabs #1, (A.H. Robbins), a combination drug that contained 10 mg d-methamphetamine hydrochloride and 65 mg phenobarbital. Similarly, Hughes (1960) evaluated the effectiveness of Du-Oria (B.F. Ascher), a combination of 25 mg d-methamphetamine hydrochloride and 0.25 mg reserpine. The weight loss effects reported in each of these studies were probably due to methamphetamine administration, but it is also likely that phenobarbital and reserpine acted to suppress symptoms of CNS stimulation (e.g., agitation and sleep disturbance), thereby masking some of the primary side effects of methamphetamine. Each of these investigations is summarized in greater detail below.

Bayly (1960) published a one-page report on the use of methamphetamine as an aid in controlling weight gain in pregnant patients. The drug or a placebo was administered under double blind conditions. Patients in the drug treatment group received a single 10 mg oral dose of methamphetamine in a sustained-release formulation (Desoxyn® Gradumet®, Abbott Laboratories) each morning. Thirty patients received methamphetamine and thirty received placebo. Criteria for selection of patients to be included in the study were not specified; it appears that they were simply chosen as they enrolled at the prenatal clinics of the Chicago Maternity Center. The initial weight of the methamphetamine-treated group averaged 174

pounds, "…though height and habitus would suggest an optimal average of 127 pounds." Similarly, the initial weight of the placebo group averaged 156 pounds, although the ideal weight for these women would have been 128 pounds. A reference for the ideal weights that were cited was not provided.

The results of the study are summarized in the table below.

	Treatment Duration (weeks)	Weight Gain (pounds/week)	Number Gaining No Weight	Number Given a Diuretic	Cases of Nausea	Cases of Nerv
Meth (n=30)	15	0.302	8	9	0	1
Placebo (n=30)	16	0.534	2	13	1	2

Data from Bayly (1960). "Cases of Nerv" refers to the number of cases of nervousness in each group.

Upon questioning, nine patients in the methamphetamine treatment group admitted that they did not take their tablets regularly, while 13 were "occasionally delinquent" in the placebo group.

The results suggest that women taking methamphetamine gained less weight than women administered the placebo. Also, methamphetamine treatment was associated with a four-fold increase in the number of women who gained no weight during the course of treatment. A low incidence of side effects (nausea, nervousness) was noted in both groups, but side effects were actually lower in the methamphetamine treatment group than in the placebo group. Diuretics may be of use in reducing weight gain during pregnancy, but in this study a greater proportion of women in the placebo group received a diuretic (13 out of 30) than in the methamphetamine group (9 out of 30). Therefore, it does not appear that the use of diuretics in this study could account for the reduced rate of weight gain in women treated with methamphetamine.

These results are consistent with those of the Chapman (1961) study. For comparison, in the Chapman study, the average weight gain of women administered the placebo was 0.948 pounds per week, while those administered 10 mg Desoxyn® Gradumet® gained 0.397 pounds per week. Treatment durations in the two studies were virtually identical (15-16 weeks).

Shutter and Garell (1966) evaluated the effectiveness of methamphetamine as a treatment for obesity in 78 children and adolescents, 5 through 18 years of age. The 12-week study was conducted under double blind, placebo controlled conditions with a crossover at six weeks. The drug was administered orally as an enteric-coated, controlled release extended action tablet (Ambar Extentabs #1, A.H. Robbins), containing 10 mg methamphetamine hydrochloride and 65 mg phenobarbital.[22] Weight loss was greatest in the first six weeks of the study regardless of treatment (Ambar or placebo), suggesting a significant initial placebo effect. However, during the second six weeks, children who received Amber lost more weight than those receiving placebo. Over the course of the study, the mean weight loss for children receiving Ambar was 6.6 pounds while those receiving placebo lost 3.4 pounds. According to the authors of the study,

[22] The composition of Ambar Extentabs #1 was not indicated in the report by Shutter and Garell. Composition data was taken from an earlier report by Stuart (1962), although the isomeric composition of methamphetamine (d-isomer or racemic) was not specified.

"No side effects were observed during this study," although this statement is difficult to evaluate given the lack of any description of assessment methods for side effects.

Simkin and Wallace (1960) also evaluated the effectiveness of Ambar Extentabs for treatment of obesity. All study participants were registered in a special outpatient obesity clinic of a large hospital. Two studies were conducted, the first under double blind conditions and the second under subject-blind conditions. In the double blind study, 30 patients were placed on the active drug and 23 on the placebo. Patients in this study ranged in age from 50 to 53 years. In the single blind study, 27 were placed on the active drug and 21 on placebo. These patients ranged in age from 43 to 48 years. Most of the patients were women, but the precise number of female and male patients in the two studies was not specified.

In both studies, a single Ambar Extentab #1 (10 mg methamphetamine hydrochloride plus 65 mg phenobarbital) was taken immediately before breakfast, and a lower dose tablet ("Ambar," containing 3.33 mg methamphetamine hydrochloride and 20 mg phenobarbital) was taken at 5 PM. All study participants were placed on a 1000-calorie high protein diet. During the initial four weeks of treatment, the patients were seen by a physician on a weekly basis. Thereafter, they were seen every two weeks for a maximum of 20 weeks. Treatment durations varied, and ranged up to 20 weeks.

As shown in the table below, there was a significant decline in the number of patients participating in the two studies with duration of treatment. However, there was no difference in patient persistence between the active drug and placebo groups.

		Patients in Each 4-Week Period				
Type of Study	**Medication**	**1st**	**2nd**	**3rd**	**4th**	**5th**
Double Blind	Ambar	27	21	17	14	10
	Placebo	22	20	15	9	7
Single Blind	Ambar	26	23	15	10	4
	Placebo	19	18	11	7	3

Data from Simkin and Wallace (1960). Number of patients in each treatment group persisting in treatment from the fourth week of the investigation through the twentieth week.

Greater weight loss was observed in patients receiving the combination drug treatment than placebo. (Data reproduced below.) A placebo effect is apparent during the first four-week interval, as patients in both studies lost more weight during this period than any other. However, in subsequent weeks, patients receiving placebo lost significantly less weight than those treated with the methamphetamine-phenobarbital combination. On average, patients administered Anbar lost approximately one pound per week over the entire course of the study, while those receiving placebo lost just 0.2 pounds per week.

TABLE 2.—WEIGHT LOSS PER PATIENT PER WEEK BY 4-WEEK PERIOD

Type of Study	*Medication*	*Average Pounds Lost per Patient per Week*				
		Period 1	*Period 2*	*Period 3*	*Period 4*	*Period 5*
Double-blind	Ambar	1.8 ± 0.2*	1.2 ± 0.2	0.9 ± 0.1	1.0 ± 0.2	0.7 ± 0.1
	Placebo	1.3 ± 0.2	0.2 ± 0.2	0.1 ± 0.1	0.3 ± 0.2	0.2 ± 0.2
Single-blind	Ambar	1.9 ± 0.1	1.4 ± 0.1	1.1 ± 0.2	0.5 ± 0.2	0.6
	Placebo	0.9 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	−0.1 ± 0.5	0

*Mean and Standard Error of the Mean.

Data from Simkin and Wallace (1960).

Matthews (1970) conducted a study to evaluate the effectiveness of a special program of dietary training and caloric control on the rate of weight gain relapse in subjects who had previously lost weight using a combination of methamphetamine and pentobarbital in a sustained release formulation (Desbutal® Gradumet®, Abbott Laboratories).

A total of fifty overweight female patients were evaluated in this study. Age and body weight statistics for the control and the trained groups are shown below.

	Body Weight (pounds) mean (range)	**Age (years)**
Instructed Group (n=26)	156.3 (132 – 218.3)	36.5
Control Group (n=24)	155.9 (126 – 223.5)	38.9

Initially, study participants were given a single tablet containing 10 mg methamphetamine hydrochloride and 60 mg pentobarbital sodium once each day for two weeks. Thereafter, the daily dose was increased to 15 mg methamphetamine hydrochloride and 90 mg pentobarbital sodium. Patients in the instructed group were treated for an average of 11 weeks and were given caloric intake diaries to afford a well-balanced diet of 1,000 calories per day. Patients in the control group were treated with the drug combination alone for an average of 16 weeks. According to the author, "Cases with slow rates of weight reduction requiring more weeks of treatment than usual were given medication intermittently to avoid possible tachyphylaxis." Within 48 hours of cessation of medication, all patients were administered a self-rating test for depression. Weekly follow-up continued for an average of seven weeks in the instructed group and 12.6 weeks in the control group.

Side effects of drug treatment were described by the author as "minor" and included the following:

- anxiety and motor restlessness (usually in the first week) in 20 percent of the patients
- insomnia in 10 percent
- changes in blood pressure (defined as variation in diastolic blood pressure of 10 mm Hg or more on one or more occasions) in 10 percent

- changes in pulse rate (defined as variation in pulse rate of 10 on one or more occasions, primarily consisting of sinus rate increase of 10 to 20 above baseline values) in 46 percent

Dependence on medication and significant post-withdrawal depression were not observed. The absence of these effects was attributed to "low dosage, slow release dosage form, the "buffering" of undesired cortical effects by pentobarbital, plus the limited, intermittent access to medication within therapeutic guidelines."

For the purpose of identifying a potential threshold dose for methamphetamine in humans, this study is limited because methamphetamine was administered in combination with pentobarbital. In addition, a control group that was not administered the drug combination was not included in the study, and data for individual patients were not provided.

Hughes (1960) evaluated the effectiveness of a methamphetamine-reserpine combination drug as an adjunct to a low-calorie diet for treatment of obesity. The drug, Du-Oria (B.F. Ascher and Company), contained of 25 mg d-methamphetamine hydrochloride and 0.25 mg reserpine in tablet form. The drug was administered orally at about 10 AM each day. Average treatment duration was 57.6 days (range: 8-147 days).

The subjects were 32 obese patients ranging in age from 14 to 68 years, although only four patients were under 30 years of age. Twenty six subjects were female and six were male. Initial body weights of the subjects averaged 179 pounds (range: 135-296 pounds).
Two subjects were diagnosed with essential hypertension. Another subject, initially diagnosed with hypothyroidism, withdrew from the study after 33 days because the drug was judged to be ineffective. Twenty-eight subjects were placed on a 1,000 calorie per day diet; the remaining four were placed on diets of 1200-1500 calories. In this regard, five patients were uncooperative and did not consistently adhere to the prescribed diet. On average, these five lost just 2.3 pounds over the course of treatment.

All but two subjects lost weight during the course of treatment. With the exception of these two subjects, average weight loss was 12 pounds after the first six-week period and 20 pounds at the end of 12 weeks.

The only side effect observed was drowsiness in four patients. One patient withdrew from the study after eight days of treatment due to severe drowsiness. The author stated, "There was a remarkable absence of any side effects such as irritability, jitters, nervous tension or overstimulation."

While somewhat informative, this study was complicated by the variation in (1) the health of the study population, (2) the age (14-68 years) and initial body weight (135-296 pounds) of the study population, (3) the diets that the patients were placed on (1000, 1200 or 1500 calories), (4) the patients' success (or lack thereof) in adhering to the diets, and (5) the duration of treatment (8-147 days). In addition, it appears that any adverse side effects potentially attributable to methamphetamine (such as anxiety or sleep disturbance) were masked by co-administration of

reserpine since the primary side effect observed in the study was drowsiness. The study also failed to include a concurrent control group (calorie restricted diet only).

High doses of methamphetamine, as might occur in cases of accidental overdose, are also associated with rhabdomyolysis (destruction of skeletal muscle cells). In a nine-year retrospective chart review, *Kolecki (1998*) identified eighteen cases of pediatric poisoning with methamphetamine and noted that rhabdomyolysis was the most common complication observed. Rhabdomyolysis could also lead to weight loss and, in extreme cases, the wasting syndrome typically associated with long-term exposure to high doses of methamphetamine in adults. However, to our knowledge, rhabdomyolysis has not been observed in persons exposed to low doses of methamphetamine typically utilized in controlled studies of the effects of methamphetamine in humans.[23]

2. Effects of Methamphetamine on Appetite and Calorie Intake

Suppression of appetite and consequent reduction of caloric intake are consistently observed in individuals taking methamphetamine and amphetamine. These effects appear to be largely responsible for the reduction in weigh gain and the weight loss reported in the studies described in the previous section. Several studies, summarized below, have examined the dose-response relationship of appetite suppression in humans.

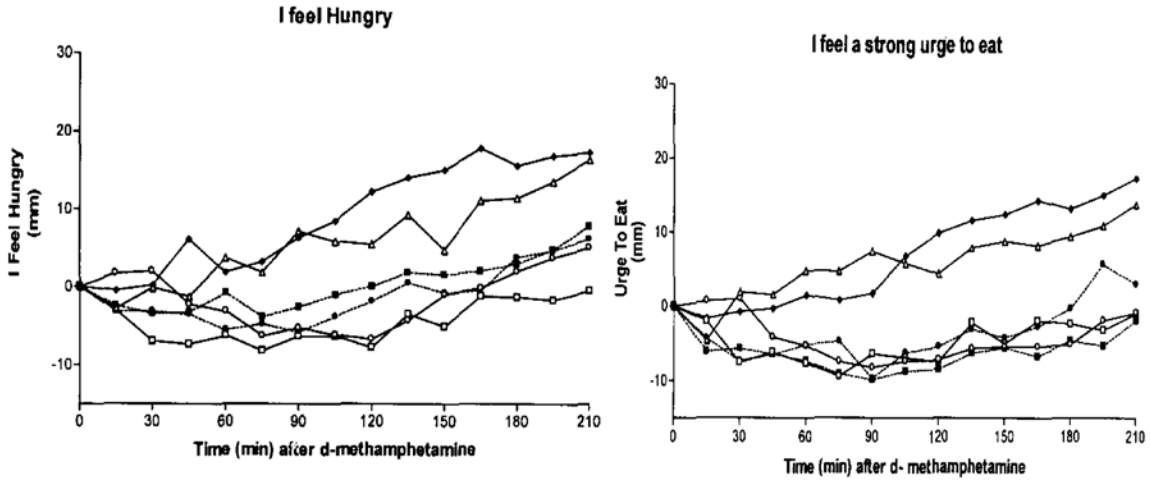
Johnson et al. (1999a) evaluated the effects of d-methamphetamine (Desoxyn®) and isradipine, a calcium channel antagonist, on somatic and psychological perceptions of hunger using a placebo-controlled, double blind, Latin Square, cross-over design in healthy male (n=11) and female (n=7) volunteers. The volunteers ranged in age from 18 to 45 years; average age was 31 years. None of the volunteers had a history of substance abuse or dependence. Two single doses of methamphetamine (0.21 and 0.42 mg/kg body weight) were tested. To provide the appropriate mg/kg doses, Desoxyn® tablets were crushed, mixed with cornstarch and administered orally in royal blue size 0 gelatin capsules. Placebo capsules contained cornstarch only.

Subjective hunger effects were evaluated using Visual Analog Scales (VAS), and all participants were trained on the use of VAS prior to commencement of the studies. VAS ratings ranged from "not at all" on the left to "extremely" on the right, and were used to rate the subjects' perception of "I feel hungry" (to rate the somatic perception of hunger) and "I feel the urge to eat" (to rate the psychological perception of hunger).

Data are shown in the two graphs below. d-Methamphetamine administration was associated with significant reductions in both somatic and psychological perceptions of hunger. Both doses produced similar responses, with the peak reduction in hunger occurring approximately two hours after dosing. Crushing the Desoxyn® tablets prior to administration may have enhanced

[23] Clinically, rhabdomyolysis is indicated by an increase in total creatine phosphokinase in urine. Evidence of rhabdomyolysis warrants aggressive measures to maintain urine output in order to prevent myoglobinuric renal failure (Kolecki, 1998).

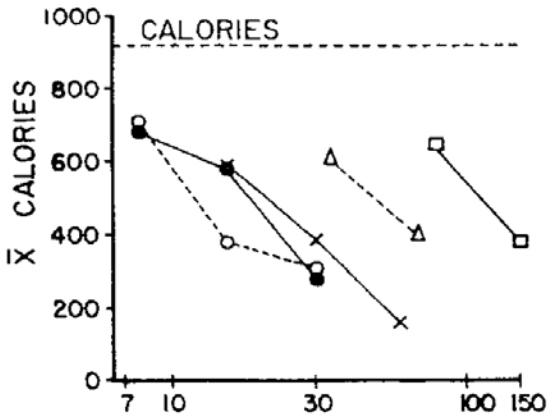
the rate of methamphetamine absorption, leading to more rapid onset of maximal effect than might otherwise have occurred.



Data from Johnson et al. (1999a). Methamphetamine-induced changes in the somatic and psychological perceptions of hunger in 18 human subjects. Placebo responses are shown by open triangles (Δ), low dose methamphetamine (0.21 mg/kg) responses are shown by open circles (○), and high dose methamphetamine (0.42 mg/kg) responses are shown by open squares (□).

Martin et al. (1971) evaluated the physiologic, subjective and behavioral effects of methamphetamine and four other centrally acting sympathomimetic amines in 12 adult male prisoners. Baseline data were collected 30-60 minutes prior to drug administration. The drugs were administered subcutaneously in a 2 ml volume under double blind conditions. The doses of methamphetamine were 7.5, 15 and 30 mg per 70 kg body weight (equivalent to 0.11, 0.21 and 0.43 mg/kg, respectively). Physiologic and subjective effects were assessed at 30 minutes and 1, 2, 3, 4 and 8 hours thereafter.

Changes in appetite were assessed 3.5 hours after methamphetamine injection by calculating the caloric content of food selected and consumed by the subjects. Data are shown in the graph below. Data obtained when the subjects were administered methamphetamine are indicated by open circles; data obtained following administration of the placebo are indicated by a horizontal dashed line. Methamphetamine produced a clear dose-related decrease in calorie intake, with the lowest dose reducing calorie intake by approximately 22 percent compared to placebo controls.



Data from Martin et al. (1971). Drug treatments represented are placebo (-----), amphetamine (●—●), methamphetamine (○---○), ephedrine (□—□), phenmetrazine (Δ---Δ) and methylphenidate (x x). The x-axis represents the log dose in units of mg/70 kg.

Martin et al. also observed that methamphetamine caused a significant dose-related increase in urinary excretion of epinephrine. Twenty years later, Perez-Reyes et al. (1991b) suggested that this finding may reflect methamphetamine-induced release of epinephrine from the adrenal medulla.

In their discussion of these results, the authors stated, "On the basis of physiologic response as well as subjective changes [data not shown], amphetamine and methamphetamine were equipotent with respect to most parameters, and no evidence was obtained that supported the view that the central stimulatory actions of methamphetamine relative to its peripheral effects are greater than those of amphetamine in man when then two drugs are administered subcutaneously."

Comer et al. (2001) evaluated the effects of repeated oral doses of methamphetamine in seven volunteers in a 15-day residential study.[24] Oral methamphetamine[25] (5 and 10 mg, twice each day) was administered on days 4 through 6 and 10 through 12; placebo was administered on all other study days. The first three days of the study were referred to as "placebo baseline days." During the first dosing period (days 4 though 6), four of the participants received the low dose and the other three received the high dose. During the second dosing period (days 10 through 12), subjects who had earlier been given the low dose were given the high dose, and *vice-versa*. Throughout each day, subjects completed a battery of psychomotor tasks and responded to questionnaires rating their subjective perceptions.

All participants in this study reported previous experience with stimulants. Several participants reported current use of cocaine (n=1), caffeine (n=5), alcohol (n=4), marijuana (n=1) and cigarettes (n=4).

[24] An eighth participant who began the study left because of difficulty sleeping following methamphetamine administration. The report does not state explicitly whether this individual received the high dose or the low dose, although it appears that he/she was in the group that was given the high dose (10 mg, BID) during the first dosing period.

[25] Desoxyn® (Abbott Laboratories), 5 mg tablets in white #00 opaque capsules with lactose filler

Relative to placebo baseline results, only two positive subjective ratings ("I feel a good drug effect" and "I feel high") were elevated, but these results were statistically significant only on the first day that the high dose was administered. (Data reproduced below.) The authors believed that the return to baseline was an indication of the rapid development of tolerance (i.e., tachyphylaxis) to these effects.

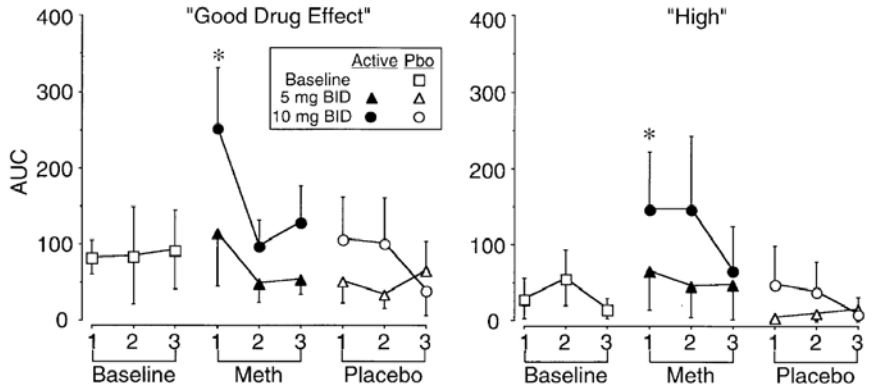


Fig. 1 Area-under-the-curve (*AUC*) values for visual analog scale ratings of "good drug effect" (*left panel*) and "high" (*right panel*) during the 3 placebo baseline days, the 3 days of active methamphetamine administration, and the 3 days of placebo administration immediately following administration of each of the active methamphetamine doses. *Error bars* represent ±1 SEM. An *asterisk* indicates a significant difference between that day and placebo baseline ($P<0.01$)

Data from Comer et al. (2001). Pbo: placebo; BID: twice each day; SEM: standard error of the mean

A number of negative ratings (e.g., "I feel dizzy" and "I feel flu-like symptoms") were also elevated. In contrast to the positive ratings, negative ratings generally became more apparent on the third day of the 3-day dosing periods. Negative ratings were clearly dose related, with the variety and frequency of negative subjective effects being much more apparent at the high dose.

Both doses of methamphetamine reduced total caloric intake on all three days of dosing. Caloric intake on the first placebo day after the 3-day methamphetamine dosing period was also reduced relative to intake during the baseline placebo period. In part, the reduction in caloric intake was attributable to a decrease in the number of eating occasions throughout the day. (Data reproduced below.)

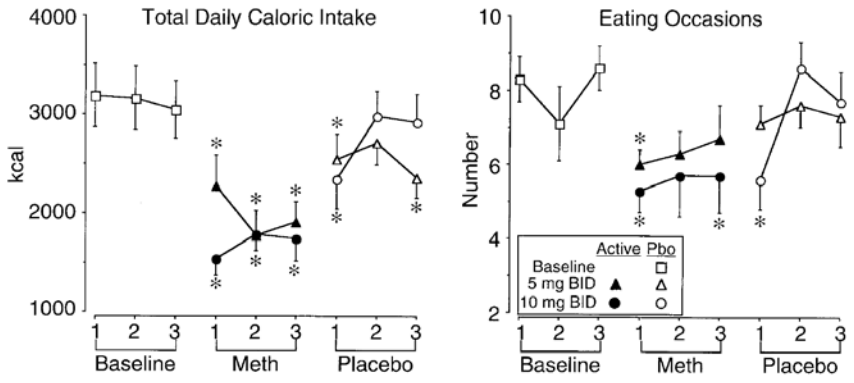
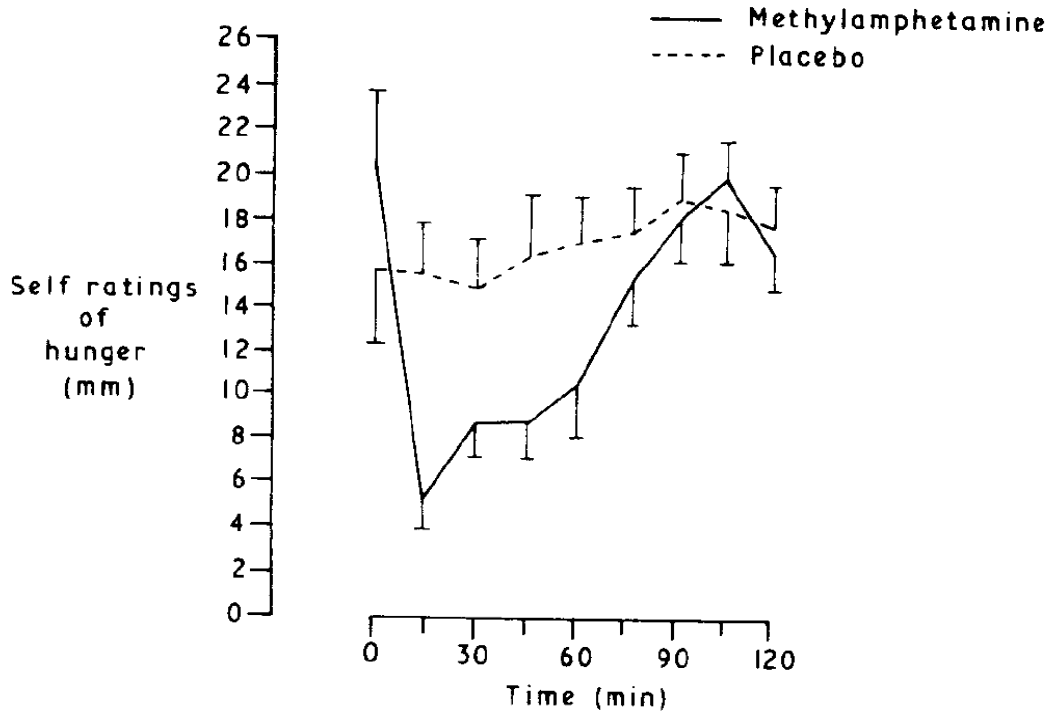


Fig. 3 Total daily caloric intake (*left panel*) and number of eating occasions (*right panel*). For details, see Fig. 1

Data from Comer et al. (2001).

On the first night of treatment with 5 mg methamphetamine, subjective ratings of "fell asleep easily" decreased significantly and ratings of "woke up often" increased significantly. On the second and third nights, no changes in sleep patterns were observed. A number of changes in sleep patterns were observed on the first night of treatment with 10 mg methamphetamine, including decreased total sleep time, sleep efficiency and total non-REM (rapid eye movement) sleep, and increased ratings of "woke up often." Alterations in the objective and subjective measures of sleep occurred primarily on the first day, but not on the second or third day, of 10 mg methamphetamine administration. These results suggest that rapid tolerance to the sleep disrupting effects of methamphetamine occurred in this study.

Ong et al. (1983) investigated the effects of methamphetamine on eating behavior in eight patients (seven female, one male) with bulimia nervosa. The drug (15 mg/75 kg body weight) was administered intravenously under double blind conditions. The study focused changes in mood, hunger and food intake under laboratory conditions. Subjective ratings of hunger, anxiety, urgency to eat, well-being, helplessness, tension, and distress were made by the patients before drug injection and at 15 minute intervals for 2 hours after drug injection. Two hours after drug injection, each patient was allowed to eat and the caloric content of food consumed in 30 minutes was determined. After injection of the placebo, patients consumed 943 ± 222 (mean ± standard error) calories. After methamphetamine injection, intake was just 224 ± 111calories. Self ratings of hunger (data reproduced below) dropped rapidly within 15 minutes of injection of methamphetamine and remained low for approximately one hour. Although this study evaluated effects of methamphetamine in bulimic patients, the primary effects that were observed (reduced subjective sensation of hunger and reduced caloric intake) are typical of those observed at the same dose (0.2 mg/kg) in normal individuals.



Data from Ong et al. (1993). Self ratings of hunger in bulimic patients administered 0.2 mg/kg methamphetamine by intravenous injection. Relative hunger ratings were quantified using a 100 mm visual analog scale. Appetite suppression was also indicated by substantially reduced caloric intake when the patients were allowed to eat, two hours after drug injection.

3. Effects of Methamphetamine on Fatty Acid Mobilization

Pinter and Pattee (1968) examined the effects of several adipokinetic substances [chemicals capable of causing release of free fatty acids (FFA) from adipose tissue], including methamphetamine, in lean and obese volunteers of both sexes. In a typical investigation, three venous blood samples were withdrawn at 20 minute intervals to establish baseline conditions. Methamphetamine or another test compound, dissolved in 50 ml of normal saline, was then infused into the antecubital vein over a period of 15 minutes. The dose of methamphetamine was 0.2 mg/kg. Blood samples were collected at the tenth minute of the infusion and at 0, 10, 20, 30, 45, 60 and 90 minutes after the infusion. Fat mobilizing effects of methamphetamine were evaluated in six subjects.

Methamphetamine infusion caused a significant increase in the plasma FFA, but no changes were found in blood glucose, total serum fat or triglyceride concentrations. In comparison with the immediate effect of exogenously administered epinephrine, the peak effect of methamphetamine on plasma FFA was consistently delayed by about 20 minutes (data reproduced below). Kinetic studies, utilizing successive injections of ^{14}C-labeled, albumin-bound palmitic acid, indicated that methamphetamine augmented the plasma FFA pool by increasing the rate of FFA production.

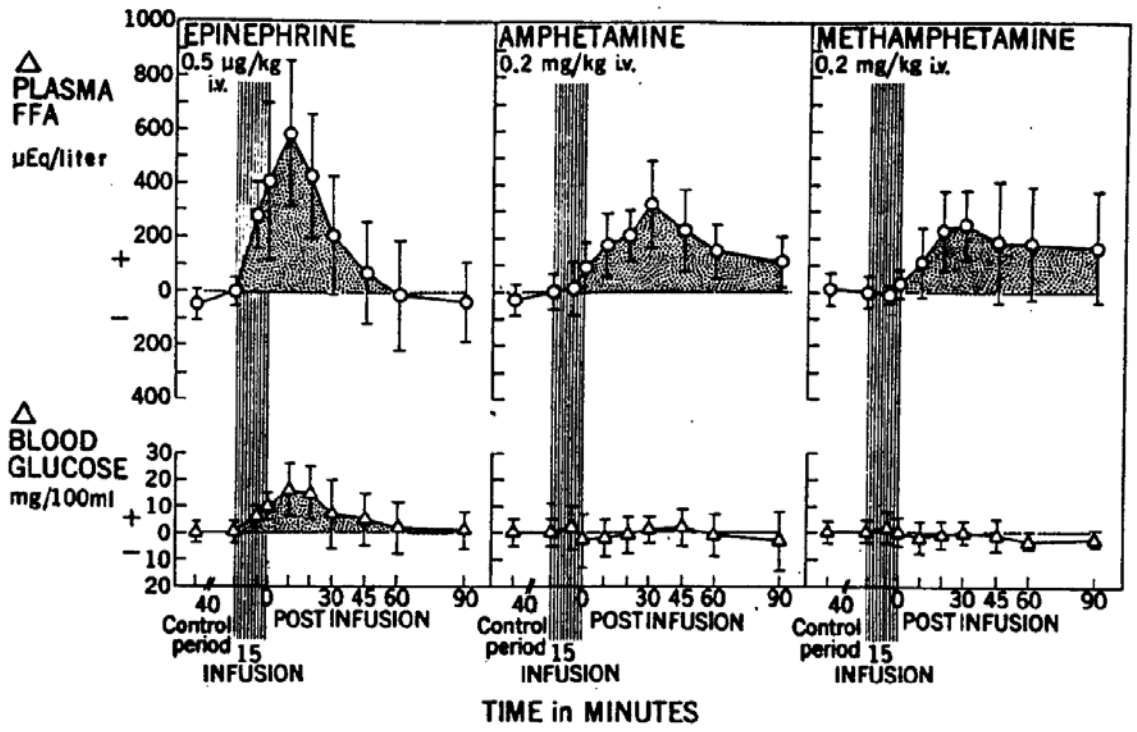


FIGURE 1 The effect of intravenous epinephrine, amphetamine, and methamphetamine infusions on plasma FFA and blood glucose levels (in 14, 15, and 6 subjects respectively). The individual curves show the mean changes ($\bar{\Delta}$) ± SD in relation to the base line levels obtained in the control periods. The shaded areas represent the + ΔFFA and + Δ blood glucose areas; bounded by the temporal plot of ΔFFA and Δ blood glucose from the beginning of the infusions up to 90 min and by a horizontal line drawn at the level of base line concentrations.

Data from Pinter and Pattee (1968).

Additional studies were conducted to clarify the role of endogenous catecholamine release in the FFA response. Catecholamine depletion, achieved by six intramuscular injections of 5 mg reserpine at eight hour intervals, nearly completely abolished the adipokinetic effect of amphetamine (Benzedrine sulfate, 0.2 mg/kg, administered by intravenous infusion). In contrast, epinephrine given after reserpine pretreatment produced an enhanced response in comparison to the response when the same individuals were not pretreated with reserpine. These data were interpreted as evidence for the dependence of amphetamine-induced fat mobilization on endogenous catecholamine release, although a direct action of amphetamine in fat mobilization could not be ruled out entirely.

Taken together, the results of this study were interpreted as evidence that amphetamines cause increased fat mobilization from adipose tissue.

A subsequent investigation by the same authors (Pinter and Pattee, 1970) demonstrated that intravenous infusion of 0.2 mg/kg methamphetamine in four subjects increased in plasma corticoids. The authors speculated that changes in pituitary-adrenal hormone secretions may contribute to the indirect adipokinetic action of amphetamines. Furthermore, they suggested that

…needless hypermobilization of fat caused by the abuse of [amphetamines]… theoretically, may lead to adverse consequences, such as acceleration of thrombogenesis, increased endogenous triglyceride formation and hyperlipidemia with fatty infiltration of the liver, and decreased carbohydrate tolerance. On the other hand, the possibility exists of decreasing the mass of adipose tissue by a metabolic action (fat mobilization) independent of appetite regulation.

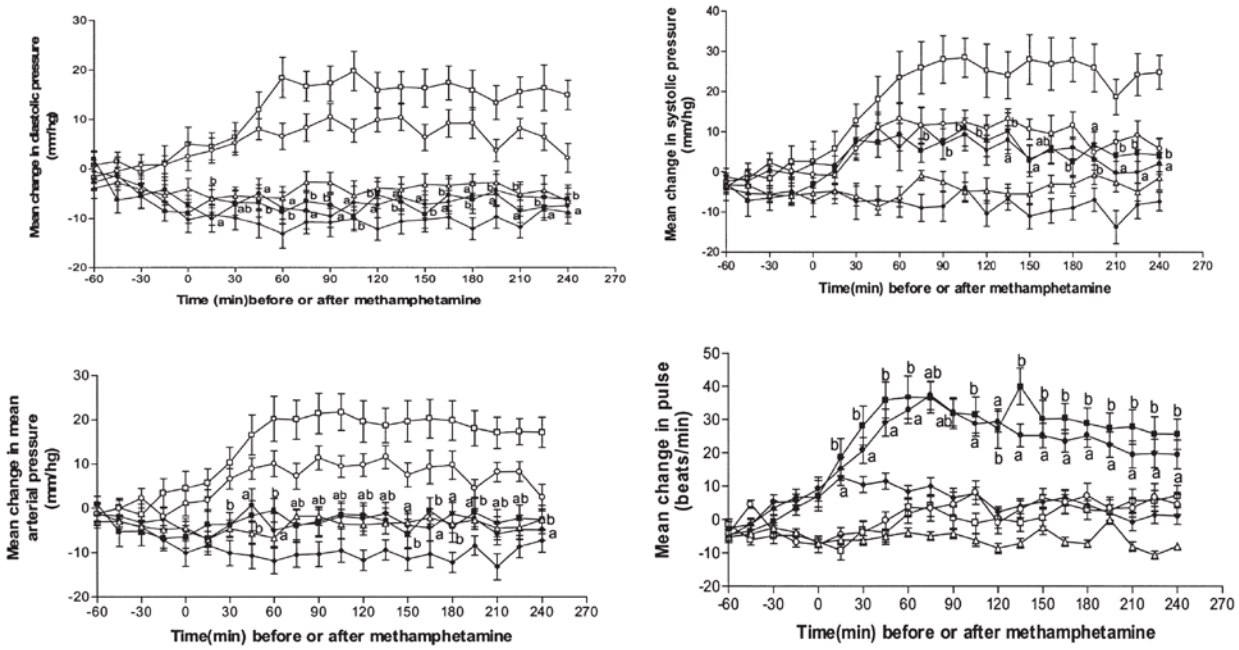
4. Endocrine Effects of Methamphetamine

Besser et al. (1969) examined the behavioral and psychomotor effects of methamphetamine and their relationships to plasma corticosteroid, adrenocorticotrophic hormone and growth hormone levels. Subjects were six healthy male volunteers, 20 to 29 years of age. The drug was administered intravenously via an indwelling catheter at two doses, 7.5 and 15 mg, at various times during the day. Results following methamphetamine administration were compared with those obtained after administration of a placebo. Treatments were allocated on a double-blind, crossover, randomized basis using a Latin square design. There was a seven-day interval between treatments for each subject. Dose-related increases in plasma corticosteroid levels were observed 30, 45 and 60 minutes after methamphetamine administration. The rise was most pronounced after evening administration of the drug. Growth hormone levels also rose in a dose-related fashion but the increase was statistically significant only at the higher dose.

Rees et al. (1970) examined the effects of methamphetamine on plasma corticosteroids and growth hormone in six normal adult male subjects ranging in age from 19 to 34 years. Subjects were pre-treated with an intravenous injection of thymoxamine (a relatively specific α adrenergic blocking agent), propranolol (a β adrenergic blocker) or placebo. Five minutes later, 15 mg (approximately 0.1 mg/kg) intravenous methamphetamine was administered. Blood samples were collected before and 15, 30, 45 and 60 minutes after methamphetamine administration for determination of plasma levels of growth hormone and corticosteroids. Treatments were administered at seven-day intervals using a double blind crossover method and a Latin square design. Methamphetamine alone produced a modest rise in plasma corticosteroids and growth hormone over the one-hour observation period. The rise in corticosteroids was prevented by prior administration of thymoxamine and enhanced by prior administration of propranolol. In contrast, the rise in growth hormone levels was enhanced by both thymoxamine and propranolol.

5. Cardiovascular and Sympathomimetic Effects of Methamphetamine

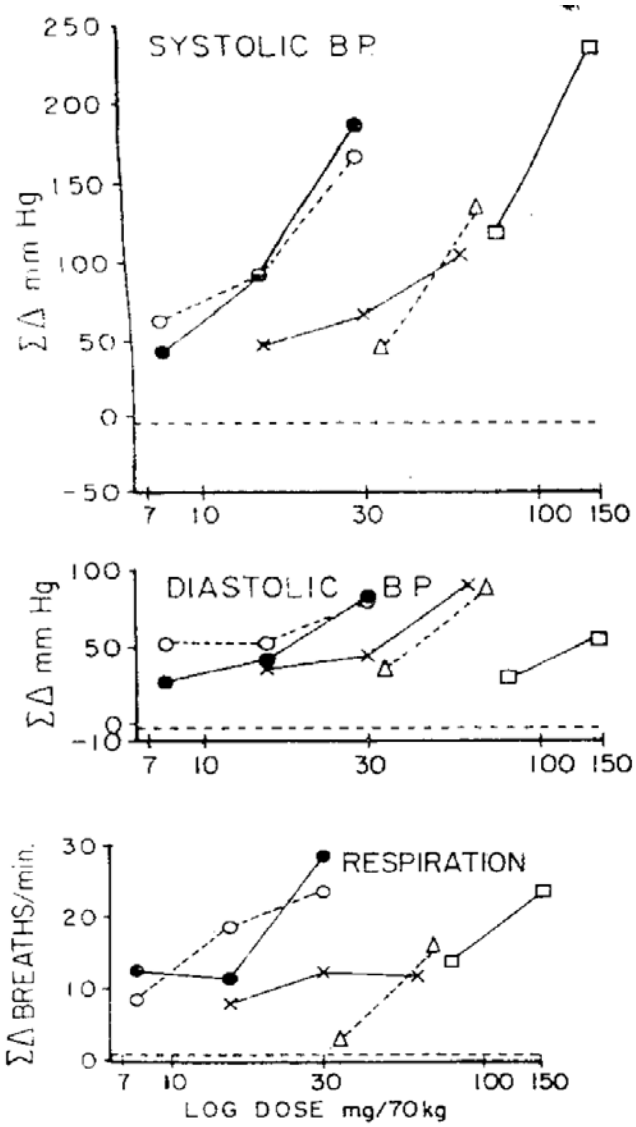
Johnson et al. (2000) examined the utility of isradipine in treating d-methamphetamine induced hypertension and changes in cognitive function. As described above, two doses of d-methamphetamine (0.21 and 0.42 mg/kg, oral) were evaluated in a placebo-controlled, double blind, Latin Square, cross-over design. d-Methamphetamine increased systolic and diastolic blood pressure, mean arterial pressure and pulse rate in a dose-dependent fashion. The drug also improved attention, accuracy of reasoning ability and performance on computerized cognitive functioning tasks. Cardiovascular changes are shown in the graphs below.



Data from Johnson et al. (2000). Methamphetamine-induced cardiovascular changes in 18 human subjects. Data points are mean ± SE. Placebo responses are shown by open triangles, low dose methamphetamine (0.21 mg/kg) responses are shown by open circles, and high dose methamphetamine (0.42 mg/kg) responses are shown by open squares.

Martin et al. (1971) evaluated the physiologic of methamphetamine and four other centrally acting sympathomimetic amines in 12 adult male prisoners. The drugs were administered subcutaneously in a 2 ml volume under double blind conditions. Baseline data were collected 30-60 minutes prior to drug administration. The drugs were administered subcutaneously in a 2 ml volume under double blind conditions. Physiologic and subjective effects were assessed at 30 minutes and 1, 2, 3, 4 and 8 hours thereafter.

Changes in respiration and systolic and diastolic blood pressure are shown in the graphs below. Note that changes in blood pressure and respiration are indicated as the summation of changes across all subjects. Methamphetamine produced a dose-related increase in systolic blood pressure, a slight increase in diastolic blood pressure, and a dose-related increase in the rate of respiration.



Data from Martin et al. (1971). Drug treatments represented are placebo (-----), amphetamine (●—●), methamphetamine (○---○), ephedrine (⊡—⊡), phenmetrazine (Δ---Δ) and methylphenidate (x x).

In a study undertaken to test the suitability of methamphetamine as a drug for the treatment of narcolepsy, Mitler et al. (1993) evaluated the effectiveness of the drug in eight pairs of subjects, consisting of a narcoleptic and a control matched on the basis of age, sex, educational background and job. Treatment conditions (baseline, placebo, low and high doses of methamphetamine) were randomized and administered under double blind conditions. Each treatment condition was evaluated on four successive days followed by three days of washout. The total duration of the study was 28 days. The drug was administered once in the morning. Doses were 20 or 40-60 mg for narcoleptic patients and 5 or 10 mg for controls. Tests were conducted to assess daytime sleep tendency, nighttime sleep parameters, performance on a computer-based driving task, cardiovascular effects (blood pressure, pulse rate and respiration rate), and possible treatment-associated side effects.

In control and narcoleptic subjects, there were no treatment-related effects on systolic and diastolic blood pressure, pulse rate, or respiration rate. (Data reproduced below).

TABLE 6. *Measures of blood pressure, pulse rate and respiratory rate listed according to group and measure (vertically) and experimental condition (horizontally). ns: not significant*

	Experimental conditions				p-level of *F*-ratio for conditions
	Baseline	Placebo	Low dose 20 mg	High dose 40–60 mg	
Narcoleptics					
Systolic BP	122.8 ± 21.8	117.3 ± 19.3	115.8 ± 20.1	118.4 ± 19.4	ns
Diastolic BP	68.9 ± 15.7	66.1 ± 10.5	66.4 ± 10.4	70.9 ± 10.7	ns
Pulse rate	67.9 ± 3.6	70.8 ± 5.7	67.5 ± 7.0	71.8 ± 6.5	ns
Respiration rate	18.5 ± 3.3	18.3 ± 3.7	17.1 ± 3.5	17.8 ± 3.9	ns
	Experimental conditions				p-level of *F*-ratio for conditions
	Baseline	Placebo	Low dose 5 mg	High dose 10 mg	
Controls					
Systolic BP	124.6 ± 30.1	115.0 ± 6.7	115.4 ± 12.2	116.8 ± 8.5	ns
Diastolic BP	66.9 ± 6.3	64.6 ± 6.1	66.8 ± 10.5	67.1 ± 7.0	ns
Pulse rate	63.0 ± 7.9	63.0 ± 8.8	60.3 ± 75.8	63.3 ± 9.6	ns
Respiration rate	16.0 ± 3.6	17.0 ± 4.5	16.4 ± 2.6	17.9 ± 3.2	ns

Data from Mitler et al. (1993).

In general, possible treatment-related side effects were dose-dependent. These consisted primarily of central nervous system effects (nervousness, insomnia and headaches) and gastrointestinal effects (nausea, abdominal pain and loss of appetite) and dry mouth. According to the authors of the study, "No complaints were judged severe enough to necessitate medical intervention, termination of drug treatment or exclusion from the study. Likert scale intensity data revealed that the side effects were generally mild to moderate (Likert rating <7) and did not interfere with normal daily activity." Behavioral changes noted in both narcoleptic and control subjects were increased talkativeness and increased willingness to take on new projects at home and work. Side effects data from this study are reproduced below.

TABLE 7. *Number of narcoleptic and control subjects who reported possible treatment-associated side effects. Data are presented according to organ system (vertically) and experimental condition (horizontally)*

	Narcoleptics (n = 8)				Controls (n = 8)			
			LD	HD			LD	HD
Symptoms by system	BL	PL	20 mg	40–60 mg	BL	PL	5 mg	10 mg
Nervous								
Nervousness	0	0	2	2	0	0	1	2
Insomnia	0	0	2	5	0	0	0	3
Dizziness	0	0	1	0	0	0	0	1
Headache	1	0	3	4	0	0	1	2
Akathisia	0	0	2	3	0	0	0	1
Dyskinesia	0	0	0	0	0	0	0	1
Chest discomfort	0	0	1	1	0	0	0	1
Gastrointestinal								
Nausea	0	1	0	0	0	0	0	1
Abdominal pain	0	0	1	1	0	0	0	1
Loss of appetite	0	0	4	3	0	0	1	2
Weight loss	0	0	1	1	0	0	0	0
Eyes, ears, nose and throat								
Dry eyes	0	0	1	1	0	0	0	0
Dry mouth	0	0	0	3	0	0	1	4
Blurred vision	0	0	0	0	0	0	0	1
Difficulty in accommodation	0	0	0	0	0	0	0	0
Skin								
Pain	0	0	0	0	0	0	0	0
Itching	0	0	1	0	0	0	0	1
Peeling	0	0	0	0	0	0	0	0
Discoloration	0	0	0	0	0	0	0	0
Other								
Impotence (n = 3 males)	0	0	0	0	0	0	0	0
Libido change	0	0	0	0	0	0	0	0
Irritability	0	0	0	0	0	0	0	0

Data from Mitler et al. (1993).

6. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Amphetamine-Naïve Subjects

Schepers et al. (2003) evaluated the pharmacokinetics and pharmacodynamics of short-term administration of Desoxyn® Gradumet® (a sustained-release form of *d*-methamphetamine) in eight normal (amphetamine-naïve) individuals. Four males and four females participated in the study. Their average age was 35 ± 4 years (range 26-40 years) and their mean weight was 72 ± 18 kg (range 55-103 kg). All eight participants received the low dose regimen of methamphetamine (four daily oral doses of 10 mg, administered over a seven day period). Three weeks later, five individuals from the original group of eight received the high dose regimen of methamphetamine (four daily oral doses of 20 mg methamphetamine). Drugs were administered in gelatin capsules with lactose. Placebo capsules contained lactose only. All drug treatments were administered under subject-blind conditions. After administration of the drug, blood samples were collected for up to 24 hours and oral fluid samples were collected for up to 72 hours. Pharmacodynamic effects (systolic and diastolic blood pressure, heart rate, pupil diameter, core and skin temperature, respiratory rate and blood oxygen saturation) were evaluated for 12 hours following drug administration.

According to the report, dissolution tests of the Gradumet® formulation demonstrated that 20-40 percent of methamphetamine is released after 30 minutes, 35-55 percent after one hour, and 60-80 percent after four hours. It was not clear whether these data were generated by the authors or provided by Abbott Laboratories, the manufacturer of Desoxyn® Gradumet®.

Following administration of the first 10 mg dose, maximum plasma concentrations averaged 20.2 ± 6.4 µg/L, in very good agreement with results obtained by Perez-Reyes et al (1991a), discussed below. After the 20 mg dose, the average maximum plasma concentrations averaged 32.4 ± 7.7 µg/L. Plasma methamphetamine half-lives were 9.3 ± 3.7 and 11.1 ± 7.2 hours for the low and high dose, respectively, providing an overall mean half-life of 10.0 ± 5.2 hours. Oral fluid concentrations of methamphetamine were on average two-fold higher than those detected in plasma but were highly variable. In one subject, the concentration of methamphetamine in oral fluid exceeded 300 µg/L after the 10 mg dose.

Diastolic blood pressure and heart rate both showed significant dose-related increases following methamphetamine administration. Systolic blood pressure, core and skin temperature, blood oxygen saturation, and pupil diameter were not significantly altered by drug treatment.

Shappell et al. (1996) investigated the pharmacokinetics and pharmacodynamics of a single dose of methamphetamine administered in the morning or evening. Subjects were ten male Marine Corps officers ranging in age from 23 to 29 years. All were nonsmokers with a history of little or no alcohol use and were not taking any prescription medications at the time of the study. The subjects were divided into two groups of five each. They were administered 30 mg/70 kg oral d-methamphetamine hydrochloride in two sessions, the first starting at 6:30 AM and ending at 9:00 PM (day session; methamphetamine administered at 8:40 AM) and the second starting at 6:30 PM and ending at 9:00 AM (night session; methamphetamine administered at 8:40 PM). A crossover design was adopted with each subject serving as his own control. Cognitive ability, subjective fatigue and blood pressure were evaluated beginning 1.5 hours before drug administration and continued every half hour until 12.5 hours after administration. Over the same time period, blood and urine samples were collected for analysis of methamphetamine and one of its primary metabolites, amphetamine.

No differences in the day *vs.* night pharmacokinetics of orally administered methamphetamine were found. Apparent peak serum drug concentrations (mean ± standard deviation) were 94.1 ± 70.9 and 60.4 ± 16.9 ng/ml for the daytime and nighttime sessions, respectively. (Data reproduced below.) In comparison to results obtained by Schepers et al. (2003), higher peak blood concentrations were achieved in this study because (1) a higher dose was administered (30 mg *vs.* 10 and 20 mg) and (2) Schepers et al. evaluated the pharmacokinetics of a slow release formulation, which would be expected to reduce the rate of drug absorption and reduce peak blood levels. Apparent terminal elimination half-lives were 9.1 ± 4.0 and 10.8 ± 8.0 hours for the daytime and nighttime sessions, respectively, which is virtually identical to the half-lives reported by Schepers et al. (2003).

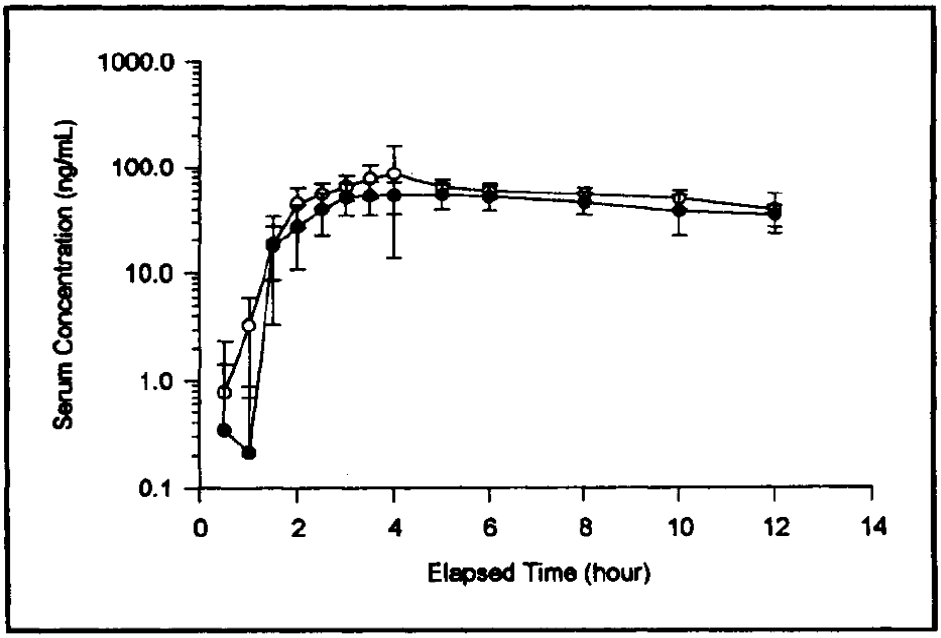
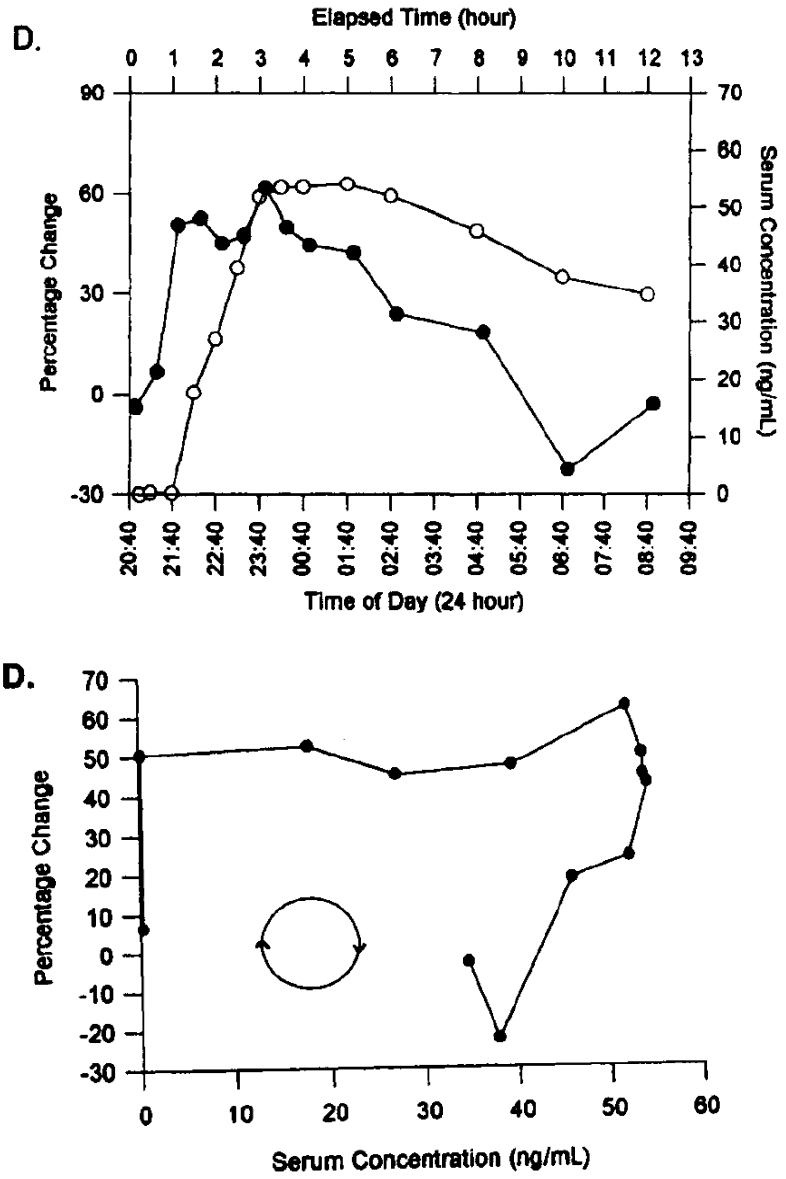


Figure 1. Logarithmic mean serum concentration of methamphetamine as a function of time after drug administration during the day (open circles) and night (filled circles).
Data from Shappell et al. (1996).

Methamphetamine significantly increased systolic blood pressure (25-30 mm Hg increase, baseline to peak) and diastolic blood pressure (7-13 mm Hg increase).
Maximal changes in both parameters were observed before the maximum serum concentrations of methamphetamine were attained. Daytime dosing produced improvements in cognitive performance and reduced subjective fatigue, but these effects were suppressed during a circadian trough, which occurred at approximately 4:30 AM (eight hours into the night session). However, improved cognitive performance and reduced subjective fatigue were *not* correlated with serum concentrations of methamphetamine. For example, nighttime fatigue declined markedly as serum methamphetamine concentrations rose, but it set in once again later on in the study even though serum concentrations of the drug remained above 30 ng/ml. (Data reproduced below.) The authors used the term "clockwise hysteresis loop" to describe this phenomenon, where less effect was observed at the same serum concentration at later time points.



Data from Shappell et al. (1996). Upper graph: Subjective fatigue, mean percentage change from baseline (●) and serum methamphetamine concentration (○) as a function of time after nighttime drug administration. Lower graph: subjective fatigue, mean percentage change from baseline (●) as a function of serum methamphetamine concentration, demonstrating discordance ("clockwise hysteresis loop") between subjective effects and serum methamphetamine level.

7. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Recreational Amphetamine Users

Perez-Reyes et al. (1991a) evaluated the pharmacokinetics of methamphetamine in six male volunteers who had previously used amphetamines for recreational purposes. Average lifetime use of amphetamines (amphetamine, dextroamphetamine and methamphetamine) was 8 ± 3.9 times. However, subjects were asked to abstain from using amphetamines or any other illegal

drug two weeks prior to commencement of the study and throughout its duration. Compliance with this request was verified by analysis of daily urine samples. The age of the subjects was 24 ± 2 years, and they weighed 72.6 ± 1.1 kg.

Subjects were administered daily oral doses of 10 mg d-methamphetamine hydrochloride in a sustained-release formulation (Desoxyn® Gradumet®, Abbott Laboratories) for 13 consecutive days (days 2-14 of the study). On days 1 and 15, the subjects were challenged with 0.125 mg/kg mg of deuterated methamphetamine hydrochloride to investigate both the pharmacological effects and the disposition of methamphetamine. Deuterated methamphetamine was administered orally in gelatin capsules and was *not* prepared as a slow release formulation. The drug was deuterated in order to differentiate plasma levels of the challenge doses from the residual levels undeuterated methamphetamine remaining after the daily doses. Subjective drug effects were evaluated by having the subjects rate the effects of the drug using a visual analog scale (VAS). The scale ranged from 0 to 100, with 0 representing no drug effects and 100 representing the "highest" they had ever experienced after using amphetamines. Cardiovascular parameters were examined prior to methamphetamine administration (i.e., baseline conditions) and at 2.5 and 3.5 hours after administration of the drug.

The time course of plasma concentrations of deuterated methamphetamine was virtually identical on test days 1 and 15. The peak plasma concentration of methamphetamine was approximately 22 ng/ml and was achieved approximately three hours after dosing. After 10 hours, the plasma concentration was approximately 15 ng/ml.

Over the same time period, the plasma concentration of non-deuterated methamphetamine, administered once/day on the previous 13 days as a sustained release formulation, remained relatively stable. The initial plasma concentration (measured before administration of the challenge dose of deuterated methamphetamine) was approximately 5 ng/ml, and declined slowly to approximately 3 ng/ml over the ensuing 10 hours. After 48 hours, the drug was no longer detected in plasma.

Consistent with the plasma concentrations of deuterated methamphetamine obtained on challenge days 1 and 15, there were no differences in the subjects' ratings of a drug related "high" at the beginning and end of the study. However, in comparison to results obtained on day 1, there was a significant decrease in the acceleration of heart rate produced in response to the methamphetamine challenge on day 15.

According to the authors, "These findings indicate that the disposition of methamphetamine and its subjective effects were not altered by this [13 day] period of daily exposure to a low dose of the drug. In contrast, tolerance to the heart-rate accelerating effect was observed."

A similar study was conducted on a different group of subjects by several members of the same research team (Cook et al., 1992). The study design was virtually identical to that adopted by Perez-Reyes et al. (1991): on day 1, a single oral dose of deuterated methamphetamine was administered; on days 2-14, a single 10 mg tablet of Desoxyn® Gradumet® was administered orally each morning; and on day 15, a second challenge dose of deuterated methamphetamine was administered orally. In this study, however, two dose levels of deuterated methamphetamine

were used: 0.125 and 0.250 mg/kg. Subjects were eight paid, informed volunteers who had previously used amphetamines for recreational purposes. All were required to abstain from using amphetamines or any other drug for two weeks prior the beginning of the experiment. Samples of blood, saliva and urine were collected and analyzed for methamphetamine and amphetamine.

The average elimination half-life of methamphetamine was 10.1 hours (range: 6.4 – 15.1 hours). Evaluation of methamphetamine pharmacokinetics following the lower challenge dose (0.125 mg/kg) of the deuterated drug revealed no statistically significant differences. However, at the higher challenge dose (0.250 mg/kg), the peak plasma concentration was slightly but significantly greater at the end of the 13-day oral dosing period than it was at the beginning of the study. (Data reproduced below.) There was no evidence that sub-chronic treatment with low doses of methamphetamine resulted in induction of metabolism.

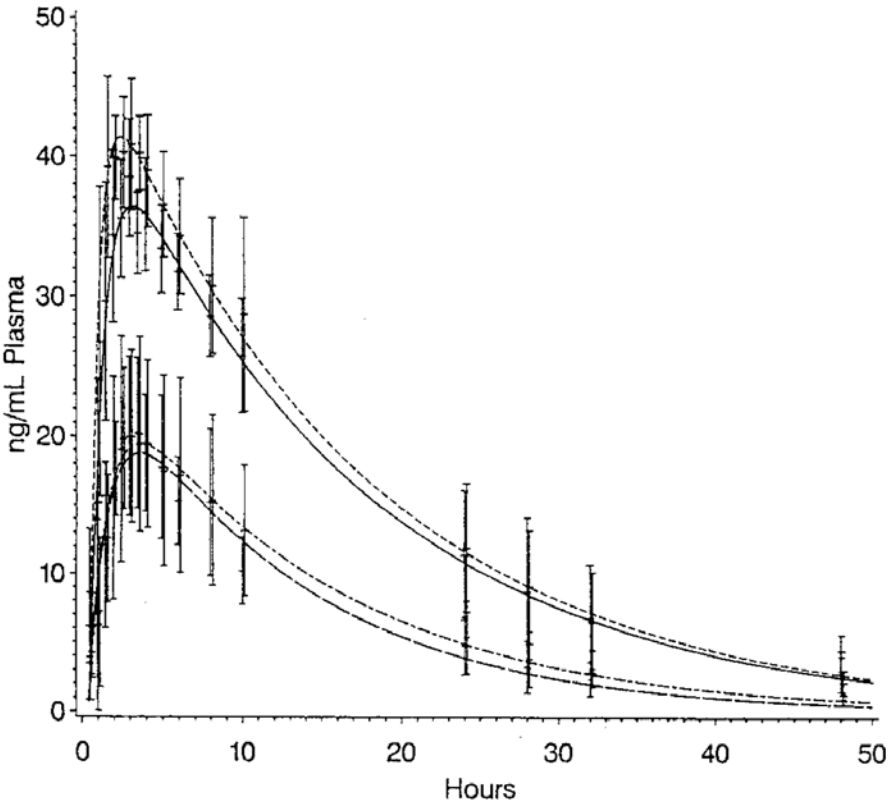


FIG. 1. *Concentration of S-methamphetamine-d_3 in plasma.*

Vertical bars show mean ± SD. *Curves* are computer fit of average pharmacokinetic data. *Curves* are day 1, 0.125 mg/kg dose (– –); day 15, 0.125 mg/kg (– - – -); and day 1, 0.250 mg/kg (——); day 15, 0.250 mg/kg(– – – –).

Data from Cook et al. (1992).

In a subsequent report (Cook et al., 1993), the authors used the data from this study to estimate an average oral bioavailability of 67.2 ± 3.1 percent. This value applies to methamphetamine

hydrochloride, not the sustained release form of the drug (Desoxyn® Gradumet®) that the subjects received on days 2-13 of the study.

Saliva concentrations of deuterated methamphetamine were on average 7.8 times higher than those detected in plasma. The correlation between plasma and saliva concentrations was modest ($r^2 = 0.62$), and large inter-individual variation was observed. These results suggest that saliva concentrations, which are frequently used for drug testing purposes, cannot reliably be used to predict plasma concentrations.

The same researcher team also examined the clinical effects of inhaled methamphetamine vapor in recreational amphetamine users (Perez-Reyes et al., 1991b). Six healthy male volunteers (age 26.7 ± 1.7 years, weight 84.1 ± 5.2 kg) participated in the study. All had significant experience using amphetamines [17.7 ± 4.3 times (range 6-35)]. Methamphetamine vapor was produced using a glass pipe that was placed in an aluminum block pre-heated to 305 ºC. Preliminary studies with this setup demonstrated that pyrolytic degradation of the drug was negligible. The pipe was capped to prevent escape of methamphetamine vapors to the atmosphere. Subjects were asked to rate their subjective impression of a methamphetamine "high" using a visual analog scale (described above), and cardiovascular effects (heart rate, blood pressure, systemic vascular resistance and indices of myocardial contractility) were determined at various intervals up to three hours after vapor inhalation. Blood samples were collected up to 48 hours after inhalation and analyzed for methamphetamine.

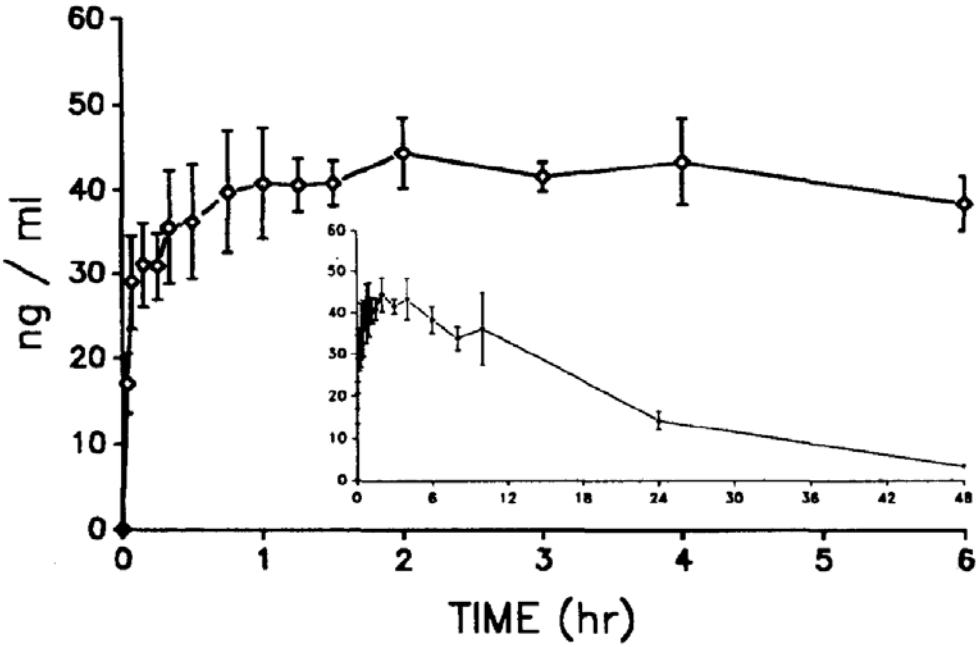
Dose range-finding studies were conducted to investigate the subjective and cardiovascular effects produced by progressively increasing doses of methamphetamine (20, 25, 30 and 40 mg). According to the authors,

> *…20 and 25 mg doses produced minimal subjective and cardiovascular effects, while the 30 mg dose produced more distinct and sustained effects. However, on one occasion in which a 40 mg dose was administered, it produced extreme subjective effects characterized by feelings of omnipotence and omniscience that were highly seductive and frightening…[this subject] experienced hypomanic symptoms for approximately two hours, intense craving for further dosing, decreased appetite, difficulty in concentration, memory lapses, and insomnia.*

Consequently, 30 mg was selected as the dose to use for the investigation to produce moderate subjective effects. Subsequent analysis of the amount of drug remaining in the pipe after inhalation indicated that the actual inhaled dose was 22.0 ± 0.3 mg (range: 20.7 – 22.6 mg), or 73 percent of the amount placed in the pipe. Using the assumption that the other three doses were similarly reduced by adherence to the pipe, it may be concluded that inhalation of 14.6 – 18.3 mg methamphetamine produced minimal subjective effects in this particular cohort of subjects, and 29.2 mg produced extremely euphoric (and thereby potentially reinforcing) subjective effects. Based on an average body weight of 84.1 kg, the delivered doses used in this study were equivalent to 0.17, 0.22, 0.26 and 0.35 mg/kg.

Methamphetamine levels in plasma rose rapidly, reaching approximately 30 ng/ml within the first five minutes after inhalation and continuing to rise during the subsequent two hours. Peak

plasma concentrations reached 45 ng/ml and remained above 30 ng/ml for 10 hours after drug administration (data reproduced below).



Data from Perez-Reyes et al. (1991b). Time course of plasma methamphetamine concentrations in six subjects following vapor inhalation (smoking) of the drug. Data points are means ± SEM.

Subjective ratings of methamphetamine "high" reached a peak at 18 ± 2 minutes after the beginning of inhalation of the drug. Subjective effects completely subsided within eight hours even though plasma levels of the methamphetamine were still in excess of 30 ng/ml. The authors believed this finding was suggestive of the development of acute tolerance (tachyphylaxis).

Peak changes in cardiovascular parameters generally appeared within 10-20 minutes of inhalation. Heart rate, systolic and diastolic blood pressure, stroke volume, cardiac output, and myocardial contractility were all increased, while systemic vascular resistance was decreased. The authors of the study suggested that the pattern of cardiovascular effects observed in this study resembled those produced by circulating norepinephrine, and was probably a result of methamphetamine-induced release of norepinephrine from the adrenal medulla. In support of this hypothesis, they cited the 1971 study by Martin et al., who observed that subcutaneous injection of methamphetamine caused a significant dose-related increase in urinary excretion of epinephrine.

In a subsequent report (Cook et al., 1993), the authors used the data from this study to estimate an average inhalation bioavailability of 90.3 percent for smoked methamphetamine hydrochloride.

8. Assessment of Euphoric and Dysphoric Effects of Methamphetamine

(Johnson et al., 1999b) evaluated the effects of isradipine on the positive subjective effects associated with the abuse liability of methamphetamine in the same cohort of 18 subjects discussed above.[26] Doses (0.21 and 0.42 mg/kg, oral) and experimental design were the same as described above. Prior to commencement of the experiments, subjects were trained to use the Addiction Research Center Inventory (ARCI) and Visual Analog Scales of Mood (VAS-M) to assess their subjective psychological status. The ARCI incorporates five sub-scales that reflect the subjective effects of different classes of abused substances: Amphetamine and Benzedrine group (A and BG scales; stimulation), Morphine-Benzedrine group (MBG scale; euphoria), Pentobarbital, Chlorpromazine and Alcohol group ((PCAG scale; sedation), and Lysergic Acid Diethylamide (LSD scale; dysphoria). VAS-M provided a means of scoring subjective ratings ranging from "not at all" to "extremely" for positive mood items (e.g., "cheerful," "feel good," "alert"), negative mood items ("lethargy" and "not liking drug effects") and craving ratings ("urge to use" and "if offered I could refuse").

d-Methamphetamine generally produced dose-dependent measures of both stimulation and mood. At both doses maximal euphoric effects were reported two hours after administration of the drug. As noted above, crushing the methamphetamine (Desoxyn®) tablets prior to administration to the subjects may have enhanced the rate of drug absorption, thereby affecting the time course of subjective effects.

Wachtel et al. (2002) evaluated the haloperidol, a drug that primarily blocks D_2 dopamine receptors, and risperidone, a drug that blocks both dopamine and serotonin receptors, on the physiological effects and subjective responses to a single 20 mg oral dose of methamphetamine. Subjects were male (n=22) and female (n=14) volunteers ranging in age from 18 to 35 years.[27] The study was a double-blind, placebo-controlled, within-subject, 2 x 2 repeated measures design. The subjects were divided into two groups of 18 subjects each: haloperidol (3 mg) was administered to one group and risperidone (0.75 mg) was administered to the other. Thus, each subject participated in four test sessions, receiving all combinations of antagonist or placebo followed by methamphetamine or placebo. Sessions were separated by at least one week. Methamphetamine was administered in size 00 gelatin capsules with dextrose filler. However, the manufacturer of the drug and its physical form (tablet or powder) were not specified in the report. Identical placebo capsules contained dextrose only.

According to the authors, a 20 mg oral dose of methamphetamine was selected "…to match previous studies with *d*-amphetamine on prototypical subjective, behavioral and physiological measures." Furthermore, "Methamphetamine is roughly equipotent with *d*-amphetamine on most measures in humans, and it substitutes readily for *d*-amphetamine in drug procedures in this dose range."

Methamphetamine alone produced stimulant effects similar to those that have been observed in human subjects who were administered *d*-amphetamine. Effects peaked 1-2 hours after administration of the drug and declined over the subsequent 3-4 hours. Responses on the 49-item Addiction Research Center Inventory (ARCI) Amphetamine (ARCI-A) and Benzedrine

[26] See Johnson et al. (1999a), summarized on pages 26-27, and Johnson et al (2000), summarized on pages 33-34.
[27] Details regarding the weight, sex, race/ethnicity, education, current drug use (including alcohol and cigarettes) and lifetime drug use of all subjects were provided in the report.

Group (ARCI-BG) scales (both of which are indices of stimulant effects) as well as the Morphine-Benzedrine (ARCI-MBG) scale (an index of euphoria) were highly statistically significant. (ARCI-A data reproduced below.) Systolic blood pressure and heart rate were significantly elevated in both groups. Neither haloperidol nor risperidone consistently reduced the acute euphoric and reinforcing effects of methamphetamine, suggesting that the reinforcing subjective effects of methamphetamine in humans are not mediated solely via dopamine and serotonin receptors.

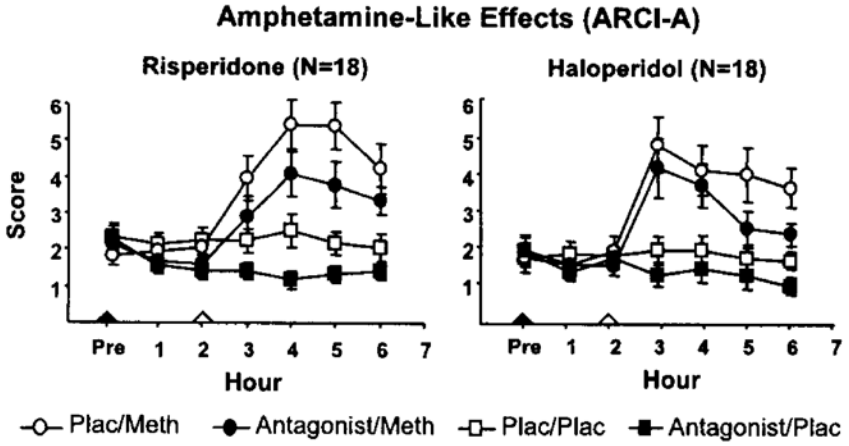


Fig. 1. Mean (±SEM) scores on the ARCI A scale, a measure of amphetamine-like effects. Circles represent methamphetamine conditions and filled symbols represent antagonist pretreatment (risperidone or haloperidol). Filled triangles on the *x*-axis indicate when the pretreatment capsule was administered; open triangles indicate when the methamphetamine or placebo was administered. In the Risperidone experiment on this measure there were main effects of both risperidone and methamphetamine, but no interaction between the two. In the Haloperidol experiment on this measure there was a main effect of methamphetamine but no effect of haloperidol.

Data from Wachtel et al. (2002). ARCI-A: Addiction Research Center Inventory scale that reflects the effects of Amphetamine drugs (stimulation).

In a similar comprehensive investigation of the subjective effects of methamphetamine, Söderpalm et al. (2003) conducted a study to determine whether acute stress alters the subjective responses to a single low (10 mg) oral dose of methamphetamine (Desoxyn®, Abbott Laboratories) in adult males. The drug was dissolved in 20 ml water and 20 ml orange juice to enhance absorption and ensure rapid onset of effects. Twenty-eight healthy men, 18-24 years of age with an average body weight of 73 kg, were recruited to participate the study. They were randomly divided into two groups that received methamphetamine (n=16) or placebo (n=12) on two successive sessions, separated by a minimum of 48 hours. Each participant was subjected to stress during one session and no stress during the other, in random order. Methamphetamine or placebo was administered immediately after the stress or no stress session. Acute stress was

induced using a modified version of the Trier Social Stress Test[28], a psychosocial stressor that has been demonstrated to reliably induce cardiovascular and endocrine responses, increase subjective ratings of stress, and increase plasma levels of the adrenal steroid corticosterone. Thus there were four experimental conditions: stress + methamphetamine, no stress + methamphetamine, stress + placebo, and no stress + placebo. Subjective mood effects, salivary cortisol levels and cardiovascular effects (blood pressure and heart rate) were assessed periodically for 90 minutes after drug administration.

Methamphetamine increased feelings of stimulation and decreased feelings of fatigue and sedation. (Data reproduced below.) These effects became apparent as early as 20 minutes after drug administration and generally peaked at 60-90 minutes, although this is difficult to conclude definitively because no data were collected beyond 90 minutes. Stress appeared to have little effect on the subjective responses to methamphetamine, particularly at the later time points. For example, methamphetamine increased scores on the ARCI MBG scale (euphoric effects) and the A scales (stimulant effects), and reduced scores on the PCAG scale (sedative effects) at multiple post-drug time points in both the stress and no stress sessions. Similarly, 30 to 90 minutes after drug administration, methamphetamine produced several of its prototypical subjective effects (e.g., increased ratings of "outgoing," "stimulated," "lively," and "want more drug") and increased heart rate irrespective of whether or not the subjects had been subjected psychosocial stress. Nevertheless, it is clear that a number of methamphetamine's characteristic subjective effects were only observed during the no stress session (e.g., increased ratings of "jittery," "alert," "on edge," and "focused," as well as increased scores on the ARCI BG scale (stimulant effects).

[28] In this procedure, subjects were required to face two observers and count backwards from 1754 in intervals of 13 for 10 minutes. They were informed that the test was being recorded and their performance would be analyzed for accuracy. If they hesitated or stopped, they were instructed to continue. Four subjects were tested together, and they were called upon in random order to perform the arithmetic task.

Table 3 Times (in min after stress) at which significant differences (*t*-tests) were obtained between stress and no stress within the groups (*columns 3* and *4*), or between the groups on either the stress or no stress sessions (*columns 1* and *2*). Letters denote the direction of the differences. *M* METH, *P* PLAC, *S* Stress, *NS* No stress

Dependent measures	Stress METH vs PLAC	No stress METH vs PLAC	METH Stress vs No stress	PLAC Stress vs No stress
Salivary cortisol	–	–	S>NS, 20*	S>NS, 0**,20***, 40*
Systolic BP	–	M>P, 40**, 60*, 90*	S>NS, 0*	S>NS, 0*
Diastolic BP	–	–	S>NS, 0*	S>NS, 0*
Heart rate	M>P, 90*	M>P, 60*, 90**	S>NS, 0*	S>NS, 0*, 20*, 60*
Like drug	M>P, 60*, 90*	–	–	–
Want more drug	M>P, 20*, 40*, 90*	M>P, 60*	S>NS, 20*	–
Energetic	P>M, 20*, 40*	M>P, 60*	NS>S, 20*, 40*	–
Sedative	M>P, 20*, 40*	–	S>NS, 60*	–
Anxious	–	–	S>NS, 0**	S>NS, 0*, 20*
Cheerful	M>P, 60*, 90*	–	–	–
Restless	–	P>M, 20**	–	–
Slow	M>P, 40*	–	–	–
Dreamy	M>P, 20*, 40*	–	S>NS, 20*	–
Outgoing	M>P, 40*, 60***, 90***	M>P, 40*, 60*, 90**	–	–
Drowsy	–	P>M, 60*, 90*	–	–
Focused	–	M>P, 40**, 60**, 90*	–	–
Heavy	M>P, 40*	–	–	NS>S, 40*
Stimulated	M>P, 60*, 90***	M>P, 60*, 90*	–	–
Peace	M>P, 20*, 60*, 90*	–	–	–
Tired	P>M, 60*	P>M, 60*, 90*	S>NS, 20*	–
Sluggish	–	P>M, 60*	–	NS>S, 60*
Lively	M>P, 60*, 90*	M>P, 90*	–	–
Jittery	–	M>P, 20*, 90**	–	–
Alert	–	M>P, 60*, 90*	–	–
On edge	–	M>P, 20*	–	–
Worn out	–	P>M, 60*	–	NS>S, 40*
Calm	–	P>M, 40*	NS>S, 0*	NS>S, 0**, 20*, 60*, 90*
Nervous	–	–	S>NS, 0*	S>NS, 0**
Content	M>P, 60*	P>M, 20**	–	NS>S, 20*, 40*, 60**, 90*
Relaxed	–	P>M, 20**	–	NS>S, 20**, 40*, 90*
Happy	M>P, 60**	–	–	–
Uneasy	–	–	–	NS>S, 0**
Mellow	–	–	–	NS>S, 40*, 90*
ARCI A	M>P, 60*, 90**	M>P, 60*	–	NS>S, 90*
ARCI BG	–	M>P, 60*, 90*	NS>S, 20**, 40*	–
ARCI MBG	M>P, 40*, 60**, 90**	M>P, 60*, 90*	–	–
ARCI PCAG	P>M, 90**	P>M, 20*, 60**, 90*	–	–

*$P<0.05$, **$P<0.01$, ***$P<0.001$

Data from Söderpalm et al. (2003). ARCI: Addiction Research Center Inventory scales, consisting of 49 true or false questions, that reflect effects of Amphetamine (A) and Benzedrine Group (BG) drugs (stimulation), Morphine-Benzedrine Group (MBG) drugs (euphoria), and Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) drugs (sedation). Subjective mood effects were evaluated using visual analog scales [ranging from "not at all" (0) to "extremely" (100)] to score each participant's feelings in relation to each of 30 adjectives.

9. Effects of Methamphetamine on Psychomotor Performance, Resistance to Fatigue, Decision Making and Memory

Shappell et al. (1992) examined the capacity of a single low dose of d-methamphetamine (10 mg/70kg, or 0.14 mg/kg) to ameliorate the detrimental effects of simulated sustained flights operations (SUSOPs) in 13 male U.S. Marine Corps commissioned officers, 22-28 years of age. Twelve control subjects received a placebo. The study was conducted under double blind conditions, and diet was strictly controlled. The SUSOP scenario consisted of a 9-hour planning session followed by 4 hours of rest and a 14-hour mission. After 6 hours of rest, the same 9 hour work /4 hour rest /14 hour work pattern was repeated. Methamphetamine was administered 4 hours and 20 minutes into the second "mission." As the simulated SUSOP scenario progressed, control subjects appeared to shift from a conservative to a more risky decision strategy. Administration of methamphetamine reduced subjective fatigue, improved scores on a generic

performance assessment battery, and reduced apparent risky behavior on two spatial memory tasks.

A similar study was conducted by Stanny et al. (1993) to evaluate the effects of a single dose of d-methamphetamine hydrochloride on fatigue-induced deficits in long-and short-term memory. Thirteen subjects, all male Navy and Marine aviation candidates, participated in this study. All subjects were extensively trained to perform tasks that required long-and short-term memory. Performance on these tasks was assessed at 90-minute intervals over a 13.5-hour sustained performance session, beginning at 7:30 PM and ending the following day at 9:00 AM. At 1:16 AM, seven received a single capsule containing 10 mg/70 kg methamphetamine in cornstarch filler. Six received a placebo, identical capsules containing cornstarch alone. The study was conducted under double blind conditions.

Performance (accuracy) on both tasks declined during the night. Methamphetamine reversed the decline in performance and improved decision speed within two hours of administration of the drug. However, improved performance was not a result of risky, impulsive responding, since there was an absence of any effect on impulsive responses ("fast guesses"). The positive drug effects were maintained through the remainder of testing, about seven hours after drug administration.

Wiegmann et al. (1996) examined the effects of methamphetamine on vigilance and tracking in a 13.5-hour sustained-performance session. Subjects were male naval aviation candidates 24 ± 1.4 years of age weighing 79.7 ± 9.3 kg (mean ± SD). Three groups of ten subjects each were evaluated after administration of a placebo, 5 mg/70 kg methamphetamine or 10 mg/70 kg methamphetamine. Treatments were administered under double blind conditions.

Subjects were trained on two computer-administered objective performance tasks, a high event rate vigilance (running memory) task and a two-dimensional compensatory tracking task, for four days prior to the sustained performance session. The sustained performance session began at 7:30 PM on day of the last practice session and ended at 7:00 AM the following morning. The session consisted of nine testing blocks spaced 90 minutes apart, and the drug or placebo was administered approximately halfway between the fourth and fifth block.

In the placebo group, performance on both tests degraded markedly during the sustained performance session: response accuracy declined and the rate of non-responses (lapses) and tracking errors increased. However, within approximately three hours of drug administration, methamphetamine reversed these deteriorations. Furthermore, at this point in the session, the two doses of the drug appeared to be equally effective. Nevertheless, by the end of session, the effects of the 5-mg dose had disappeared while the 10-mg dose continued to be effective. (Example data from the tracking task are reproduced below.)

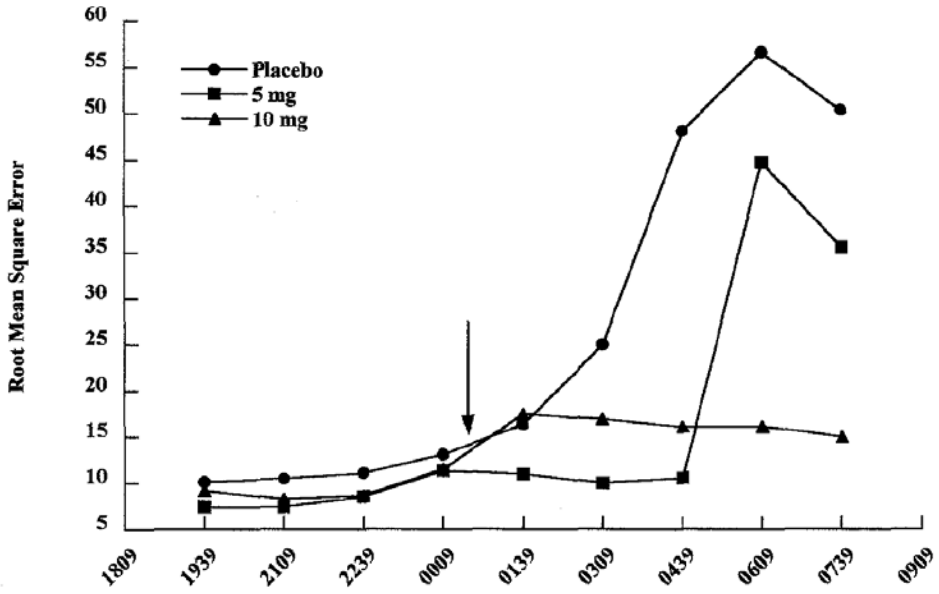


FIGURE 4 Tracking error versus time for the placebo and amphetamine groups. The arrow indicates drug administration.

Data from Wiegmann et al. (1996). In the two-dimensional tracking task, subjects were required to use a joystick to compensate for random directional changes in a continuously moving cursor displayed on a computer screen. The objective was to keep the cursor's *X-Y* position centered on a set of crosshairs in the middle of the screen. This task lasted about 9 minutes.

Mewaldt and Ghonheim (1979) evaluated the effects of physostigmine, scopolamine and methamphetamine on memory in human subjects. Subjects ranged in age from 18 to 32 years; average age was 22.6. Two doses of methamphetamine (0.2 and 0.3 mg/kg) were each administered intramuscularly to five subjects. Treatments were determined by randomized block procedure, and drugs were administered under double blind conditions. Following administration of the drug, subjects were administered a subjective rating questionnaire and several tests requiring immediate recall, delayed recall, and delayed recognition. Both doses of methamphetamine produced feelings of mental and physical arousal and generally increased feelings of happiness and friendliness or extroversion. The drug had no effect on retrieval of information learned prior to injection, and performance on two immediate recall tasks was similarly unaffected. In contrast, methamphetamine produced significant improvement in delayed recall of information that was acquired while the subjects were under the influence of the drug. However, the drug also produced a large increase in incorrect recall of words learned after injection. According to the authors of the study, the latter effects may reflect a change in the subjects' response strategy, i.e., improvement in both correct and incorrect recall may have been an artifact of improved confidence and reduced inhibition of recall.

10. Utilization of MRI to Identify Brain Regions Affected by Methamphetamine: Correlation with Subjective Effects

Völlm et al. (2004) utilized functional magnetic resonance imaging (fMRI) to identify areas of the brain that become activated as a result of methamphetamine administration in drug-naïve

subjects. Subjects were healthy volunteers (four female, three male, average age 29 years) with no history of psychostimulant use. The study was a single-blind within-subjects design. Baseline imaging and behavioral ratings were established during a 10-15 minute period of i.v. saline infusion. Thereafter, methamphetamine (0.15 mg/kg) was administered intravenously (i.v.) over a 1-minute period. According to the authors, "The choice of this specific dose was based on pilot data obtained from drug-naïve volunteers where it was established as the smallest i.v. dose that reliably separated the effects of methamphetamine from placebo on subjective ratings." The entire session lasted 41 minutes (i.e., 26-31 minutes after infusion of the drug). During this period, fMRI images were obtained and subjects rated themselves for the subjective experience of "mind racing" at one-minute intervals. Subjective ratings ranged from 0 (no mind racing) to 4 (high), and a clear description of the term "mind racing" was provided to the subjects.[29]

All subjects experienced an increase in "mind racing" within 2-3 minutes of i.v. methamphetamine infusion. Peak response occurred 10-15 minutes after the infusion. By the end of the session, subjective ratings had dropped significantly. (Data reproduced below.) Post-session interviews indicated that the subjects experienced the subjective effects of the drug as positive and rewarding.

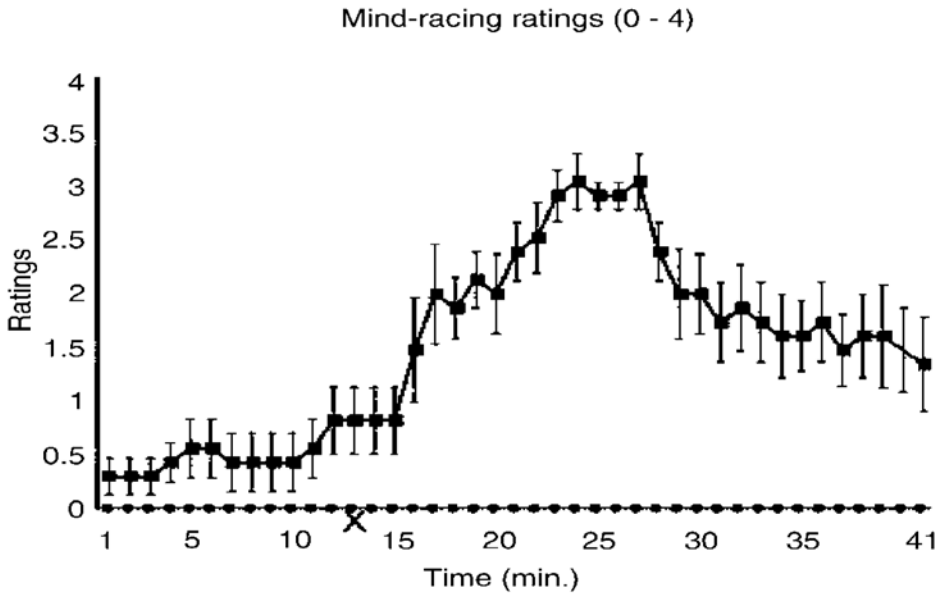


Figure 1 Averaged (mean ± SEM) behavioral ('mind racing') ratings given by subjects across the experiment. The 'X' in the time axis shows the average time of the amphetamine infusion.

Data from Völlm et al. (2004). (In the figure legend, "amphetamine" actually refers to methamphetamine.)

[29] Specifically, "Mind racing is a condition you would not normally experience in day to day life. It is a state where your thoughts run far too quickly as if they were racing. One thought is replaced by another very quickly and it is difficult to hold on to your thoughts. You might have experienced a similar condition when you were very anxious or excited."

fMRI imaging demonstrated activation of the medial orbitofrontal cortex, the rostral portion of the anterior cingulated cortex and the ventral striatum. (fMRI images reproduced below.) Activations of the latter two regions correlated with ratings of "mind racing." Activations of the medial orbitofrontal cortex were observed during the entire post-infusion period and were independent of any motor-related activity (i.e., responses required to make subjective ratings). The authors suggested that these results provide evidence of activation of classical reward circuitry in the brain, and that activation of the orbitofrontal cortex may play a central role in drug reinforcement and the development of drug addiction.

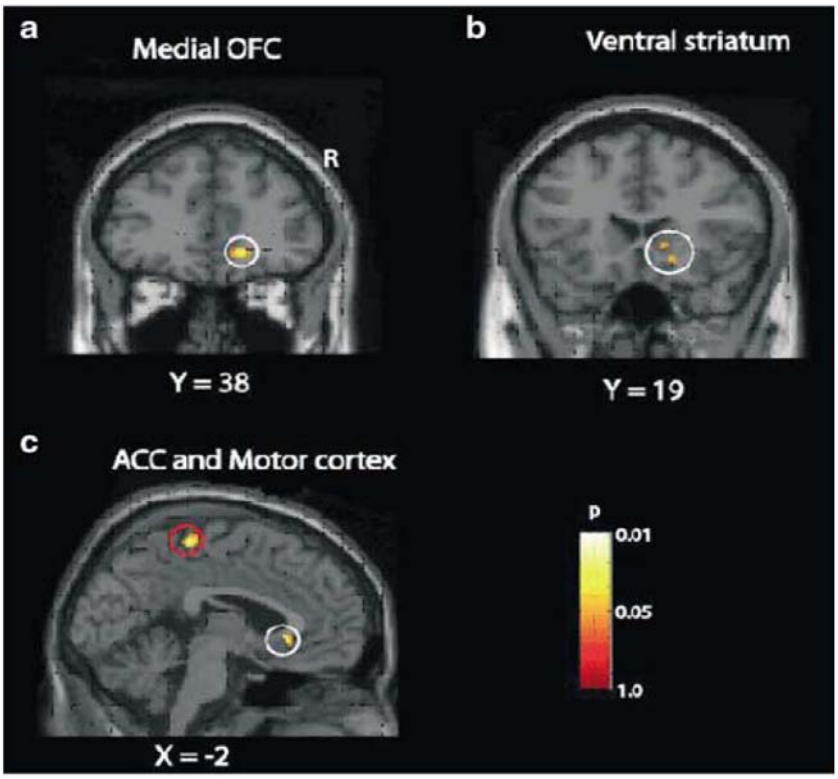


Figure 2 Results of the comparison Amphetamine–Saline. Activations (shown within the white circles) were found in (a) the medial orbitofrontal cortex, (b) ventral striatum, and (c) anterior cingulate cortex, and motor cortex (red circle). The *p*-values shown are with the small volume correction procedure (SVC, see 'Materials and methods').

Data from Völlm et al. (2004). (In the figure legend, "amphetamine" actually refers to methamphetamine.)

11. Studies Evaluating the Use of Methamphetamine to Treat Children for Enuresis

Young and Turner (1965) conducted a study to test the hypothesis that stimulant drugs would facilitate conditioning (negative reinforcement) in the treatment of nocturnal enuresis (bed wetting) in children. As summarized in the table below, 299 children 4-15 years of age were placed in one of three treatment groups.

Treatment Groups:	n	Mean Age (years)	Duration (months)
Conditioning alone	105	8.1	2.2
Conditioning + Dexedrine (d-amphetamine)	84	8.0	2.0
Conditioning + Methedrine (d-methamphetamine)	110	7.1	1.9

In conditioning treatment, a buzzer alarm is triggered by the discharge of urine onto an electronic detector placed under the sleeping child. The alarm wakens the child very soon after enuresis begins and therefore serves as negative reinforcement for bed wetting. Successful treatment was defined as 14 consecutive "dry" nights. The average treatment duration for all three groups was approximately two months, although some children were treated for as long as four months. If a child had not achieved the criterion for success after four months, the case was considered a failure.

The groups were not matched according to sex. In the control group (conditioning alone) 57.4 percent of the children were boys. In the conditioning + Methedrine group, 72.2 percent of the children were boys. Using mean number of wet nights as a measure of success, girls slightly outperformed boys, although the differences between girls and boys were not statistically significant.

For children under five years of age, the initial dose of methamphetamine was 2.5 mg, but was increased to 5 mg and maintained at this level or reduced if side effects became apparent. Children of five years of age and older received an initial dose of 5 mg and were maintained at this level or reduced, again depending on the appearance of side effects. For three children the dose was increased to 7.5 mg, with 2.5 mg given between 4-5 PM and 5 mg at bedtime. One child received 10 mg in divided doses. These higher doses were tolerated without any side effects. With the exception of these four cases, parents were required to administer the drugs at bedtime.

The parents of children who participated in this study were closely involved in treatment. Parents and children were seen at the clinic together at 14-day intervals; regular attendance at these interviews was made a condition of treatment. Parents were specifically questioned about any disturbance of sleep pattern. In the 189 cases where drugs were administered, side effects were experienced by four children taking Dexedrine and by eight children taking Methedrine. These side effects disappeared when dosages were reduced.

Sleep disturbance and insomnia are widely recognized, characteristic side effects of amphetamines and other stimulants (e.g., methylphenidate). In this study, the children were administered the drugs at bedtime, greatly increasing the likelihood that CNS stimulation and consequent sleep disruption would be observed. While the published report does not state this explicitly, it appears that the eight children in the conditioning + Methedrine group who experienced sleep disturbance were receiving 5 mg/day. When the dose was reduced to 2.5 mg/day, these effects disappeared. Thus, 8 of 110 children dosed with methamphetamine experienced adverse effects at 5 mg but not at 2.5 mg. Based on this study, the critical effect of methamphetamine would be defined as sleep disturbance (insomnia). The LOAEL was 5 mg per day, and the NOAEL was 2.5 mg/day. Since the average body weight of a 7 year-old child is

25.1 kg (Exposure Factors Handbook; U.S. EPA, 1997), the LOAEL and NOAEL are equivalent to 0.2 and 0.1 mg/kg-day, respectively.

Methamphetamine treatment improved the success rate and reduced the duration needed to achieve the criterion for treatment success. In the control group (conditioning alone), 68 percent of the children were treated successfully. In contrast, 90 percent of children receiving conditioning + methedrine) were treated successfully. Mean number of wet nights (14.2 for conditioning alone vs. 10.1 for conditioning + Methedrine) also indicated that methamphetamine improved treatment outcome.

A 1969 report by Kapoor and Saksena also evaluated the effects of d-methamphetamine (Methedrine, Burroughs Wellcome) for treatment of enuresis in children. Thirty children were placed on a single oral dose of 5-10 mg methamphetamine each day, and fifteen children received a placebo. The ages of these children ranged from 5-14 years. Additional study details are lacking, although it appears that the parents of the children administered the drug. Parents were asked to report any adverse reactions, including insomnia and loss of appetite, immediately. The duration of treatment was not specified. The investigators assessed each child's progress with weekly follow-ups. If no improvement was noted after one week of treatment, the daily dose was increased (presumably, from 5 mg/day to 10 mg/day, although this was not stated explicitly). Results are shown in the table below.

	Methamphetamine (n=30)	**Placebo (n=15)**
Complete cessation of enuresis	15	1
Great improvement (2-3 wet nights/week)	4	3
Moderate improvement (4-5 wet nights/week)	8	2
Unchanged (6-7 wet nights/week)	2	9

Three of the children receiving methamphetamine experienced drug-related side effects (insomnia, constipation, dry mouth and anorexia) and the dose of the drug was reduced (presumably, from 10 mg/day to 5 mg/day, although this was not stated explicitly). Drug treatment of one child had to be stopped, presumably due to the occurrence of significant side effects. The authors concluded that methamphetamine produced earlier and more complete cessation of enuresis than placebo.

In a study designed to replicate the findings of Young and Turner (1965), Kennedy and Sloop (1968) evaluated the use of d-methamphetamine as an adjunct to conditioning treatment of nocturnal enuresis in normal and institutionalized retarded children.

Among the non-retarded children, three boys and one girl received 5 mg/day Methedrine (d-methamphetamine hydrochloride) just before bedtime. The control group, which consisted of five boys and one girl, was treated with conditioning alone using a commercially available alarm system similar to the device used by Young and Turner. The non-retarded children ranged in age from 6 to 12 years. Eight institutionalized retarded children were 9 to 12 years of age and had measured IQs ranging from 26 to 65. Five retarded children were treated with conditioning

alone, and three received conditioning plus Methedrine. The criterion for successful treatment was 14 consecutive dry nights.

The authors concluded that methamphetamine failed to enhance either the rate of achieving success or completeness of success compared to conditioning alone. However, among the retarded children, the data do not necessarily support this conclusion (see graph below). Furthermore, the small size of the study probably precludes drawing definitive conclusions about the relative success of the two treatments.

12. Case Studies of Children Treated with Methamphetamine

Zike (1972) described a case study of treatment of an 8-year old child with "developmental dyslexic learning disability" with methamphetamine. Initially, the child was observed for a period of five days. On days 6 to 18, one placebo tablet was given at 7:00 AM each day. This was followed by daily doses of 5 mg methamphetamine[30] on days 19 to 29, also at 7:00 AM. On days 30 and 31, the dose of methamphetamine was increased to 10 mg/day. On each day of the study, the child was rated for thirty minutes on the following:

- attention-to-task ("not looking away from the boundaries of his desk, ignoring surrounding stimuli unless physically involving, and carrying out the task assigned")
- talks-outs ("speaks without raising his hand for the teacher's attention or speech is inappropriate to the task assigned or he vocalizes in any other way which is not acceptable")
- jump-ups ("leaves his seat without permission or direction from teacher")

Observations were made at the same time each day by the same observer, who was blind to treatment.

Details regarding the outcome of treatment were not provided, and side effects were not discussed. However, a single chart showing baseline behavior, behavior during treatment with the placebo and behavior during treatment with methamphetamine (reproduced below) indicates that the drug was successful in improving attention to task and reducing talk-outs and jump-ups.

[30] The drug administered was "desoxyephedrine [methamphetamine] in a time-release form" but details regarding the manufacturer or the form of the drug were not provided.

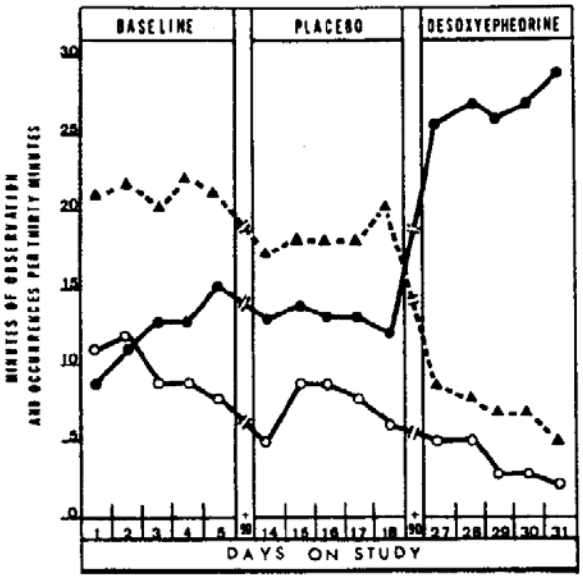


Fig. 2. Eight-year-old DYSLX-LD hyperkinetic boy of normal intelligence. Drug: desoxyephedrine, time-release form, 5 mg orally 7.00 a.m. daily (days 19 to 29); 10 mg orally 7.00 a.m. (days 30 to 31).
●——● attention-to-task; ○——○ talk-outs; ▲- - -▲ jump-ups.

Data from Zike (1972).

Bussing and Levin (1993) described a case study of an 11-year-old boy with obsessive-compulsive disorder (OCD), major depression and ADHD who was successfully treated with a combination of fluoxetine and methamphetamine. Fluoxetine (Prozac®) was started initially to treat OCD and depression. The initial dose was 20mg every other day, and after one week was increased to 20 mg/day. After three weeks, OCD and symptoms of depression showed significant improvement, but ADHD symptoms increased. Consequently, a stimulant was added to the fluoxetine regimen. Initial twice daily oral doses of 5 mg dextroamphetamine produced an increase in symptoms of hyperactivity. The authors suspected this may have been caused by the presence of FD&C Yellow No. 5 (tartrazine) in the medication. Consequently, they switched stimulant medication to methamphetamine (which does not contain tartrazine), 5 mg orally twice each day. Other reasons for selecting methamphetamine were its reliable and rapid onset of action and its lack of potential for altering the metabolism of fluoxetine. Eventually, the dose was changed to 10 mg of a sustained-release form of methamphetamine every morning. Given that the body weight of the child was 37 kg, the daily dose of methamphetamine was 0.27 mg/kg-day.

Treatment with methamphetamine produced marked reduction of symptoms associated with ADHD. The authors noted that the child "….has tolerated this regimen of fluoxetine and methamphetamine without untoward effects." Unfortunately, no long-term follow-up information on this case was available (Regina Bussing, personal communication).

13. Potential Developmental Toxicity of Methamphetamine

Sussman (1963) reported on four case studies of women who used methamphetamine during pregnancy and the effects on their delivery and infants. Salient features of these cases are summarized in the table below. Two of the infants were born prematurely, and one case was complicated by breech delivery. On admission to the hospital, all four mothers were asymptomatic. In two cases, the time period since the last methamphetamine dose was at least ten days, and neither infant experienced withdrawal symptoms. In the other two cases, the time since the last methamphetamine dose was unknown, and both of the infants born to these mothers experienced withdrawal symptoms. Physical examination of one infant (case #4) at four months of age was normal, although both the weight and head size of this infant were small. An associated finding in this case was "suspect hepatitis" but the report did not elaborate on this.

The cases presented in this report exemplify several of the problems associated with attempts to assess methamphetamine's potential to adversely affect prenatal development. The author noted, "The exact drug dose taken by a pregnant addict is rarely known. The drug purchased illegally is often diluted, and the history referable to this point is usually inaccurate." Other factors such as multiple drug use and poor nutrition during pregnancy have significant potential to adversely affect prenatal development, but obtaining accurate information on them is equally difficult.

Last "Fix," Pre-delivery	Weight (kg)	Withdrawal Symptoms	Onset of Withdrawal	Associated Findings	Follow-Up Age (mo)	Follow-Up Findings
unknown	2.7	shrill cry, irritable, jerky, moro	5 hours	respiratory distress at & after birth	none	
unknown	2.9	irritable, sneezing	1st day	none	none	
10 days	2.4	none	—	none	none	
6 months	2.2	none	—	suspect hepatitis	4	normal; weight 3 percentile head 10 percentile

Data from Sussman (1963). Summary of case studies of infants born to mothers who were users of methamphetamine. Details of each case were limited and not discussed in detail. In the first case, "moro" refers to a small abscess or tumor resembling a mulberry. Two of the births were premature, but the author did not identify the two premature births among the four cases.

Smith et al. (2001) examined morphological changes and biochemical markers of neurotoxicity in the brains of young children born to mothers who were addicted to methamphetamine during pregnancy.[31] Results were compared to a healthy control group of children whose mothers had no history of drug use. Characteristics of the exposed and control groups are shown in the table below.[32]

	Methamphetamine Exposed	**Control**
Number of subjects	12	14
Average age (years)	8.1 ± 0.8	7.3 ± 1.1
Maternal tobacco use[a]	6	1
Maternal alcohol use[b]	4	0
Maternal cocaine use[c]	2	0

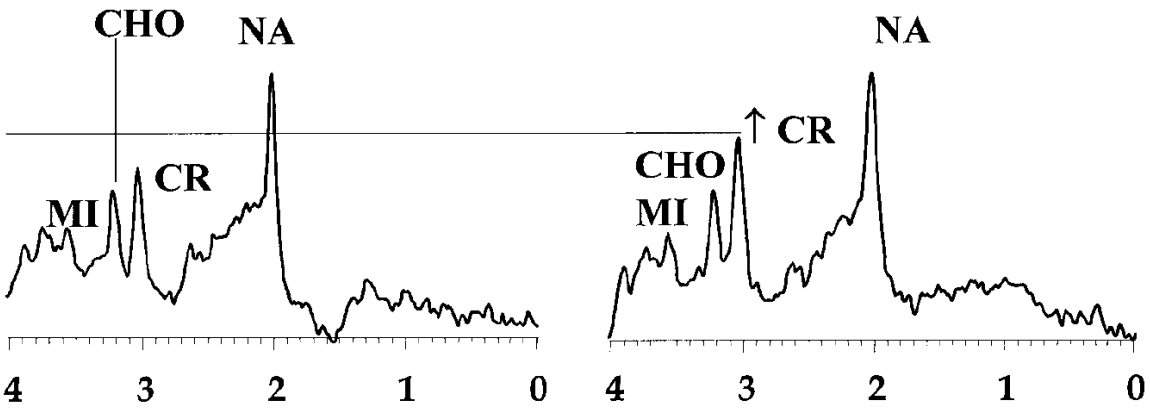
[a] Average number of cigarettes smoked per day: 17 ± 8
[b] Of the four methamphetamine-addicted women who also consumed alcohol during their pregnancy, all reported less than 0.5 ounces of absolute alcohol/day.
[c] Two methamphetamine-addicted women also reported "trying" cocaine during their pregnancy "on a limited number of occasions."

Children born to methamphetamine-addicted mothers were shown to have a higher concentration of creatine and phosphocreatine (Cr) in the basal ganglia, suggesting potential abnormality in energy metabolism. The authors suggested that altered energy metabolism in the basal ganglia may have important clinical implications because executive functioning in the brain is thought to be mediated in part by the frontal-striatal pathway.

Concentrations of N-acetylaspartate (NA), a marker of neuronal integrity that is reduced in conditions of neuronal damage or loss, were not significantly different in the two groups. Additionally, examination of the brains of both groups of children using magnetic resonance imaging (MRI) indicated no visible structural abnormalities, and assessments using the Child Behavior Checklist parental rating revealed no significant differences in the incidence of reported behavior problems.

Methodological shortcomings of this study include the small numbers of children in the exposed and control groups, and reliance on maternal self-reporting of use of other psychoactive substances. The interpretation of results is also limited by significantly higher rates of concurrent tobacco, alcohol and cocaine use in the methamphetamine-addicted mothers compared to the controls. Although the two groups of children differed in age by almost ten months, the authors reported that no age-related changes in creatine and several other biochemical markers of neuronal and glial integrity were detected.

[31] Children were included in the methamphetamine-exposed group only if their mother was diagnosed as methamphetamine dependent [according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV)] for at least two-thirds of her pregnancy.
[32] All biochemical data were reported as mean ± SEM. The report does not state specifically that age and tobacco use information were also reported as mean ± SEM, but this would appear to be a logical conclusion.



Data from Smith et al. (2001). Proton magnetic resonance spectra from the right basal ganglia of a control child (left) and a child whose mother was addicted to methamphetamine during pregnancy. Compared to the control child, the prenatally exposed child shows a 7.7 percent increase in creatine and phosphocreatine (CR) concentration, possibly indicating altered energy metabolism in this portion of the brain. Other biochemical markers [N-acetylaspartate (NA), myoinositol (MI) and choline (CHO)] were not significantly different.

Chang et al. (2004) conducted a pilot study to examine the effects of prenatal methamphetamine exposure on brain morphometry using magnetic resonance imaging (MRI). Global intracerebral brain volumes, subcortical brain structures and cerebellum were evaluated. In addition, global cognitive functioning was assessed using a battery of neurocognitive tests, with particular emphasis on tests of attention and motor development.

Characteristics of children in the methamphetamine-exposed and control groups are summarized in the table below.[33] Some of the subjects in this study also participated in the study conducted by Smith et al. (2001), reviewed above. Data on concurrent maternal use of other psychoactive substances (tobacco, alcohol and cocaine) during pregnancy were not provided. However, the authors noted that some of the children smoked cigarettes and consumed "low doses" of alcohol. Neurocognitive assessments were only completed on ten of the methamphetamine-exposed and nine of the control children.

	Methamphetamine Exposed	**Control**
Number of subjects	13	15
Boys, girls	4, 9	6, 9
Average age (years)	6.9 ± 3.5	7.8 ± 3.2
Age range (years)	3 - 16	3 - 15

[33] Children were included in the methamphetamine-exposed group only if their mother was diagnosed as methamphetamine dependent [according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV)] for at least two-thirds of her pregnancy.

Methamphetamine-exposed and control children were recruited from similar lower and middle socioeconomic groups but were not matched for parental education level, which might influence performance on cognitive tests.

MRI-based morphometry showed that whole brain volumes of children in the two groups were comparable, but the putamen, globus pallidus and hippocampus were all smaller in methamphetamine-exposed children. The reduction in size of these structures correlated with lower scores on tests of sustained attention and delayed verbal memory. Children exposed prenatally to methamphetamine also scored lower on measures of visual motor integration, attention, verbal memory and long-term spatial memory. No differences in motor skills, short delay spatial memory or measures of non-verbal intelligence were detected.

A common limitation in interpreting the results of the studies by Smith et al. (2001) and Chang et al. (2004) is the inability to determine which (if any) of the reported effects are attributable to prenatal methamphetamine exposure and which are due to the postnatal environmental in which these children were raised. As Wouldes et al. (2004) point out, "Risk factors related to maternal psychosocial functioning and the home environment have been found to adversely affect child development independent of the mother's use of substances during pregnancy…Thus, converging evidence…suggest that there may be a double jeopardy in which these children are at risk due to the combination of prenatal exposure effects and postnatal environmental effects."

Smith et al. (2003) evaluated fetal growth and the incidence of withdrawal symptoms in term infants exposed to methamphetamine in utero. This retrospective study involved 134 methamphetamine-exposed and 160 unexposed infants. Significant differences ($p<0.001$) in prenatal care and concurrent psychoactive substance use by the two groups of mothers were reported (see table below). There were no differences in growth parameters of infants exposed prenatally to methamphetamine and unexposed infants. Nevertheless, the growth of neonates exposed to methamphetamine throughout gestation was decreased relative to the growth rate of infants exposed for only the first two trimesters. The growth of infants born to methamphetamine-addicted mothers who also smoked cigarettes was reduced significantly relative infants exposed prenatally to methamphetamine alone. Four percent of methamphetamine-exposed infants experienced withdrawal symptoms serious to require pharmacologic intervention.

	Methamphetamine Exposed	**Control**
Number of women	134	160
Poor prenatal care, percent (<5 visits)	57	21
Cigarette smokers, percent	63	10
Alcohol use, percent	33	0
Marijuana use, percent	44	0

Smith et al. (2008) reported preliminary findings from the Infant Development, Environment and Lifestyle (IDEAL) study, a 36-month longitudinal investigation of neurodevelopmental outcomes in children with prenatal methamphetamine exposure. The study involved 74

methamphetamine-exposed and 92 control mother-infant pairs. Characteristics of the mothers are summarized in the table below.

	Mean (SD)/number (percent)	
	Exposed (N=74)	Comparison (N=92)
Race		
White	33 (45%)	38 (41%)
Hispanic	14 (19%)	19 (21%)
Pacific Islander	10 (14%)	11 (12%)
Asian	12 (16%)	13 (14%)
Black	4 (5%)	8 (9%)
Other	1 (1%)	3 (3%)
Low SES (Hollingshead V) *	29 (39.2%)	11 (12.0%)
Household income <0,000	21 (32%)	18 (21%)
No partner*	43 (58.1%)	33 (35.9%)
Public insurance	62 (83.8%)	77 (83.7%)
Education <12 years	38 (51.4%)	38 (41.3%)
Age, year	25.1 (5.4)	23.9 (5.8)
Gest age 1st prenatal visit, week *	15 (7.7)	9 (5.1)
Out of home placement *	20 (28.2%)	2 (2.2%)
Prenatal heavy METH use	12 (16.7%)	
Prenatal tobacco use *	58 (78.4%)	25 (27.2%)
Heavy tobacco use *	22 (29.7%)	8 (8.7%)
# of cigarettes per day (median & range) *	3.83 (0–20)	0 (0–25)
Prenatal alcohol use *	28 (38%)	15 (16%)
Heavy alcohol use *	3 (4.1%)	0
# of absolute alcohol per day (median & range) *	0 (0–1.36)	0 (0–0.14)
Prenatal marijuana use *	24 (32%)	7 (7.6%)
Heavy marijuana use *	15 (20.3%)	6 (6.5%)
# of joints per day (median & range) *	0 (0–4)	0 (0–1.36)

* $P<0.05$.

Data from Smith et al. (2008). "Heavy" METH use was defined as using any methamphetamine three or more days per week. Similarly, "heavy" tobacco use ≥ 10 cigarettes per day, "heavy" alcohol use was ≥ 0.5 oz. of absolute alcohol per day (1 standard drink), and "heavy" marijuana use was defined as ≥ 0.5 joints per day. All other uses of these substances were defined as "some use."

Consistent with earlier studies of children whose mothers were addicted to methamphetamine while they were pregnant (discussed above), the exposed mothers in this study were two- to four-times more likely to use tobacco, alcohol and marijuana as well. Mothers who self-report cocaine use during pregnancy were excluded from the study. Most of the women in the exposed

group smoked cigarettes (78 percent *vs.* 27 percent of controls), and slightly less than one-third were heavy smokers (30 percent *vs.* 9 percent of controls). These women were also more likely to be in a lower socioeconomic group and without a partner.

Patterns of methamphetamine abuse in the exposed group by trimester are summarized in the table below. The data represent frequency of use only. Amounts of the drug consumed were not provided because "The quantity of MA [methamphetamine] use in the exposed study population was deemed unreliable in the study set because many [mothers] did not know the grams conversion of the street term amount they were using."

MA use	Trimester					
	First		Second		Third	
	N	(%)	*N*	(%)	*N*	(%)
Daily	11	(15.3%)	4	(5.6%)	2	(2.8%)
3–6 days/week	19	(26.4%)	10	(13.9%)	7	(9.7%)
1–2 days/week	9	(12.5%)	7	(9.7%)	5	(6.9%)
1–3 days/month	8	(11.1%)	6	(8.3%)	3	(4.2%)
1–2 days/3 months	13	(18.1%)	14	(19.4%)	13	(18.1%)
Not at all	12	(16.7%)	31	(43.1%)	42	(58.3%)

Data from Smith et al. (2008)

Smoking was by far most common route of methamphetamine administration, having been used by 81 percent of the mothers who admitted using the drug. Other routes were snorting (28 percent), injection (14 percent), and ingestion (7 percent). Approximately 18 percent of admitted users took the drug by two or more routes.

The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) was administered to most full-term infants within 5 days after birth. The NNNS provides a means of assessing neurologic, behavioral, and stress/abstinence neurobehavioral function. Heavy methamphetamine use[34] by mothers was associated with lower arousal scores (suggesting hypo-arousal), higher lethargy scores, and higher physiological stress scores in their infants. These effects were not observed in the infants whose mothers only reported "some use" of methamphetamine during pregnancy. First trimester methamphetamine use was associated with greater stress/abstinence in the infants.[35] Third trimester use was associated with poor "quality of movement" in the infants, indicating that the neonates were more likely to be jittery with little or no smooth movement of the arms and legs, were more easily startled, and had higher overall activity.

[34] Heavy use was defined as use of any methamphetamine three or more days per week. Just 12 of the 74 methamphetamine-using women in the study were identified as heavy users.

[35] The stress/abstinence scale is based on observations made throughout the examination. It is divided in to physiologic, autonomic, CNS, skin, visual, gastrointestinal and state sub-scores.

In evaluating the significance of research on the potential adverse effects of prenatal exposure to methamphetamine on childhood neurodevelopment, the conclusions of a 2006 literature review conducted by National Abandoned Infants Assistance Resource Center (AIA) are pertinent. The authors of this report stated,

> *Research findings concerning the effects of prenatal substance exposure on children's development are often inconclusive and controversial…The development of infants exposed prenatally to substances may be simultaneously affected by numerous factors, including exposure to multiple substances and prenatal care…Specifically, mothers who gave birth to infants prenatally exposed to illegal substances were also found to have used greater amounts of alcohol and tobacco while pregnant compared to mothers whose children were not exposed and were also less likely to have received prenatal care or had fewer prenatal care visits…Other moderators, such as the type of substance (both licit and illicit), amount of exposure, frequency of use, and timing during pregnancy, may also affect child outcomes.*
>
> *Perhaps the most important limitation of the current research is the complexity and difficulty presented in attempting to tease out the specific developmental effects of drug exposure from the effects of the child's home environment. How and by whom the child exposed to substances in-utero is raised can have profound effects on growth and development.*

To various extents, the research limitations noted in the AIA review are applicable to all the studies summarized in this section. For the purposes of developing a reference dose, lack of information on the amount of drug consumed by the women in these studies is problematic because reported effects cannot be related to a specific dose or even a range of doses. However, the results reported by Smith et al. (2008) suggest that relatively heavy use (and consequent high doses) of methamphetamine is required to adversely affect neurodevelopment, at least when neurodevelopmental assessment is conducted shortly after birth. We anticipate that additional findings from this 3-year longitudinal study will help refine our understanding of the consequences of *in utero* exposure to methamphetamine.

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Response to Comments on the Draft Document, *Development of a Reference Dose (RfD) for Methamphetamine* (OEHHA, December 2007)

I. Comments from Dr. John Martyny, Associate Professor, Division of Environmental and Occupational Health Sciences, National Jewish Medical and Research Center, Denver, Colorado

a) *On page 8 (top), you discuss some of the adverse effects and indicate in rare cases children developed cognitive impairment, etc. The article may not discuss this but what is rare - 1 percent or 10 percent or 0.01 percent?*

The statement that children with ADHD who receive methylphenidate (Ritalin®) or amphetamine (e.g., Adderall®) "…may experience cognitive impairment, psychosis, mood disturbances or hallucinations" is essentially a re-statement of one of the conclusions of the three reports that were reviewed in this section. An estimate of the frequency of occurrence of these effects was not provided, most likely because this conclusion was probably based on individual case reports. Obtaining a "ballpark" estimate of the incidence of severe side effects is further complicated by the fact that children who are given stimulants for treatment of inattentiveness and/or impulsivity may actually have more severe psychological illness. Therefore, in some cases, the severe side effects that are linked with stimulant medications may actually be part of the spectrum of symptoms the child is already experiencing.

b) *On page 9 (second paragraph), you indicate that surface residue will be depleted over time due to cleaning and transfer to other surfaces. I am not sure that is true. I do believe that many surfaces might be depleted such as tables, etc. In the real world, however, rarely do people wash down their walls or ventilation ducts. In addition, our experience with carpet cleaners does not suggest that much contamination is removed. Vacuuming and even steam cleaning do not seem to drastically reduce carpet levels of many contaminants. Since we were never able to do the long-term study, we don't know how long meth will stay but we found some very high levels in houses that had been occupied for some time. We did not sample carpets in those homes but we did look at other smooth items. My guess is that the carpeting will serve to contaminate other smooth surfaces that have been cleaned.*

Our analysis of exposure in a post-cleanup scenario incorporated the assumption that surface methamphetamine residues do not become depleted over time. Nevertheless, in order for a child to be exposed via the dermal route, surface-to-skin transfer of methamphetamine must occur. A logical consequence of this transfer is that the surface concentration will be depleted with each successive contact. In essence, we have incorporated health protective principles into the analysis: surface-to-skin transfer is the mechanism whereby exposure occurs, but we assume that this transfer does not deplete the concentration of methamphetamine on any surface. This

assumption leads to a higher estimate of exposure than would occur if we were to assume that the surface concentration becomes depleted over time.

We recognize that removing methamphetamine residue from surfaces – particularly carpet – is difficult. Nevertheless, exposure via the dermal route (and indirectly, the ingestion route) requires transfer of methamphetamine residue from the contaminated surface to skin. If no transfer occurred, there would be no exposure and consequently there would be no health risk. Transport of residues from highly contaminated areas to areas that are less contaminated also requires surface-to-surface transfer (e.g., carpet-to-shoes).

c) *On page 17, one of the bullets refers to the significance of the inhalation as a pathway of exposure. I think that inhalation may still be a problem since vacuuming a carpet does seem to result in a major exposure. Although many individuals only vacuum once a week or less and it may not be a major exposure. Simply walking on a carpet may allow some release for inhalation.*

We agree that vacuuming and walking across heavily contaminated carpet or flooring will kick up chemical residues into the air. However, it's important to recall that our analysis is based on a post-remediation exposure scenario. In this scenario, all surfaces have been cleaned and the concentration of methamphetamine does not exceed the designated target remediation standard. The small amount of methamphetamine that remains on the surface is the residue that is most difficult to remove. As you note in your previous comment, vacuuming and even steam cleaning of carpet does not appear to drastically reduce the levels of contaminants on carpets. Therefore, we believe it is very unlikely that simply walking across a remediated surface will result in re-entrainment of methamphetamine residues into the air.

II. Comments from Dr. Kent Olsen, Medical Director of the San Francisco Division of the California Poison Control System and Clinical Professor of Medicine and Pharmacy at UC San Francisco

a) *Did you find any additional developmental toxicity information in animals that might help shed light on potential teratogenic effects of methamphetamine exposure during the first trimester of pregnancy?*

The potential teratogenicity of methamphetamine and other amphetamine compounds was extensively reviewed in the report, *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Amphetamines* (National Toxicology Program, Center for the Evaluation of Risks to Human Reproduction, July, 2005). This report examined the potential for amphetamines to cause adverse effects on reproduction and development in humans. It concluded that methamphetamine may cause adverse developmental effects in humans, specifically on growth and neurobehavioral development. This conclusion was based on "…evidence from studies in experimental animals [indicating that] prenatal and

postnatal exposures to methamphetamine produce neurobehavioral alterations, small litter size, and low birth weight."

The CERHR report provided detailed summaries of the developmental toxicity studies in experimental animals that were cited to support its conclusions. In most of these studies, methamphetamine was administered to pregnant rats by subcutaneous injection. In summarizing the results of several such studies, the expert panel that authored the report concluded

> *…the studies suggest that prenatal methamphetamine exposure can result in decreased litter size (≥ 10 mg/kg bw/day), delayed eye opening (≥ 3 mg/kg bw/day), reduced postnatal body weight gain (≥ 3 mg/kg bw/day), and increased stillbirth or postnatal mortality (≥ 20 mg/kg bw/day). One study* [Acuff-Smith et al., 1996] *demonstrated that increases in stillbirths and postnatal mortality are greater with late- (GD 13-18) versus mid- (GD 7-12) gestational exposures.*

Note that all the doses utilized in these studies are substantially higher than 0.08 mg/kg bw/day, the LOAEL based on data from Chapman (1961).

The CERHR report did not identify any reports that specifically examined the developmental toxicity of methamphetamine in animals exposed during the first trimester of gestation.

In response to this comment and others that we received from OEHHA staff, we expanded the final section of the RfD report that addresses the potential neurodevelopmental toxicity of methamphetamine in humans. A study by Smith et al. (2008) tracked the frequency of methamphetamine use during the first, second and third trimesters of pregnancy. In general, there was a pattern of decreasing methamphetamine use and increasing abstinence during the course of pregnancy, suggesting that the effects reported in this investigation may by attributable primarily to use of the drug during the first trimester. However, as discussed in our review of this report, it is not clear that any of the reported effects are attributable to methamphetamine use because concurrent use of other psychoactive substances (both licit and illicit) was significantly higher in the women who took methamphetamine than in the controls. Furthermore, data from individual women were not provided, precluding identification of effects specifically attributable to first trimester drug use.

b) *Taken as a whole, the proposed human reference dose appears to be prudent and based on sound scientific knowledge, methods and practices.*

No response required.

c) *Regarding the study design of the Chapman (1961) study: were patients really* ***not*** *assigned randomly to a treatment group? How was assignment done?*

The Chapman (1961) report provides the following information regarding the assignment of individual women to a specific treatment (dose) group:

- Patients were chosen for inclusion in the study "…because of overweight or excessive weight gain in the course of the pregnancy."
- Patients were given the 5 mg dose if their initial weight was 100 to 120 pounds (45-54 kg), 10 mg if their initial weight was 120 to 165 pounds (54-75 kg), and 15 mg if their weight exceed 165 pounds (>75 kg).
- If a patient could not tolerate the initial dose, the next smaller dose was utilized.

In fact, it does not appear that strict adherence to the weight criteria for dose assignment was maintained. For example, five of the ten women in the 5 mg dose group weighed more than 120 pounds at the beginning of their pregnancy, and seven of the women in this group weighed more than 120 pounds at the beginning of the study. In contrast, only a few of the women in 10 mg group weighed in excess of 165 pounds. As a result, the average body weights of the 5 and 10 mg dose groups at the beginning of the study differed by just 14 pounds, and women in the 10 mg group received almost twice the dose on a mg/kg body weight basis as women in the 5 mg group. In part, these results may reflect the dose adjustments that were made early in the course of the study to accommodate those women who did not tolerate the initial dose.

III. Comments from Dr. Tim Wiegand, Assistant Adjunct Professor of Medicine, UC San Francisco and the California Poison Control Center – San Francisco Division

a) *Selecting the study involving pregnant women (Chapman) included a potentially 'sensitive' sub-population. Use of the critical effect, "weight loss" compared to 'sleep disturbance' (Young and Turner study) based on the possibility of development of tolerance to the critical effect, 'sleep disturbance', in particular in children, was pertinent. In fact, many of the effects elicited by methamphetamine may be tampered* [sic] *by tolerance.*

We agree that tolerance to some of the central effects of methamphetamine can occur, and the development of tolerance to weight loss was also a concern in selecting the Chapman study as a basis for development of an RfD. The Physician's Desk Deference indicates that Desoxyn® Gradumet® may be used for treatment of obesity "…as a short-term (i.e., a few weeks) adjunct to a regimen of weight reduction based on caloric restriction…" Furthermore, "Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued." Over the 15-16 week exposure period of the Chapman study, tolerance to the anorectic effect of Desoxyn® Gradumet® may indeed have occurred, but the report did not provide the data needed to substantiate this possibility. Nevertheless, it is clear that methamphetamine produced a dose-related reduction in

body weight gain over the course of the study, suggesting that the participants in this study did not develop tolerance to the drug.

b) *This method of dosing…did not account for overlap in weights of women in placebo, 5, 10 and 15 mg/kg groups. Thus the mg/kg dose did not vary linearly when moving from 5 to 10 to 15 mg/kg doses.*

The total daily doses given to the women in this study were 0, 5, 10 and 15 mg; these were not mg/kg body weight doses. As noted in our response to comment II(c) above, the body weight criteria for assigning individual women to a specific dose group were not rigorously applied. As a result, the average daily doses in the four treatment groups were 0, 0.08, 0.15 and 0.17 mg/kg body weight. Therefore, while the nominal doses spanned a three-fold range, the range of doses expressed as mg/kg body weight was slightly more than two-fold.

c) *Some dropout patients were not included in the studies final analysis thus somewhat limiting the findings.*

In summarizing the results of this study, we excluded twelve women who withdrew from the study (designated "intolerant" by the study's author) and nine women who were treated with a diuretic (in addition to methamphetamine) to control weight gain. Nevertheless, the number of women who remained in the study throughout the dosing period was sufficient to ensure that the overall effect was dose-related and highly statistically significant. The numbers of women who withdrew from the study or were treated with a diuretic in each dose group are summarized in the table below.

Treatment	Initial n	"Intolerant"	Administered diuretic	Final n
0	25	2	0	23
5 mg/day	17	5	2	11
10 mg/day	43	4	4	35
15 mg/day	20	1	3	16

d) *The review and explanation of limits and relevance for each section (not only for the primary study but also for the supporting literature/reviews) in regards to how the critical factors were selected; as well as applicability to the 'at-risk' groups at risk for sub-chronic exposure to wastes/chemicals in structures previously used for clandestine methamphetamine production, was thorough and supportive of the findings in regards to the RfD.*

No response required.

e) *The depth and breadth of the review was adequate. I agree with excluding an intensive review of the literature regarding animal toxicity for the reasons mentioned in the report: there is a large species dependent difference in sensitivity to effects of the drug…However, there has been some very interesting*

work done on neurotoxicity of methamphetamine and imaging in primates (although the doses used were substantially higher than any doses encountered in this population at risk or a population exposed to a dose within orders of magnitude of the RfD). These studies could simply be referenced or commented on in regards to discussion of particular neurologic lesions/toxicity from methamphetamine exposure.

As stated in the report, we intentionally avoided review and evaluation of the effects of methamphetamine in common laboratory animals, such as rats and mice, for the reasons noted in Dr. Wiegand's comment. We believed these reports would not have a material effect on the conclusions of our report, although they may have provided an additional support for including an additional 3-fold uncertainty factor in the RfD calculation to account for gaps in the toxicity database.

The RfD report did review one study (Völlm et al., 2004) that utilized functional magnetic resonance imaging (fMRI) to identify regions of the brain that are activated when methamphetamine is administered to drug-naïve human subjects. Several other studies have utilized various brain imaging technologies to examine various effects of the drug in humans, but these have focused primarily on changes in long-term methamphetamine abusers. The same imaging techniques have been used to study the actions of the drug on the brains of non-human human primates. For example, Fowler et al. (2007) utilized positron emission tomography (PET) to examine the pharmacokinetics of *d*-methamphetamine, *l*-methamphetamine and cocaine and assess the saturability and pharmacologic specificity of binding to the dopamine and norepinephrine transporters or the vesicular monoamine transporter (VMAT). At this point, we believe the primary value of these studies lies in elucidation of the biochemical mechanisms of action of methamphetamine rather than identification of subtle changes that might be indicative of toxicity. Of course, this situation could change in the future as additional studies utilizing brain imaging are conducted.

It is worth noting that the range of effective doses of methamphetamine in humans and non-human primates appears to be similar. For example, Melega et al. (2008) evaluated the effects of long-term (33 weeks) methamphetamine administration in vervet monkeys and utilized a dose of just 0.1 mg/kg-day (intra-muscular) during the first four weeks of the study. This suggests that primates may be a relevant animal model for studying the effects of the drug at the biochemical and cellular level.

f) *Limits in the supporting data, although most of the limits were pointed out in the EPA protocol, include reviews which discussed stimulants other than methamphetamine used to treat conditions that methamphetamine (or generally a 'stimulant' type of medication) is used for. Although, the adverse events reported in these studies are consistent with adverse events reported when exposures to methamphetamine have occurred – as during studies directly involving methamphetamine or inadvertent exposure occur; and use of a variety of 'stimulants' as treatments, in particular for children, consistently uncovered common side effects such as: anorexia, nausea, jitteriness or anxiety and*

decreased sleep, and that minimal difference in efficacy when using varied stimulants to treat the same underlying condition is reassuring (studied in multiple as well as individual subjects). However, methamphetamine, being more potent than other stimulants such as: amphetamine or methylphenidate, will produce the 'similar' adverse effects, but at lower doses (I agree with this statement and point made in the paper after review of the literature). Thus there cannot be a direct comparison to methamphetamine and other stimulants in terms of adverse or critical effects.

The RfD document summarized the conclusions of three reviews that evaluated the legitimate pharmaceutical uses of stimulant medications other than methamphetamine. These reviews were conducted by the American Medical Association's Council on Scientific Affairs (1997), the National Institutes of Health (1998), and the American Academy of Pediatrics (2001).

We agree that comparing methamphetamine with pharmacologically and chemically similar stimulants such amphetamine and methylphenidate is problematic, and did not intend to suggest that methamphetamine is "just another stimulant." Without question, methamphetamine is more potent, produces greater effects on the central nervous system and has a higher abuse potential. Our purpose in reviewing the literature on the effects of less potent stimulants in children was to examine the possibility that results of studies of drugs with similar spectrum of biologic effects might inform our understanding of the adverse effects of methamphetamine, and raise any "red flags" about methamphetamine's potential to adversely affect children's health and (in particular) neurological development.

In a health risk assessment, hazard identification is the qualitative process of determining the nature of the adverse health effects that may arise as a result of exposure to a particular chemical. Dose-response assessment is the quantitative process of characterizing the relationship between the dose of the chemical and the incidence of a particular adverse effect. We believed that authoritative evaluations of the adverse effects stimulants in children might provide useful information for the hazard identification step of a risk assessment for methamphetamine. We did not plan on using this information to derive a dose-response relationship for methamphetamine

In comparison to the handful of studies examining the adverse effects of methamphetamine in children, the scientific literature on the effects of methylphenidate (Ritalin®) and amphetamine (e.g., Adderall®) in children is extensive. Although they are less potent, these drugs are structurally and pharmacologically similar to methamphetamine. The available evidence suggests that treatment with low doses of these two stimulants for periods up to 14 weeks is not associated with adverse neurobehavioral consequences. Had there been any evidence suggesting that methylphenidate or amphetamine adversely affect neurological development in children, we likely would have increased the uncertainty factor for incompleteness of methamphetamine's toxicity database from 3 to 10.

g) *This will also be particularly relevant in discussion of general exposure to the residue from clandestine labs, not in reference to individual chemicals, but taken as exposure to different combinations of chemicals, from different synthetic routes, with different contaminants and different yields of byproducts from the reaction –how this may effect symptoms and the overall sub-chronic exposure to this type of environment may be very different than isolated sub-chronic exposure to individual chemical entities at REL's* [reference exposure levels].

Clandestine synthesis of methamphetamine generates multiple chemical by-products that contaminant the interior space where the synthesis occurred. The possibility exists that the adverse effects of exposure to methamphetamine residues may be significantly enhanced by simultaneous exposure to other environmental contaminants. Therefore, a target remediation standard for methamphetamine that is based solely on toxicity data for the drug – and does not consider concurrent exposure to other environmental contaminants – may not completely protect the health of future residents. We agree that this is a legitimate concern.

Former clandestine methamphetamine labs should probably be regarded as hazardous waste sites. If this were the case, simultaneous exposure to multiple contaminants could be accounted for by conducting a health risk assessment, which would assume that the response to multiple chemical contaminants is additive. Therefore, the target cleanup standard for each contaminant would be reduced in proportion to the total number of contaminants present.[36] However, at the present time, former clandestine methamphetamine labs are not regarded as hazardous waste sites and, to our knowledge, a health risk assessment for a former clandestine lab has never be conducted.

Currently, methamphetamine is the primary "indicator chemical" for remediation of former clandestine methamphetamine labs. Fortunately, the cleanup methods that are required to meet the target cleanup standard for methamphetamine are likely to be at least partially effective at removing residues of other chemical contaminants from interior surfaces. Furthermore, given the time required to remediate a clandestine methamphetamine lab, it is very likely that any airborne contaminants (such as solvent vapors) will have dissipated by the time the property is approved for re-occupancy.[37] Therefore, while exposure to multiple contaminants in a post-cleanup scenario is possible, the levels of all contaminants are likely to be low enough that significant toxicological interactions would not be anticipated.

h) *Most of the supplementary documentation was consistent with, and supported, the primary study, however a group of reports that described dosing of methamphetamine in conjunction with a sedative (phenobarbital, chlorpromazine or pentobarbital), in my opinion, need to be interpreted with significant*

[36] Health risk assessments generally do not account for synergistic (greater than additive) interactions between chemicals. Fortunately, synergistic interactions in toxicology are rare.

[37] Justification for the assumption that airborne contaminants are no longer present once the remediation of a former clandestine methamphetamine lab is complete is provided in the draft report, "Assessment of Children's Exposure to Surface Methamphetamine Residues in Former Clandestine Methamphetamine Labs, and Identification of a Risk-Based Cleanup Standard for Surface Methamphetamine Contamination" (OEHHA, 2007).

limitation. These preparations do not mimic the methamphetamine exposure as described elsewhere, in particular in the primary study (Chapman). The use of a sedative, in particular, a barbiturate, will attenuate many of the adverse reactions/sympathomimetic effects seen with methamphetamine and other stimulant drugs… The limits of using these studies (which relied on methamphetamine doses in admixtures with other drugs) is described somewhat when discussing a study which involved administration of a methamphetamine/reserpine combination.

Four studies reviewed in the RfD report utilized methamphetamine in combination with a sedative for treatment of obesity. The authors and the pharmaceutical formulations used in these studies are summarized in the table below.

Study	**Pharmaceutical**	**Meth-HCl**	**Sedative**[38]
Shutter & Garell (1966)	Ambar Extentabs #1	10 mg	65 mg phenobarbital
Simkin & Wallace (1960)	Ambar Extentabs #1	10 mg	65 mg phenobarbital
Matthews (1970)	Desbutal Gradumet	10-15 mg	60-90 mg pentobarbital
Hughes (1960)	Du-Oria	25 mg	250 µg reserpine

These studies were reviewed because they provide additional experimental evidence that methamphetamine is an effective pharmaceutical for reducing weight gain and/or promoting weight loss in obese individuals. However, all four of these studies have methodological shortcomings that severely limit their utility in identifying low-dose adverse effects of methamphetamine.

As Dr. Wiegand points out, combining a sedative with methamphetamine probably masked many of the adverse side effects of methamphetamine such as insomnia and jitteriness. For this reason, these studies are not useful for identifying any effect other than appetite suppression. Even this conclusion is somewhat uncertain because sedation may lead to reduced physical activity and lower caloric demand. If this were the case, treatment with the stimulant-sedative combination would be expected to produce less weight loss than methamphetamine alone.

The report by Shutter and Garrell (1966) was of interest because the subjects of the investigation were children 5 through 18 years of age, and we had identified young children as the population of greatest concern for the purpose of establishing a risk-based

[38] Phenobarbital is a long-acting barbiturate with a half-life of 24-96 hours; pentobarbital has a short- to intermediate-term duration of action and a half-life of 21-42 hours. Reserpine is a "hit and run" antipsychotic agent, insofar as behavioral effects appear slowly and persist long after the drug is gone from the body.

cleanup standard for methamphetamine. The results of the study confirmed the effectiveness of methamphetamine in the treatment of obesity, but shortcomings in the experimental design – particularly the use of a methamphetamine-sedative combination drug and the failure to include a protocol to track the occurrence of side effects – greatly limit the significance of these results.

In additional to using a methamphetamine-sedative combination, Simkin and Wallace (1960) placed all participants in their studies on a restricted 1000-calorie high protein diet, making it impossible to ascertain the relative significance of drug treatment and caloric restriction on weight loss.

Both Shutter and Garell (1966) and Simkin and Wallace (1960) were reviewed in the RfD report because they demonstrated a significant placebo effect during the first 4-6 weeks of treatment. That is, subjects in both the active drug and the placebo groups experienced more weight loss during the first few weeks of the study than in subsequent weeks, but those who received the active drug continued to lose weight at a significantly greater rate than the placebo controls.[39] These findings demonstrate the importance of conducting weight loss studies in humans (1) under placebo-controlled conditions and (2) over a duration that is long enough to ensure that a placebo effect can be distinguished from a legitimate drug effect. The fact that the Chapman (1961) study met these two criteria was one of the primary reasons it was selected as the basis for the RfD.

Matthews (1970) also evaluated a methamphetamine-sedative combination drug for weight loss, but the primary emphasis of the study was to evaluate the effectiveness of dietary training on the subjects' ability to keep from re-gaining weight they had lost. The study was included in the RfD document because it included a description of the side effects of drug treatment, including anxiety and motor restlessness, insomnia, and changes in blood pressure and heart rate. In addition, post-treatment depression, a potential side effect of withdrawal from methamphetamine treatment, was not observed. Nevertheless, the incidence of stimulant-induced side effects was undoubtedly altered by concurrent administration of pentobarbital. Hughes (1960) provided details on the side effects of a methamphetamine-reserpine combination drug in a diverse group of obese subjects ranging in age from 14 to 68. Unlike the other three studies where a methamphetamine-sedative combination was used to treat obesity, the primary side effect observed in this study – drowsiness – appears to be attributable to the sedative. Methodological shortcomings of this study were discussed in the RfD report.

We believe the findings reported by Matthews (1970) and Hughes (1960) are interesting and add breadth to the analysis of methamphetamine's biological effects. However, we agree that they are of little relevance to the development of an RfD for methamphetamine.

i) *Finally, the case reports (when discussing possible developmental toxicity), which described possible developmental toxicity, and in particular the reports that focused on methamphetamine obtained through non-pharmaceutical sources, are of limited use in that there is often significant confounding variables ("…multiple*

[39] See Table 2 from Simkin and Wallace (1960), reproduced on page 24 of the external review draft.

drug use, poor nutrition during pregnancy…") which limit interpretation. Obtaining accurate information may be very difficult.

We agree. Furthermore, given the binge dosing (i.e., multiple doses taken periodically over a period of several hours) that frequently occurs with individuals who are addicted to methamphetamine, obtaining a reasonably accurate estimate of the dose of the drug is a challenge. The case reports were included in the RfD report because they provide limited qualitative information on the potential of methamphetamine to adversely affect pre- and postnatal development. They did not affect the derivation of the RfD for methamphetamine.

Since the draft RfD report was prepared, we identified several additional studies examining the potential neurodevelopmental toxicity in children whose mothers took methamphetamine during pregnancy. Summaries of these reports have been added to Section 13 of the report ("Potential Developmental Toxicity of Methamphetamine"), but they did not alter the derivation of the RfD.

j) *It would be useful, to place the RfD in context, to discuss the findings of various measurements at particular clandestine methamphetamine labs as well as "controlled" methamphetamine 'cooks' –e.g., in a fume hood. In one review I looked at the mean of methamphetamine obtained from "single swab wipes" (from 97 wipe samples) of 499 mcg of methamphetamine/sample (described as 499 mcg/100cm2). Discussion on translating this to a chronic exposure value would be needed as well. This may fit well when the specific REL is discussed for methamphetamine.*

Utilization of the RfD to derive a risk-based cleanup standard for methamphetamine on indoor surfaces is described in the draft report, *Assessment of Children's Exposure to Surface Methamphetamine Residues in Former Clandestine Methamphetamine Labs, and Identification of a Risk-Based Cleanup Standard for Surface Methamphetamine Contamination* (OEHHA, 2007). This document describes use of the U.S. EPA's Stochastic Human Exposure and Dose Simulation (SHEDS) model to estimate the total exposure a 6-to18 month old child would receive as a result of living in a residential environment that is uniformly contaminated with methamphetamine residues on all interior surfaces. In essence, SHEDS translates a given surface residue concentration (in units of ug/100 cm^2) into a estimate of exposure (in units of mg/kg-day).

This report also describes some of the results environmental data that John Martyny et al. have obtained following controlled "cooks" (synthesis) of methamphetamine, as well as analytical results from wipe samples that were collected from surfaces of former clandestine methamphetamine labs.[40]

k) *Some of these comments are placed in italics in that a particular response may be more pertinent when included in the follow up discussion/report regarding REL's*

[40] Dr. Martyny's reports are available at http://www.nationaljewish.org/news/y2005/meth_research_results.aspx

or follow-up reports on the clandestine methamphetamine labs and sub-chronic exposures to their environments. I included my thoughts simply for consideration.

We appreciate the comment. As noted in the responses to comments received from James Morrison (below), we believe comprehensive analysis of the potential health risks of chemicals encountered at former clandestine methamphetamine labs requires completion of a health risk assessment. This is the standard planning tool used to analyze risks associated with most hazardous waste sites, and former clandestine methamphetamine labs certainly qualify as hazardous waste sites. Development of an RfD for methamphetamine will provide a means of incorporating the drug into a multi-chemical, multi-pathway assessment of potential health risks.

l) *Overall this report was well done and based upon sound scientific literature, method and practice. The RfD derived is extremely reasonable in that considerations of safety have been thoroughly addressed as well as the variables involved in extrapolating existing data to such an exposure as is being addressed in this report.*

No response required.

IV. Comments from James Morrison, PG, Technical Programs Manager, Tennessee Department of Environment and Conservation, Division of Remediation

a) *It should be noted that some of the assumptions of the study do not correlate with symptoms and complaints that are common from people inadvertently living in former clandestine methamphetamine labs (CML) here in Tennessee. The common symptoms reported are:*

- *Breathing difficulties similar to allergy.*
- *Extreme breathing difficulties with multiple hospital visits for newborns*
- *Nosebleeds*
- *Headaches*
- *"Jittery or restless feelings" (There is no consensus as to specifics of this category. Each individual describes it differently. This could be partially a placebo effect from one believing they have been exposed to stimulants.)*

The RfD report represents a comprehensive summary and review of published research describing the toxic effects of methamphetamine in humans. Jitteriness and restlessness are consistent with known symptoms of methamphetamine exposure, but the other symptoms listed – particularly those relating to breathing difficulty – are not. This suggests that other contaminants may be responsible for these effects. Other contaminants would likely be present in a former clandestine methamphetamine lab if it had not been remediated or had been improperly remediated. Some of these contaminants (such as ammonia and solvent vapors) are acute pulmonary irritants that could cause breathing difficulties, nosebleeds and headaches.

The RfD report did not review the range of toxic symptoms experienced by humans who have been exposed to chemicals encountered in a clandestine methamphetamine lab environment. Dozens of chemicals are present in these labs, and the results of studies conducted by Martyny et al. indicate that the concentrations of these chemicals during a "cook" and immediately thereafter are often high enough to produce adverse health effects. Unremediated or improperly remediated chemical spills or disposal sites could also produce emissions of volatile chemicals that would have the potential to adversely affect health, and in particular compromise pulmonary function.

b) *Some of the symptoms described above may be caused by chemicals other than methamphetamine. If this is the case methamphetamine may not be the critical chemical to assess the risk of reoccupation of a former meth lab.*

We agree that several of the symptoms listed in the first comment are probably not indicative of methamphetamine exposure. However, methamphetamine is clearly the primary indicator chemical for remediation of former clandestine methamphetamine labs in many states, including Tennessee. Furthermore, the provisions of California Senate Bill 536 (Bowen, Chapter 587, Statutes of 2005) required that OEHHA develop guidance for a risk-based target remediation for methamphetamine to ensure protection of the health of all persons who subsequently occupy a former clandestine methamphetamine lab. The Department of Toxic Substances Control will use this guidance to develop the methamphetamine remediation standard.

A comprehensive health risk assessment would need to be completed in order to determine which contaminant(s) have the greatest potential to adversely affect the health of persons living in a former clandestine methamphetamine lab. This would require RfD values for methamphetamine and all other detected contaminants. To our knowledge, a health risk assessment of a former clandestine methamphetamine lab has never been conducted.

c) *The model of this study assumed no inhalation exposure. This does not seem to parallel the symptoms we get from complaints (breathing difficulties and nosebleed).*

Justification for eliminating inhalation as a significant pathway of exposure to methamphetamine in a properly remediated former clandestine methamphetamine lab is provided in the exposure assessment report. A more detailed response to this comment is included with responses to comments on the exposure analysis.

d) *The model does not consider newborns as a likely sensitive receptor. The complaints we have received would indicate otherwise.*

We agree that newborns may be particularly sensitive to methamphetamine. In fact, justification for incorporating an additional 3-fold uncertainty factor in the derivation of

the RfD was based in part on methamphetamine's potential to cause neurological toxicity during pre- and postnatal development (see pages 15-16 of the draft RfD report).

e) *Methamphetamine is the only chemical modeled in the paper. As we all know methamphetamine labs frequently have many chemicals of concern (frequently there are significant unknowns). The scope of this proposed health-based standard should be kept in mind as it only applies to hazards from the drug itself and not the many other contaminants of drug manufacture.*

Both the RfD report and the exposure assessment report addressed methamphetamine as the sole chemical of concern. The scope of both documents was dictated by the legislation that provided the resources for completing this work. As noted above, the provisions of California Senate Bill 536 (Bowen, Chapter 587, Statutes of 2005) required that OEHHA develop guidance for a risk-based target remediation for methamphetamine to ensure protection of the health of all persons who subsequently occupy a former clandestine methamphetamine lab.

Without question, other chemicals are present in former clandestine methamphetamine lab environments. However, in order to assess aggregate health risks from multiple chemicals, a multimedia health risk assessment – which requires an RfD for each of the environmental contaminants detected – must be conducted. Reference doses for many of the contaminants encountered at clandestine methamphetamine labs have already been developed. The availability of an RfD for methamphetamine will allow the drug to be included as a chemical of concern in a health risk assessment.

V. Comments from Dave McBride, Washington State Department of Health, Office of Environmental Health Assessments

a) *The current cleanup standard of 0.1 µg/100 cm^2 used by Washington State was established in 2000 and was based primarily on what was believed at that time to be technologically feasible...While no human studies have been conducted sense* [sic] *Washington established a clean up standard, several animals studies have been conducted that help better understand the possible health effects from low dose exposures.*

We respectfully disagree with the statement that no low-dose studies of methamphetamine toxicity in humans have been conducted since 2000. In fact, numerous investigations of this type have been conducted since that time and were cited in our report. Furthermore, new studies have been published in the short time since the draft OEHHA RfD report was made available for public comment (e.g., Hart et al., 2007).

All additional comments and analysis from Mr. McBride are related to exposure analysis and derivation of a risk-based cleanup standard for methamphetamine, and as cited in OEHHA's companion document on the subject.

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Response to Comments on the Revised Draft Document, *Development of a Reference Dose (RfD) for Methamphetamine* (OEHHA, December 2008)

I. Comments from Mr. Tony Ohrazda, Environmental Health Specialist II, Clandestine Drug Lab Remediation Program, Tacoma-Pierce County Health Department, Tacoma, Washington

1. The argument for using a subchronic RfD is that as exposure via dermal transfer occurs, there is a direct ongoing depletion of the source. Therefore, over a subchronic period of time enough depletion of the source will have occurred to eliminate exposure.

   Comment: If it could be shown that depletion is temporary, and media (e.g. gypsum wallboard) can become repeatedly "re-contaminated", would OEHHA consider applying an uncertainty factor to extrapolate to a chronic RfD? If so, what would be the calculated chronic RfD?

   Response: If the contractor in charge of cleanup did not do a thorough job and left unremediated source(s) of methamphetamine residue in a home, re-contamination of previously cleaned surfaces might occur. However, we believe this scenario reflects the adequacy (or lack thereof) of the cleanup operations. It does not undermine the validity of the proposed cleanup standard.

   In evaluating the appropriateness of a sub-chronic exposure scenario, another consideration was target population identified in our analysis. Children 6-18 months of age are a "most exposed" population by virtue of their behavior – specifically, mouthing behavior and contact with the floor for long periods of time. These behaviors occur over a relatively short age range. It would not be reasonable to assume that a child exhibits the behavior of a 6-18 month old for several years. As a child gets older, the behaviors that enhance daily exposure to surface residues diminish.

2. The primary study used for development of an RfD for methamphetamine was a study of a drug's efficacy in reducing weight gain during pregnancy (Chapman, J.D., 1961). This study determined a LOAEL of 0.08 mg/kg-day, based on the critical effects of appetite suppression and subsequent decrease in weight gain (in pregnant women). The study lasted 15-16 weeks.

   Comment: Several questions come to mind when considering this study. Is it possible that pregnant women would have "stronger appetites" than non-pregnant women? If pregnant women do have stronger appetites than non-pregnant women, is it possible that other health effects would occur prior to noticeable appetite suppression/reduction in weight gain (such as agitation, hypertension, CNS stimulation), and at a lower dose? Has OEHHA considered these questions, and if so, how are they addressed?

   Response: A fundamental principle of toxicology is that the severity or effects and/or the proportion of a population affected must be related to the dose of a chemical. The 1961

Chapman study included an evaluation of nervousness, insomnia and increased blood pressure – all characteristic of low-dose methamphetamine exposure – in all four treatment groups. None of these effects was related to the dose of methamphetamine. (See Table 3, page 12 of the Revised Draft.)

We have acknowledged that a single study involving 84 pregnant women probably does not represent the range of human sensitivity to methamphetamine. To better understand the range of sensitivity to the drug, we also reviewed several dozen other studies characterizing the dose-response relationships of methamphetamine in a variety of human populations. The weight of evidence from these studies supports the conclusion that the lowest effective dose of methamphetamine in humans is around 5 mg/day. To account for variation in human sensitivity to the drug (including the hypothetical variation attributable to differences in appetite), a 10-fold uncertainty factor was included in the calculation of the RfD.

3. The Chapman study was conducted over a period of 15-16 weeks.

   Comment: Compared to the scenario of critical sub-populations living in a structure contaminated with residual levels of methamphetamine, this seems to be a very short period of time. Was an additional uncertainty factor applied to account for this? If so, what was it? If an additional factor wasn't applied, why not?

   Response: The RfD was developed assuming a sub-chronic exposure scenario. As noted in our response to comment #1, children 6-18 months of age were identified as a "most exposed" population by virtue of their behavior, and it would be unreasonable to assume that a child exhibits the behavior of a 6-18 month old for several years. Furthermore, in our exposure scenario the mass of contamination on surfaces is finite, and exposure cannot occur without causing depletion of surface residue levels. This process of depletion via contact and removal, combined with occasional cleaning, will lead to depletion of surface residue concentrations.

   It is not unusual to extrapolate the results of a subchronic study to durations longer than the duration of the study. In addition, the results of the Chapman study suggest that exposure for a longer duration would not produce qualitatively different adverse effects from those that were observed.

4. The Chapman study describes four different dosage groups; placebo, 5mg, 10mg, and 15 mg.

   Comment: If the dosages are predetermined and set, then how can the LOAEL be measured? Isn't it possible that appetite loss (or intolerance) could occur at a dosage between placebo and 5mg? *Note that the lowest dosage group (5mg) had the highest percentage of side effects (Sum 41%).*

   Response: The results of a number of studies suggest that a daily dose of 5 mg methamphetamine is sufficient to produce pharmacological response(s) in children and

adults. The 1961 Chapman study was not the only experimental basis for this conclusion. Other studies that were reviewed in the RfD document (e.g., Young and Turner, 1965), also support this conclusion.

A LOAEL is based on experimental data. The doses used in the Chapman study were probably based on the dose-response database that existed at the time the study was conducted as well as the doses that Abbott Laboratories had made commercially available in an extended release formulation. Lower doses may also have been effective, but the weight of evidence from other studies of methamphetamine's pharmacological activity in humans suggests that doses very much lower than 5 mg would probably have been ineffective.

In analyzing data from the Chapman study, the rates of various side effects were summed in order to evaluate the possibility that that there was a dose-related increase in total adverse effects potentially attributable to methamphetamine. (See Table 3 on page 12 of the Revised Draft). No such dose-related increase was apparent: the summation of all side effects in the 0, 5, 10 and 15 mg/day groups was 28, 41, 35 and 40 percent, respectively.

5. 41% of the lowest dose population had to be excluded from the Chapman study due to edema and/or "intolerance". Intolerance includes "nervousness, gastrointestinal complaints, tachycardia, and insomnia".

   Comment: Does OEHHA consider these to be critical effects? If not, why? If so, how were they incorporated?

   Response: In our analysis of the Chapman data, we excluded two groups of women: those who developed edema and were administered a diuretic, and those determined to be "intolerant." As noted in the response to the previous comment, "intolerance" was not well defined and appeared to reflect the occurrence of one or more individual symptoms or complaints. None of these symptoms was dose-related.

   In the 5 mg group, 5 of the 17 women (29%) who began the study were judged to be intolerant and discontinued participation in the study. None of the women in the 5 mg group experienced nervousness or insomnia, even though both these symptoms were cited by the author a basis for intolerance.

   In the placebo group, 2 of the 25 women (8%) who began the study were judged to be intolerant, but an additional 3 women (15%) experienced nervousness and 1 woman (4%) complained of insomnia. In total, 6 women (24%) in the placebo group were identified as intolerant or experienced symptoms that were consistent with the author's definition of intolerance.

   In the 10 mg group, 9 of the 43 woman (21%) who began the study were judged to be intolerant or experienced nervousness or insomnia. Similarly, in the 15 mg group, 4 of

the 20 women (20%) who began the study were judged to be intolerant or experienced nervousness or insomnia.

On the basis of these data, we concluded that the combined incidence of nervousness, insomnia and intolerance was not dose-related and therefore not related to methamphetamine exposure.

This conclusion is supported but the authors statement that "…when intolerance was found….the dosage was diminished and the symptom pattern was found to be the same." However, four patients were switched to the placebo instead of receiving a lower dose, but they continued to experience symptoms of "intolerance." These results suggest that other factors – such as concern over participation in a study where the participants were given an unknown amount of an unknown drug – may have influenced the frequency of nervousness, insomnia and intolerance reported in all four treatment groups.

6. The subchronic RfD that was determined is based on a critical literature review of approximately 160 published research reports. Two studies constitute the primary support for the subchronic RfD, Chapman (1961) and Young & Turner (1965).

   Comment: Environmental risk assessment / toxicity assessment has changed significantly since the Chapman and Young & Turner studies of nearly 50 years ago. If significant changes have occurred in methods, procedures, etc. in the last half century, how might it affect the studies outcome or relevancy? Is this a concern for OEHHA, and if so, how is it addressed?

   Response: Both of the cited studies were published in peer reviewed medical journals. Their results are consistent with other similar studies published at about the same time, and are consistent with the results of studies published much more recently. A placebo-controlled, double blind study is still regarded as the gold standard for research on the effects of chemicals and drugs in humans.

7. The second study (Young & Turner, 1965) evaluated the use of methamphetamine for the treatment of bed-wetting in 299 children between the ages of 4-15 years of age. Sleep disturbance was the critical effect. The US EPA defines critical effect as the first adverse effect, or its known precursor, that occurs to the ***most sensitive species*** as the dose rate of an agent increases (emphasis added). The youngest child involved in this study was 4 years of age, the average age was 7.

   Comment: What consideration was given to the fact that the population of this study was considerably older than the most sensitive population? *Note that the uncertainty factor discussed on page 9 regarding age seems to only address age as it relates to the ADHD studies' relevance.*

   Response: As noted in the discussion on pages 52-54 of the Revised Draft, the results of the Young and Turner (1965) study suggested a Lowest Observe Adverse Effect Level (LOAEL) of 5 mg/day (0.2 mg/kg-day) and a No Observed Effect Level (NOEL) of 2.5

mg/day (0.1 mg/kg-day). The LOAEL identified on the basis of the Chapman (1961) study was 0.08 mg/kg-day. Therefore, the decision to use the Chapman study as the experimental basis for the RfD resulted in a LOAEL that was 2.5 times lower than the LOAEL suggested by the results of the Young and Turner study.

The available data suggest that children may actually be *less* sensitive to methamphetamine than adults, as the initial dose for both groups for treatment of ADHD and obesity is 5 mg/day. Nevertheless, to account for the possibility that children 6-18 months of age are significantly more sensitive to methamphetamine than older children or adults, a 10-fold uncertainty factor was added to the RfD calculation.

As noted on page 3 of the Revised Draft, the scientific evidence clearly indicates that humans are indeed considerably more sensitive to methamphetamine than rats or mice. On this basis, we believe our evaluation of the available data is consistent with the U.S. EPA's definition of critical effect.

8. The critical effect of the Young & Turner study was sleep disturbance. This was measured by parents observing that their children were having difficulty sleeping.

   Comment: Were other non-subjective parameters, that could be considered critical health effects, being monitored? If so, would OEHHA consider using those instead of sleep disturbance?

   Response: The report does not mention monitoring for any other non-subjective parameters.

   Comment: How likely is it that sleep disturbance would occur prior to an increase in heart rate, blood pressure, etc?

   Response: Relative sensitivity to the low-dose effects of methamphetamine probably varies from person-to-person. For some individuals, sleep disturbance may occur at a dose that is lower than the amount required to elicit an increase in heart rate or blood pressure. For others, the opposite situation may hold.

   One problem with comparing these effects is that sleep disturbance is assessed qualitatively (e.g., slight, moderate or severe), while heart rate and blood pressure are assessed quantitatively. With quantitative measures, statistical significance becomes an issue. Also, all three endpoints could be affected by the testing environment. Anyone (particularly children) may have difficulty falling asleep knowing that they are sleeping on an electronic moisture sensor that's attached to a buzzer alarm. Similarly, the act of inflating a pressure cuff around an adult or child's arm could cause his or her blood pressure to rise.

   Comment: What consideration has been given to the absence of trained clinical staff using standard methods to measure this effect?

Response: Parents were required to assess their child's success or failure in eliminating nocturnal enuresis by keeping track of the nights that the buzzer alarm went off, and to provide information on disturbance of sleep patterns. The former task does not require specialized training and the latter – if conducted under controlled scientific conditions – could only be completed in a laboratory setting, which probably would have reduced the size of the study considerably. One could also argue that parents are better able to detect subtle changes in their own child's behavior than trained clinical staff.

The results of this study were cited to support the primary conclusions of the overall risk appraisal process. They were not used to derive the RfD. Therefore, concern that the children were not evaluated directly by trained clinical staff using standardized methods was not a critical aspect of our analysis.

9. A 3 fold uncertainty factor has been applied to address incompleteness of the database.

Comment: This seems very low. Is a 3 fold uncertainty factor enough to address the multiple instances of uncertainty, such as; no research on the effects of methamphetamine on 1-2 year old children, pharmacokinetics of stimulants compared to methamphetamine (remember that the only difference between meth and pseudo is an OH group), human studies look at symptoms vs. physiology, etc.?

Response: Our rationale for adopting a 3-fold uncertainty factor to account for incompleteness of the toxicity database is summarized on pages 15-17 of the Revised Draft.

There are always unknowns and uncertainties in our knowledge of the biological effects of chemicals. However, the breadth and depth of toxicity information for methamphetamine is exceptional: more than 100 studies of the pharmacological effects of methamphetamine in humans have been published in the peer reviewed scientific literature. Several studies concurrently evaluated both physiological responses (such as increased heart rate and blood pressure) and psychic effects (such as agitation, nervousness and euphoria).

The uncertainty factors used in our analysis were selected and justified in a manner consistent with the current practice of human health risk assessment. In fact, in comparison to risk appraisals conducted for other chemicals, a compelling argument could be made that the aggregate uncertainty of 300 we used on our assessment is excessive. For example, the U.S. EPA's chronic RfD for the pesticide DDT is based on a 27-week feeding study in rats and an aggregate uncertainty factor of 100. In contrast, the sub-chronic RfD for methamphetamine was based a 15-week placebo-controlled, double blind study in humans and an aggregate uncertainty factor of 300.