Inhalant Abuse Among Children and Adolescents:
Consultation on Building an International Research Agenda

MEETING SUMMARY

National Institute on Drug Abuse/Fogarty International Center
Rockville, Maryland, November 7–9, 2005

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Table of Contents

Executive Summary **1**
Defining the Problem 1
Epidemiology 2
Neuroscience and Clinical Research 3
Prevention and Treatment 4
Conclusion and Next Steps 5

Keynote Presentation: The Public Health Impact of Inhalant Abuse **5**

World Reports: Epidemiology of Inhalant Abuse **6**
Epidemiology of Inhalant Abuse in Mexico: Impact on Public Health 6
What the Data Tell Us About Solvent Abuse in Canada 7
Epidemiology of Inhalant Use in the United States: Correlates and Consequences 8
Inhalant Abuse among Juvenile Delinquents in the United States 8
Summary of Russian Regional Data on Inhalants 9
Epidemiology of Inhalants in Peru 10
Isolating Precursors from Consequences of Inhalant Use 10
Impact of Inhalant Use in Venezuela 11

Special Reading From "An Ex-Mas Feast" and Commentary **11**

Impact of Inhalants on the Brain: Neuroscience and Clinical Research **12**
Solvents and Ethanol: More Alike Than We Thought 12
Comparing Effects of Nitrous Oxide to Various Anesthetics and Alcohol 12
Novel Cellular Targets for the Effects of Abused Solvents 12
Recent Imaging Approaches to Studying Pharmacokinetics of Solvents 13
Early Research and New Opportunities for Neuroscience and Clinical Research at the Mexican National Institute of Psychiatry 13
Fetal and Neonatal Effects of Inhalant Abuse 14
Animal Models for Assessing the Effects of Maternal Inhalant Abuse 14
Inhalant Abuse and Related Toxicity: The Philippine Experience 14
Pharmacologic Quagmire 15

Inhalant Abuse: Interventions for Prevention and Treatment 15

Issues on Developing Prevention Interventions 15

Issues on Developing Treatment Interventions 16

The Work of Friends-International in Cambodia from Mainstream to Gateway: Inhalants Among Cambodian Street Children 16

Inhalant Abuse by Street Children in Brazil: Causes and Consequences 17

Glues or Paint Thinner: Understanding the Nature and the Extent of Inhalant Use in Turkey 18

Lessons from the Validation of Multisystemic Therapy (MST) for Substance-Abusing Adolescents 18

Finding Answers From Within: Interventions With Aboriginal Young People and Their Families 19

Inhalant Abuse Prevention Research in Alaska 20

Reformulation of Products With Abuse Liability: Industry Responses to Research 20

Abuse Liability 20

Industry Response to Research 20

Research Funding Opportunities 21

John E. Fogarty International Center 21

Canadian Institute of Health Research: Research Funding Opportunities 22

NIDA Support for Inhalant Abuse Research 22

Consejo Nacional Contra las Adicciones (National Council Against Addictions) 23

Discussion, Research Needs, and Next Steps 23

Epidemiology 23

Neuroscience 26

Prevention and Treatment 28

Appendix A: Agenda

Appendix B: Participant List

Executive Summary

An international meeting of scientists has concluded that despite differences in the underlying causes, abused substances, and patterns of use, inhalant abuse is a growing public health problem for rich and poor nations worldwide that requires urgent action by the international drug abuse research community. To consider what is currently known on this topic and to help set the direction for future international research and practice collaborations, institutions in the United States, Canada, and Mexico jointly convened the meeting *Inhalant Abuse Among Children and Adolescents: Consultation on Building an International Research Agenda* on November 7–9, 2005. Cosponsors included the National Institute on Drug Abuse (NIDA) International Program and the John E. Fogarty International Center (FIC) from the United States; the Canadian Institute of Neurosciences, Mental Health, and Addiction (INMHA) and the Institute of Aboriginal Peoples' Health (IAPH) at the Canadian Institute of Health Research (CIHR); and the Mexican Consejo Nacional Contra las Addicciones (CONADIC).

The scientists called for specific collaborative international efforts to expand research into the causes, consequences, prevention, and treatment of inhalant abuse, and for increased neuroscientific studies to explain the effects of inhalants at the cellular and organic levels. The following priority research areas emerged from the discussion: (1) standardizing and adapting existing surveillance methods and coordinating data collection procedures internationally to better measure the extent of inhalant abuse; (2) designing, implementing, and evaluating treatment and prevention interventions tailored to inhalant abuse; (3) expanding basic science studies to better understand the mechanisms of action of inhalants on developing brains; and (4) investigating the interaction among underlying factors that may contribute to inhalant abuse and the consequences of that abuse. Meeting participants expressed particular interest in qualitative research, longitudinal studies to compile data about subjects before they begin using inhalants, and research that explores chronic versus episodic and isolated versus communal use patterns.

Defining the Problem

Inhalants are breathable chemical vapors that can be inhaled to induce a psychoactive or mind-altering effect. These volatile substances are relatively inexpensive and are available as legal components of many common household products. The easy accessibility and relatively low cost of inhalants are major reasons why they are most likely to be abused by children and adolescents, who are especially vulnerable to their highly toxic effects. Although adequate epidemiological information is lacking, the apparently growing problem of inhalant abuse among children and adolescents has raised concerns in both affluent and developing nations. Despite an expanding body of knowledge and promising new avenues of research, formidable challenges still confront efforts to prevent and treat inhalant abuse among young people around the world.

The specific objectives of the consultation meeting were to review the state of knowledge on the nature and extent of inhalant abuse, the neuroscience of the effects of inhalants on the brain and behavior, and the prevention and treatment of inhalant abuse among children and adolescents around the world; to identify knowledge gaps and research needs; and to encourage research on all aspects of inhalant abuse. Topics included findings from epidemiological, behavioral, neurobiological, and clinical studies that helped elucidate the antecedents, consequences, and underlying mechanisms of inhalant use and abuse. Other presentations provided examples of prevention and treatment interventions that targeted aboriginal youth, street children, and other young people who use inhalants. Another session addressed the issue of product reformulation to reduce abuse potential.

Representatives of the three cosponsoring nations welcomed 55 participants from 10 different countries. These speakers established that inhalant abuse is a significant and growing problem not only in their

respective countries but also around the world. Subsequent presentations provided more details on the extent of this international problem and the efforts being made to address it. Discussions after each session and within four workgroups generated recommendations to address knowledge gaps, research needs, and next steps.

Epidemiology

The meeting's keynote address by Dr. Robert L. Balster and subsequent presentations examined the international problem of inhalant abuse based on various national and regional data sets as well as on special population-based surveys. These presentations set the stage for discussion of knowledge and shortcomings in research information as well as differences and similarities between developed and developing nations' issues with inhalant abuse.

Issues in Measuring the Nature and Extent of Inhalant Abuse

The keynote address focused on the crucial issue of defining the public health impact of inhalant abuse. Dr. Balster reviewed approaches for assessing the public health problems associated with the generally high prevalence of inhalant abuse among U.S. adolescents and examined relevant data from seven indicators: death, other medical emergencies, chronic health problems, inhalant use disorders, risk for other substance use disorders, risk for other psychiatric disorders, and social disruption. Discussion among participants raised the issues of whether data are providing an accurate picture of the public health impact; whether national data sets are useful in understanding local phenomenon within small, often isolated populations; and whether relative risk is greater in countries or subpopulations with higher prevalence.

Recommendations that emerged from this discussion included several strategies to address measurement problems, including using international partnerships to design better data extraction tools; segregating data by subcategories (e.g., types of inhalants and users); and strengthening the ongoing monitoring and efficient use of existing data. Other recommendations included exploring additional approaches to assess the public health impact of inhalant abuse, such as using additional indicators (e.g., HIV/AIDS and other infectious diseases) and direct measures (e.g., costs). Another identified priority was addressing the issue of stigma and its possible impact on underreporting of inhalant abuse. Recommended next steps included standardizing and comparing use and outcome measures across countries.

Trajectories, Practices, and Patterns of Inhalant Use

Reports on the epidemiology of inhalant abuse from a number of countries with high prevalence showed variations in data collection systems as well as in rates of prevalence and treatment. Several presenters detailed high and often increasing rates of inhalant abuse among U.S. incarcerated youth; Russian adolescents; street children in Mexico, Peru, Venezuela, Cambodia, and Turkey; and Canadian aboriginal youth. Several of the reports provided evidence of the use of inhalants as a gateway to other drug abuse. The presentations also revealed differences in the motivations for inhalant use. For example, although inhalants may be used recreationally in some developed nations, street children in developing nations tended to use inhalants to help them function on the streets by suppressing hunger, fear, and physical or emotional distress.

Participants recommended that future research address the trajectories of inhalant use, including the course of use from initiation to escalation to cessation as well as outcomes in morbidity/disease and other drug use. Other recommended research topics included detailed microanalyses of practices and patterns of use, such as the frequency, quantity, methods, and settings of inhalant use, as well as patterns of polydrug use to better understand chronic versus episodic, isolated versus communal, and single drug versus polysubstance use patterns. Identified knowledge gaps included the reasons why children and

adolescents start and escalate inhalant use, why lifetime inhalant use rates decline with age, and trends in the types of inhalants used.

Etiologic/Risk Factors and the Consequences of Inhalant Use
Several speakers presented findings on the correlates, predictors, and consequences of inhalant use and abuse. These findings indicated that factors such as depression, symptoms of post-traumatic stress disorder, and higher levels of emotional and physical abuse might be associated with drug abuse among youth. U.S. adolescents with inhalant use disorders tended to report coexisting problems such as delinquent behaviors, multiple drug abuse and dependence, and the use of mental health services. Researchers also found high rates of head injury and diagnosed mental illness among incarcerated youth who abused inhalants.

Participants from several countries recommended further study of the association of inhalant abuse with violence and other trauma, head injuries, depression, stress, and higher levels of adversity. Additional studies of the relationship between inhalant abuse and the abuse of alcohol and other drugs were also suggested. Other identified priorities included research on the short- and long-term consequences of inhalant use and acute inhalant intoxication—including mortality (e.g., sudden sniffing death), morbidity (e.g., injuries), psychiatric problems, and cognitive impairment—as well as studies of the factors that predict individuals' susceptibility to these adverse consequences.

Neuroscience and Clinical Research

Presentations on neuroscience and clinical research described new findings on inhalants' mechanisms of action at cellular sites, effects of inhalants on the brain, and consequences of prenatal exposure to inhalants.

Mechanisms of Action
Presentations about research on the similarities between solvents (e.g., toluene) and ethanol demonstrated progress toward an understanding of the basic mechanisms by which these compounds affect the function of cells. However, studies also found evidence of some differences, including instances of opposing action at the cellular level. These findings indicated that that toluene and ethanol affected many different types of channels selectively. A comparison of the alcohol-like effects of nitrous oxide (N_2O) and volatile anesthetics found significant differences that were consistent with the substances' putative mechanisms of action. (See Bale, A.S., Tu, Y., Carpenter-Hyland, E.P., Chandler, L.J. and Woodward, J.J. Alterations in glutamatergic and gabaergic ion channel activity in hippocampal neurons following exposure to the abused inhalant toluene, *Neuroscience*, 130(1): 197-206, 2005.)

Participants recommended that research further explore the effects of alcohol and solvents and their mechanisms of action (e.g., similar mechanisms involved in intoxication, dependence, and withdrawal; activation of behaviorally relevant systems). Research to answer key questions about solvents (e.g., structure-activity relationships, interaction with other drugs of abuse) also was suggested. Other recommendations included research to better characterize inhalants, including defining inhalants (e.g., properties that cause intoxication, dependence, and neurotoxicity; doses that cause intoxication, loss of consciousness, or death); addressing concerns about the classification of different substances (e.g., nitrites, N_2O) as inhalants; and separating two effects (i.e., dependence, toxicity) in the different substances. Participants also cited the need for studies of the relation of inhalant abuse to stress, HIV and other diseases, and other environmental conditions (e.g., nutrition).

Neuroimaging Studies and Animal Models
Presentations from neuroimaging studies revealed that various inhalants affect the brain differently by affecting disparate brain regions and exhibiting dissimilar pharmacokinetic properties. Other

neuroimaging and behavioral studies used animal models of inhalation and conditioned place preference response to study the addictive properties of inhalants. These studies provided evidence that the rewarding effects of inhaled toluene were at least partially related to levels of brain dopamine.

Participants recommended the use of imaging studies to look at more volatile or highly aerosolized substances and to identify those that would have less abuse liability. International collaborations between institutions with neuroimaging capabilities (e.g., Brookhaven National Laboratory, the Mexican Institute of Psychiatry) were suggested. Participants noted the need for new animal models to study inhalant abuse, including models of binge toluene exposure and models that used self-administration techniques. A related recommendation was the design of laboratory studies that simulated real-life human exposures (e.g., doses, frequency of doses) to inhalants.

Consequences of Prenatal Exposure

Several studies examined the consequences of prenatal exposure to inhalants. A review of medical records showed that metabolic acidosis did occur as a complication of maternal inhalant abuse, and a clinical study confirmed neonatal withdrawal from prenatal exposure to inhalants. A literature review and blinded cohort study raised doubts about whether fetal solvent syndrome (FSS) was a phenotype that was distinct from fetal alcohol syndrome (FAS). An animal model of gestational exposure to toluene showed that repeated exposures to high concentrations were associated with adverse effects on fetal growth and early postnatal development and behavior.

Participants recommended further research to elucidate the short- and long-term consequences of prenatal exposure and to address key questions about FSS, including characteristics that might help clinicians recognize the syndrome and distinguish it from FAS.

Prevention and Treatment

Presenters described various issues and approaches related to interventions that focused on preventing and treating inhalant abuse in children and adolescents.

Efficacy and Effectiveness

Several presenters described strategies that generated positive outcomes from prevention and treatment efforts. U.S. prevention programs that sought to warn young children about the dangers of inhalants as "poisons" by educating parents and other influencers were able to reduce inhalant abuse rates or increase recognition of the problem of inhalant abuse. Inhalant-specific treatment programs for Canadian First Nations and Inuit youth that used strength-based techniques and culturally appropriate holistic approaches improved client retention rates and educational achievement. Multisystemic therapy (MST) for children and adolescents with serious behavior problems (e.g., delinquency, substance abuse, sex offenses, physical or mental illness, abusive families) showed success in decreasing youth problems and preventing costly out-of-home placements (e.g., incarceration, residential treatment) and might have implications for treating inhalant use.

Participants emphasized the need for research to evaluate the efficacy and effectiveness of prevention strategies, programs, and messages as well as to assess the short- and long-term effectiveness of treatment. Research should evaluate effective approaches to inhalant abuse prevention (e.g., regulation, reformulation, and education/awareness) and should investigate treatment models (e.g., strength-based treatment, cognitive-behavioral therapies) that are effective for adolescents. Efforts should focus on action research that incorporates feedback from the field into the development of practical interventions. Studies on therapeutic medications (e.g., naltrexone, vigabatrin) are also needed. The development of best prevention practices and consensus-based treatment guidelines as well as research on the validity and cost-effectiveness of these approaches are crucial needs.

Population-Specific Strategies
Presentations described various strategies for interventions focused on specific populations of youth who abused inhalants. Friends-International fostered inhalant abuse prevention and rehabilitation among Cambodian street children by offering real alternatives to street life (e.g., education, job training, social and physical support networks) and helping these children reintegrate into society. A study of inhalant use among street children in Brazil identified user characteristics (e.g., severe toluene intoxication, use of other drugs) that indicated the need for targeted prevention approaches and treatment plans. An inhalant addiction treatment program for street children and other adolescents in Istanbul, Turkey, incorporated knowledge of these youth (e.g., frequent family and psychological problems) into interventions that included group and individual therapy for adolescents and group education for families.

Participants noted the need for population-based prevention strategies that tailored approaches based on characteristics such as age, gender, ethnicity, and geographic region. They also suggested research to better understand specific populations of inhalant users (e.g. aboriginal youth) and acute versus chronic users. Participants recommended studying comorbid conditions and chronic stressors as well as the hallucinations that often were reported by inhalant users. In addition to population-specific strategies, there was a call for research to identify approaches and interventions effective across cultures.

Conclusion and Next Steps

In addition to the specific recommendations for international collaboration in the fields of epidemiology, neuroscience and clinical research, and prevention and treatment, meeting participants identified two overarching priorities that require cooperation by many nations and institutions. The participants recommended that (1) an international workgroup of pharmacologists and epidemiologists be created to classify substances and develop questions for use in screening instruments and surveys and (2) the sponsors establish a mode for communication and exchange of information on issues related to inhalants research. One important role for NIDA might include the coordination and facilitation of U.S., international, and collaborative research and the dissemination of findings related to inhalant abuse. NIDA invites its partners in the United States, Canada, and Mexico to join with us to forge effective international approaches to address inhalant abuse.

Keynote Presentation: The Public Health Impact of Inhalant Abuse

Robert L. Balster, Ph.D., Virginia Commonwealth University, United States

Dr. Balster addressed difficulties in translating what is known about inhalant use into an understanding of what this means for the health and functioning of society. His presentation focused on a strategy for assessing the public health impact of inhalant abuse using available U.S. national data sets, including the National Household Survey on Drug Abuse, now called the National Survey on Drug Use and Health (NSDUH); Monitoring the Future (MTF); the Drug Abuse Warning Network; and the Treatment Episode Data Set. Dr. Balster reviewed the following epidemiological data, which set the context for the public health impact:

- Past-year use of inhalants among youth age 12 to 17 was 4.5 percent in 2003. This prevalence was about a third of the rate for marijuana use and considerably higher than the rate for cocaine use in this age group. (NSDUH)
- Inhalant abuse was more prevalent among younger users, with rates higher among 8th-grade students than among 10th- and 12th-grade students. (MTF)
- After years of decline since the mid-1990s, past-year inhalant use began to rise in the past few years, especially among eight-graders. (MTF)

Dr. Balster reviewed approaches for assessing the public health problems associated with the generally high prevalence of inhalant abuse among U.S. adolescents, including comparing inhalant abuse to the known impact of other abused substances, such as marijuana, cocaine, and alcohol, and comparing inhalant abuse prevalence to harm. He also proposed examining data for seven different indicators of public health problems: (1) deaths directly related to inhalant exposure (e.g., "sudden sniffing death"); (2) other medical emergencies; (3) chronic health problems (e.g., neurotoxicity, fetal solvent syndrome); (4) inhalant use disorders; (5) risk for other substance use disorders; (6) risk for other psychiatric disorders; and (7) social disruption (e.g., delinquency, school dropout).

After reviewing unpublished data analyses for each of the seven indicators, Dr. Balster presented the following tentative conclusions based on the current data collection and reporting methods:

- Lethality and other medical emergencies might not be major impacts of inhalant use.
- Estimating the extent of neurotoxic consequences of inhalant abuse is problematic.
- Although the prevalence of inhalant dependence is fairly high among adolescents, inhalants are significantly underrepresented in adolescent treatment admissions.
- Inhalant use is a significant risk factor for, and could be considered an early indicator of risk for, other substance use disorders.
- A risk of other psychiatric disorders is not associated with inhalant use.
- Inhalant use appears to be a significant risk for delinquency but not for school dropout.

The indicator of public health impact that is strongest for U.S. inhalant use is the higher risk of other substance use disorders. However, it is not clear whether the link is causal or merely associative. Dr. Balster questioned whether certain indicators (i.e., those showing that inhalant use might be less dangerous than the abuse of other drugs) were providing an accurate picture of the public health impact. He also raised the issues of whether other population indicators were available for study, whether the public health impact in the United States was different from that in other countries, and whether relative risk was greater in countries or subpopulations with higher prevalence. Finally, Dr. Balster suggested considering strategies other than comparing the relative risk for inhalant adverse effects to those for other drugs. One possibility is to obtain more direct measures of public health impact, such as costs.

In responses to questions from participants, Dr. Balster acknowledged that stigma might play a role in the potential underreporting of inhalant-related indicators (e.g., deaths, emergency room visits, and treatment admissions) as well as in the lack of research on inhalant abuse. It was suggested that the national data sets might not be useful in understanding local phenomena within small, often isolated populations. Dr. Balster agreed with the suggestion that data should be separated by types of inhalants (e.g., nitrous oxide [N_2O] vs. volatile solvents) and types of users (e.g., social users vs. chronic users). It was suggested that association between inhalant use and death might be subtler than a direct cause of death. For example, inhalant use might contribute to medical conditions (e.g., impaired liver or kidney function) that enhance the likelihood of mortality. Moreover, polydrug use may obscure assessments of the impact of inhalant abuse.

World Reports: Epidemiology of Inhalant Abuse

Epidemiology of Inhalant Abuse in Mexico: Impact on Public Health

María Elena Medina-Mora, Ph.D., National Institute of Psychiatry, Mexico

Dr. Medina-Mora presented data collected from national household surveys, student surveys, and information systems on treatment demand. A survey of underage workers (age 6 to 17) in 101 Mexican cities found that 8 to 17 percent of the underage workers lived in the streets; the rest of the children lived with their families and worked in the streets. She identified three types of inhalant users: experimenters,

polydrug users, and daily inhalers who had periods of abstinence. Toluene was the preferred substance among street children because it gives greater effects, produces less "hangover," and does not leave marks on the face.

National household surveys in Mexico indicated that inhalants were the most common first drug of abuse, but rates of inhalant abuse had declined over several years. However, a comparison of data from the household survey and the street worker survey found that inhalant abuse among adolescents was much more prevalent in the latter population, especially among adolescents who lived in the streets. An analysis of risk factors for problem behaviors among minors who worked in the streets indicated that going to school was a protective factor for drug abuse and other risky behaviors, and living with parental figures was associated with school attendance. The places where children worked were an important factor related to drug abuse. Although friend and family member use of inhalants was significantly associated with children's inhalant use when comparing inhalant users with nonusers, these factors were no longer significant when inhalant users were compared to users of other drugs. In the latter comparison, socioeconomic factors and antisocial behaviors were predictors of inhalant use.

In response to questions from participants, Dr. Medina-Mora explained that the high treatment rates she presented represented an increase in both the availability of services and the number of people seeking treatment. She noted that cocaine was overtaking inhalants as the main drug of abuse, and as the percentage of people in treatment for cocaine had increased, the percentage of people in treatment for inhalants had decreased. Inhalant abusers tended to enter treatment at a younger age (about 5 years younger) than other drug abusers. A participant pointed out that different treatment rates in the United States, Mexico, and Canada also reflected differences in the availability of treatment centers and treatment programs that accepted inhalant abusers.

What the Data Tell Us about Solvent Abuse in Canada
Colleen Anne Dell, Ph.D., Canadian Centre on Substance Abuse, Canada

Dr. Dell reported that data on volatile solvent abuse (VSA) among youth in Canada were scarce because the country lacks a national data collection system. The 2004 Canadian Addiction Survey collected data from the general Canadian population for the first time since 1994. Results indicated that 1.9 percent of males and 0.7 percent of females reported lifetime volatile solvent use, an increase from 1.2 percent and 0.3 percent, respectively, in 1994. Among solvent users, 67 percent reported first-time use between 12 and 16 years of age; 13 percent tried solvents before the age of 12. According to the 1998–1999 National Longitudinal Survey of Children and Youth, 10 percent of 12- and 13-year-olds reported that their friends had tried glue or solvents.

Although provincial and territorial school surveys varied in their approach to data collection, some general observations were possible. For example, there was no large difference in the rates of past-year VSA among males and females, and VSA declined with grade among secondary school students. Research and practice among selected populations indicated higher rates of VSA among youth who experienced poorer life conditions.[1] For example, a 2003 report from Pauingassi First Nation in Manitoba revealed that half of the children on the reserve who were under age 18 had abused solvents. However, such findings had to be considered in the context of aboriginal peoples' poverty and unemployment, history of discrimination, and health disparities. Dr. Dell suggested that an international research agenda on inhalant abuse would call attention to the importance of collecting national-level data in various

[1] National data on the rate of solvent use among aboriginal youth in Canada are not yet available. However, national data from the First Nations and Inuit Longitudinal Health Survey became available after the consultation meeting was held.

countries to help understand similarities and differences in prevalence, treatment, and other aspects of the problem.

Epidemiology of Inhalant Use in the United States: Correlates and Consequences
Li-Tzy Wu, Sc.D., Duke University School of Medicine, United States

Dr. Wu reported findings about inhalant abuse in the United States that were based on analyses of various data sets. An analysis of aggregated 2000–2001 NSDUH data showed that among adolescents age 12 to 17, the prevalence of lifetime use and past-year use of inhalants was 8.8 percent and 3.5 percent, respectively, with no significant gender differences. Among past-year adolescent users, 19.8 percent used inhalants weekly and 10.9 percent had an inhalant use disorder. About half (50.9 percent) of adolescent inhalant users reported using more than one type of inhalant, and nearly half (46.4 percent) first used inhalants before the age of 13. The analysis showed that adolescents with inhalant use disorders reported coexisting delinquent behaviors, multiple drug abuse and dependence, and use of mental health services for other emotional problems. Dr. Wu suggested that this finding indicated a need for prevention efforts to target young children.

An analysis of marijuana and inhalants as gateway drugs examined the likelihood of progression to other substance use disorders among adolescents who reported lifetime use of (1) both marijuana and inhalants, (2) marijuana, but not inhalants, (3) inhalants, but not marijuana, or (4) other drugs, but not marijuana or inhalants. The analysis found that adolescents who used both marijuana and inhalants had a much higher prevalence of alcohol use disorder (35.0 percent) and drug use disorder (38.9 percent) than the other three types of drug users. These users might constitute a high-risk group that deserves more attention from investigators and clinicians.

Dr. Wu also presented findings from an analysis of inhalant use and psychiatric disorders among adults based on data from the 2000–2001 National Epidemiological Survey on Alcohol and Related Conditions (NESARC). The analysis found that the prevalence of most past-year mood disorders and anxiety disorders was higher among lifetime inhalant users who began inhalant use before the age of 18 than among those who began use at a later age. Gender differences were not significant for adult lifetime inhalant users who had one or more lifetime or past-year psychiatric disorders. For lifetime inhalant users, the age of onset of inhalant use disorder (between 16 and 18 years) was younger than the age of onset of other psychiatric disorders (between 19 and 28 years), with the exception of social phobia and specific phobia (between 13 and 14 years).

Dr. Wu clarified anomalous NESARC findings regarding no significant gender differences and low prevalence rates for lifetime inhalant use. She noted that NSDUH data indicated no gender differences in adolescent inhalant abuse and dependence, and speculated that low prevalence rates might be due to forgetting, underreporting, stigma, or possible cohort effects.

Inhalant Abuse among Juvenile Delinquents in the United States
Matthew O. Howard, Ph.D., University of Michigan, United States

Dr. Howard described a study of 723 youth incarcerated in 32 facilities in Missouri. A unique aspect of the study was its examination of the acute health and psychological consequences of acute inhalant episodes. The analysis found that inhalant use was endemic among the incarcerated youth, as evidenced by a 37-percent prevalence of lifetime inhalant use. In addition, polyinhalant use was the norm among those who used inhalants. Nearly half of all inhalant users had used four or more types of inhalants, and 80 percent had used two or more types. These high rates indicate that youth involved in the juvenile justice system need to be a major part of any inhalant prevention and treatment initiatives.

The finding that most youth used inhalants in their home (35.2 percent) or a friend's home (28.5 percent) indicated the need to educate parents. Other findings indicated that mere education of youth might not be enough to prevent inhalant use. For example, about two-thirds of adolescent inhalant users already perceived moderate or great risk in experimental use, and nearly fourth-fifths of users perceived such risk with regular use. Dr. Howard reported that if the Volatile Solvent Screening Inventory used in the study had been limited to the 12 most commonly used inhalants, it would have identified 97 percent of the inhalant users detected by the extensive screen of 55 inhalants.

Various analyses comparing inhalant users with nonusers and comparing groups categorized according to lifetime frequency of inhalant use showed that use and greater frequency of use were associated with significant levels of psychopathology and criminality. Areas of special concern were the high rates of head injury with an extended period of unconsciousness (nearly one-fifth) and diagnosed mental illness (more than half) and symptoms of cognitive and neurological impairment among users. Girls who had high rates of inhalant and polyinhalant use were another concern. If these girls became pregnant, they and their offspring might be at high risk for negative consequences.

In response to a question about antisocial behavior and attention deficit hyperactivity disorder (ADHD), Dr. Howard theorized that youth with sensation-seeking and impulsive temperaments might have an autonomic responsivity to external stimuli that makes them more likely to try inhalants. The disinhibiting effects of inhalants could then lead to antisocial behavior. He also speculated that, similar to some alcohol users, youth with ADHD might be self-medicating to deal with their attention deficits.

Summary of Russian Regional Data on Inhalants
Edwin Zvartau, M.D., Ph.D., D.M.Sci, Pavlov State Medical University, Russia

Dr. Zvartau presented a summary of Federal and regional data on inhalant use in Russia. He explained that separate statistics were collected for alcohol dependence (alcoholism) and alcohol abuse; narcotic drug dependence (narcomania) and narcotic drug abuse; and dependence on toxic, non-narcotic psychoactive substances (PAS), which is known as toxicomania, and abuse of these substances.
Dr. Zvartau reported that the use of PAS, of which volatile solvents constitute about 90 percent, was widespread in the Russian Federation. Federal-level data for 2002 indicated that nearly 46 percent of adolescents were dependent on volatile solvents, and 48 percent of adolescents abused these substances. In the same year, adolescents comprised the largest proportion of newly registered patients with mental and behavioral disorders related to PAS, including 42 percent of those who were dependent on PAS and 47 percent of those who were abusing the substances. Statistics from the Ministry of Education found that in 2003, 16 percent of teenagers and young adults (age 11 to 24) used inhalants regularly (2 to 3 times a week). These data also indicated a gateway effect for inhalants, with half of youth who began substance abuse with inhalants later using marijuana, 20 percent using prescription drugs, and 10 percent using opiates.

Statistics from a report of the Adolescents' Narcological Service showed that in the Leningrad region, 40 percent of registered patients suffering from toxicomania used volatile organic compounds such as varnish and paints, and 55 percent used gasoline and glue. According to forensic medical examiners, 76 inhalant-related deaths in 2004 included sudden deaths resulting from respiratory depression or asphyxia and from arrhythmia and cardiac arrest. Trend data for the incidence and mortality of toxicomania among the underage population in the Leningrad region showed some declines in the early 1990s, followed by gradual increases until 1998. Since then, incidence has undergone wave-like changes with peaks in 2002 and 2004; mortality rates have remained stable since significant increases occurred in 2002. Rates of newly registered toxic substance abusers showed a pattern similar to that of incidence, with decreases in the early 1990s, followed by increases and then wave-like changes, with substantial increases in 2004. Russia has official recommendations for the treatment of inhalant intoxication, withdrawal, and

remission, as well as a new prevention and rehabilitation initiative for street children that involves a network of Federal, municipal, and nongovernment partners. Dr. Zvartau concluded that the problem of inhalants was of great concern in Russia because of the expected increase in toxic substance dependence and abuse and the growing proportion of psychiatric and somatic disorders caused by toxic damage to the central and peripheral nervous system.

Epidemiology of Inhalants in Peru
Inés Verónica Bustamante, M.P.H., M.H.S., Universidad Peruana Cayetano Heredia, Peru

Ms. Bustamante presented an overview of inhalant use in Peru based on data from household and school population studies and from studies of specific populations such as street children. She noted that the National Commission for Life Free of Drugs (DEVIDA) has implemented a surveillance system to gather data on mortality and treatment. In addition, the National Household Survey on Drug Use has been conducted since 1998. Data indicated that inhalants were the fourth most commonly used illegal drug among Peruvians and the most commonly used drug among street children. In 2002–2003, past-year prevalence for inhalant use was 0.44 percent. Adolescents age 14 to 16 reported the highest past-year inhalant use as well as the highest annual incidence of use. Ms. Bustamante noted that whereas early users of inhalants were almost exclusively boys, that proportion changed during middle adolescence. For the 17- to 19-year-old age group, girls reported higher past-year rates of inhalant use than did boys. Ms. Bustamante pointed out that in the younger age group of 12- to 13-year-olds, the annual incidence was higher for inhalants than it was for other illegal drugs. However, by age 14 to 16, annual incidence of marijuana use surpassed that of inhalants.

Ms. Bustamante also reported results from a study conducted by CEDRO in 1997 that surveyed 125 street children ages 8 to 15 years. The study distinguished between children who worked on the streets but returned to their homes and children who lived on the streets and were homeless. Findings showed that the highest lifetime prevalence for drug use among street children was for glue (58 percent). This prevalence was much higher among homeless children (86 percent) than among children who lived in homes (31 percent). The age of first use was 10 to 12 years for most children (59 percent). However, 16 percent of the children reported first use at age 7 to 9, and nearly one-quarter started at age 13 to 15. In response to questions, Ms. Bustamante explained that further study was needed to address the issue of why girls in late adolescence had higher rates of past-year prevalence than males; she suggested that experimental use among girls might account for some of the difference.

Isolating Precursors from Consequences of Inhalant Use
Diana H. Fishbein, Ph.D., Research Triangle Institute-International, United States

Dr. Fishbein reported general findings about inhalant users based on the U.S. literature. She noted that past research used retrospective designs and focused on adolescents who already used inhalants. Because such studies could not capture baseline data before the onset of inhalant use, they could not credibly identify risk or protective factors or distinguish between the consequences of inhalant use and preexisting deficits that might be exacerbated by such use. Dr. Fishbein described how the Inhalants Project, a longitudinal study funded by NIDA, is designed to overcome these limitations. The project is a prospective study that collects data before and after the onset of inhalant use. Researchers identified a study cohort based on Safe Schools Healthy Students data, which showed that Cicero, Illinois, had the highest rate of past-30-day inhalant use in the country (more than 18 percent of seventh-grade students).

The study focuses on neurocognitive function, with the intent of distinguishing between neurocognitive deficits that might be precursors to inhalant use and those that are consequences of such use. The researchers are particularly interested in the ways in which the prefrontal cortex (PFC) modulates deficits

in executive cognitive function (e.g., heightened sensitivity to reward, impulsivity, and inattention) and emotional responses (e.g., ascribing feelings to environmental inputs), which may then feed back to executive function. The researchers believe that a disconnect in this regulatory system might make people vulnerable to engaging in high-risk behaviors such as drug abuse. Moreover, because this circuitry is very sensitive to developmental insults, researchers are interested in how stress and exposure to adversity can impair PFC development in adolescents.

The Inhalants Project recruited 553 youth and currently is collecting the second of at least three waves of data collection. Background data show that 90 percent of these youth are Hispanic/Latino (primarily from migrant families), and only 39 percent think that inhalants are more harmful than other illicit drugs. Youth who have experienced adverse situations (e.g., exposure to violence or trauma) tend to have multiple experiences of adversity. Preliminary data have identified some factors that appear to predict dysregulation, a measure that has been shown to be a precursor to drug abuse. These factors include depression, symptoms of post-traumatic stress disorder, and higher levels of emotional and physical abuse and physical neglect. Analyses of interactions between potential factors indicate that in the presence of child abuse, cognitive deficits lead to dysregulation, and in the presence of depression, IQ is one of the strongest predictors of dysregulation. Dr. Fishbein expected data collection for the project to be completed in early 2007.

Impact of Inhalant Use in Venezuela
Elvia Amesty, M.S.G.c., José Félix Ribas Foundation, Venezuela

Ms. Amesty presented epidemiological data about drug use in Venezuela that were gathered from high school students, risk groups, and drug abusers in treatment. These data indicated a continued increase in legal and illegal drug use during adolescence and a decrease in the age of first use. Surveys in Zulia State showed that inhalants were the first drug abused by high school students at the mean age of 11. Lifetime prevalence of inhalant use among these students increased from 0.8 percent in 1996 to 3.6 percent in 2004. Among high school students in seven Central and South American countries, Venezuelan students had the highest past-month prevalence and actual use of inhalants. Data collected from street youth, youth offenders, and addicts showed that street youth had the lowest age for first-time use of inhalants and had the same prevalence of lifetime inhalant use (6 percent) as youth offenders. Data from drug abusers in treatment showed that requests for treatment by vulnerable youth (e.g., children in the street, foster homes, the judicial system, or institutions for behavior problems) increased in the past 3 years and that drug use patterns among these youth were different than in the general treatment population (i.e., people of all ages, socioeconomic status, and education levels). Whereas only 1 percent of the general treatment population reported actual inhalant use, 12 percent of drug-abusing adolescents in a youth program reported such use.

Special Reading From "An Ex-Mas Feast" and Commentary
Uwem Akpan, S.J., University of Michigan, United States

Patricia Needle, Ph.D., of NIDA introduced Fr. Uwem Akpan, who read excerpts from his story, "An Ex-Mas Feast," which was published in June 2005 in the *New Yorker*. Fr. Akpan explained that the story was about a street family whose oldest daughter had taken up prostitution to help support her family. He noted that the story showed the dichotomy between inhalant abuse in the developing world and in the developed world. Whereas children in the developed world usually sniff inhalants to get high, children in developing countries use inhalants because they want to stave off the pains of hunger. Fr. Akpan hoped that participants at the meeting would encourage research on inhalant use in Africa. It was suggested that associating the problem of inhalants with other diseases such as AIDS might stimulate support for research.

Impact of Inhalants on the Brain: Neuroscience and Clinical Research

Solvents and Ethanol: More Alike Than We Thought
Silvia L. Cruz, Ph.D., Department of Pharmacobiology, Cinvestav, Mexico

Dr. Cruz presented research findings about the similarities between solvents and ethanol. She made distinctions between several different types of organic solvents, including alcohol (ethanol) and aromatic hydrocarbons (benzene, toluene). Dr. Cruz described an early hypothesis that anesthetics produced a nonspecific effect by entering and changing the properties of membranes. However, researchers in the early 1980s raised doubts about whether membrane changes were the main mechanism of action in anesthetic effects. Noting that toluene and ethanol had similar effects in humans and animals, Dr. Cruz and colleagues examined whether these solvents inhibited the same receptor activity. Their studies of toluene's mechanism of action showed that, like ethanol, the solvent blocked a ligand-gated ion channel that was regulated by N-methyl-D-aspartate (NMDA) receptors. Subsequent studies by several groups of researchers showed that ethanol, toluene, and other solvents had effects on all ligand-gated ion channels, including those regulated by gamma-aminiobutyric acid A ($GABA_A$), glycine receptors, nicotinic acetylcholine (nAch) receptors, and the serotonin 5-HT_3 receptor. This research showed that the general mechanism of solvents is to increase the inhibitory effects and decrease the stimulant effects of these receptors. Other studies are beginning to look at the effect of solvents on voltage-gated ion channels.

Comparing Effects of Nitrous Oxide to Various Anesthetics and Alcohol
Diana J. Walker, Ph.D., University of Chicago, United States

Dr. Walker described a study that compared the effects of N_2O to volatile anesthetics (i.e., sevoflurane, isoflurane) and alcohol. The research attempted to overcome safety, dosing, and ethical issues associated with human studies by using a human laboratory model of inhalant abuse. The model involved adult subjects (age 21 to 39) who were recreational drug users with a history of inhalant use or exposure but no history of drug dependence. The study compared N_2O and the two volatile anesthetics for their effects, including states of intoxication, behavioral toxicity, and physiological effects. The results showed that for doses at which subjects gave similar ratings of drug-effect strength, N_2O produced greater euphoria and psychedelic-like effects than the volatile anesthetics; the anesthetics produced greater sedation and psychomotor impairment than N_2O. When examining the alcohol-like effects of the three drugs, the researchers typically found that stimulant-like effects were more likely from N_2O, sedative-like effects were more likely from the volatile anesthetics, and cognitive and psychomotor impairment was greater from the volatile anesthetics. These findings were consistent with several of the drugs' putative mechanisms of action, including the supposed roles of the NMDA receptor for N_2O and the GABA receptor for alcohol and volatile anesthetics.

Novel Cellular Targets for the Effects of Abused Solvents
John J. Woodward, Ph.D., Medical University of South Carolina, United States

Dr. Woodward supplemented Dr. Cruz's presentation by describing recent studies on other alcohol-sensitive ion channels that are sites of action for abused inhalants. These studies have shown that although the effects of alcohol and abused solvents such as toluene are targeted to many of the same cellular mechanisms, inhalants and alcohol have very different effects on some of the channels. Toluene was found to inhibit gap junction communication, a disruption that could be important for disorders such as the toluene-induced form of deafness. Toluene and related solvents also were potent inhibitors of voltage-sensitive calcium channels, which are important to heart function and the release of neurotransmitters in the brain. However, unlike alcohol, solvents also affected the sensitivity of calcium

channels to activation, which could cause dysregulation of normal channel function and possibly contribute to problems such as sudden sniffing death. Toluene and ethanol appeared to have opposing actions on calcium-activated potassium channels and a distinct type of G-protein inwardly rectifying potassium (GirK) channel. Two other types of GirK channels appeared to be insensitive to toluene but sensitive to ethanol. These studies indicate that although toluene and ethanol affect many different types of channels, they do so with subunit selectivity among different receptors. Moreover, evidence of opposing action on certain channels indicates that these sites probably are not important for a common mechanism or behavioral action that toluene and alcohol might share. One participant pointed out that the selective effects of solvents suggest that these compounds can be studied like other drugs, thus helping to legitimize inhalant research in the basic research community.

Recent Imaging Approaches to Studying the Pharmacokinetics of Solvents
Stephen L. Dewey, Ph.D., Brookhaven National Laboratory, United States

Dr. Dewey discussed findings from various imaging studies that examined the effects of solvents on the brain. He noted that the work originated with a school-based outreach program that shows brain images of people who have abused drugs. Dr. Dewey presented images made with positron emission tomography (PET), which showed how brain function was affected by various inhalants, including toluene, acetone, butane, and propane. PET studies in animals found that, contrary to some expectations, not all inhalants were alike. These substances differed not only in their regional distribution in the brain but also in their pharmacokinetics (i.e., they do not all go to the same parts of the brain at the same time). Dr. Dewey also described neuroimaging and behavioral studies that provided evidence about the addictive properties of inhalants. For example, PET studies showed a marked, dose-dependent increase in brain dopamine after exposure to toluene. Behavioral studies using an animal model of self-administration showed that animals exposed to toluene and to acetone expressed a dose-dependent preference for the chamber in which they had received the solvent. Another experiment found that gamma-vinyl GABA (vigabatrin), a substance that blocks the biochemical effects of alcohol and drugs such as cocaine and heroin, also appeared to block the effect of toluene. Results from these and other studies led Dr. Dewey to conclude that the rewarding effects of inhaled toluene were at least partially related to brain dopamine and, therefore, subject to GABAergic modulation by vigabatrin. In addition, toluene produced persistent and profound decreases in 18-flurodeoxyglucose (^{18}FDG) uptake that appeared to recover partially over time.

Early Research and New Opportunities for Neuroscience and Clinical Research at the Mexican National Institute of Psychiatry
Dr. Jorge J. González Olvera, National Institute of Psychiatry, Mexico

Dr. González Olvera reviewed early research in inhalant abuse that had been conducted at the National Institute of Psychiatry in Mexico and informed participants about new opportunities for neuroscience and clinical research at that institution. Dr. González Olvera described early work that used animal models to study the effects of inhalants (e.g., toluene, thinner, benzene) on the central nervous system, brain, and heart. More recent work has addressed the effects of inhalants on sleep disorders and neuropsychological function. A major drawback of most of these studies is that they were published only in Spanish and thus are seldom cited in the literature. Current research opportunities at the National Institute of Psychiatry include brain imaging studies using technologies such as magnetic resonance imaging, spectrometry, and electroencephalography. The institute also offers the opportunity to work with special populations that have been identified through the epidemiological work of Dr. Medina-Mora.

Fetal and Neonatal Effects of Inhalant Abuse
Milton Tenenbein, M.D., FRCPC, University of Manitoba, Canada

Dr. Tenenbein discussed his studies on metabolic acidosis and withdrawal in neonates born to mothers who abused inhalants. He explained that metabolic acidosis was a known complication of chronic toluene abuse, but it was not known whether neonates were at risk for this condition. Dr. Tenenbein's medical record review of neonates born to mothers who abused inhalants showed that metabolic acidosis did occur as a complication of maternal inhalant abuse and that severity was variable and likely related to the degree of inhalant exposure immediately before birth. A 4-year study of neonates born to inhalant-abusing mothers revealed the following: neonatal withdrawal from inhalants did occur, the Finnegan Neonatal Abstinence Scoring System was useful for describing gradation, inhalant odor on the baby was a marker for withdrawal, and pharmacotherapy with phenobarbital seemed to be worthwhile.
Dr. Tenenbein also reported on a review of the literature that found several descriptive reports suggesting the existence of a "fetal solvent syndrome (FSS)." However, the phenotype was virtually identical to that of fetal alcohol syndrome (FAS). His subsequent, blinded cohort study showed that all the infants who had the features of FAS/FSS had been exposed to both inhalants and alcohol, whereas the infants exposed only to inhalants had no dysmorphic features. Dr. Tenenbein concluded that these data did not support the existence of a FSS physical phenotype; rather, the observed dysmorphic features probably were attributable to *in utero* exposure to alcohol. However, Dr. Tenenbein emphasized that these data did not mean that children were not harmed *in utero* by exposure to inhalants. Moreover, the small sample size and the frequent co-occurrence of inhalant and alcohol use among the mothers made it difficult to differentiate which drug was responsible for the negative consequences observed.

Animal Models for Assessing the Effects of Maternal Inhalant Abuse
Scott Earl Bowen, Ph.D., Wayne State University, United States

The fact that females now comprise more than half of chronic inhalant abusers in the United States has increased concerns about the developmental effects on children born to pregnant women who abuse inhalants. Dr. Bowen reported that human studies indicated a range of adverse effects, including higher rates of spontaneous abortion, congenital malformations, and other abnormalities. However, one research question has been how to develop an animal model that would allow researchers to study human inhalant abuse in a laboratory setting. Dr. Bowen described a study that used an animal model of gestational exposure to toluene. In the study, repeated exposures to high concentrations of toluene were associated with adverse effects on fetal growth (e.g., initially lower postnatal weights) and on early postnatal development and behavior (e.g., dysmorphologies; developmental delays; higher locomotive activity, particularly among males; and less ability to wait for rewards). However, the long-term impact of gestational exposure to toluene has yet to be determined.

Inhalant Abuse and Related Toxicity: The Philippine Experience
Irma Makalinao, M.D., University of the Philippines, Republic of the Philippines

Dr. Makalinao reported that it was difficult to estimate the magnitude of solvent abuse in the Philippines among children and adolescents. However, she provided estimates based on data from the Dangerous Drugs Board (DDB) and the Poison Control Unit. DDB data from rehabilitation centers indicated that the prevalence of methamphetamine, the most commonly abused drug in the Philippines, was 84.45 percent, whereas the prevalence of inhalant abuse was 3.38 percent. However, previous research has not included samples of street children, who are at the highest risk of inhalant use and abuse. UNICEF data indicate that there are 75,000 to 80,000 street children in the Philippines, and this number is estimated to increase by 6,365 annually. However, nongovernment organizations estimate that the population of street children in the Philippines is 1.5 million.

About half of Philippine street children will at some time in their lives snort "ruby" (primarily toluene) and other aromatic solvents, usually to assuage hunger pangs. The longer these children live on the streets, the more likely they re to use methamphetamines. Dr. Makalinao and colleagues conducted a study of chronic solvent abuse among Filipino street children in Manila. Preliminary results showed cognitive dysfunction, particularly memory impairment; hyperactivity; malnutrition and anemia; and poor performance on the groove peg board test in this population. Dr. Makalinao noted that street children who used inhalants also were likely to have high rates of exposure to lead from vehicle emissions (e.g., lead gasoline), which might confound the preliminary findings. She also described aspects of solvent toxicity (e.g., pharmacokinetics, biologic markers for exposure and toxicity, clinical manifestations, and biphasic response) that have been observed in street children who come to the National Poison Control Center.

Pharmacologic Quagmire
Charles Sharp, Ph.D., National Institute on Drug Abuse, United States

Dr. Sharp highlighted several issues in pharmacologic research on inhalant abuse that he hoped would stimulate further discussion. He noted the following important research questions:

- **Definition of an inhalant**—How important is the odor of a compound, and do inhalant users prefer certain odors? Is intoxication based on chemical properties? What defines a desired product (e.g., is the ingredient being sought a solvent, propellant, or a main component)? What is the affective amount of the substance? Are various substances fads or dependence-producing inhalants?
- **Consequences of inhalant use**—What quantity (e.g., the degree or amount of use) produces serious hazards? What frequency or quantity of use defines an addict? How long or intense is an episode that produces a quick "drunk" or leads to hospitalization? What is the rate of mortality among inhalant users?
- **Disease modalities**—How can research further elucidate related neurologic problems such as hearing loss, effects of brief exposures on cognitive ability, brain damage after excessive exposure, and peripheral neuropathy?
- **Product interpretation**—How can the formulation of products be better interpreted (e.g., identification of product ingredients such as solvents, propellants, and inert ingredients)? What are the effects of changes in formulation (e.g., from fully halogenated to partially hydrogenated products) and "pure" products containing primarily one ingredient?
- **Study problems**—How can better human studies be designed and conducted? How can animal chambers be created to reflect human patterns of inhalant use more accurately? How can the administration of mixtures best be controlled?

Inhalant Abuse: Interventions for Prevention and Treatment

Issues on Developing Prevention Interventions
Harvey Weiss, M.B.A., National Inhalant Prevention Coalition, United States

Mr. Weiss focused on the awareness/education approach to preventing inhalant use and described strategies that have been used by programs in Texas (1990 to 1995) and Tennessee (January 2005 to present). The focus of these programs has been to educate very young children about the dangers of inhalants by increasing the awareness and skills of parents, educators, and other influencers in the community. A key facet of the programs was redefining the problem of inhalant abuse as a public health issue, rather than as a substance abuse issue. Parents were encouraged to talk to their children about inhalants being "poisons" and to emphasize the dangers of misusing these products. This paradigm shift facilitates the involvement of a broader group of community partners, including nurses, emergency room

personnel, medical associations, and poison control centers. Equating inhalants with poisons and the misuse of other products also helps parents and schools to begin educating children at very young ages.

A major focus of the prevention interventions has been developing and providing educational materials and other resources to families, schools, communities, media, and other potential change agents. Products include staff training and curricula for schools, resources to teach parents skills (e.g., how to talk to young people about reading product labels and using products safely), resources for peer leadership programs, and materials to help engage the media in talking about the problem of inhalant abuse. Other program activities have included linking statewide and local constituencies to form and sustain partnerships or coalitions and maintaining communications through e-newsletters. Outcomes of these programs have included a significant reduction in inhalant abuse rates in Texas in 1994 to 1995 and widespread recognition of the problem of inhalant abuse in Tennessee. Mr. Weiss posed several questions for the research agenda that are included in the list of research needs for prevention and treatment.

Issues on Developing Treatment Interventions
Debra Dell, Youth Solvent Addiction Committee, Canada

Ms. Dell related lessons learned from her experiences in residential treatment programs for youth who are abusing inhalants, including inhalant-specific programs for First Nations youth. She noted that the eight Inhalant Specific Treatment Centres located throughout Canada initially faced several challenges, including working in isolation from each other, varied policies and procedures, staff recruitment and retention difficulties due to remote locations, and negative research reports on the treatment potential for inhalant-abusing clients. In 1998, the centers started the Youth Solvent Addiction Committee (YSAC) and began working together to develop proactive approaches to addressing common problems. YSAC and its centers developed an accreditation program, standardized reporting and data collection, and forged partnerships with government agencies and research institutions. Today the centers focus on strength-based techniques and show improved rates for client and staff retention. Schools that exist at all but one of the centers show client educational improvement of up to 1.5 grade levels in math and English during the 6 months that youth were in the program.

YSAC recognizes that treatment needs to consider impact on physical, emotional, spiritual, and mental health. Outcome indicators (e.g., school scores, a pre- and post-resiliency scale, and entry/exit motor coordination tests) address these four domains. Ms. Dell reported that the best outcomes were achieved at centers that had characteristics such as gender-specific programs; small client loads (i.e., 9 to 10 teens); lower staff turnover; and treatment approaches such as the use of family components, holistic resiliency models, and traditional aboriginal health methods. Ms. Dell also acknowledged that residential treatment was not a sufficient response to widespread inhalant abuse and emphasized the importance of prevention and early intervention. A program that she developed in Saskatchewan sends an outreach worker to communities that request treatment for a cluster of teens. Community-based interventions include providing free prevention manuals and posters. Since the implementation of the outreach program, Saskatchewan accounts for only 8 percent of the centers' client load, compared to 18 percent before program implementation.

The Work of Friends-International in Cambodia from Mainstream to Gateway: Inhalants among Cambodian Street Children
Sebastien Marot, Friends-International, Cambodia

Mr. Marot provided a field perspective from Cambodia, a country that has some of the lowest indicators of human development and health in Asia. For example, 80 percent of the population is poor, high rates of HIV infection are expected to orphan 140,000 children this year, and the capital city of Phnom Phen has 20,000 street children. Mr. Marot explained that Friends-International works to support street

children and help them reintegrate into society by initiating new programs, providing technical support to existing programs, and supporting governments and organizations that want to start new programs. When the organization began its drug project, Mith Samlanh (Friends), in 1994, there was virtually no substance use in Cambodia because war had isolated the country for 25 years. Substance abuse among street children was first observed as solvent use at the Thailand border and quickly spread throughout the country as these children fled to escape arrest. By 1999, 91 percent of street children sniffed glue. Within a few years, heroin and amphetamine-type substances (ATS) overtook inhalants as the most commonly used substances. Today, 71 percent of street children under age 15 regularly use inhalants, primarily glue. The use of this gateway drug tends to decrease as street children get older and move to "cooler" drugs, especially ATS. However, the cost of ATS and heroin has increased dramatically in recent months, and the still inexpensive solvents have returned to the mainstream of substance use, even among older children. Adult dealers—who buy, promote, and sell glue to children—have emerged where shops refuse to sell to children.

Mr. Marot emphasized several risks of solvent use observed in Cambodia, including the risk of overdose and accidental death, unprotected sex and HIV infection, and accidental injuries. He described Friends-International's approach to prevention, which focuses on what matters to street children. For example, materials use pictures rather than text, and messages emphasize the effects of inhalants on looks rather than the risk of death. Other crucial components of the project are peer education, support to substance users through outreach visits and drop-in centers, detoxification assistance, and rehabilitation/relapse prevention. Mr. Marot emphasized that offering real alternatives to street life is essential to changing behavior.

Inhalant Abuse by Street Children in Brazil: Causes and Consequences
Helena Maria Tannhauser Barros, M.D., Ph.D., Fundação Faculdade Federal de Ciências Médicas de Porto Alegre, Brazil

Dr. Barros presented data on drug use in Brazil based on surveys of students, street children, and households. These data show that compared to other nations, Brazil has the highest rates of experimental use of solvents among students. Inhalants are the first illicit drug used by children, and inhalant use remains high among adults. Although the rate of past-month use of inhalants among street children has changed over the years, it has been consistently high. The intensity of inhalant use varies according to the children's contact with family and their attendance at school, with rates being much higher among children who sleep in the streets than among children who live with their families and go to school. Many children who sleep in the streets are there because of family problems, the negative influence of friends, poverty, or the desire for freedom. These children are more likely to use drugs, drop out of school, commit crimes, and eventually get caught in a spiral of drug dependence and violence.

Dr. Barros described a study of intense daily toluene use among 65 children who used a government night shelter. Toluene blood levels for most of these children were in the ranges for severe intoxication or for risk of death. High levels of urinary hippuric acid (UPA) were correlated with high toluene blood levels but not clinical pathology as indicated by urine and blood analyses. Toluene and UPA levels indicated that children binged on toluene throughout the day and night. Most of the children in the study also used marijuana, usually because they had become anorexic from toluene use and needed marijuana to stimulate their appetite. Toluene appeared to be a gateway drug for marijuana and cocaine use in this population, but street children also continued to use toluene because they liked its effects. Dr. Barros noted that these children need prevention approaches and treatment plans that are adapted to their special situation. For example, all organizations working with street children need to connect as a network to help this population.

Glues or Paint Thinner: Understanding the Nature and Extent of Inhalant Use in Turkey
Kultegin Ögel, M.D., Bakirköy State Hospital, Turkey

Dr. Ögel presented an overview of inhalant use, inhalant users, and a treatment program in Istanbul, Turkey. He reported that the most commonly used inhalants were glues and paint thinners, as well as N_2O among more affluent people. A survey of 10th-grade students indicated that lifetime prevalence was higher for inhalants than for marijuana or ecstasy and that these rates had increased in 2004, reversing a downward trend noted in 2001. In 2001, 76.4 percent of inhalant users reported that they were planning to quit inhalant use, but 45.9 percent reported difficulty in quitting. Street children had high rates of past-year drug use, especially for thinners, glues, alcohol, and marijuana. Street children tended to prefer thinners, which have more toluene and produce higher sedative and anesthetic effects than glue. Dr. Ögel listed characteristics of inhalant users, including earlier onset of drug use, lower levels of education and socioeconomic status, prevalent cognitive impairment and developmental deficiencies, high criminality, frequent family and psychological problems, and high stigmatization. He noted that these characteristics indicated the need for school-based prevention programs for early ages, social support programs, family interventions, harm reduction activities, and efforts to reduce stigma.

Dr. Ögel described the Treatment Program in Inhalant Addiction Center in Turkey, which includes beds for street children and adolescents who live with their parents. Interventions for both outpatient and inpatient programs include group therapy and individual therapy for adolescents as well as group education and, when necessary, therapy for families. The center also uses medical interventions (i.e., assessment and detoxification); psychosocial interventions (e.g., family trainings and therapy); individual interventions (i.e., dialectical behavioral therapy and relapse prevention); and general and health education programs. Although effectiveness data are not available, the center has 3-month dropout rates of 18 percent for the inpatient program and 26 percent for the outpatient program. Dr. Ögel emphasized that inhalant use is a complex and complicated type of drug use and requires comprehensive and targeted treatment programs. For example, the YENIDEN Health and Education Foundation in Turkey has developed an inhalant use severity questionnaire specifically for adolescents. Treatment programs need to be adapted to specific types of inhalant users, such as children living with their families versus those living in the street, male users versus female users, and users of glue versus users of paint thinner. Dr. Ögel suggested that a better understanding of the natural course of inhalant use would aid the design of more effective treatment programs.

Lessons From the Validation of Multisystemic Therapy (MST) for Substance-Abusing Adolescents
Scott W. Henggeler, Ph.D., Medical University of South Carolina, United States

Dr. Henggeler described the work of the Family Services Research Center, which develops, tests, and disseminates family- and community-based treatment and interventions for children and adolescents with serious behavior problems, such as substance abuse, violence, and suicidality. He hoped that information about the effective treatment services developed by the center might have implications for treating other kinds of antisocial behaviors such as inhalant use. He also explained that multisystemic therapy (MST) is an intensive treatment aimed at decreasing youth problems and preventing costly out-of-home placements (e.g., incarceration, residential treatment). Because caregivers are considered the key to positive long-term outcomes, MST devotes the bulk of its clinical resources to empowering and building a support system for parents and other caregivers. Studies have shown that this approach decreases arrests, substance use, and out-of-home placements while improving family relations and school attendance. A recent study of substance use outcomes for adolescents showed that drug courts were more effective than family courts and that drug courts combined with evidence-based interventions, such as MST and contingency management, were even more successful.

Dr. Henggeler reviewed outcomes research for evidence-based practices that had been effective for delinquent adolescents because delinquency and substance use are highly associated and have many common risk factors and service system issues. He noted that three such practices—MST, functional family therapy, and multidimensional foster care—shared several common features, including a comprehensive approach to addressing risk factors, a family focus, efforts to remove barriers to service, use of behavioral intervention techniques, and strong quality assurance protocols to support treatment fidelity. Dr. Henggeler commented that MST was expensive because it is an intensive service; however, it is cost-effective if targeted to youth who otherwise would require costlier placement or incarceration. He added that Dr. Michael French at the University of Miami has a tool that measures the cost-effectiveness of the drug court system; Dr. French currently is adapting the tool for easy use in research on adolescent substance abuse.

Finding Answers From Within: Interventions with Aboriginal Young People and Their Families
Grant Charles, Ph.D., R.S.W, University of British Columbia, Canada

Dr. Charles followed up Ms. Debra Dell's earlier presentation with a discussion of aboriginal children who were in one of Canada's first solvent abuse treatment programs in the 1990s. He reported that most of these children had concurrent abuse of other drugs (70 percent) and had come from families that had at least one other substance-abusing member (90 percent). Many of the children had experienced numerous other difficulties, such as a history of physical or sexual abuse (53 and 45 percent, respectively); a recent death in the family due to suicide, accident, or homicide (50 percent); and family violence (36 percent). Almost two-thirds of the children (60 percent) had been hospitalized even though they lived in isolated communities, and many experienced medical or developmental problems, which initially were thought to be permanent but later showed improvement after 3 months in treatment. Inhalant use among these youth was initiated at an earlier age than youth in studies (an average age of 9.7 vs. 11.5 and 13.1 years) and involved primarily gasoline (used by 91 percent of youth). Two years after treatment, 86 percent of these youth had returned to their home communities and 51 percent had used inhalants, but usually not until late in the 2-year period.

Dr. Charles described several challenges to treatment interventions in aboriginal children, including outdated or inappropriate treatment services when children return to their home communities; cultural conflict, including between different aboriginal cultures; racism and marginalization, often manifested as resistance to having treatment centers located in a community; and families' suspicion of residential programs as a result of a history of residential schools and efforts to suppress aboriginal culture.
Dr. Charles described a framework developed by Fred Matthews, who conceptualized children's services according to the needs of three groups of young people:

- The majority (70 percent) of children, who are loved and supported. These children will do well regardless of their communities, schools, and medical systems.
- A smaller group (20 percent) of children, who are more vulnerable. Most of these children will do well if they have support and services; children without support and services will not do well.
- A small group (5 percent) of children who will struggle regardless of the services in the community because they were born with difficulties or were in highly abusive families.

The framework suggests that prevention education works well with the first group of children but needs to be supplemented with community and crisis intervention services for the second group. Short-term crisis intervention could help many children in the second group avert the need for residential treatment. Children in the third group have many needs and are disruptive; they should be treated in small, individualized settings rather than mixed with other children in residential programs. Dr. Charles raised several research questions, which are included in the list of research needs for prevention and treatment.

Inhalant Abuse Prevention Research in Alaska
David Collins, Ph.D., PIRE Louisville Center, United States

Dr. Collins briefly described a new research project that is implementing inhalant abuse prevention programs in four relatively small communities in Alaska. The programs use environmental strategies that were tested in earlier efforts to reduce alcohol trauma. In the first year, the project mobilized the interest of communities to ensure their buy-in and the cultural appropriateness of the programs. Next steps include setting up retailer, family, and school environmental strategies and testing a prevention curriculum for fifth-graders that is based on life-skills training for Native Americans. Subsequent efforts will involve testing the school-based curricula in 16 other Alaskan communities.

Reformulation of Products With Abuse Liability: Industry Responses to Research

Abuse Liability
Scott Earl Bowen, Ph.D., Wayne State University, United States

Dr. Bowen discussed several approaches to managing the abuse potential of consumer products, including restricted distribution, more prominent warning labels, and changes to the formulation of products. He gave an example of how reformulated products can be studied to explore whether the new compounds still have abuse potential. Dr. Bowen and his colleagues conducted several tests comparing 1,1,1-tricholoroethane (TCE), an ingredient in a correction fluid that had been widely abused, with Isopar-E™, an isoparaffin compound that replaced TCE in the reformulated product. Evaporation studies showed that Isopar-E™ was clearly less volatile than TCE; however, heating Isopar-E™ increased its volatility. Results from animal studies of function (e.g., activity, reflexes) indicated that whereas TCE produced significant behavioral disruptions on most measures, Isopar-E™ resulted in only minor disruptions. Both substances appeared to produce similar dose-dependent sedative effects in animals performing an operant (lever-pressing) task and similar ethanol-like responses in animals performing a drug discrimination task. Unlike TCE, Isopar-E™ caused some seizures and one death at very high doses. Another animal study showed that Isopar-E™ produced cross-dependence with TCE. According to Dr. Bowen, that the ethanol-like effects and seizure outcomes produced by Isopar-E™ suggested that more study was warranted before the compound was determined to be safe from inhalant abuse.

Industry Response to Research
Edwin Zvartau, M.D., Ph.D., D.M.Sci, Pavlov State Medical University, Russia

Dr. Zvartau described interactions with Russian companies that manufactured products containing solvents. In the late 1980s, a glue made with a toluene-based thinner and other types of solvents became widely abused by children in St. Petersburg. Dr. Zvartau and colleagues assessed the addictive potential of the glue's vapors using a series of animal studies, including tests of stimulus discrimination, place conditioning, rate-intensity function, and rate concentration. The researchers concluded that the ability of solvents to reinforce conditioning in the place preference paradigm and to activate the brain reward system in intracranial self-stimulation (ICSS) suggested that such experiments might be useful for predicting the addictive potential of inhalants. In the mid-1990s, industry sought to confirm and extend earlier findings by testing additional solvents such as cyclohexane, acetone, and petroleum benzine as well as an additional testing procedure—a new autotitration ICSS protocol. Dr. Zvartau reported results from rate-intensity, autotitration ICSS, and intravenous self-administration protocols. These studies showed that several solvents could facilitate brain stimulation and activate the brain reward system. Experiments showed that drug- and experimentally naive mice would self-administer toluene and TCE, suggesting that researchers could use intravenous self-administration protocols to study the abuse

potential of these volatile compounds. Perhaps one of the most important contributions of this research was the reformulation of the glue product to exclude toluene.

In the discussion that followed the presentations by Dr. Scott and Dr. Zvartau, Dr. Balster reminded participants that although animal models have been used for decades to assess the abuse potential of medications, abuse potential assessment of solvents for product reformulation is at a very early stage. He pointed out that a key to the success of the studies reported by Dr. Scott and Dr. Zvartau was the ability to attract industry funding. Dr. Balster suggested that with a concerted effort and more developed models, it would be possible to use animal tests to obtain some level of predictive value for the abuse liability of solvents. It then would be possible to develop a list of solvents from which industry could choose for inclusion in its products. Dr. Zvartau added that it was important to have some preclinical testing of new products using classical animal addiction models and that solvents should be studied like any other psychoactive chemical components. Dr. Cruz suggested that the availability of self-administration animal models, conditioned place preference measurements of withdrawal, and molecular targets could now enable the inhalant research community to develop guidelines for comparing solvents for safety. Mr. Ken Newman, who represented Falcon Safety Products, Inc., a company that makes a frequently abused product (i.e., computer duster spray), suggested that more research was needed to understand the reasons (e.g., chemical ingredient, peer pressure, product labeling) that inhalant abusers preferred certain products. He envisioned three roles for industry: reformulation, prevention, and research. He proposed that researchers approach industry from a partnership perspective with the offer to provide science-based information on abuse potential.

Research Funding Opportunities

John E. Fogarty International Center
Kathleen Michels, Ph.D., John E. Fogarty International Center (FIC), United States

Dr. Michels reported that NIH funds international research directly to foreign sites, through domestic awards to U.S. scientists with foreign components in their projects, and through programs specifically targeted to international research and research collaborations. Unlike other NIH Institutes that support some international research, FIC devotes all its efforts to this area. The Center focuses specifically on reducing disparities in health and advancing health research in low- and middle-income countries. FIC works with the other Institutes, including NIDA, to cover the full spectrum of NIH-funded research. The Center supports research and training, particularly partnerships and collaborations. FIC research grants include broad programs such as the Fogarty International Research Collaboration Award (FIRCA); Brain Disorders in the Developing World; and Stigma and Global Health Research Program, which FIC hopes to recompete. Dr. Michels noted that a unique feature of FIC programs is that applications for foreign grants do not need to meet certain more restrictive criteria required by other NIH Institutes. FIC also supports international collaborations through grants that fund the training of researchers in low- to middle-income countries. Training programs generally involve collaborations between U.S. and foreign institutions, with trainings conducted in the United States or the home country and research conducted in the home country. Training programs potentially of interest to participants include the International Clinical, Operational, and Health Services Research and Training Award (ICOHRTA) and the Framework Programs for Global Health. More information on these and other programs is available at the FIC Web site at http://www.fic.nih.gov.

Canadian Institute of Health Research: Research Funding Opportunities
Richard Brière, Ph.D., Institute of Neurosciences, Mental Health, and Addiction, Canada

Dr. Brière reported that in 2003, a forum on alcohol and illicit drugs in Canada identified a comprehensive list of research themes that became the focus of a Request for Applications (RFA). Four Institutes at the Canadian Institute of Health Research (CIHR) and four partner organizations sponsored the RFA, which uses five funding tools:

- **Team grants** to support the creation of new research teams or the development of small existing teams comprised of investigators undertaking collaborative, multidisciplinary research.
- **Policy research grants** to stimulate research that will influence and guide or have direct impact on policy decisions (Dr. Brière noted that this type of research is important for a topic like addiction.)
- **Knowledge synthesis grants** to assess current knowledge foundations and help identify knowledge gaps and priorities (Dr. Brière noted that research on inhalants would be a good subject for these grants.)
- **High-risk seed grants** to encourage novel, innovative, and inventive research in the area of alcohol and illicit drug use, abuse, and addiction.
- **Secondary analysis grants** to provide an opportunity for expert analysis of existing data sets.

Two additional Canadian research programs include the following:

- **International Opportunities Program**, which includes a development planning grant and collaborative research project grants. The program is sponsored by CIHR and requires Canadian partners.
- **Teasdale-Corti Team Grants**, which support the development of multiyear programs involving teams of Canadian and low- and middle-income country researchers and research users. The grants are sponsored by CIHR and three other partners.

More information on these and other research opportunities is available at http://www.cihr-irsc.gc.ca.

NIDA Support for Inhalant Abuse Research
David Shurtleff, Ph.D., National Institute on Drug Abuse, United States

Dr. Shurtleff explained that NIDA views drug addiction as a complex behavioral and neurological disorder that encompasses a variety of historical, environmental, and physiological factors. To develop a complete understanding of drug abuse and addiction, NIDA must study all these areas and use multiple levels of analysis, ranging from genes to social networks. Dr. Shurtleff reported that in 2002, NIDA issued an RFA (DA02-002) on inhalant abuse that supported broad-based research approaches. The 13 grants awarded covered a broad range of research issues, including several projects on inhalant use in children and adolescents. In 2005, NIDA released a Program Announcement (PA-05-099) encouraging the research community to submit broad-based research approaches to the problem of inhalant abuse, including epidemiology, prevention, treatment, and basic research. NIDA recently issued a new Program Announcement (PA-06-050) to support international collaborations on drug abuse and addiction outside the United States, with inhalant abuse cited as a priority issue. NIDA plans to continue to address the problem of inhalant abuse by informing the public through multiple channels (e.g., a Web site devoted to inhalant abuse [http://inhalants.drugabuse.gov]) and to international drug abuse research collaboration [http://www.international.drugabuse.gov]), community bulletins, research reports, and popular news articles) and conducting program outreach (e.g., encouraging a broad array of research, supporting scientific meetings, preparing special journal articles).

Consejo Nacional Contra las Adicciones (National Council Against Addictions)
Dr. José Ángel Prado García*, *Colonia Juárez Delegación Cuauhtémoc, Mexico

Dr. Prado García reported that the National Council Against Addictions focuses on public policy related to prevention and treatment rather than research. However, the council does lobby to obtain financial support for research. Dr. Prado García named several institutions in Mexico that conduct research on drugs, alcohol, and tobacco. He added that the primary funding source for research was the National Council on Science and Technology, which supports epidemiology, neuroscience, clinical research, social behavior, and medicine. Awards are based on quality rather than the subject of the research. Dr. Prado García noted that the primary challenge in Mexico was to increase collaboration between its research institutions and with research institutions in other countries.

Discussion, Research Needs, and Next Steps

Discussions among the full body of participants after presentations and within four workgroups at the end of the consultation addressed the knowledge gaps, research needs, and next steps for moving forward in the areas of epidemiology, neuroscience and clinical research, and prevention and treatment. Participants cited the need for specific collaborative international efforts to expand research into the causes, consequences, prevention, and treatment of inhalant abuse, and for increased neuroscientific studies to explain the effects of inhalants at the cellular and organic levels. The following priority research areas emerged from these discussions:

- Standardizing and adapting existing surveillance methods and coordinating data collection procedures internationally to better measure the extent of inhalant abuse
- Designing, implementing, and evaluating treatment and prevention interventions tailored to inhalant abuse
- Expanding basic science studies to better understand the mechanisms of action of inhalants on developing brains
- Investigating the interaction among underlying factors that may contribute to inhalant abuse and the consequences of that abuse.

Meeting participants expressed particular interest in qualitative research, longitudinal studies to compile data about subjects before they begin using inhalants, and research that explores chronic versus episodic and isolated versus communal use patterns.

Highlights of recommendations in each area are presented below.

Epidemiology

Research Needs

Develop strategies to address the suspected underreporting of inhalant abuse, including:

- Work with the Substance Abuse and Mental Health Services Administration's Office of Applied Studies and NIDA's Community Epidemiology Work Group to find ways to strengthen the ongoing monitoring of existing data and to use the data more efficiently.
- Work with colleagues in Mexico, where some reported rates are higher, to identify more systematic ways of looking at available indicator data.
- Use international partnerships to develop better tools (e.g., better survey questions) for extracting data on inhalant use. These tools should work in every cultural setting.
- Consider ways to address political barriers to reporting.
- Include data from interviews with emergency medical service workers and police.

Separate collected data according to various subcategories, including:

- Types of inhalants (e.g., nitrites, volatile solvents)
- Types of inhalant users according to:
  - Gender (even if prevalence does not appear to differ significantly by gender)
  - Social/casual/occasional users versus chronic users
  - Users who want to get high (recreational use) versus users who want to forget their life situation versus users who want to stave off hunger
  - Casual users for whom the perception of risk is a deterrent versus users for whom the perception of risk encourages use (e.g., those for whom "a scare is a dare")
- Special populations of users (e.g., people who are homeless, incarcerated, or institutionalized in mental hospitals).

Explore approaches to assessing the public health impact of inhalant abuse. Consider:

- Whether comparing the relative risk of inhalant abuse to other drugs of abuse is the best strategy
- Whether current indicators give an accurate picture of the public health impact
- Whether other indicators (e.g., coexisting infectious diseases such as AIDS) would be valuable
- Whether direct measures (e.g., costs) would be valuable.

Examine the following aspects of the public health impact:

- Whether the impact in the United States is similar to or different from that in other countries, including developing countries
- Whether relative risk is greater in countries or subpopulations where prevalence is higher
- Ways to understand the impact of local phenomena within small, often isolated, populations.

Address the issue of stigma (including within the inhalant-using community) and its possible impact on underreporting and research support.

Support research on the various ingredients in inhalants (e.g., solvents, propellants) to define the most prominent and correlated chemicals in terms of:

- What induces individuals to start using the substance
- What causes dependence on the substance
- What causes short- and long-term health problems.

Encourage research on consequences of inhalant use, including:

- Mortality (e.g., sudden sniffing death) and morbidity (e.g., injuries from explosions of butane cans)
- Long-term medical and psychiatric consequences
- Cognitive impairment in children and adolescents
- Effects of prenatal inhalant exposure on neonates and child development, including the prevalence and impact of fetal solvent syndrome
- Outcomes such as depression and other substance abuse
- Correlates of inhalant use disorders in children and adolescents
- Characteristics and consequences of asthma inhaler abuse
- Association of inhalant abuse with head injuries, violence and other trauma, stress, and higher levels of adversity
- Distorted sleep cycles in homeless children.

Encourage research to understand particular aspects of inhalant use, including:

- Why youth start and escalate inhalant use
- Why lifetime inhalant use rates decline with age (e.g., youth redefine "inhalants" as they get older)

- Trends in the types of inhalants used (e.g., less use of glue and more use of products without residue such as computer dusters and butane)
- Frequency/quantity of use (e.g., experimental vs. other patterns of use)
- Patterns and predictors of polydrug use
- Factors that predict individuals' susceptibility to the adverse medical and health-related consequences of inhalants
- Assessment of inhalant user characteristics by geographic region (e.g., who is at risk and where are they at risk?)
- Assessments of trajectories of inhalant users over time, including:
  - Outcomes in morbidity/disease
  - Other drug abuse
  - Other outcomes.
- Assessment of risk factors in students (Currently, more is known about risk factors in street children.)
- Impact of adversity (e.g., poverty, trauma) and severe home environments (e.g., homes with harsh parental discipline) as well as the compounding effect of the interaction between inhalant use and stress
- Potential gender differences in underlying pathologies (e.g., boys are exposed to more violence, but girls are more affected by violence, particularly sexual abuse; affected boys are more likely to abuse drugs, whereas girls are more likely to become depressed)
- Issue of girls who work in the street and become pregnant. Their babies are at risk not only because of exposure to their mothers' pre- and postnatal use of inhalants but also because of their postnatal exposure to inhalant use by their parents and other people in close environments.

Support the following types of studies:

- Small-scale qualitative studies, possibly in indicator areas, whose results could be shared with other countries
- Longitudinal studies on the life course of inhalant use to understand better why some youth start using, why some escalate use, and why some stop use
- Longitudinal studies to examine the long-term medical and psychiatric consequences of early inhalant use and the consequences of acute episodes of inhalant intoxication
- Epidemiological studies on the prevalence and correlates of inhalant use and dependence disorders in children and adolescents
- Ethnographic studies to obtain a detailed microanalysis of actual inhalant use practices and patterns
- Research on the taxonomies and typologies of inhalant users to support the development of subtypes of users.

Foster interdisciplinary approaches and perspectives, including the perspectives of inhalant users:

- Develop guidelines and other training and educational tools for medical examiners, treatment providers, physicians, pediatricians, nurses, emergency department personnel and other hospital staff, and educators.
- Collect data from inhalant users on what inhalant products they have used, how they use the products, reasons for starting and stopping use, perceived risks of use, and other contexts of their inhalant use.

Next Steps

- Standardize measures across countries for inhalant use and outcomes, including mortality, disease, and other outcomes.
  - Develop an international workgroup of pharmacologists and epidemiologists who can classify substances and develop questions for use in international surveys.
- Conduct cross-pharmacologic and basic research to better characterize inhalant use.

- Compare data across countries and use these data to develop and implement culturally specific interventions.
- Develop better studies of user trajectories that identify risk factors and characterize inhalant users.

Neuroscience

Research Needs

Conduct research to better define inhalants:
- Study what aspects of inhalants (e.g., chemical properties) cause intoxication effects and what factors lead to dependence.
- Determine the relevant concentrations of substances (e.g., doses that cause intoxication, loss of consciousness, death).
- Address concerns about the classification of different substances as inhalants, particularly nitrites but also N_2O.
- Address a concern about grouping substances as "poisons."

Conduct research to understand the relative nature of dependence that occurs with any solvent or gas.

Further explore effects of alcohol and solvents and their mechanisms of action:
- Compare N_2O and volatile solvents directly with alcohol.
- Study the determinants and modulators of effects related to abuse liability, especially reinforcing effects.
- Include studies of other compounds such as halothan.
- Study related mechanisms of action in which alcohol and solvents act in the same ways to affect intoxication, dependence, and withdrawal.
- Explore the relationship between cellular targets for the effects of abused solvents, including sudden sniffing death.
- Examine the coexpression of channels that are sites of action for abused inhalants.
- Study more complex, behaviorally relevant systems (e.g., reward areas of the brain) that are activated with solvent use.
- Focus on channel subtypes and use molecular/transgenic techniques to define sites of action and to examine the multiple mechanisms and behavioral actions involved.
- Conduct more research on pharmacologic interactions.
- Consider revisiting relevant earlier experiments that were not understood at the time and reproduce them using new knowledge about mechanisms of action.

Address other key questions about solvents:
- Do solvents have the same physiologic effects with chronic use and dependence?
- Do the same treatment and rehabilitation interventions that work for alcohol or drug abuse also work for solvent abuse?
- What can future research on solvents learn about structure-activity relationships, solvent mixtures, and interactions with other drugs of abuse?
- Do multisolvent exposures involve additive or synergistic effects?
- What is the relation of solvent abuse to stress, HIV or other diseases, or other environmental conditions (e.g., nutrition)?

Use imaging studies to look at more volatile or highly aerosolized substances and to identify those that would have less abuse liability.

Separate and compare two important effects—dependence relationships and toxicity—in different inhalants.

Answer questions about inhalant users' choices of other inhalants and other drugs.

- Conduct more studies to understand which products are being used and which product characteristics are influencing this choice (i.e., are users more interested in one chemical substance?).

Develop new animal models to study inhalant abuse, including:

- Animal models of binge toluene exposure
- An extension of Dr. Bowen's animal model that includes using toluene doses that are lower than a toxic range and testing the animals for seizure threshold
- Animal models that use self-administration techniques (to facilitate preclinical research on dependency)

Research key questions about FSS:

- Is FSS a syndrome that is distinct from FAS?
- If so, is there is a way to recognize FSS?

Design laboratory studies that simulate real-life human exposures (e.g., doses and frequency of doses, including binge exposure) to inhalants. (Detailed microanalyses of ethnographic data could facilitate the development of such studies.)

Recruit a broader basic research community to study neurobiological aspects of inhalant abuse:

- Find ways to overcome current isolation. Impediments include stigma (not only with reporting inhalant use but also among inhalant researchers); misconceptions that inhalants cannot be studied effectively (e.g., they evaporate too quickly); technological challenges (e.g., creating self-administrated exposure chambers); and lack of awareness of the high-quality research currently being done in this area.
- Promote inhalant research internationally to attract other neurobiologists. Sponsor satellite symposiums.
- Address the lack of financial support, especially in resource-poor countries.
- Use a variety of dissemination channels (e.g., submitting review articles to journals in the field, competing in study sections, using conference grants to hold satellite meetings) to show that neuroscience research on inhalants is using cutting-edge techniques and is on a par with the work being done on other drugs of abuse.

Approach manufacturers of products that are abused as inhalants to support efforts to increase awareness.

Consider international collaborations:

- Brookhaven National Laboratory and the Mexican National Institute of Psychiatry could consider collaborating on imaging studies to conduct cultural comparisons.
- Use impending tripartite agreements now being discussed by the United States, Canada, and Mexico as an opportunity to obtain funding for future initiatives (e.g., on indigenous peoples).

Next Steps

- Set up a Web site or other computer-based portal for scientists and other interested persons to access vital information or contacts in different countries.
- Set up Web-based conferencing to allow researchers and other interested persons from different countries to talk about various issues. (An example is the process instituted by the National Institute of Mental Health.)

Prevention and Treatment

Research Needs

Empirically validated best practices for the prevention of inhalant abuse are needed. (Validated curricula and approaches for drug abuse prevention usually are nonspecific and rarely measure inhalant abuse.)

Research is lacking on different approaches to inhalant abuse prevention and what works.
Research is needed to address the following prevention questions:

- Do inhalants constitute a gateway to other substance use?
- What are the primary techniques to prevent inhalant abuse (e.g., regulation, education, reformulation of products)?
- What are the ramifications of legal approaches to prevention (e.g., laws restricting access to toluene in the United Kingdom led to more deaths from butane)?
- What are effective prevention strategies, programs, and messages?
- Who are the key players in inhalant abuse prevention?
- How do we talk about inhalant abuse (e.g., as a poison/safety issue vs. a drug abuse issue, as an abstinence vs. a harm reduction issue)?
- How do we frame inhalant abuse as a public health issue? (e.g., Is inhalant abuse a gateway to other substance abuse? Can the prevention/harm reduction of inhalant abuse reduce exposure to HIV/AIDS?)
- What are the primary prevention messages? Is there a universal theme?
- Who is best suited to deliver the messages (e.g., poison control centers vs. drug abuse prevention curricula)?
- Who are the target audiences? Are there distinct target audience segments (e.g., experimenters vs. chronic users)? What are the unique characteristics and commonalities of these segments?
- Should prevention strategies consider tailored approaches based on characteristics such as age, gender, and ethnicity?
    - How do we implement age-appropriate approaches? At what age should we start prevention efforts?
- How can we better understand inhalant users and user trends?
    - What factors influence the initiation of inhalant use? Why are certain subgroups at higher risk in specific regions (e.g., girls in the United States, boys in Cambodia)? What are the implications of findings in these areas for prevention?
    - What more can we learn about the following factors:
        - Comorbid conditions (e.g., antisocial personality disorder, depression, attention deficit hyperactivity disorder, post-traumatic stress disorder)
        - Chronic stressors
        - Characteristics prior to initiation of use
        - American Society of Addiction Medicine Patient Placement Criteria
        - Risk and protective factors
        - Triggers
        - How and where users get high

- What are effective cross-cultural approaches to prevention that can work in various countries?
- What constitutes a good public health campaign (e.g., what will interest the media, who are crucial partners)?
- What programmatic vehicles should we use (e.g., how to develop infrastructure and resources, how to get people to work together)?
- Is it better to include messages in drug abuse prevention curricula or to keep messages about inhalant use completely separate?
- How can we apply the current science to prevention efforts (e.g., how to integrate neuroscience findings into curricula or other approaches)?
- What is the role of stigma in inhalant abuse prevention?

Research is needed to address the following treatment questions:

- What is the short- and long-term effectiveness of treatment?
- What is the effectiveness of the following treatment models?
  - Strength-based treatment programs
  - Turkish model that includes individual and group therapy for adolescents and their parents
  - Cognitive-behavioral therapies
  - Disease models (especially 12-step programs) are ineffective for adolescents
- Manual-based treatment guidelines may replace one rigid system with another.
- How can success in treatment be defined to address the goals of both the agencies providing funds (e.g., getting children to stop using inhalants) and communities (e.g., keeping children alive)?
- What is the effectiveness of therapeutic medications such as naltrexone and vigabatrin?
- What is the impact of chronic exposure to other substances such as environmental pollutants and leaded versus unleaded gasoline?

Research is needed to address the following questions about services:

- Who are young, aboriginal inhalant users and their families? Can better distinctions be made according to children's vulnerability and their need for services (e.g., as described by Dr. Charles)? Can distinctions be made between acute versus chronic users?
- What children are best served by specific kinds of services at specific times? What are the least intrusive services that children need at specific times?
- How can services for rural and remote communities be effective, cost-efficient, and respective of culture?
- How can services become less stand-alone and segmented and more integrated?
- How can "mainstream" services be aligned with culturally based services?
- How can community ownership of interventions be ensured?
- What family and community interventions are effective across cultures?
- How can we better train outreach workers?

Research is needed to better understand hallucination-seeking among chronic inhalant users, including the following issues:

- Why do users seek hallucinations (i.e., view hallucinations positively)?
- How do treatment providers view hallucinations?
- What consistent themes are reported in hallucinations across cultures and across genders?
- What relationships exist between cultural traditions of vision-seeking and inhalant-induced hallucinations?

More action research is needed to bridge the gap between researchers and people in the field. Researchers need to develop interventions that will work in the field and to incorporate feedback from the field into their studies.

Next Steps

- Evaluate effective approaches to inhalant abuse prevention, including regulation, reformulation, education/awareness, and combinations of these approaches.
- Identify effective treatment programs.
- Develop consensus-based treatment guidelines.
- Conduct research on the validity and cost-effectiveness of consensus-based treatment guidelines.
- Publish research results.
- Develop a listserv to foster sharing of information on inhalants. Include people involved in neuroscience research.
- Fund an international inhalant research seminar to discuss basic science, prevention, and treatment. Involve other Federal and other U.S. Department of Health and Human Services agencies (e.g., Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment, other NIH Institutes).

APPENDIX A: AGENDA

Inhalant Abuse Among Children and Adolescents: Consultation on Building an International Research Agenda

National Institute on Drug Abuse/Fogarty International Center

AGENDA

Monday, November 7, 2005

9:00 a.m. **Welcome and Introductions**
Kathleen Michels, John E. Fogarty International Center
Steven W. Gust, National Institute on Drug Abuse
Sharon Hrynkow, John E. Fogarty International Center
Timothy P. Condon, National Institute on Drug Abuse
Laura E. Commanda, Institute of Aboriginal Peoples' Health, Canada
José Ángel Prado García, Consejo Nacional Contra las Adicciones, Mexico

9:20 a.m. **Objectives: Assessing the Problem, Setting the Agenda**
Steven W. Gust, National Institute on Drug Abuse
Kathleen Michels, John E. Fogarty International Center

9:30 a.m. **Keynote Presentation:**
The Public Health Impact of Inhalant Abuse
Robert L. Balster, Virginia Commonwealth University

10:15 a.m. **Break**

10:45 a.m. **World Reports: Epidemiology of Inhalant Abuse**
Section I
MODERATORS/FACILITATORS:
Wilson Compton, National Institute on Drug Abuse
Laura E. Commanda, Institute of Aboriginal Peoples' Health, Canada

PRESENTATIONS:

10:50 a.m. **Epidemiology of Inhalant Abuse in Mexico: Impact on Public Health**
María Elena Medina-Mora, Mexican Institute of Psychiatry

11:15 a.m. **What the Data Tell Us about Solvent Abuse in Canada**
Colleen Anne Dell, Canadian Centre on Substance Abuse

11:35 a.m. **Epidemiology of Inhalant Use in the United States: Correlates and Consequences**
Li-Tzy Wu, Duke University School of Medicine

12:15 p.m. **Lunch**

1:30 p.m. **Special Reading from "An Ex-Mas Feast" and Commentary**
Uwem Akpan, University of Michigan

2:00 p.m. **World Reports: Epidemiology of Inhalant Abuse**
Section II

MODERATORS/FACILITATORS:
Moira O'Brien, National Institute on Drug Abuse
Lourdes Schnaas, Instituto Nacional de Perinatología, Mexico

PRESENTATIONS:

2:05 p.m. **Inhalant Abuse among Juvenile Delinquents in the United States**
Matthew O. Howard, University of Michigan

2:35 p.m. **Summary of Russian Regional Data on Inhalants**
Edwin Zvartau, Pavlov State Medical University, Russia

3:05 p.m. **Epidemiology of Inhalants in Peru**
Inés Verónica Bustamante, Universidad Peruana Cayetano Heredia, Peru

3:35 p.m. **Isolating Precursors from Consequences of Inhalant Use**
Diana Fishbein, Research Triangle Institute-International

3:55 p.m. **Impact of Inhalant Use in Venezuela**
Elvia Amesty, José Félix Ribas Foundation, Venezuela

4:15 p.m. **Discussion of Knowledge Gaps and Research Needs**

5:00 p.m. **Adjourn**

Tuesday, November 8, 2005

8:45 a.m. **Welcome**
Steven W. Gust, National Institute on Drug Abuse

9:00 a.m. **Impact of Inhalants on the Brain: Neuroscience and Clinical Research**
Section III

MODERATORS/FACILITATORS:
David Shurtleff, National Institute on Drug Abuse
Richard Brière, Institute of Neurosciences, Mental Health and Addiction, Canada

PRESENTATIONS:

9:10 a.m. **Solvents and Ethanol: More Alike Than We Thought**
Silvia L. Cruz, Department of Pharmacobiology, Cinvestav, Mexico

9:40 a.m. **Comparing Effects of Nitrous Oxide to Various Anesthetics and Alcohol**
Diana J. Walker, University of Chicago

10:05 a.m. **Novel Cellular Targets for the Effects of Abused Solvents**
John J. Woodward, Medical University of South Carolina

10:30 a.m. **Break**

10:50 a.m. **Recent Imaging Approaches to Studying Pharmacokinetics of Solvents**
Stephen L. Dewey, Brookhaven National Laboratory

11:15 a.m. **Early Research and New Opportunities for Neuroscience and Clinical Research at the Mexican National Institute on Psychiatry**
Jorge González Olvera, Mexican Institute of Psychiatry

11:45 am **Discussion of Knowledge Gaps and Research Needs**

12:15 p.m. **Lunch**

1:30 p.m. **Impact of Inhalants on the Brain: Neuroscience and Clinical Research Section IV**

MODERATORS/FACILITATORS:
Charles Sharp, National Institute on Drug Abuse
Silvia L. Cruz, Department of Pharmacobiology, Cinvestav, Mexico

PRESENTATIONS:

1:35 p.m. **Fetal and Neonatal Effects of Inhalant Abuse**
Milton Tenenbein, University of Manitoba, Canada

2:05 p.m. **Animal Models for Assessing the Effects of Maternal Inhalant Abuse**
Scott Earl Bowen, Wayne State University

2:35 p.m. **Break**

3:00 p.m. **Inhalant Abuse and Related Toxicity: The Philippine Experience**
Irma Makalinao, University of the Philippines

3:30 p.m. **Pharmacologic Quagmire**
Charles Sharp, National Institute on Drug Abuse

4:00 p.m. **Discussion of Knowledge Gaps and Research Needs**

5:00 p.m. **Adjourn**

Wednesday, November 9, 2005

8:45 a.m. **Welcome**
Patricia Needle, Consultant, National Institute on Drug Abuse

9:00 a.m. **Inhalant Abuse: Interventions for Prevention and Treatment**
Section V
MODERATORS/FACILITATORS:
Patricia Needle, Consultant, National Institute on Drug Abuse
Colleen Anne Dell, Canadian Centre on Substance Abuse

PRESENTATIONS:

9:05 a.m. **Issues on Developing Prevention Interventions**
Harvey Weiss, National Inhalant Prevention Coalition

9:20 a.m. **Issues on Developing Treatment Interventions**
Debra Dell, Youth Solvent Addiction Committee, Canada

9:35 a.m. **The Work of Friends International in Cambodia**
From Mainstream to Gateway: Inhalants among Cambodian Street Children
Sebastien Marot, Friends International, Cambodia

10:00 a.m. **Inhalant Abuse by Street Children in Brazil: Causes and Consequences**
Helena Maria Tannhauser Barros, Fundação Faculdade Federal de Ciências Médicas, Brazil

10:25 a.m. **Break**

10:45 a.m. **Glues or Paint Thinner: Understanding the Nature and Extent of Inhalant Use in Turkey**
Kültegin Ögel, Bakirkoy State Hospital, Turkey

11:10 a.m. **Lessons from the Validation of Multisystemic Therapy (MST) for Substance-Abusing Adolescents**
Scott Henggeler, Medical University of South Carolina

11:35 a.m. **Finding Answers from Within: Interventions with Aboriginal Young People and Their Families**
Grant Charles, University of British Columbia, Canada

11:50 a.m. **Inhalant Abuse Prevention Research in Alaska**
David Collins, PIRE Louisville Center

12:00 p.m. **Discussion of Knowledge Gaps and Research Needs**

1:00 p.m. **Lunch**

2:00 p.m. **Reformulation of Products with Abuse Liability: Industry Responses to Research**

MODERATOR:
Robert L. Balster, Virginia Commonwealth University

PRESENTATIONS:

2:10 p.m. **Abuse Liability**
Scott Earl Bowen, Wayne State University

2:30 p.m. **Industry Response to Research**
Edwin Zvartau, Pavlov State Medical University, Russia

3:00 p.m. **Research Funding Opportunities**

MODERATORS:
Steven W. Gust, National Institute on Drug Abuse
Kathleen Michels, John E. Fogarty International Center

PRESENTATIONS:

3:00 p.m. **CANADA**
Richard Brière, Institute of Neurosciences, Mental Health and Addiction

3:20 p.m. **UNITED STATES**
Kathleen Michels, John E. Fogarty International Center
David Shurtleff, National Institute on Drug Abuse

3:40 p.m. **MEXICO**
José Ángel Prado García, Consejo Nacional Contra las Adicciones

4:00 p.m. **Closing Remarks and Summary**
Steven W. Gust, National Institute on Drug Abuse
Kathleen Michels, John E. Fogarty International Center

4:15 p.m. **Adjourn**