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Hair Tests Offer Advantages In Forensic and Clinical Uses

By Jeri D. Ropero-Miller

Hair can be an alternative or complementary matrix to blood and urine in forensic and clinical drug testing. Hair's advantages include an ability to document a longer history of ingestion and/or exposure, ease of collection, chemical stability, and less susceptibility to intentional adulteration. Issues that continue to challenge the field include non-standardized laboratory techniques, inconsistent proficiency testing material and laboratory certification, variability of results, an inability to discriminate between use and environmental contamination, and a lack of knowledge about potential differences in drug incorporation caused by hair color, ethnicity, and other factors. The validity of these concerns remains unclear and they continue to be investigated.

Hair testing for metals in clinical and forensic applications began in the 1950s and drugs-of-abuse testing using hair began in the early 1980s. Hair testing continues to develop, as indicated by the publication of more than 300 scientific manuscripts focusing on its applications in the past 10 years alone. Table 1 summarizes a PubMed search using the keywords "hair analysis and drug" for publication dates from 1996 through 2007.

Current applications include forensic drug screening, clinical testing, and death investigations, and potential new applications include reinstatement of driving privileges, detection of doping agents, and testing for drugs used in a criminal act. This article is excerpted from an original manuscript by the author to be published later this year in *Forensic Science Review* (1).

Testing process

The general process of a hair drug test can be summarized as follows, although each step can vary

among collection sites and laboratories. A 10- to 100-mg hair specimen about the diameter of a standard pencil-top eraser is collected (usually cut close to the skin with an instrument such as scissors) from the posterior vertex of the scalp (e.g., the circular skull cap area including the crown) or other adequate anatomical site (e.g., axillary, pubic). The hair is kept in correct orientation with the root-end noted by the collector.

The laboratory receives the specimen under chain-of-custody protocol. A 10- to 50-mg sample is weighed, with a representative sample consisting of hair strands 1 to 4 cm in length, measuring from the root-end for most current drug exposure. It is washed of surface contaminants such as dirt, shampoo, and external drug. Prior to analysis, the hair matrix may be degraded by mechanical pulverization and/or digestion to free any drug. The drug analytes are isolated from the hair and analyzed by a screening technique such as an immunoassay. Presumptive positives are confirmed and quantitated by a separate analytical technique, including gas chromatography/mass spectrometry, liquid chromatography/mass spectrometry, tandem mass spectrometry, and two-dimensional gas chromatography with cryogenic focusing. Tandem mass spectrometry has proved its ability to quantitate low-concentration analytes such as Δ^9 -tetrahydrocannabinol-9-carboxylic acid, fentanyl, and benzodiazepine metabolites.

Forensic drug screening

Drugs-of-abuse testing is commonly performed in workplace programs, "at-risk" environments, and child protection arenas. Every year millions of speci-

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Buprenorphine is Alternative For Treatment of Addiction

By Loralie Langman

An estimated 810,000 to 1,000,000 individuals were heroin addicts in the United States in the year 2000, more than in any year since the mid-to-late 1970s (1). A significant number of treatment programs help individuals fight this addiction. Treatment programs using prescription drugs generally rely on maintenance drugs that are opiate agonists, such as methadone or levomethadyl acetate hydrochloride, or on narcotic antagonists such as naltrexone. Buprenorphine is a relatively new drug with mixed agonist-antagonist properties.

Like methadone and other opioids, buprenorphine can be used to treat moderate to severe pain and to treat opiate agonist dependence (2). An advantage of its use for the treatment of opiate agonist dependence is that the total weekly dose can be given over three days, in contrast to methadone, which must be given daily (2).

Buprenorphine was first approved for the treatment of moderate or severe pain by the Food and Drug Administration (FDA) in December 1981 as Buprenex, a 0.3-mg/mL parenteral formulation. In October 2002, the FDA approved Subutex (buprenorphine alone) and Suboxone (buprenorphine with naloxone) as sublingual pills for the treatment of opiate agonist dependence (3).

Naloxone is an antagonist at the mu-receptor in the central nervous system (CNS), so if the combination is taken intravenously, naloxone neutralizes any buprenorphine-induced mu-receptor agonist activity, which leads to withdrawal symptoms in those who inject it to get high. In contrast, when the combination is taken sublingually, there is very low absorption of naloxone, so it does not affect the efficacy of buprenorphine.

Method of action

Buprenorphine, which is chemically [5 α ,7 α (S)]-17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethenomorphinan-7-methanol, is a semisynthetic derivative of thebaine (2). It is 25 to 50 times more potent than morphine (4, 5). Buprenorphine is a CNS partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Mu-receptors are considered the classic morphine-receptor type because their stimulation produces supraspinal analgesia, respiratory depression, euphoria, and physical dependence. Actions at

kappa-receptors are believed to produce alterations in the perception of pain and the emotional response to pain. Buprenorphine dissociates very slowly from the mu-receptor, which likely accounts for its longer duration of action than morphine, the unpredictability of its reversal by opioid antagonists, and its low level of physical dependence. Because it is a partial mu-receptor agonist, there is a ceiling to buprenorphine's pharmacological effects, in which increased doses do not produce increased effects after a certain point (3). The danger of overdose, abuse, and toxicity may therefore be less than with full opioid agonists.

Buprenorphine with naloxone is preferred over buprenorphine alone for maintenance treatment, especially when patient drug administration will not be supervised. Single-agent buprenorphine should be used only for unsupervised administration in those patients who cannot tolerate buprenorphine with naloxone. In addition, single-agent buprenorphine may be preferred for induction treatment. Buprenorphine or buprenorphine with naloxone is administered sublingually as a single dose typically in the range of 12 to 16 mg (6).

Side effects and concentrations

Buprenorphine's side effects are similar to those of other opioids (3, 4, 6). The most frequent side effect is sedation, which occurs in approximately two-thirds of patients. Less frequent adverse reactions are nausea, dizziness, and vertigo, which occur in 5–10% of patients. Sweating, hypotension, vomiting, miosis, and headache occur in 1–5% of patients. A rare side effect is respiratory depression, which can potentially result in death. Most of the fatal cases occur in combination with other CNS depressants such as alcohol or benzodiazepines (3). Although sublingual buprenorphine is indicated for the treatment of opioid dependence, in high doses it can actually precipitate withdrawal effects, especially when administered as the combination buprenorphine-naloxone formulation (3, 4, 6).

Comparable plasma concentrations of buprenorphine are achieved with sublingual administration of buprenorphine with and without naloxone. Plasma concentrations of buprenorphine are linearly related to the dose administered over the typical dose range. Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin (3, 6). Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can undergo further glucuronidation (6). Little unchanged buprenorphine appears in the urine. It undergoes extensive enterohepatic circulation. The mean elimination half-

life of sublingual buprenorphine is 37 hours.

Although the incidence is rare when used for pain management, buprenorphine can cause psychological dependence, which can lead to substance abuse in some patients. As a partial mu-agonist, buprenorphine has some potential for misuse, including being sold by patients to other addicts.

Urine drug screens are used frequently to confirm that patients are complying with therapy and to detect any abuse. In general, opiate immunoassays do not detect buprenorphine, so are not suited for monitoring therapeutic use, compliance, or abuse. Buprenorphine can be detected using specific immunoassay kits, with confirmation and quantitation performed by gas chromatography electron capture, gas chromatography/mass spectrometry, liquid chromatography, liquid chromatography/mass spectrometry, or other robust methods (5).

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Hair Testing

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mens are analyzed in government-regulated and non-regulated drug-testing programs; most likely less than 10% are performed using hair.

Urine is the most common matrix for workplace drug testing, but hair testing lends itself to pre-employment, random, and follow-up testing, with the first two applications currently the most accepted. Hair testing is more expensive and time-consuming than urine testing, but many employers maintain that hair's extended detection window warrants the additional costs. Almost every state permits the use of hair in workplace drug testing in the non-regulated, private sector market (2-4). The 2005 National Survey on Drug Use and Health estimated that among

Table 1. PubMed Search of Hair Drug Testing from 1996 to 2007

| Discipline | Country of First Author | | | TOTAL |
|--------------------------------|-------------------------|----------------|----------------|-------|
| | United States | European Union | Other Country* | |
| Forensic drug screening | 17 | 37 | 14 | 68 |
| Clinical applications | 39 | 45 | 26 | 110 |
| Death investigation | 2 | 19 | 3 | 24 |
| General technical | 16 | 49 | 28 | 93 |
| Recent and future applications | 5 | 23 | 4 | 32 |
| TOTAL | 79 | 173 | 75 | 327 |

*Other countries: Australia, Brazil, Canada, Chile, China, Croatia, India, Israel, Japan, Jordan, Korea, New Zealand, Norway, Russia, Singapore, Switzerland, Turkey.

unemployed adults, 17.1% were current illicit drug users, while an estimated 12.9 million full- or part-time employees were illicit drug users (5).

Drugs tested for in workplace programs include amphetamines, cocaine, cannabis, phencyclidine, and opiates. Employers can add analytes for hair testing such as benzodiazepines, oxycodone, and hydrocodone. Several organizations have published guidelines for hair testing; however, currently there are no globally accepted practices, although several states have mandated specific procedures. The guidelines that do exist are used for only a small proportion of samples tested for workplace purposes. The Substance Abuse and Mental Health Services Administration and the European Workplace Drug Testing Society have guidelines on workplace drug testing, but both regulate only urine testing (6, 7).

Prevention, prevalence, and chronicity

Targeted populations such as adolescents, prison inmates, known drug users, domestic violence victims and perpetrators, and people living in low socioeconomic environments where drug use is more widespread are often evaluated for drug-use prevalence. In addition to prevention, other reasons to monitor drug use in these populations include clinical relevance, societal impact, and success of treatment and rehabilitation programs. Hair testing can capture a more realistic measure of prevalence because of its increased window of detection.

Drug monitoring of young adults is another area in which drug-use history can be relevant. Behavioral effects of drugs are complicated and sometimes difficult to detect, so knowledge of drug use is the first step to restoring normality. Substance use by adolescents is a major public health problem in the United States. The 2001 Monitoring the Future study indicated that 37% of eighth graders surveyed had smoked tobacco, 51% had used alcohol, 20% had used marijuana, and 15% had used other drugs (8).

Parents, schools, and sports organizations use hair testing for adolescents because they believe identifying “at-risk” adolescents as early as possible can increase the success of future prevention.

Child custody and child abuse

Hair testing is used to prosecute cases of child abuse and to decide custodial rights. For both of these circumstances it is paramount to establish, historically, the extent of the child’s exposure to drugs or toxins. Gestational and childhood drug exposure put the child’s health at risk, and legal action may be pursued when a parent or guardian exposes a child to these conditions. A case report of a cocaine-exposed child follows.

Case report: environmental cocaine exposure

A six-year-old child was admitted to an emergency room after experiencing distress symptoms, including generalized malaise associated with mild agitation, tachycardia, arterial hypertension, and mydriasis. Because of his parents’ history of crack addiction, toxicological testing was ordered to determine cocaine intoxication. The prosecutor also ordered hair analysis of the child to determine potential previous cocaine exposure. Spot urine tests detected significant amounts of cocaine (109 ng/mL) and benzoylecgonine (145 ng/mL), consistent with acute cocaine intoxication. Multiple hair aliquots showed mean concentrations of 16 ng/mg for cocaine and 0.6 ng/mg for benzoylecgonine. Police investigation determined that the shared living environment included a microwave that was used to heat food as well as crack cocaine. Hair analysis indicated that the child was involuntarily exposed to cocaine that subsequently led to passive cocaine consumption and intoxication (9).

Research-specific clinical populations

There are specific clinical populations for which drug-use history is important for treatment and recovery. These populations are “at-risk” for abusing drugs, and self-reporting of drug use can be inaccurate. Knowing their new drug-use pattern is critical for medical and psychological treatment and safe confinement within treatment facilities. Clinical populations for which hair analysis has been investigated include alcoholics and pregnant women.

Indirect biological markers are used to diagnose excessive alcohol consumption. First detected in the liver, ethylglucuronide (ETG) is a synthetase enzyme that catalyzes the formation of fatty acid ethyl esters (FAEE) in the presence of ethanol triglycerides, lipoproteins, phospholipids, and free fatty acids. ETG was identified in hair roots in the late 1990s. Con-

sequently, FAEE were investigated in hair and at least four have been identified (ethyl myristate, ethyl palmitate, ethyl oleate, and ethyl stearate). Several authors have concluded that ETG and FAEE are suitable markers for detection of heavy alcohol consumption. Detection of these biomarkers using segmental hair analysis may be useful in withdrawal treatment to look at compliance and recovery (10).

Similarly, hair analysis as a tool for retrospective detection of drug use during pregnancy also shows promise. Many studies have investigated the presence of drugs in the hair of pregnant women, fetuses, neonates, and infants. These studies have been used to determine the incidence of drug exposure and abnormal birth conditions, neurological conditions, premature deaths, and other public health concerns.

Fetal hair grows in the last trimester of pregnancy. Hair is accessible months after delivery, making it useful long after meconium, the infant’s first stool collection after delivery, is no longer available. In most cases, a positive neonatal hair test indicates maternal use after she knew she was pregnant, a strong indicator of maternal addiction.

Hair analysis studies of mothers and their infants have indicated that high drug exposure may be associated with preterm deliveries, low birth weights, smaller head circumference, neonatal withdrawal syndromes, central nervous system deficits, and other pathological findings. Much of these data are limited and actual prevalence is unknown given the small populations investigated (11–15).

Therapeutic drug monitoring and compliance

Often, physicians monitor their patients to ensure that their medical treatment through prescription medication is suitable and optimally effective. Therapeutic drug monitoring (TDM) tests are usually performed to measure a specific drug in the blood. Hair has been proposed as an alternate matrix for TDM because it can give historical information on drug use that blood cannot. With most medications, the desired effect is obtained with a specific drug concentration in the blood. Some medications are toxic if the level rises too high and ineffective if the levels are too low. Health-care providers can use hair in addition to blood to maintain drug levels within an effective range.

Hair analysis can also be used to monitor compliance in taking drugs that patients tend to be refractory in taking as prescribed, such as epilepsy, tuberculosis, and psychiatric drugs. Hair testing is generally not used alone but to corroborate compliance and clinical levels in other matrices.

Compliance in drug-treatment programs

Patients participating in treatment programs are tested to verify their drug-abuse history prior to beginning the program. Drug testing is also used to determine drug exposure, including medication compliance, during the rehabilitation process.

Technical and clinical manuscripts detailing the use of hair testing to document recidivism and compliance by patients of drug-treatment facilities have been published in the past decade. Reports have documented that hair testing is suitable for monitoring relative changes in drug intake in the same individual, which makes it applicable to any drug monitoring program.

Metals determination

As early as the 1950s, researchers in forensic medicine were using hair to determine patients' heavy metal exposure and to monitor populations for environmental pollutants (16). Atomic absorption spectroscopy and atomic emission spectroscopy were instrumental in the routine analysis of metals in hair for clinical and forensic applications. At one time, metals analysis was used to diagnose an individual for disease or nutritional status, but this has become less acceptable due to large individual differences associated with age, sex, race, hair color, hair treatment, and environmental exposure. Today, neutron activation and inductively coupled plasma/mass spectrometry are the dominant analytical techniques for metals determination in hair.

Metals commonly associated with accidental or intentional poisonings include arsenic, lead, cadmium, mercury, and thallium. The species (i.e., valency and state) of a metal determines its toxicity and tendency to attack specific organs.

Adverse health effects of metal poisoning are numerous. Noteworthy effects include allergic reactions (e.g., beryllium, chromium, arsenic), neurotoxicity (e.g., arsenic, lead), nephrotoxicity (e.g., mercuric chloride, cadmium chloride), and cancer (e.g., arsenic, hexavalent chromium). Table 2 lists concentrations of metals reported in hair at normal, toxic, and lethal concentrations.

Drug-related death investigations

Hair has many advantages as a matrix in post-mortem toxicology. Hair can be collected at autopsy in cases of interest or as a routinely collected specimen. Historically, hair analysis has been used for three primary purposes in death investigations. First, hair's stability and resistance to decomposition mean that it can be analyzed when other biological fluids and tissues no longer exist. Hair of ancient Egyptian and Peruvian mummies, dating back to 950 B.C. and

1000 A.D., respectively, have tested positive for cocaine and its metabolites, with the Peruvians known to chew coca leaves as part of their daily rituals (17, 18). Second, because hair can be used as a chronological marker, with every centimeter equal to one month of growth on average, hair testing has been used to chronicle exposure of a decedent to a drug or toxin during life. Lastly, hair testing is used to corroborate other case findings, especially in suspected deaths involving drugs or toxins such as metals.

Recent and future applications: driving

In the United States in 2005, nearly 1.4 million drivers were arrested for driving under the influence of alcohol or narcotics (19). Many drivers have their licenses revoked for this offense.

Courts in several countries have investigated the utility of hair testing for the purpose of reinstating driving privileges because of its long window of detection. Currently, France, Germany, and Italy allow hair testing to be used as evidentiary information for reinstatement of driving privileges. In the future, additional countries may use hair testing to document driving ability, driving liability, or both.

Athletes' compliance with drug-use policies

Hair has recently been investigated in anti-doping testing to determine if athletes are taking a banned performance-enhancing substance. Hair testing can be used for detection of substances that are totally banned (e.g., anabolic steroids), but is not use-

Table 2. Concentrations of Metals in Hair

| Metal | Reference (µg/g) (mean) | Toxic (µg/g) | Lethal (µg/g) |
|----------|---|---------------|--------------------------------------|
| Arsenic | 0–1.92 (0.37) | Chronic: 1–47 | Acute:>200 |
| Cadmium | Nonsmoker: 1.0 Smoker: 0.5 | * | * |
| Lead | Scalp: Austria, Italy: 0.33–49.5 (1.72) Germany: 0.54–5.53 (1.72) Korea: 3.4 ± 3.5 Poland: 2.52 Pubic: Germany: 0.29–3.77 (1.05) | 4.85 ± 5.91 | 30.2 33.7 |
| Mercury | 1.4–15 (4.1) | 50 | 50 |
| Thallium | <0.01 | 0.4 | NR |

References: 20–23

* Measurement of cadmium in hair is not generally considered reliable because cadmium can bind to the outside of hair and give faulty results. Hair levels are also not reliable as a predictor of toxicity or as an indicator of occupational exposure.

ful for substances that are banned for a short time period before the athletic event (e.g., salbutamol) or banned above a designated concentration (e.g., caffeine) (24). Currently, hair testing has not been adopted by regulatory organizations, including the International Olympic Committee, World Anti-Doping Agency, or United States Anti-Doping Agency.

Several investigators have discussed the potential of testing hair for doping agents, especially anabolic steroids (25–27). Steroid concentrations from 0.6 pg/mg to greater than 250 pg/mg have been found in hair samples from body builders.

Evidence of drug-facilitated crimes

In recent years, literature reports of hair testing for agents used to incapacitate victims during the course of a crime have steadily increased. Frequently, crime victims do not report that they were assaulted or drugged until many days after the incident. At that point, urine and blood are normally not appropriate specimens to test to document drug exposure. In contrast, hair can be tested after a post-assault waiting period, allowing the hair to grow before collecting a representative sample. Hair testing for sedatives such as benzodiazepines (28, 29), gamma-hydroxybutyrate (GHB) (30), zopiclone (29), buprenorphine (31), and zolpidem (32) has been used to document drug-facilitated sexual assault and other crimes. A representative sexual assault case is detailed below.

Case report: drug-facilitated sexual assault

A 14-year-old boy was found dead at a known sexual offender's home. Pathology findings at autopsy were unremarkable, and drug testing including hair analysis was performed. Blood buprenorphine and norbuprenorphine concentrations of 1.1 ng/mL and 0.2 ng/mL demonstrated their acute presence at the time of death. A buprenorphine concentration in the hair, measured by liquid chromatography/mass spectroscopy, was up to 23 pg/mg, but the desmethyl metabolite was not detected above 0.1 ng/mL. Segmental hair testing showed repetitive administration of the drug, and the perpetrator confessed he had used buprenorphine and clorazepate over a course of weeks to sedate his victim to molest him (31).

Conclusion

In the past decade, investigators in more than 40 countries have reported the use of hair testing to identify drugs and toxins in humans. Forensic and clinical applications of hair testing include forensic drug screening for employment, prevention, prevalence measurements, child protection, surveillance of specific clinical populations, therapeutic drug monitoring, compliance monitoring, antemortem and post-

mortem metals and drug determinations, and newly emerging applications for reinstatement of driving privileges, anti doping, and investigation of drug-facilitated crimes.

Hair testing can be a remarkable tool for forensic and clinical applications, especially with the continuing new developments. Detection limits in the picogram range and the need to determine single drug exposures for a crucially timed event challenge hair-testing laboratories to improve their analytical techniques and protocols. Continual improvement is needed for hair testing to evolve and ultimately gain widespread acceptance.

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National Alcohol Per Se Law Has Decreased Fatal Crashes

By Nichole Bynum

Every 31 minutes, someone is killed in an alcohol-related motor vehicle crash (1). The National Highway Traffic Safety Administration (NHTSA) considers a crash to be alcohol-related if at least one driver or pedestrian has a blood alcohol concentration (BAC) at or above the state's established limit. This does not, however, mean that the accident or fatality was due to the presence of alcohol.

Currently, it is an offense to drive a motor vehicle with a BAC at or above 0.08 g/dL (0.08%), regardless of the driver's visible signs of intoxication or performance on roadside tests. Termed a per se law, the establishment of this national standard was a multi-step process that spanned 16 years.

In 1988, NHTSA reviewed 177 studies to examine the effect of adopting this national limit (1). Since then, NHTSA has reviewed 112 additional studies, which led it to conclude that virtually all drivers, including those with experience, are significantly impaired at 0.08% BAC (1). In a 1992 report to Congress, NHTSA recommended that all states lower the legal per se level to 0.08% for all drivers 21 years and older.

Adoption of national standard

President Clinton addressed the nation on March 3, 1998, urging that new standards be adopted to prevent the many alcohol-related injuries and deaths on the nation's roads. In 1998, the Transportation Equity Act for the 21st Century created a new federal incentive grant program to encourage states to adopt the 0.08% BAC legal per se level.

Two years later, Congress passed the DOT Appropriations Act of Fiscal Year 2001, which adopted 0.08% as the national legal limit for impaired driving. States that did not adopt this limit would be subjected to a withholding of 2% of certain highway construction funds, with a 2% increase in withholding each year until fiscal year 2007, resulting in an 8% withholding. States that adopted the new limit by Oct. 1, 2007, would receive back all the funds lost in the previous years. States that did not adopt the law by the deadline would not receive any of the withheld funds. Thus, a state could lose millions of dollars in federal assistance for highway development and maintenance.

Prior to the enactment of this bill, only 19 states, the District of Columbia, and Puerto Rico had 0.08% BAC per se laws in place. By May 2001, 49 states

did. And by 2004, with Delaware being the last, all states had adopted the legislation.

Studies of effects

Several studies have examined the impact of 0.08% legislation. Johnson and Fell studied the impact that lowering the per se limit to 0.08% had in the states of California, Maine, Oregon, Utah, and Vermont, all of which adopted the change prior to 1992, and found statistically significant reductions in driver involvement in alcohol-related fatal crashes in four of the five states (2). Hingson et al. concluded that overall these five states experienced a 16% post-law reduction in the proportion of crashes with a fatally injured driver whose BAC was at or above 0.08% (3).

In 2001, after many states adopted 0.08% as the legal limit for alcohol intoxication, NHTSA revised its alcohol reporting categories to 0.00%, 0.01–0.07%, and at or above 0.08%. The previous categories were 0.00%, 0.01–0.09%, and at or above 0.10%, so the changes make some comparisons difficult, such as determining the effect that a 0.02% change from 0.08% to 0.10% has on alcohol-related crashes.

In general, compared with 25 years ago, there has been a noticeable decrease in the percentage of alcohol-related fatal crashes. During the past few years there have been fluctuations, but in all states, alcohol-related motor vehicle crash numbers have

remained consistently below those of the years before per se laws.

Again, there has been a dramatic decrease in these crashes in recent years as compared to 1982. Although it is difficult to determine the impact the 0.08% per se law has had on the reduction of alcohol-related crashes, there appears to be a significant decrease in the percentage of crashes compared with 25 years ago.

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