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D-3.1 REPORT ON THE ANALYSIS OF THE SUITABILITY OF SCREENING AND CONFIRMATION TESTS FOR MISUSE OF ALCOHOL AND DRUGS

MESAFE – MEntal health for aviation SAFEty

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CONTRACTOR / AUTHOR:	Deep Blue / Ries Simons
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SUMMARY

The present report provides an overview of those psychoactive substances that have an impact on the ability of pilots and ATCOs to safely perform the privileges of their license. This overview is followed by a review of available methods of screening for use/misuse of psychoactive substances, and their suitability to be used in the medical examinations of pilots and ATCOs.

Based on the data of alcohol use in the European working populations, a cautious estimation is that risky alcohol use might affect around 10% of the pilot or ATCO population . The acute and hangover effects of alcohol are detrimental to flight safety. Residual or hangover effects represent a major threat to flight safety, as the consequent degradation of performance may be insidious and may not be recognised by the other crewmembers.

The use of so-called 'party drugs' is presently widespread among the general population and is not limited to specific sub-cultures anymore. Simultaneous use of different substances is popular. Although the prevalence of risky substance use by aircrew and ATCOs is unknown, it is reasonable to assume that aircrew and ATCOs have a similar risk to come into contact with drugs as a European working population aged 18-67 years, of whom the prevalence of using drugs is estimated at around 5%. All drugs mentioned in the present report have acute, prolonged, or residual effects, and/or withdrawal symptoms that are incompatible with flying or ATC duties.

In the present report screening methods for identification of psychoactive substance (mis)use in the initial Class 1 screening as well as the aero-medical examinations for renewal of Class 1 medical license and initial/renewal Class 2 and Class 3 (ATCOs) medical licenses will be discussed and the most suitable methods will be recommended.

It is emphasised that all aeromedical licence examinations of pilots and ATCOs should include physical examination and extensive history taking by the AME in which dedicated questions concerning psychoactive substance use should be included in the interview. In addition, screening methods for identification of psychoactive substance (mis)use are considered important additional tools to support AME/AeMC in their considerations about an applicant's fitness to function in a safety-sensitive aviation job.

Hair analysis appears best suited for initial Class 1 /Class 3 psychoactive substance testing because it can provide a 30-90 days alcohol/ drugs/ medication history of the applicant. For renewal of Class 1, Class 3, and all Class 2 examinations a Urine Drugs Screen (if positive, followed by a confirmation analysis) is suitable to demonstrate the use of opioids, cannabinoids, amphetamines, cocaine, hallucinogens, and sedative hypnotics over a time period covering at approximately 2 to 4 days (for most drugs) before the test is taken. When evidence has to be found for chronic excessive alcohol use, the combination of serum levels of GGT and CDT appears the most suitable method to be used in these examinations. This combination covers excessive alcohol use in the 2-3 weeks prior to the examination. For recent excessive use of alcohol, EtG in urine is suitable to demonstrate excessive alcohol use at least within 24 hours prior to the examination.

Due to its likely deterrence effect, random alcohol and drugs testing of aircrew is considered as a useful additional measure to reduce misuse of psychoactive substances and enhance flight safety.

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ABBREVIATIONS

ACRONYM	DESCRIPTION
ADHD	Attention deficit hyperactivity disorder
AeMC	Aero-medical centre
ALAT	alanine aminotransferase
ALT	alanine aminotransferase
AME	Aviation Medical Examiner
ASAM	American Society of Addiction Medicine
ASAT	aspartate aminotransferase
AsMA	Aerospace Medical Association
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AST	aspartate aminotransferase
ATC	Air Traffic Control
ATCO	Air Traffic Controller Operator
ATS	amphetamine-type stimulants
ATSB	Australian Transport Safety Bureau
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood alcohol level concentration
BEA	French Bureau d'Enquêtes et d'Analyses pour la Sécurité de l'Aviation Civile
BZD	Benzodiazepines
CAGE	Cut, Annoyed, Guilty, Eye questionnaire
CBD	Cannabidiol
CDT	Carbohydrate-deficient transferrin
CNS	Central nervous system

ACRONYM	DESCRIPTION
CRM	Crew resource management
DAST	Drug Abuse Screening Test
DBS	dried blood spots
D&A	Drug and alcohol
DMT	Dimethyltryptamine
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUDIT	Drug Use Disorders Identification Test
DWI	driving-while-intoxicated
EASA	European Union Aviation Safety Agency
EBT	Evidential Breath Test
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMIT	Enzyme Multiple Immunoassay Test
EtG	ethyl-glucuronide
EtS	ethyl-sulfate
FAA	Federal Aviation Administration
FAEE	Fatty Acid Ethyl Esters
FDA	US Food and Drug Administration
GABA	Gamma-aminobutyric acid
GBL	Gamma butyrolactone
GC-MS	gas chromatography-mass spectrometry
GGT	gamma-glutamyl transferase
GHB	Gamma hydroxybutyrate
ICAO	International Civil Aviation Organization
IQ	Intelligence quotient
ISO	International Organization for Standardization

ACRONYM	DESCRIPTION
LSD	Lysergic acid diethylamide
MCV	mean corpuscular volume
MDA	Methylenedioxyamphetamine
MDMA	3,4-methylmethamphetamine
MRO	Medical reviewer officer
NIAAA	National Institute of Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NMDA	N-methyl-D-aspartate
NPS	New psychoactive substances
NPV	Negative predictive value
NTSB	National Transportation Safety Board
N2O	Nitrous oxide
OTC	Over the counter medicine
PEth	Phosphatidylethanol
pH	potential of hydrogen
PPV	Positive predictive value
PTSS	Posttraumatic Stress Syndrome
REM-sleep	Rapid eye movement sleep
ROC	Receiver operating characteristics
SUD	Substance use disorder
TAC	transdermal alcohol concentration
THC	delta9-tetrahydrocannabinol
UDS	Urine drug screen
VSA	Volatile substance abuse
WHO	World Health Organization

ACRONYM	DESCRIPTION
XTC	Ecstasy
3-CMC	Clophedrone
3-MMC	3-Methylmethcathinone
4-FA	4-fluoroamphetamine
4-MMC	Mephedrone
5-HIAA	5-hydroxyindol-3-ylacetic acid
5-HTOL	5-hydroxytryptophol

1. Introduction

The present report provides an overview of those psychoactive substances that have an impact on the ability of pilots and ATCOs to safely perform the privileges of their license. This overview is followed by a review of available methods of screening for use/misuse of psychoactive substances, and their suitability to be used in the medical examinations of pilots and ATCOs.

Based on the data of alcohol use in the working populations, a conservative and cautious estimation would indicate that risky alcohol use might affect around 10% of the pilot or ATCO population with a range of 5-20%. The acute and hangover effects of alcohol are detrimental to flight safety. Residual or hangover effects represent a major threat to flight safety, as the consequent degradation of performance may be insidious and may not (or too late) be recognised by the other crewmembers.

The use of so-called 'party drugs' is presently widespread among the general population and is not limited to specific sub-cultures anymore. Simultaneous use of different substances is popular. Although the prevalence of risky substance use by aircrew and ATCOs is unknown, it is reasonable to assume that aircrew and ATCOs have a similar risk to come into contact with drugs as a European working population. Aircrew and ATC personnel may be at risk for using the most popular psychoactive drugs in the 'party/festival circuit' which are cannabis, ecstasy, cocaine, amphetamine s, and to a lesser extent GHB (gamma-hydroxybutyrate), 'magic mush rooms' (psilocybin), and ketamine. All drugs mentioned in the present report have acute, prolonged, or residual effects, and/or withdrawal symptoms that are incompatible with flying or ATC duties.

In the present report screening methods for identification of psychoactive substance (mis)use in the initial Class 1 screening as well as the aero-medical examinations for renewal of Class 1 medical license and initial/renewal Class 2 and Class 3 (ATCOs) medical licenses will be discussed and the most suitable methods will be recommended.

It is emphasised that all aeromedical certification examinations of pilots and ATCOs should include physical examination and extensive history taking by the AME in which several dedicated questions concerning psychoactive substance use are woven into the interview. In addition, screening methods for identification of psychoactive substance (mis)use are considered important additional tools to support AME/AeMC in their considerations about an applicant's fitness to function in a safety-sensitive aviation job.

Hair analysis appears best suited for initial Class 1 /Class 3 psychoactive substance testing because it can provide a 30-90 days alcohol/ drugs/ medication history of the applicant. For renewal of Class 1, Class 3, and all Class 2 examinations a Urine Drugs Screen (if positive, followed by a confirmation analysis) is suitable to demonstrate the use of opioids, cannabinoids, amphetamines, cocaine, hallucinogens, and sedative hypnotics over a time period covering at approximately 2 to 4 days (for most drugs) before the test is taken. When evidence has to be found for chronic excessive alcohol use, the combination of serum levels of GGT and CDT - using the formula $[0.8\times\ln(GGT)]+[1.3\times\ln(\%CDT)]$ - appears the most suitable method to be used in these examinations. This combination covers excessive alcohol use in the 2-3 weeks prior to the examination. For recent excessive use of alcohol, EtG in urine is suitable to demonstrate excessive alcohol use at least within 24 hours prior to the examination.

2. Background

Following the publication of the French Bureau d'Enquêtes et d'Analyses pour la Sécurité de l'Aviation Civile (BEA) preliminary investigation report on 6 May 2015, the EASA-led Germanwings Task Force on the accident of the Germanwings Flight 9525 examined the findings of the BEA report and assessed the adequacy of the European air safety and security rules. As a result of this work, the European Union published new safety rules on air operations in 2018, including new provisions to better support the mental fitness of air crew. The Regulation includes the following safety measures:

- carrying out a psychological assessment of the flight crew before commencing line flying;
- enabling, facilitating and ensuring access to a flight crew support programme; and
- performing systematic drug and alcohol (D&A) testing of flight and cabin crew upon employment

In the above context and considering the negative impact of psychoactive substances on flight crew and ATCOs, the present report is to provide guidance and recommendations to optimise screening of psychoactive substance use of flight crew and ATCOs. Identification of misuse of psychoactive substances is all the more relevant because in the last decennia the world is witnessing an alarming increase of use of psychoactive substances at all levels of the society (EMCDDA, 2022). Aviation personnel may not differ from the rest of the society in their relationship with psychoactive substances. So, it is appropriate to discuss the individual and aviation safety risks of psychoactive substance use and prevention of these risks.

According to the EASA guidelines the term psychoactive substances means alcohol, opioids, cannabinoids, sedatives and hypnotics, cocaine, other psychostimulants, hallucinogens, and volatile solvents, whereas caffeine and tobacco are excluded https://www.easa.europa.eu/downloads/21688/en).

To understand the mechanisms involved in taking psychoactive substances, it may be useful to know why people take drugs. In general, people take drugs for a few reasons (NIDA, 2020):

To feel good. Drugs can produce intense feelings of pleasure. This initial euphoria is followed by other effects, which differ with the type of drug used. For example, with stimulants such as cocaine, the high is followed by feelings of power, self-confidence, and increased energy. In contrast, the euphoria caused by opioids such as heroin is followed by feelings of relaxation and satisfaction.

To feel better. Some people who suffer from social anxiety, stress, and depression start using drugs to try to feel less anxious. Stress can play a major role in starting and continuing drug use as well as relapse (return to drug use) in patients recovering from addiction.

To do better. Some people feel pressure to improve their focus in school or at work or their abilities in sports. This can play a role in trying or continuing to use drugs, such as prescription stimulants or cocaine.

Curiosity and social pressure. In this respect, teens are particularly at risk because peer pressure can be very strong. Adolescence is a developmental period during which the presence of risk factors, such as peers who use drugs, may lead to substance use.

There is a wealth of evidence in the scientific literature that use of psychoactive drugs and/or alcohol (D&A) can –besides causing many physical health problems- impair cognitive functions, such as Information processing, decision making and problem solving, and may lead to slowing of reaction times, poor coordination, poor concentration, risk taking behaviour or inappropriate action, and mood changes. All these effects may endanger flight safety and apply equally to pilots and air traffic controllers (ATCOs), although their tasks are different. In this report the impact of alcohol and illicit or recreative drugs on the ability of pilots and ATCOs to safely perform their tasks will be described assuming that the psychopharmacological effects of alcohol or risky drugs will be similar for pilots and ATCOs, as both are comparable human beings and need similar cognitive functions to perform their tasks safely.

Definition of commonly used terminology

Problematic use of substances by aviation personnel

The use of one or more psychoactive substances by aviation personnel in a way that:

a) constitutes a direct hazard to the user or endangers the lives, health or welfare of others;

b) and/or causes or worsens an occupational, social, mental or physical problem or disorder.

Substance use disorder (SUD)

According to DSM-5, a substance use disorder (SUD) involves patterns of symptoms caused by using a substance that an individual continues taking despite its negative effects (Hasin et al., 2013). Based on research, DSM-5 points out 11 criteria that can arise from substance misuse. These criteria fall under four basic categories: impaired control, physical dependence, social problems, and risky use:

1. Using more of a substance than intended or using it for longer than you're meant to.
2. Trying to cut down or stop using the substance but being unable to.
3. Experiencing intense cravings or urges to use the substance.
4. Needing more of the substance to get the desired effect — also called tolerance.
5. Developing withdrawal symptoms when not using the substance.
6. Spending more time getting and using drugs and recovering from substance use.
7. Neglecting responsibilities at home, work or school because of substance use.
8. Continuing to use even when it causes relationship problems.
9. Giving up important or desirable social and recreational activities due to substance use.
10. Using substances in risky settings that put you in danger.
11. Continuing to use despite the substance causing problems to your physical and mental health.

The substance use disorder criteria explained in the DSM-5 allow clinicians to determine how severe a substance use disorder has become depending on how many symptoms are present. For example (Hasin et al., 2013):

- One symptom could indicate an individual is at risk.
- Two or three criteria point to a mild substance use disorder.
- Four or five symptoms show someone has a moderate substance use disorder.
- Six or more criteria indicate a severe substance use disorder, which signals an addiction to that substance.

In the case of aircrew and ATCOs, identifying one symptom should already alert the aeromedical examiner of a substance misuse problem that needs further evaluation.

Misuse of alcohol and/or drugs use may be a stand-alone problem, a consequence, cause, or an accompanying symptom of ill mental health (e.g., Kessler et al., 1997; LeardMann et al., 2013). Therefore, identifying a case of problematic alcohol or drugs use is likely to unveil other psychological or psychiatric problems in that case. An inverse association is also possible: cases with psychological or psychiatric problems may be more prone to

alcohol or drugs misuse in which case the AMEs and/or medical assessors could consider investigating with a focused interview and objective testing.

The use/misuse of D&A is one of the few disorders that have the potential to affect the mental health of pilots, for which screening by means of biochemical tests is available. Therefore, the present report will give an overview of those psychoactive substances that have an impact on the ability of pilots and ATCOs to safely perform the privileges of their license followed by a review of available methods of screening for use/misuse of psychoactive substances, and their suitability to be used in the medical examinations of pilots and ATCOs.

3. Overview of psychoactive substances that have an impact on the ability of pilots and ATCOs to safely perform the privileges of their license

3.1 Substance use

3.1.1 Alcohol

3.1.1.1 Effects of alcohol relevant for flight safety

Alcohol is a central nervous system depressant that causes brain activity to slow down. The following acute effects may threaten flight safety are equally applicable for pilots and ATCOs (Dry et al., 2012; Jacob and Wang, 2020):

- Impaired alertness
- Narrowing of attention: focus on one task
- Neglecting alarm signals
- Underestimation of danger
- Opting for risky solutions, risk taking behaviour
- Ignoring normal procedures
- Unawareness of impaired performance
- Impairment of vision
- Impairment of motor coordination
- Euphoria / Aggression / Anger / Withdrawal
- Boosting the effects of fatigue and certain medication
- Nausea, Headache, Flushing
- Disturbed Sleep: Next day fatigue and impaired performance
- Impaired spatial orientation (particularly important for pilots)

Effects are potentiated by hypoxia (pilots) and fatigue (both pilots and ATCOs)

3.1.1.2 Acute effects of alcohol observed using flying tasks

Based on reviews and studies by Modell and Mountz (1990), Billings et al. (1991), Ross et al. (1992), and Cook (1997), Table 1 gives a summary of the piloting tasks for which impairment has been demonstrated at various blood alcohol concentrations (BAC).

Table 1 - Flying Tasks and functions impaired by alcohol (Cook, 1997)

0.01 – 0.03%	Terrain separation
	Aircraft descent
	Performance during angular acceleration +/- dm lighting
0.03 – 0.05%	Progressive impairment of the above
	Tracking radio signals
	Target tracking
	Airport traffic control vectoring
	Flight coordination and configuration
	Traffic observation and avoidance
	Stimulus responses tasks involving use of hand sticks and foot pedals
	Complex coordination/Short term memory/Reaction time
> 0.05%	+ Oculovestibular function

Table 1 shows that the negative effects of alcohol on flying tasks can already be observed at relatively low levels of BAC. Acute ingestion of alcohol is clearly incompatible with the safe performance of flying operations.

3.1.1.3 Alcohol-Residual or Hangover effect and impaired sleep

Hangover or morning-after effects often refer to the physical symptoms after drinking alcohol the night before. These effects are mostly described as general malaise, headache, dizziness, dry mouth, stuffy nose, fatigue, upset stomach, irritability, impaired judgement, and increased sensitivity to bright light. When describing hangover effects on performance, the term “residual effects” is preferred, because after drinking moderate amounts of alcohol, performance can be impaired, even when subjects notice no subjective physical symptoms (Morrow et al., 1991).

Most airlines and/or authorities require pilots and ATCOs to obey an alcohol-free period of 8 to 10 hours before starting their duty. However, a moderate amount of alcohol consumed 8 to 10 hours before starting a duty might still have residual negative effects during the duty period. Residual or morning-after effects are a bigger threat to safety than acute intoxication because the subtle incapacitating impairments of cognitive abilities may go unnoticed to other colleagues or crew members. After drinking the night before, the next morning BAC measured by breathalyzer will be 0.00% while there is still alcohol left in cells of the central nervous system causing subtle degradation of cognitive functions and spatial orientation. Table 2 shows that evidence for impaired cognitive functioning can be found as long as 9 hours after the last alcoholic drink and a night sleep.

Table 2 - Results on residual effects of alcohol on performance. Research was only included when hangover time periods ("measured after") were studied that were considered as relevant for the airline industry. BAC=blood alcohol concentration (0.1%=1‰)

AUTHOR(S)	EVENING BAC	TYPE OF TASKS	EFFECT ON PERFORMANCE	MEASURED AFTER	BAC%
Morrow et al. (1990)	0.1%	Radio communication	impairment	8 hrs	0
Taylor et al. (1994)	0.08%	ATC communication	impairment	8 hrs	0
Simons & Valk (2003)	0.07%	Tracking & vigilance	impairment	9 hrs	0

Residual effects on cognitive functioning are often potentiated by the effects of poor sleep quality and duration which are also caused by even a moderate dose of alcohol consumed in the hours before bedtime.

Alcohol consumed at bedtime may decrease the time required to fall asleep, but is known to disrupt the sleep architecture of the remaining sleep period (Landolt et al., 1996; Vitiello, 1997; Stein and Friedmann, 2005; Pietilä et al., 2018). The result is shortened sleep latency and disturbed and fragmented sleep during the second part of the night. The resulting sleep disruption may lead to daytime fatigue and sleepiness which may have negative effects on daytime performance. The adverse effects of sleep deprivation are increased following alcohol consumption. Subjects administered low doses of alcohol following a night of reduced sleep perform poorly in a driving simulator, even with no alcohol left in the body (Roehrs et al., 1994; Krull et al., 1993). Reduced alertness may potentially increase alcohol's sedating effect in situations such as rotating sleep-wake schedules (e.g., shift work) and rapid travel across multiple time zones (Roehrs et al., 1994). Affected individuals may not recognise the extent of sleep disturbance that occurs under these circumstances, increasing the danger that sleepiness and alcohol consumption will co-occur.

Alcohol and sleep apnea

It is important to consider that evidence is found that alcohol consumption before bedtime may increase the risk of sleep apnoea by 25% (Simou et al., 2018). Alcohol may trigger obstructive sleep apnea (OSA) and/or worsen the severity of OSA, while OSA may worsen the residual effects of alcohol.

Conclusion

We conclude that the acute effects of alcohol, even of BACs as low as 0.1–0.3‰, are detrimental to flight safety. However, cases of pilots flying with measurable BACs will be rare in commercial air transport operations, because of the social control in the cockpit and high professional responsibility standards of most pilots. In contrast, use of alcohol during the evening prior to flight duties appears to be more common among pilots. It is, for instance, anecdotally known that long-haul pilots have a tendency to drink during stopovers when not in their base country. This is often a way to socialise with the crew ("landing drink"), but is sometimes also used to facilitate falling asleep especially in cases of significant time-zone crossing impacting their circadian rhythm.

It has been shown (Table 2) that pilots or ATCOs, who have a BAC of 0.7‰ (0.07%) 8–10 hours prior to their duty start, still may experience adverse effects on performance of flying or controlling tasks due to residual or hangover effects. These pilots or ATCOs will often not be aware of their hangover and will have no measurable BACs at the start of their duty, thus a breathalyzer test will be negative. Residual or hangover effects represent

a major threat to flight safety, as the consequent degradation of performance may be insidious and may not (or too late) be recognised by the other crewmembers or co-workers.

3.1.1.4 Terms related to levels of alcohol use (Reid et al., 1999, NIAAA)

Standard units of alcohol

In literature, amounts of alcohol are commonly noted as standard units or standard drink. However, it should be considered that there is no international consensus on how much pure alcohol is contained in a standard unit among EU Member States. The most commonly used value is that 10 g of pure ethanol is contained in a standard unit, but higher and lower values are used in some countries. E.g. Austria uses 20 g, Czech Republic 16 g, while Iceland uses 8 g. US studies and guidelines use standard units that contain 14 g pure ethanol and UK literature uses 8 g pure ethanol. 10g of ethanol equates to the following drinks: 100 ml of wine (at 13% vol), 100 ml of sparkling wine (at 12% vol), 250 ml beer (at 5% vol), or 30 ml spirit at 40% vol. In this report it is considered that a standard unit contains 10g of pure ethanol, but when US and UK guidelines or study results are cited, the reader should be aware of the country-specific definitions.

Alcohol dependence

Alcohol dependence is characterised by craving, tolerance, a preoccupation with alcohol, and continued drinking in spite of harmful consequences (O'Flynn, 2011).

Heavy drinking

Heavy drinking is defined as a quantity of alcohol consumption that exceeds an established threshold value. The National Institute of Alcohol Abuse and Alcoholism (NIAAA) sets this threshold at more than 14 drinks per week for men (or >4 drinks per occasion); more than 7 drinks per week for women (or >3 drinks per occasion); and more than 7 drinks per week for all adults 65 years and above. Individuals whose drinking exceeds these guidelines are thought to be at increased risk for adverse health events.

Binge Drinking

The NIAAA defines binge drinking as a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 percent (0.8 promille or 0.08 grams of alcohol per deciliter) or higher. For a typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours. People who binge drink are more likely to behave recklessly and are at greater risk of being in an accident (https://www.nhs.uk/live-well/alcohol-advice/).

Hazardous drinking

Hazardous drinking is defined as a quantity or pattern of alcohol consumption that places individuals at risk for adverse health events and is recognized by the World Health Organization (WHO) as a distinct disorder. The quantity or pattern of alcohol consumption that constitutes hazardous drinking is also specified by setting threshold values for an individual's average number of drinks consumed per week or per occasion. For example, in a recent study that examined the efficacy of the Alcohol Use Disorders Identification Test (AUDIT), hazardous drinking was defined as an average consumption of 21 drinks or more per week for men (or ≥7 drinks per occasion at least 3 times a week), and 14 drinks or more per week for women (or ≥5 drinks per occasion at least 3 times a week).

Because the definitions of hazardous and heavy drinking are similar, both terms are used to define this type of drinking disorder.

Harmful drinking

Harmful drinking is defined as alcohol consumption that results in physical or psychological harm. This disorder is defined by criteria which include (1) clear evidence that alcohol is responsible for physical or psychological harm, (2) the nature of the harm is identifiable, (3) alcohol consumption has persisted for at least 1 month or has occurred repeatedly over the previous 12-month period, and (4) the individual does not meet the criteria for alcohol dependence.

Risky drinking

For aircrew and ATCOs all above levels of alcohol use are considered as a major risk to flight safety and, therefore, alcohol use/misuse needs to be prevented through education and safety promotion, as well as early detection and management of signs of consumption and conditions that may lead to a higher risk of misuse. For aircrew and ATCOs, as for all safety relevant positions in aviation environment, the terms heavy drinking, binge drinking, hazardous drinking, and harmful drinking are all considered as risky drinking. This also applies to drinking of alcohol quantities that lead to residual or hangover effects on professional task performance.

3.1.1.5 Prevalence of harmful or risky alcohol use by aircrew and ATCOs

While detailed data of alcohol consumption of the general European population are available (Eurostat, 2021), reliable data on the prevalence of (risky) alcohol use representative for the active aircrew population are very scarce, while representative data for ATCOs are practically non-existing.

All methods of studies to gather such data have their limitations in that respect. Random breath alcohol testing only detects a small sample of pilots or ATCOs who have measurable blood alcohol levels at the time of testing and misses individuals with risky drinking causing a hangover, a most important group from the flight safety perspective. The yield of random testing on alcohol is very low. The FAA 2019 MIS random alcohol testing data show that in a total of 60,375 random tests 99.6% were negative. In 2020, the random alcohol test violation rate for aviation personnel was 0.148% (U.S. DOT, 2021). It should be considered that random testing is nor meant nor suited to provide prevalence data representative for a professional population, but is considered useful and is mandated to emphasise the deterrence aspect of drug and alcohol programs.

Results of toxicological studies on alcohol levels in fatally injured pilots, mainly performed in the US, are difficult to extrapolate to all pilots because of selection bias. Canfield et al. (2012) extracted data from the FAA toxicology database for all pilots who died from 2004 to 2008 in aviation accidents. Alcohol was identified in 7% of the population tested. No airline transport pilot (flying CFR Part 121) was found to be flying in violation of FAA alcohol regulations. Although prevalence of ethanol and drugs has been evaluated in fatally injured aviators, such evaluation has not been performed in active pilots who were not involved in accidents.

There are many published and unpublished accounts of fatal aviation accidents in which alcohol has been a contributing or major causative factor. The majority of these accidents concerned general and private aviation, but several well-documented cases have also occurred in commercial airline operations (Kraus and LI, 2006; Botch and Johnson, 2009; Mitchell and Lillywhite, 2013). It should be emphasised that many fatally injured pilots have not been examined on alcohol levels, due to scarcity of post-mortem tissue, putrefaction of tissue (produces alcohol), or omission of the post-mortem examination.

Questionnaire Surveys

In questionnaire surveys there is minimal selection bias, but respondents tend to significantly underestimate the quantity of alcohol they consume and interpretation of the results depends on the response rate and definitions of risky, harmful, or hazardous alcohol use.

An unpublished IFALPA Occupational Health Survey (James & Green, 1990) showed that 83.1% of the responding Dutch pilots uses alcohol on a regular basis (mean quantity: 11.5 units per week) and that 8.4% judges to drink too much according to their own standards (standards not specified). Mean alcohol consumption in this last group was 23.6 units per week). The response rate was not known, but was presumably quite low.

In a questionnaire survey among Dutch short-haul charter pilots, 15.6% of the respondents used more than 14 glasses alcoholic beverage per week, with extremes up to 40 drinks/week (response rate 53%; Simons et al., 1999). More than 14 drinks/week is considered as 'drinking at risk' by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). On the day before a flight, 14.7% of the respondents "almost always" used alcohol. During stopovers, 12% used alcohol in the pre-flight night and 6% admitted experiencing adverse effects of night-before alcohol intake on the day of the flight. This last percentage is a reason for concern and indicates harmful alcohol use.

Attitudes of Aircrew towards use of alcohol

The mandatory time period between the last alcoholic drink and reporting for duty ("bottle-to-throttle time") as required according to the provisions of AMC1 CAT.GEN.MPA.100(c)(1) Crew responsibilities on Alcohol consumption, the minimum requirements are that "no alcohol should be consumed less than 8 hours prior to the specified reporting time for a flight duty period or the commencement of standby" (although some operators require longer intervals). It was found that pilots most at risk of breaching these regulations are those who tend to have higher general weekly consumption of alcohol (Maxwell & Harris, 1999). This conclusion is supported by the results of the questionnaire survey of Simons et al. (1999) among Dutch short-haul charter pilots in which a significant inverse relationship ($r=-0.68$; $p<0.001$) was found between the amount of alcohol a pilot is used to consume and the bottle-to-throttle time considered to be safe in the opinion of that pilot before reporting for the next flight. In other words, the more pilots are used to drink, the shorter the bottle to throttle periods they considered to be safe. When comparing the group of moderate drinkers (consumption <14 glasses per week) with the group of "heavy" drinkers (>14 glasses/week) there appears to be consensus on the bottle-to-throttle time considered to be safe after drinking one, two, or three glasses of alcohol (i.e. 8 – 10 hours). After having four or more drinks, moderately drinking pilots think they need a longer recovery period to safely start their flying duties than "heavy" drinking pilots. When drinking >6 glasses the moderate drinkers think they need 24 hours to recover, while the "heavy" drinkers think they need only 16 hours to fully recover. These results illustrate the common public knowledge, that heavy drinkers consider themselves to be more resistant to the debilitating effects of alcohol than light drinkers or teetotallers.

The available data of random, toxicological, and questionnaire survey are not suited to determine the importance of identifying risky alcohol use of pilots and ATCOs by AMEs. For a realistic estimation it would be reasonable to assume that the percentage of risky drinkers in highly skilled aviation personnel approximates the percentage found in higher educated employees. In that context it is useful to consider that 1) approximately 9% of total workforce in the USA struggled with a substance or alcohol use disorder in the past 12 months (National Safety Council, 2021); 2) in the Netherlands 6.6% of employed population is a heavy drinker and 15% of the working population are risky drinkers because their drinking behaviour causes problems on the job, they regret their use of alcohol, or have had colleagues recommending them to drink less (Lifestyle Monitor, 2018). National estimates in Europe indicate that between 5 % and 20 % of workers are either dependent on alcohol or at risk of becoming so (EMCDDA, 2022-a). National prevalences show significant differences between states (EMCDDA, 2022-a).

3.1.1.6 Conclusions – Relevance for the aviation workplace

Based on the data of alcohol use in the European working populations, a conservative and cautious estimation would indicate that risky alcohol use might affect around 10% of the pilot or ATCO population with a range of 5-20%. Although the true prevalence is difficult to define, this estimated prevalence clearly indicates the need for timely identification of alcohol problems in pilots and ATCOs in order to safeguard flight safety. Although the physical and cognitive effects of alcohol will be similar for pilots and ATCOs, their prevalence of risky alcohol use might differ because both groups may on average have different ways of living and/or lifestyle. It applies, however, to both groups that the acute, residual, and long-term effects of alcohol misuse are incompatible with safe performance of aviation duties.

3.1.2 Psychoactive drugs

3.1.2.1 Introduction

According to the EASA guidelines, psychoactive substances means alcohol, opioids, cannabinoids, sedatives and hypnotics, cocaine, other psychostimulants, hallucinogens, and volatile solvents, whereas caffeine and tobacco are excluded (https://www.easa.europa.eu/downloads/21688/en .

The term 'recreational drugs' refers to pharmacological agents taken for personal pleasure, in contrast to medical drugs taken for the treatment of disease. Chief examples of this class are alcohol and illicit drugs. The latter term is also commonly known as 'psychotropic drugs', 'psychoactive substances'.

Illicit drugs are Schedule I drugs as defined by the US Drug Enforcement Administration. These drugs, by definition, have no accepted medical use and a high potential for abuse. Their use can lead to psychological or physical dependence. Examples include marijuana, heroin, and ecstasy. In the U.S. cocaine and amphetamine are Schedule II drugs because they are sometimes used for medical indications. However, they are mainly used for non-medical purposes (recreational) and therefore these drugs are also considered as illicit. As is the case with alcohol, most aircrew or ATCOs will not use psychoactive drugs prior to, or during their duties, because they have a professional attitude and responsibility for safety. However, they may consider use of these drugs the day or night before a duty period to be harmless, while psychoactive drugs may have residual or prolonged effects on safety-sensitive performance. Should a captain allow a first officer to smoke cannabis at the bar of a stop-over hotel? This real-life example illustrates some aspects of the problem: are residual effects to be expected during the flight the next day? In this case, further cannabis use was forbidden, leaving the first officer with the idea that he was punished for a harmless act.

The use of so-called 'party drugs' is presently widespread among the general population, and therefore is not limited to specific sub-cultures anymore. Simultaneous use of different substances is popular. Popular combinations are alcohol with cannabis, cocaine, or MDMA (ecstasy), and cannabis with ecstasy. This often leads to potentiation: aggressive behaviour after alcohol mixed with cocaine is notorious. It can be assumed that behaviour of aircrew or ATCOs concerning use of psychoactive substances at festivals or parties may not be notably different from comparable social classes in the general population. Based on the growing popularity of recreational drugs (i.e. cocaine and ecstasy) in social classes comparable with aircrew, recreational drug use in the aviation workplace is considered a growing cause for concern. Moreover, because illicit drug use is popular among high school students (EMCDDA, 2022), younger aircrew may have become acquainted (or even addicted) with the use of drugs in their youth and may consider drugs as harmless and normal 'additives' to their social life. The most commonly used drugs in Irish colleges and universities are cannabis (52%), cocaine (25%), ecstasy (23%), ketamine (16%), magic mushrooms (12%), amphetamines (9%), and new psychoactive substances (8%) (Ralph Riegel, 2022). Similar to the European working population, aircrew and ATC personnel may come in contact with the most popular psychoactive drugs in the 'party and festival circuit', viz. cannabis, ecstasy, cocaine, amphetamine s, and to a lesser extent GHB (gamma-hydroxybutyrate), 'mag ic mush rooms'

(psilocybin), and ketamine. All drugs mentioned have acute, prolonged, or residual effects, and or withdrawal symptom s that are incompatible with flying or ATC duties.

Psychedelic drugs as adjunct to psychotherapy

Psychedelic drugs have re-emerged as a promising adjunct to psychotherapy for a variety of mental health indications. Firstly, recent phase 3 clinical studies indicate 3,4-methylenedioxymethamphetamine (MDMA) is both efficacious and well tolerated in the treatment of post-traumatic stress disorder. Psilocybin—naturally found in mushrooms—appears in phase 2 studies to be efficacious in treating depression. The US Food and Drug Administration (FDA) has designated both as breakthrough therapies, fast-tracking them for approval. Secondly, commercial interest has surged, with dozens of companies investing in psychedelic drug development in what is predicted to be a multibillion-dollar market. And thirdly, if and when psychedelics are approved by the FDA, they will almost certainly be used not just for their approved indication(s) but for off-label ones as well. The influence of underground and spiritual healers may also prompt off-label or alternative uses within the medical context (Wexler & Sisti, 2022). Due to these developments, it would be possible that aviation personnel come in touch with use of psychedelic substances via spiritual healers or spiritual séances.

3.1.2.2 General effects of psychoactive drug use

The ICAO manual on prevention of problematic use of substances in the aviation workplace (ICAO, 1995) provides a general overview of effects of various psychoactive substances. The patterns and consequences of use of psychoactive substances are different from one individual to another. Variables, including the choice of substance, frequency of use and method of ingestion will determine not only the immediate effects of the substance, but also whether long-term effects will occur and what these effects will be.

The primary effects of psychoactive substances are pharmacological and psychological effects caused by introduction of the substance into the body. For example, use of amphetamines and cocaine can result in marked euphoria and a sense of enhanced physical and mental capabilities. Cannabinoids produce feelings of relaxation, while lysergic acid diethylamide (LSD) and psylocybin (magic mushrooms) can cause hallucinations and gross distortions of perception. Together with the psychological effects, most psychoactive substances may have adverse effects on cardiovascular, respiratory, gastro-intestinal, and metabolic systems. An association of illicit drug use and sudden cardiac death is described (D'Silva, 2022).

Most described effects are acute effects, whereas knowledge on the residual or long-term effects is of particular concern in the context of aviation.

The secondary effects of psychoactive substance use are associated with dependence and withdrawal. Dependence can be psychological, physiological, or both, and involves a compulsion to use the substance. Withdrawal effects may occur when an individual ceases to use a psychoactive substance. Initially, the user may focus on the memories of pleasant feelings caused by the substance used. Subsequently, this progresses to adverse symptoms such as weakness, anxiety, depression, and serious physiological symptoms. The combined effects of withdrawal are frequently sufficient to lead to re-initiation of the substance use. The problem can be exacerbated by a development of tolerance to the substance, which requires the individual to use progressively larger doses to achieve the desired primary effects.

Altered cognitive function can be viewed as a hallmark feature of substance use disorders, with reliably documented alterations in the well-known "executive" domains of attention, inhibition/regulation, working memory, and decision-making (Ramey and Regier, 2019). This has been documented, generalizable across multiple cognitive domains and substance types (Goldstein, 2022).

It is emphasized that simultaneous use of multiple substances has frequently been observed among recreational drug users in bars, clubs, discotheques, and at parties. Popular combinations are alcohol with cannabis, cocaine, or ecstasy, and cannabis with ecstasy. Effects of these combinations may differ from the

effects of the single components, often leading to potentiation (e.g. aggressive behaviour after alcohol mixed with cocaine is notorious).

In the present review only the most popular and frequently used psychoactive substances belonging to the categories of cannabinoids, sedatives and hypnotics, cocaine and other psychostimulants, opioids, hallucinogens, and volatile solvents will be discussed. There are thousands of natural and synthetic psychoactive chemicals currently available in a wide variety of herbal, medicinal, or illicit compounds. Examples of synthetic psychoactive chemicals are the so-called new psychoactive substances (NPS) of which the numbers of newly developed substances show a daily increase. NPS are defined as novel substances which are not controlled by the United Nations' 1961 Narcotic Drugs or the 1971 Psychotropic Substances Conventions. Most NPS are chemical derivatives of classic psychoactive substances and most frequently concern psychostimulants. NPS are often made to bypass national laws, because the name of the newly designed drug is not mentioned in the illicit substances law. An example of NPS is 3-MMC (3-Methylmethcathinone) which is closely related in structure to the in 2012 banned NPS mephedrone (4-MMC). After 3-MMC was banned in October 2021, its successor 3-CMC (clophedrone) was online marketed as of 1 November 2021. The effects and adverse effects of 3-MMC, 4-MMC, and 3-CMC are considered to be more or less similar to those of MDMA (ecstasy) and cocaine, although details are unknown. Some fatal intoxications have been reported although only a few involved 3-MMC only. Use of NPS is often not widespread and limited to regional centres.

The individual and safety risks of less frequently used synthetic psychoactive chemicals these NPS will not be discussed separately because the risks that will be discussed for the above-mentioned categories also stand for use of these NPS that are often used on a rather limited scale.

3.1.2.3 Prevalence in the general population

Results from the overall assessment of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2022) show that drug availability and use remain at high levels across the European Union, although considerable differences exist between countries (table 3). Approximately 83.4 million or 29 % of adults (aged 15–64) in the European Union are estimated to have ever used an illicit drug, with more males (50.5 million) than females (33.0 million) reporting use. Cannabis remains the most widely consumed substance, with over 22 million European adults reporting its use in the last year. Stimulants are the second most commonly reported category. It is estimated that in 2020 3.5 million adults consumed cocaine, 2.6 million MDMA (Ecstasy, XTC), and 2 million amphetamines. Around 1 million Europeans used heroin or another illicit opioid in 2020 (see table 3).

It is important to note that most of those with drug problems will be using a range of substances. EMCDDA is seeing considerably more complexity in drug consumption patterns, with medicinal products, non-controlled new psychoactive substances and substances such as ketamine and GBL/GHB now associated with drug problems in some countries or among some groups. This complexity is reflected in an increasing recognition that drug use is linked with, or complicates how we respond to, a wide range of today's most pressing health and social issues, such as mental health problems and self-harm (EMCDDA, 2022).

Table 3 - Estimates of use of the four most popular drugs in the European Union by adults 15-64 years. Differences between national estimates of drugs use in last year of survey are shown in the third data column (Countries indicated by ISO Country Codes; EMCDDA, 2022)

DRUG	EU LAST YEAR USE (# MILLION)	EU LIFETIME USE (# MILLION)	NATIONAL ESTIMATES OF USE IN LAST YEAR SURVEY 2015 - 2020 IN 26 COUNTRIES LOWEST – HIGHEST
Cannabis	7.7% (22.2)	27.3% (78.6)	3.4% (HU) – 22.9% (FR)
Cocaine	1.2% (3.5)	5.0% (14.4)	0.2% (SV) – 5.6% (UK)
MDMA (Ecstasy)	0.9% (2.6)	3.7% (10.6)	0.2% (PT) – 7.7% (NL)
Amphetamines	0.7% (2.0)	3.1% (8.9)	0.0% (PT) – 4.2% (NL)

Of the working population aged 18-67 years in the Netherlands 7.2% used cannabis, 4% ecstasy (XTC), 1,5% amphetamines, 1.9% cocaine, and 2,5% laughing gas (N2O) and 5.9% of the Dutch working population reported sick due to use of drugs in the last 12 months (Lifestyle monitor, 2018).

3.1.2.4 Prevalence of drugs use among aircrew and ATCOs

Caused by similar problems as mentioned for the prevalence of alcohol use, there are no data concerning use of psychoactive recreational drugs by aircrew or ATCOs that enable determination of the magnitude of the problem in these groups. The yield of random drugs testing is low. In U.S. aviation personnel the random drug test positive rate was 0.771% (U.S. DOT, 2021). As already mentioned in the case of alcohol misuse, random testing is nor meant nor suited to provide prevalence data representative for a professional population, but it is considered useful and is mandated for its deterrent effects on aircrew and ATCOs.

Toxicological test results of fatally injured pilots may be useful to study associations of performance impairing drugs with safety, but are difficult to extrapolate to all pilots because of selection bias. Obviously, such data do not exist for ATCOs. Figure 1 shows toxicology test results of 952 pilots (1 pilot (<1%) was flying under Part 121, 28 pilots (3%) were flying under Part 135, and 924 pilots (97%) were conducting GA operations) who were fatally injured in the United States between 2013 and 2017 (NTSB, 2020). Figure X shows that cases in which illicit drugs were found have gradually increased over the years to 5% in the fatally crashed pilots. Cannabis was the drug that was most frequently found. During the 5 years ending in 2017, 28% fatally injured pilots tested positive for at least one potentially impairing drug, 15% pilots tested positive for at least one drug indicating a potentially impairing condition, and 10% pilots' test results indicated evidence of use of at least one controlled substance.

It is noteworthy that sedating antihistamines continued to be the most common category of potentially impairing drugs found in pilots who died during the report period, with 11.9% testing positive for at least one drug in this category, which increased from 9.9% during the preceding 5 years. Sedating pain relievers, a

category that includes opioids, was the second most common category of potentially impairing drugs at 5.3%. Of the 50 pilots who tested positive for sedating pain relievers, 46 were positive for at least one opioid (NTSB, 2020).

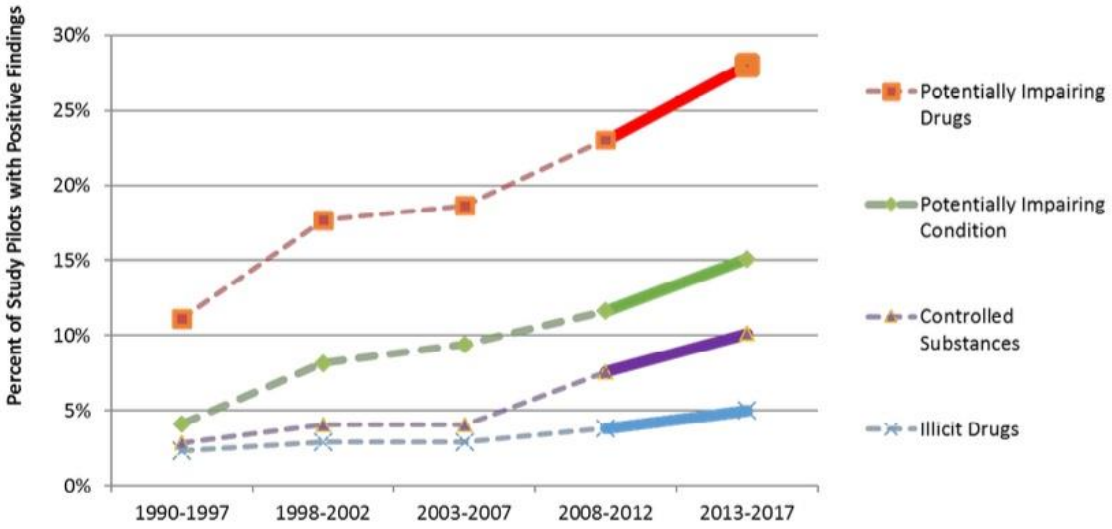


Figure 1 - Toxicology test results of 952 pilots who were fatally injured in the United States between 2013 and 2017 (NTSB, 2020)

Questionnaire surveys will likely give unreliable prevalence data because 1) aircrew and ATCOs are likely to hide their drugs use because it may have unwanted consequences for their job; 2) there is a widespread public stigma on substance misuse and mental health problems; 3) pilots and ATCOs may be unaware about the impact of their substance use and mental health problems on professional performance and health; 4) the experience with surveys on alcohol use by aircrew indicates that low response rates are to be expected.

It can be concluded that the prevalence of risky substance use by aircrew and ATCOs is unknown due to a lack of representative data. For an estimation of the prevalence it would be reasonable to assume that the percentage of risky psychoactive substance users in highly skilled aviation personnel approximates the percentage found in educated employees. In that context it is useful to consider that approximately 5% of the working population aged 18-67 years in the Netherlands used recreational drugs in the month before the survey was held. Cannabis was the most frequently used drug followed by ecstasy (XTC), amphetamines, and cocaine (Lifestyle Monitor 2018). This picture might well be representative for Western-Europe, but it should be considered that the prevalence of drugs use by employees might considerably differ between countries within Europe due to cultural differences and local availability (table 3; EMCDDA, 2022).

It is reasonable to assume that aircrew and ATCOs have a similar prevalence of drug use as the European working population aged 18-67 years, whose lifetime risk is estimated at around 5%.. Because differences between countries are known to be significant, it is recommended to take national and regional patterns in psychoactive drug use into account when NAAs have to determine the scope of their screening requirements.

3.1.3 Opioids

All opioids, such as buprenorphine, codeine, dextropropoxyphene, dihydrocodeine, fentanyl, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, tapentadol, tilidine, and tramadol, are chemically related and interact with opioid receptors on nerve cells in the body and brain. Heroin is a highly addictive painkiller synthesized from morphine, which comes from the seeds of the poppy plant. It is a potent opiate with a very intense effect on the brain's reward system and therefore highly addictive. Although heroin

use in the general population is rather low, the numbers of people starting to use heroin have been steadily rising since 2007. This may be due in part to a shift from misuse of prescription pain relievers to heroin as a readily available, cheaper alternative (NIDA, 2018).

Addiction to opioid pain relievers, such as oxycodone, hydrocodone, codeine, morphine, fentanyl, and tramadol is far more prevalent than addiction to heroin. These pain relievers are often prescribed by a doctor to treat pain, but because they produce euphoria in addition to pain relief, they can be misused and taken in a larger quantity than prescribed, or taken without a doctor's prescription. Even as prescribed by a doctor, regular use can lead to dependence and, when misused, opioid painkillers can lead to addiction, overdose incidents, and deaths. The start of an opioid addiction is often in a hospital where opioids are prescribed as painkiller. After successful treatment of opioid addiction individuals are prone to a relapse of the addiction.

Common side effects of opioid use include sedation, sleepiness, dizziness, nausea, vomiting, constipation, physical dependence, respiratory depression, and tolerance. Opioids are notorious for causing addiction. Addiction is often treated with buprenorphine or methadone. These are also opioids and may have adverse effects that are incompatible with aviation safety. Methadone- and buprenorphine-treated groups showed significant impairments in visuospatial memory tasks but not the abstinent groups. Impairments in visuospatial memory strongly correlated with higher mood and anxiety symptom severity scores (Tolomeo et al. 2019).

In Europe the most frequently prescribed opioid painkillers are oxycodone, tramadol, fentanyl, and morphine. Fentanyl is a synthetic painkiller that is up to 100 times as potent as morphine. When used in conjunction with other painkillers such as heroin, fentanyl can quickly lead to overdose and other dangerous side effects.

Individuals with opioid dependence have cognitive deficits during their abuse period in attention, working memory, episodic memory, and executive function. After protracted abstinence, consistent cognitive deficit has been found in complex working memory, executive function, and fluid intelligence (Rapeli et al., 2006). The pattern of neuropsychological performance among patients with opioid use disorders appears to reflect mild generalized cognitive dysfunction, with a large effect in complex psychomotor abilities (Wollman et al., 2019).

Withdrawal from opiates can occur any time long-term use is stopped or cut back. Symptoms of withdrawal include: agitation, anxiety, muscle aches, increased tearing, insomnia, runny nose, sweating, yawning, abdominal cramping, diarrhoea, dilated pupils, goose bumps, nausea, and vomiting. Symptoms usually start within 12 hours of last heroin usage and within 30 hours of last methadone exposure.

Relevance for the aviation workplace

Opioid painkillers are quite frequently administered in hospitals to treat severe pain and often some opioid medication will be continued in the first days or weeks out of the hospital. Thus, opioids might also occasionally be prescribed as painkillers for aircrew or ATCOs. Because they produce euphoria, some individuals will continue to use opioids even when they have no pain. Regular use may lead to dependence and addiction. The adverse effects and cognitive dysfunction caused by use of opioids as well as the withdrawal symptoms preclude safe functioning as pilot or ATCO.

3.1.4 Hallucinogens

3.1.4.1 Cannabinoids: Cannabis or Marijuana

Cannabis is the most popular drug in Europe with 22.2 million users in 2020 (EMCDDA, 2022). Cannabinoids have a long history of recreational and medical use. The primary active constituent of the hemp plant (Cannabis Sativa) is delta9-tetrahydrocannabinol (delta9-THC, in brief "THC"). Commonly used names for this class of drugs are cannabis and marijuana. Dronabinol is chemically synthesized delta-9-tetrahydrocannabinol (THC). It is the sole pharmaceutical source of THC and has psychoactive effects that may present safety issues.

Psychoactive cannabinoids increase the activity of dopaminergic neurons in the human brain. Since these dopaminergic circuits are known to play a pivotal role in mediating the reinforcing (rewarding) effects of most drugs, the enhanced dopaminergic drive elicited by cannabinoids is thought to underlie the reinforcing and abuse properties of marijuana (Ameri, 1999). Another ingredient of the hemp plant is cannabidiol (CBD) which –in contrast to delta9-THC- has no psychoactive effects (Bhattacharyaet al., 2010). CBD is increasingly used to treat a broad range of symptoms and ailments, such as chronic pains, sleep problems, Alzheimer's disease, arthritis, cardiovascular disease, and epilepsy with variable success according to anecdotal evidence. However, it is important to note that many CBD products may contain some level of THC. Federal law requires that hemp-derived CBD products contain less than 0.3% of THC. Research has found that 70% of CBD products contain significantly more THC than their labels suggest. Whereas pure CBD products are not addictive and have no psychoactive effects, impure bogus products might have a potential for THC-like effects.

Cannabis is commonly smoked and in this way is rapidly absorbed through the lungs. With the less common practice of gastro-intestinal ingestion (via “space cake”), absorption is slower and effects are less predictable. The physiological effects of the drug become apparent shortly after absorption, persisting for four to six hours unless administration is repeated.

THC is excreted in urine. The elimination half-life of THC in naive users has been established at 18.2 ±5 h (Johansson et al., 1990). In infrequent users, THC has been detected in urinary specimens up to 12 days after the last dose.

Psychological and physiological effects of psychoactive cannabinoids include euphoria, enhancement of sensory perception, tachycardia, difficulties in concentration, cognitive impairment, and memory impairment. Current research provides evidence for mild to moderate acute cannabis effects on episodic and working memory, processing speed, and executive functions. Mild residual impairing effects were also observed in these same cognitive domains, suggesting that adverse effects following cannabis intoxication persist at least days or weeks following cannabis abstinence (Bourque and Potvin, 2021). Cannabis use has been shown to impair cognitive functions on a number of levels—from basic motor coordination to more complex executive function tasks, such as the ability to plan, organize, solve problems, make decisions, remember, and control emotions and behaviour (Crean et al., 2011).

As the potency of cannabis products has increased, together with regular and frequent cannabis use, cannabis use disorders and psychiatric comorbidities have also risen in Europe (EMCDDA, 2022).

There is discussion about the effect of marijuana/cannabis on intelligence. Systematic reviews and meta-analyses of cross-sectional data assessing the effect of cannabis on intelligence show inconsistent results. Assessing marijuana's impact on intelligence quotient (IQ) has been hampered by a lack of evaluation of subjects before they begin to use this substance (Power et al., 2021).

Cannabis use in adolescence is consistently associated with poorer mental health outcomes including increased risk of mood disorders, self-harm and suicidality (Gobbi et al., 2019; Twomey, 2017). There is strong evidence demonstrating an association between cannabis and psychotic disorders, particularly frequent use of high tetrahydrocannabinol potency cannabis (Di Forti et al., 2019).

Relevance for the aviation workplace

Experience with cannabis starts often at high school, and therefore younger aircrew may consider its use as a normal leisure activity. As mentioned above, cannabis use has been shown to impair cognitive functions on a number of levels and this may have harmful implications for car and train driving, aeroplane piloting, and highly-safety sensitive performance such as air traffic management (ATSB, 2004). The cognitive deficiencies of cannabinoids appear to be persistent after withdrawal (Ameri 1999).

It is concluded that acute effects and prolonged use are incompatible with flight safety. Longer term use may affect mental health. Based on the elimination half-life of THC, flight safety can be assumed to be at risk up to

48 hours after a single dose of THC containing substances, but it should be considered that there is large variation in the quantities and ways of administration (smoking, ingestion) of cannabis that are used and it is therefore often difficult to estimate how much has in fact being used. Withdrawal symptoms may jeopardize flight safety for a longer time period depending on occasional or chronic use withdrawal symptoms can be manifest for several days to weeks. It should be considered that large differences exist in the duration of withdrawal symptoms.

Some countries, such as Canada, where cannabis is legalized have regulated the use of cannabis by flight crews and ATCOs with a new policy prohibiting flight crews and flight controllers from consuming cannabis for at least 28 days before being on duty (https://tc.canada.ca/en/aviation/general-operating-flight-rules/better-pilot-decision-making/cannabis-legalization).

3.1.4.2 Psilocybin ("magic mushrooms") and Lysergic acid diethylamide (LSD)

The hallucinogenic agents psilocybin and LSD are structurally related and have similar physiological, pharmacological, and clinical effects. Psilocybin is derived from a common mushroom species, whereas lysergic acid diethylamide, which was also originally extracted from a fungus, is now usually manufactured synthetically. Many young Europeans are experimenting with hallucinogenic ("magic") mushrooms. The phenomenon may be driven by a broader consumer trend for young people to actively seek out intense experiences and 'natural highs' and by an increasing interest in organic products. Surveys in 12 EU Member States indicate that, among people aged 15 to 24 years old, ever in lifetime use of hallucinogenic mushrooms ranges from less than 1% to 8%. Drug surveys conducted in club settings show that prevalence of illegal drug use is consistently higher than prevalence among the general or school populations and use of hallucinogenic mushrooms is more common among young people who have used other illegal drugs than among young people who have not (https://www.emcdda.europa.eu/publications/thematic-papers/mushrooms_en).

Lysergide (LSD) is a semi-synthetic hallucinogen and is one of the most potent drugs known. Recreational use became popular between 1960 and 1980 but is now less common.

Both psylocybin and LSD are indole derivatives and chemically resemble serotonin. They act as agonist, partial agonist, and antagonist at various serotonin, dopaminergic, and adrenergic receptors in the human brain (e.g., Fuentes et al., 2020). Both drugs are usually ingested orally, with LSD being 100 times more potent than psilocybin. Following ingestion, the effects on the central nervous system begin within 15 to 45 minutes and usually last for 4 to 6 hours. LSD is metabolized by the liver and has a plasma half-life of 100 minutes. The elimination half-life of psilocybin is unclear, as there are no controlled studies available.

These psychoactive substances are known for their mind-altering properties, typically causing feelings of euphoria, anxiety, paranoia, as well as visual and auditory hallucinations. Physical symptoms that correspond to general sympathetic stimulus include dilated pupils, tachycardia, hypertension, and hyperreflexia (Abraham & Aldridge 1993). Evidence supports the association of LSD use with panic reactions, prolonged schizoaffective psychoses and post-hallucinogen perceptual disorder, the latter being present continually for as long as 5 years (Abraham & Aldridge 1993).

LSD and psilocybin are considered as potential therapeutic agents in psychiatry; the evidence to date is strongest for the use of LSD in the treatment of alcoholism, but studies are underway to assess their efficacy in the treatment of anxiety and depression (Fuentes et al., 2020). Therapeutic use of hallucinogens like LSD and psilocybin should always be under psychiatric expert control and supervision because the administration of classical hallucinogens carries some risks. One of them is the so-called "bad trip" or "challenging experience", described as an acute state of anxiety, dysphoria and confusion, which can lead to adverse effects causing panic reactions ('bad trips') may be sufficiently severe to require medical support. In recreative users it was observed that patients usually recover within a few hours but occasionally hallucinations last up to 48 hours and psychotic states may last for 3–4 days. Another possible risk is the exacerbation of psychotic disorders or the generation of prolonged psychotic reactions, which could be related to the subject's previous predisposition.

Relevance for the aviation workplace

Popularity of LSD as recreative drug is considered to decline and is currently not commonly used. The popularity of “magic mushrooms” is increasing. Although “magic mushrooms” is a potential candidate drug for use by aircrew and ATCOs, its use seems more frequent among groups experimenting with organic hallucinogenic products. Acute effects and prolonged use are incompatible with flight safety. After cessation of LSD use, the post-hallucinogen perceptual disorder precludes flying duties for a longer time. Data on prolonged effects or withdrawal symptoms of “magic mushrooms” are lacking.

3.1.4.3 Ketamine

Ketamine (ketamine hydrochloride or Ketalar) has hallucinogenic and neuro-depressive properties. It is an anaesthetic that has some hallucinogenic effects. Ketamine is an intravenous anaesthetic that has been approved for both human and animal use in medical settings since 1970; about 90% of the ketamine legally sold is intended for veterinary use. Since 1970 it was the most widely used battlefield anaesthetic. The drug acts as a N-methyl-D-aspartate (NMDA) receptor antagonist in the brain. Ketamine is available in tablet, powder, and liquid form. In powder form, the drug can be snorted or sprinkled on tobacco or marijuana and smoked; in liquid form it can be injected.

Ketamine is known by the street names are: K, Special K, K2, Vitamin K, Super K, Super C, Lady K, Ket, Kit Kat, Ketaset, Ketaject, Jet, Super Acid, Green, Purple, Mauve, Super Acid, Special LA Coke, Cat Tranquilizers, Cat Valium.

Ketamine is often used in combination with MDMA (ecstasy), amphetamine, methamphetamine, or cocaine. Ketamine use can be fatal in combination with alcohol intoxication.

When properly medically administered, a therapeutic dose of ketamine will leave a patient feeling calm and relaxed. During their state of sedation patients will also experience immobility, amnesia, and relief from pain. The S(+) enantiomer of ketamine, esketamine is approved for treatment-resistant depression and for patients with major depression and acute suicidal ideation or behaviour.

Ketamine is a dissociative drug that distorts perceptions of sight and sound, produces hallucinations, and provides the user with feelings of detachment from both the environment and self. Due to these effects, the recreational use of ketamine has gained popularity as a “club drug” that is used at dance clubs and raves. The liquid drug is usually injected or mixed in drinks, or it is heated and provided as a powder that can be snorted or smoked.

Mental effects of ketamine include hallucinations, dreamlike states, feelings of invulnerability, anxiety, agitation and aggressive behaviour, amnesia, confusion, reduced awareness of environment, disorientation, out of body experiences, and dissociation (Rosenbaum et al., 2021). Individuals who take a high enough dose of ketamine are at risk of entering a “K-hole,” which is characterised by intense visual and auditory hallucinations coupled with a frightening detachment from reality (Muetzelfeldt et al., 2008).

Physical effects of ketamine include sedation, double vision, involuntary eye movements, slurred speech, seizures, tachycardia, increased blood pressure, slowed breathing, lack of coordination, muscle rigidity and bronchodilation. At high doses, ketamine can cause delirium, amnesia, impaired motor function, respiratory distress, paralysis, increased cardiac output (leading to risk of heart failure or stroke), coma, and death (Rosenbaum et al., 2021).

The onset of ketamine effects depends on how the drug is administered. If the drug is smoked, it takes effects immediately. Snorting produces effects in 5-10 minutes, and oral administration will produce effects in 15-20 minutes. The effects will last 30-45 minutes after injection, 45-60 minutes after snorting, and 1-2 hours after oral ingestion, but judgement, senses and coordination may be affected for up to 24 hours or longer. Three

days after drug ingestion, recreational users showed evidence for semantic memory impairment (Curran & Morgan 2000).

Because ketamine is a relatively short-lasting drug, some people repeatedly use the drug to get high and re-administer the drug when they begin to crash.

Long-term mental effects may include memory impairment and impaired executive functioning, mood swings, decreased sociability, attention deficit or dysfunction, flashbacks, and depression (Strous et al., 2022).

Frequent, repeated abuse of ketamine can cause damage to various major organs, including the digestive tract, urinary tract, and brain. Drug abuse also strains the heart, liver, and kidneys, and it can lead to permanent damage. One of the major physical harms caused by ketamine is ulcerative cystitis.

The chronic abuse of ketamine can result in psychological dependence, causing users to experience intense cravings when not taking the drug. Someone who becomes psychologically dependent on ketamine may go through withdrawal if use of the drug is suddenly stopped. This can result in anxiety, depression, insomnia, and flashbacks (Lin et al., 2016).

Relevance for the aviation workplace

Use of ketamine as a recreational drug is soaring in Europe (EMCDDA, 2022) and aircrew or ATCOs might be at risk when visiting dance clubs and raves. The acute and long-term effects of ketamine use are clearly incompatible with safety-sensitive jobs such as flying or ATM, as well as personal health.

3.1.5 Stimulants

3.1.5.1 Amphetamine / Methamphetamine

Amphetamines are potent central nervous system stimulants. The chemical structure of amphetamines closely resembles that of adrenaline and noradrenaline, stimulants that occur naturally in the human body. Based on potency, amphetamines can be divided into 3 basic groups:

- Methamphetamine or methyl-amphetamine, which is the most potent.

- Dexamphetamine or dextro-amphetamine, two times weaker than methamphetamine.

- Amphetamine, four times weaker than methamphetamine.

The pharmacological working mechanism of these three basic groups is similar and effects and adverse effects differ mainly in severity due to the difference in potency between the groups.

The market for “captagon”, an illicitly manufactured substance containing various concentrations of amphetamine, continues to flourish in the Middle East. Cathinone (Khat), the active ingredient of the Khat plant, is a stimulant with similar effects to amphetamine.

Some types of amphetamines are prescribed to treat medical conditions such as attention deficit hyperactivity disorder (ADHD) and narcolepsy. Amphetamines have also been used to treat Parkinson’s disease. Other types of amphetamines are produced and sold illegally. Amphetamines are widely used as performance enhancing drugs. The most potent form is crystal methamphetamine (“crystal meth” or “ice”), which has long-lasting effects (Ruiz & Strain, 2014). Illegally produced amphetamines can be a mix of drugs, binding agents, caffeine and sugar. New psychoactive substances (NPS), such as 4-fluoroamphetamine (4-FA) may also be added.

Methamphetamine (and the other amphetamines) releases high levels of the neurotransmitter dopamine, which stimulates brain cells, enhancing mood and body movement. It also appears to have a neurotoxic effect, damaging brain cells that contain dopamine and serotonin.

Methamphetamine is a white, odourless, and bitter tasting crystalline powder, readily soluble in water or alcohol. It is used orally or intranasally, by intravenous injection, and by smoking. Five to ten seconds after smoking or intravenous injection, the user experiences an intense “rush” that lasts only a few minutes and is described as extremely pleasurable. Snorting (inhale the drug up into the nasal passages) or ingesting produces a “euphoria high” but not the rush that comes with smoking or injecting. Snorting produces effects within 3 to 5 minutes, and oral ingestion produces effects within 15 to 20 minutes.

The central nervous system actions that result from taking even small amounts of stimulants of the amphetamine family, such as methamphetamine, include increased wakefulness, increased physical activity, decreased appetite, euphoria, feelings of power, strength, self-assertion, and enhanced motivation. Other effects include irritability, insomnia, confusion, tremors, convulsions, anxiety, paranoia, and aggressiveness. Physical effects of methamphetamine include increased respiration, respiratory problems, hyperthermia, cardiac arrhythmia, and extreme anorexia. Its use can result in cardiovascular collapse and death (McKetin et al., 2019).

On average, when taking moderate doses, the effects of amphetamines will last about 4 to 12 hours, often followed by listlessness, drowsiness, and depressed mood. After cessation of amphetamine, withdrawal symptoms, such as irritability, depressed mood, and depression are observed. These symptoms may lead to continuing the use of amphetamine and addiction (McKetin et al., 2019; Zorick et al., 2010).

Side effects of amphetamine use include athetosis (writhing, jerky, or flailing movements), irritability, insomnia, confusion, tremors, anxiety, chest pain, fever, difficulty in breathing, dizziness, irritability, nervousness, nausea, hot flashes, dryness of the mouth, sweating, palpitations, and hypertension.

Excessive doses can produce mental confusion, severe anxiety, paranoia, hyperthermia, and convulsions. In addition, amphetamines cause increased heart rate and blood pressure that can lead to irreversible damage to blood vessels in the brain, producing strokes.

Recreational use of amphetamine generally involves much larger doses, which have a greater risk of serious adverse drug effects than dosages used for therapeutic purposes, such as treatment for attention deficit hyperactivity disorder (ADHD) and narcolepsy.

Frequent use of amphetamines was observed in military operations in the Second World War and Vietnam War and this has resulted in widespread addiction problems.

Herbal products containing ephedra

The herb ephedra is the basis of several popular herbal products available in vitamin shops and fitness centres. These products, initially marketed as slimming pills, are popular as party drug, erotic stimulant or lifestyle pill. One of the alkaloids in ephedra is ephedrine, which causes amphetamine-like effects. Adverse reactions include stroke, heart attack, cardiac arrhythmias, seizures, and psychotic disorders (Hooft & Stricker, 2002). Taking ephedra may also cause anxiety, dizziness, dry mouth, headache, irritability, nausea, personality changes, and insomnia. Although ephedra is banned in many countries, it is still available via internet. The general public is often unaware of the risks, because herbal products are considered as “natural”. The acute effects are not compatible with flying duties. Knowledge on longer-term effects and withdrawal symptoms is sparse.

Relevance for the aviation workplace

Of the working population aged 18-67 years in the Netherlands 1,5% used amphetamines. Although it is far less popular than cannabis or MDMA (ecstasy) use of amphetamines and its derivatives is increasing in Western Europe and therefore AMEs should be aware of the possibility that some pilot or ATCO might be using -or have used- amphetamines.

Amphetamines have been used as “go pills” in strictly defined military missions. Because of its enhancing effects on alertness and activating effects, amphetamines are taken to combat the symptoms of fatigue and enhance

alertness in military aviation personnel. In this context, it is anecdotally known that some civil pilots use low doses of amphetamines to stimulate their in-flight alertness when they are severely fatigued. It should, however, be emphasised that fatigue and amphetamines form a dangerous combination because fatigue as well as amphetamines may lead to risky behaviour and lack of self-criticism and therefore should not be used in a civil aviation environment. Aircrew may not be aware of the adverse effects of ephedra containing herbal slimming or party-pills. Acute effects and prolonged use of amphetamine or amphetamine-like drugs are incompatible with flight safety. After cessation of use, withdrawal symptoms should be carefully evaluated and return to aviation duties should only be possible after approval of the medical assessor of the licensing authority in coordination with AME and aviation psychiatrist.

3.1.5.2 Cocaine

Cocaine is a strong central nervous system stimulant that interferes with the re-uptake of the neurotransmitter dopamine in the midbrain, a chemical messenger associated with pleasure and movement. Dopamine is released as part of the brain's reward system and is involved in the “high” that characterizes cocaine consumption. The major routes of administration of cocaine are sniffing or snorting, injecting, and smoking.

The acute effects of cocaine are a euphoric ‘high’ with hyperstimulation, reduced fatigue, mental clarity, peripheral vasoconstriction, pupillary dilatation, tachycardia, increased blood pressure, and hyperthermia. Some users may show restlessness, irritability, anxiety, paranoia (high doses). Cocaine-related deaths due to cardiac arrest or seizures followed by respiratory arrest have been reported.

After cessation of use a “crash” may follow with symptoms of anxiousness, dysphoria, restlessness, and hypersomnolence.

The duration of cocaine's immediate euphoric effects, which include hyperstimulation, reduced fatigue, and mental clarity, depends on the route of administration. The faster the absorption, the more intense the “high”, but the shorter the duration of action. The high from snorting lasts 15 to 30 minutes, while that from smoking may last 5 to 10 minutes. Increased use can reduce the period of stimulation. High doses of cocaine and/or prolonged use can trigger paranoia. Prolonged cocaine snorting can result in ulceration of the mucous membrane of the nose and can damage the nasal septum enough to cause it to collapse.

Data on elimination rates of cocaine in chronic users vary considerably. The mean cocaine elimination half-life is 1.5 - 4.1 h, however longer elimination half lifes have been found (19.0 +/- 4.2 h). A terminal elimination phase was also observed for cocaine metabolites with half-life estimates ranging from 14.6 to 52.4 h (Jufer et al., 2000).

Relevance for the aviation workplace

While cocaine was long considered as a popular drug among people with a high economic and social status, nowadays cocaine use is more widespread use among the general population. In several European countries cocaine now overtakes ecstasy as second most popular illegal drug among college students, “clubbers”, and “ravers”. Of the Dutch working population aged 18-67 years 1.9% has used cocaine in 2018 (Lifestyle Monitor,(2018). Aircrew and ATCOs are considered at risk to get in touch with cocaine and cocaine users.

Acute effects as well as prolonged use are incompatible with flight safety. After cessation of use, the so-called crash period of several days precludes any flying duties.

3.1.5.3 MDMA (3,4-methylmethamphetamine, ecstasy, XTC)

MDMA is a synthetic, psychoactive drug with both stimulant (amphetamine-like) and hallucinogenic (LSD-like) properties. It is popular among clubbers and ravers who love it for its euphoric and energizing effects. Its chemical structure, 3-4 methylenedioxymethamphetamine, is similar to methamphetamine (stimulating effect), methylenedioxyamphetamine (MDA), and mescaline (hallucinogenic effect). MDMA is believed to the increase the net release of monoamines (serotonin, dopamine and noradrenaline) from their respective axon

terminals (Huether et al. 1997). The release of dopamine and noradrenaline is mainly responsible for the physical effects that MDMA shares with amphetamine. The release of serotonin and (in)direct stimulation of post-synaptic serotonergic receptors are believed to be responsible for the mental effects observed during MDMA intoxication. The peak plasma concentrations of MDMA and its metabolite MDA are achieved at approximately 2 hours after intake. Physiological and mental effects of MDMA can last up to 6 hrs after intake (de la Torre et al 2004). The drug produces a "high" that can last from several minutes to an hour.

MDMA is most often available in tablet form and is usually ingested orally. The average recreational dose of ecstasy in tablet form is between one and two tablets. One tablet of ecstasy contains approximately 60-120 mg MDMA, but dangerously higher levels have been observed nowadays. The drug is also available as a powder and is sometimes snorted and occasionally smoked, but rarely injected. Some easily available MDMA tablets may also contain other drugs, which is often unknown by its users.

The acute effects after MDMA/ecstasy administration are euphoria, elevated self-confidence and increased sensory awareness, well-being, happiness, stimulation, increased energy, extroversion, feeling close to others, increased empathy, increased sociability, enhanced mood, mild perceptual disturbances, changed perception of colours and sounds, increase of blood pressure and heart rate, mydriasis, and moderate derealisation but not hallucinations.

Acute adverse effects include moderate derealisation and depersonalization, cognitive disturbances, elevated anxiety and decreased appetite (Vollenweider et al., 1998). Commonly reported acute adverse physiological effects include tachycardia, bruxism, trismus, pupillary dilation, gait instability and nausea (Downing 1986; Peroutka et al., 1998; Cohen 1995; Davison & Parrott 1997). In addition, in high doses MDMA can cause a sharp increase in body temperature resulting in malignant hyperthermia leading to muscle breakdown, kidney failure, and cardiovascular system failure.

Following the acute subjective effects, ecstasy users generally report a 24- to 48-h period characterized by the persistence of the acute effects and the onset of additional effects that are reminiscent of the "crash" phenomenon reported after psychostimulant administration. The most common subacute symptoms include muscle aches, fatigue, depression, irritability, difficulty in concentrating, and headache (Peroutka et al. 1988; Davison & Perott 1997). The longer term effects of MDMA are evident in increased ratings for "discontented", "sad", and "bored" over 4 days after self-administration of the drug. MDMA users exhibited lower mood than alcohol users the day after taking the drug, but were even more depressed 4 days later, at which point the depression scores of some users were within the range for clinical depression (Curran & Travill 1997).

MDMA appears to impair visual paired associates learning in new users, suggesting serotonergic dysfunction in hippocampal regions as a consequence of MDMA use (Wagner et al., 2013). Continued use of MDMA was associated with progressive decline in terms of immediate and delayed recall. After extensive use, abstinent MDMA users show evidence for impairment in verbal and visual memory. There is evidence that this memory impairment is caused by MDMA-induced serotonin (5-HT) neurotoxicity (Zakzanis & Young, 2001; Quednow et al., 2006). Moreover, there is evidence that chronic, heavy, recreational use of ecstasy is associated with sleep disorders, depressed mood, persistent elevation of anxiety, impulsiveness, impairment of episodic memory, working memory and attention (Morgan, 2000).

Immediate and long term effects depend on choice of substance, frequency of use and method of ingestion.

Relevance for the aviation workplace

After cannabis, MDMA (ecstasy) is the second most used drug on raving and dance parties and aircrew may have easy access to the drug. Of the Dutch working population aged 18-67 years 4% has used MDMA (ecstasy) in 2018 (Lifestyle Monitor, 2018). There is convincing evidence that memory impairments are a central characteristic of individuals who use ecstasy on a recreational basis Ecstasy users are at significant risk of sleep disorders, persistent cognitive impairments and disturbances of affect and personality. Some of these problems

may remit after abstinence, but residual neurotoxicity and decline of serotonergic function may result in recurrent psychopathology and cognitive decline.

It is concluded that acute and longer term effects are incompatible with flight safety. Subacute effects are observed up to 48 hours after ingestion and mental health effects up to 4 days after taking the drug. Both subacute effects and prolonged psychological effects are incompatible with flying duties.

3.1.6 Central Nervous System depressants

Depressants impact the gamma-aminobutyric acid (GABA) neurotransmitter in the brain. When this happens, the brain's activity slows, often leading to relaxation, sleepiness, and reduced inhibitions.

3.1.6.1 Gamma hydroxybutyrate (GHB)

GHB or Gamma Hydroxybutyrate is a central nervous system (CNS) depressant that is commonly referred to as a "club drug" or "date rape" drug. GHB is abused by teens and young adults at bars, parties, clubs and "raves" (all night dance parties), and is often mixed with alcoholic beverages. GHB and its analogs have been shown to increase brain dopamine levels (Hechler, 1993).

Euphoria, increased sex drive, and tranquillity are reported positive effects of GHB abuse. Negative effects may include sweating, sedation, loss of consciousness or coma, nausea, auditory and visual hallucinations, headaches, vomiting, exhaustion, lethargy, amnesia, and confusion (e.g. Stomberg et al., 2014). GHB takes effect in 15 to 30 minutes, and the effects last 3 to 6 hours.

Approximately 95% of GHB is metabolized in the liver, and its half-life ranges from 30 to 60 minutes. It is metabolized to carbon dioxide and eliminated through the lungs. Only 5% is excreted via the kidneys. Detection of GHB in the urine may be difficult after 24 hours due to its short half-life.

GHB is bought on the streets or over the Internet in liquid form or as a white powdered material for illicit use. It is taken orally and is frequently combined with alcohol. GHB may be adulterated with unknown contaminants that may worsen its toxicity. The production of GHB usually involves the use of lye or drain cleaner mixed with gamma butyrolactone (GBL), a chemical analogue of GHB and an industrial solvent often used to strip floors. Analogues that are often substituted for GHB include GBL and 1,4 BD (1,4-butanediol). These analogues are available legally as industrial solvents. They are also sold as supplements for bodybuilding, fat loss, reversal of baldness, improved eyesight, and to combat aging, depression, drug addiction, and insomnia. Identification of abuse of these GHB analogues is difficult because routine toxicological screens do not detect the presence of these analogues.

GHB is potentially addictive if used repeatedly. Withdrawal effects may include insomnia, anxiety, tremors, sweating, increased heart rate and blood pressure, or psychotic thoughts. Adverse events during withdrawal include hypertensive crisis, severe agitation, delirium and epileptic seizures. Users may experience these withdrawal symptoms within 1 to 6 hours of their last dose, and the symptoms may persist for months.

Combined use with alcohol, or other CNS depressants such as benzodiazepines may result in nausea, vomiting and aspiration, loss of consciousness or coma, and severe depression of respiration and heart rate depression, which in some cases may lead to death. High doses of GHB, even without other illicit substances or alcohol, may result in profound sedation, seizures, coma, severe respiratory depression and death (Corkery et al., 2015).

In Australia GHB users appeared to be a stable, highly educated and well-functioning group. They had extensive experience with a range of drugs, and GHB was typically used in conjunction with other drugs. The proportion reporting significant negative side effects when using GHB was high (99% reported at least one), and the mean number of side effects ever experienced was 6.5. Notably, 52% reported becoming unconscious, 53% reported vomiting, 58% reported profuse sweating, an d 8% reported having a fit or seizure (Degenhardt et al., 2002).

Relevance for the aviation workplace

The use of GHB/GBL is, generally, low in the EU (EMCDDA, 2022) but there is evidence of some sub-populations, settings and geographical areas where it is commonly used, such as in nightclubs where GHB is popular as 'party drug'. Aircrew or ATCOs, who are involved in the 'party circuit', may try and use it. GHB's acute physiological and euphorogenic effects are incompatible with flight safety. Frequent GHB use may induce prolonged withdrawal symptoms, which are also incompatible with flight safety.

3.1.6.2 Benzodiazepines and non-benzodiazepines

Benzodiazepines (BZDs) are among the most prescribed sedative hypnotics and among the most misused and abused medications by patients, in parallel with opioids. Benzodiazepines, often called benzos, are prescribed to treat sleep disorders (e.g. temazepam), anxiety (e.g. oxazepam, alprazolam), and seizures (valium). By stimulating the neurotransmitter GABA (γ-aminobutyric acid), benzodiazepines can have a sedative effect, a sleep-inducing effect, and an aborting impact on convulsion and ability to relax the muscles. Most benzodiazepines are designed for short-term (e.g. 5 days) use and in the smallest dose possible. With longer use they carry a significant risk of dependence. After opioids, BZDs have been the drug class most frequently involved in drug-related suicide attempts (Jones & McAninch, 2015).

There is significant evidence from toxicology results of illicit tablets being sold as diazepam, temazepam and alprazolam linked to hospitalisations and deaths, and from police seizures, that some illicit drugs sold as benzodiazepines are causing harm. In fact these tablets contain dangerously potent illicit benzodiazepines or their analogues such as flubromazolam, flualprazolam and etizolam (Public Health England, 2020).

BZD adverse effects

Benzodiazepines may have residual effects, such as somnolence and decreased alertness on the job which may lead to subtle incapacitation of pilots or ATCOs and is known to cause occupational injuries (Garbarino et al., 2021). Other adverse effects are suppression of REM-sleep, memory impairment, impairment of information processing speed, impaired alertness and attention, impairment of visual processes and motor coordination, rebound insomnia, and withdrawal symptoms which may lead to benzodiazepine dependency. Withdrawal symptoms after longer or heavy use of benzodiazepines are insomnia, anxiety and panic attacks, depression, tremors, delirium or detachment from reality, muscle spasms, convulsions or seizures (after severe misuse), abnormal body sensations, nausea, and strong cravings for the drug (Pétursson, 1994).

Non-benzodiazepines

Although originally marketed as safe –non-addictive- alternatives to the potentially dependence -causing benzodiazepines, there is presently convincing evidence that the non-benzodiazepines zolpidem, zopiclone, eszopiclone, and zaleplon ("Z-drugs") also have the potential of abuse, dependence, and withdrawal symptoms (Schifano et al., 2019). Like benzodiazepines, these Z-drugs are agonists of the GABA receptor complex and therefore enhance GABA-mediated neuronal inhibition. Their binding selectivity and pharmacokinetic profiles have initially been reported to minimize the possibility of side-effects similar to those produced by benzodiazepines, for example, next day sedation, dependence, and withdrawal. However, many cases of Z-drugs abuse and dependence were reported around the world. These cases showed that zolpidem, zopiclone, and eszopiclone can exert residual effects causing sedation, abuse capability, euphoric mood, tolerance, and a withdrawal syndrome. (Victorri-Vigneau et al., 2007; Cubala et al., 2008; Heydari & Isfeedvajani, 2013; Schifano et al., 2019).

There is sufficient evidence from epidemiologic and experimental studies to establish a strong causal relationship between BZD or Z-drug use to motor vehicle accidents, falls and fractures as a consequence of psycho-motor impairment (Brandt & Leong, 2017).

Known adverse reactions of Z-drugs are paradoxical reactions with anterograde amnesia in some patients. Zolpidem, zopiclone, and eszopiclone are associated paradoxical reactions such as sleep-walking, sleep-driving, and engaging in other activities while not fully awake. The U.S. Food and Drugs Administration urged health care professionals to caution all patients (men and women) who use zolpidem about the risks of next-morning impairment for activities that require complete mental alertness, including driving. Women appear to be more susceptible to this risk because they eliminate zolpidem from their bodies more slowly than men (FDA, 2019). Fatalities were reported for all Z-drugs, although this typically occurred mostly with zolpidem and zopiclone, both typically ingested in a poly-drug misuse scenario (Casula et al., 2013; Gunja, 2013).

It is hypothesized that there may be 2 subsets of individuals misusing BZDs and/or Z-drugs: one group may include patients with psychiatric comorbidities (Zammit, 2009; Lin et al., 2017), who were originally started with these molecules for insomnia but who developed tolerance and withdrawal phenomena, therefore requiring increasing dosages overtime (Griffiths and Johnson, 2005); and another group that includes young people, who are using large Z-drug dosages in combination with other recreational compounds to achieve better euphoria.(Schifano et al., 2019).

Relevance for the aviation workplace

There are no useful data on the prevalence of benzodiazepine misuse by pilots or ATCOs. Toxicology test results of 952 fatally injured pilots, of which 97% were conducting GA flights, showed that benzodiazepines were found in 3.0% of the cases (NTSB, 2020). It is, however, not clear how many cases concerned misuse or medically indicated short or single use of benzodiazepines. Pilots or ATCOs may be occupationally prone to sleep problems (e.g. due to time-zone crossing, shift work), while sufficient sleep of good quality is important to guarantee optimal alertness during their work. Therefore, they might occasionally be candidates to use prescription hypnotics. In these cases acute and residual effects of BZDs or Z-drugs should be taken into account. In case of occasional single use it should be considered that the duration of the sedative effects may show inter-individual variation and differ for different hypnotic agents. This might have negative consequences for safe performing of tasks the day after single dose ingestion. The safe “hypnotic to throttle/duty” time after occasional or longer use depends on age, weight, ethnicity, metabolism, liver function, dosage, length of time period the drug is taken, interacting medications, smoking, co-use of alcohol (dangerous combination can be fatal). Acute and residual effects, as well as withdrawal symptoms and BZD/Z-drugs dependency are incompatible with aviation safety. Dependency should be identified and treated.

3.1.6.3 Tranquillizers

Tranquillizers are divided in two types: 1) minor tranquillizers (anxiolytics) used to treat anxiety, such as BZDs (oxazepam, alprazolam) and, very rarely prescribed, some barbiturates and carbamates; and 2) major tranquillizers: antipsychotics or neuroleptics.

Anxiolytics

The adverse effects, withdrawal symptoms, dependency risk, and consequences for aviation safety of the BZDs have been discussed in section 6.4.2. It is important to obey a safe “hypnotic to throttle/duty” time after a pilot or ATCO has successfully stopped to use BZD anxiolytics. Factors that determine how long a dose of BXDs will persist in the body include: age, weight, ethnicity, metabolism, liver function, dosage, length of time taking the drug, interacting medications, smoking, co-use of alcohol (dangerous combination can be fatal). In the context of resuming aviation duties, it should be considered that it takes about five half-lives for 98% of a drug dose to clear the body, so alprazolam would take up to 4 days to be fully eliminated from the body. The elimination half-life of oxazepam ranges from 4 to 15 hours. Based on these numbers it could take from 20 to 75 hours for all of a dose of oxazepam to be eliminated.

Barbiturates (e.g., pentobarbital, phenobarbital) were used extensively in the 1960s and 1970s as a treatment for anxiety, insomnia, and seizure disorders. Barbiturates have largely been replaced, both medically and

recreationally, by benzodiazepines. Nowadays barbiturates are mainly prescribed for epilepsy, anaesthesia, and (physician-assisted) suicide. The correct dose of barbiturates is difficult to predict and even a slight overdose can cause coma or death. Barbiturates are addictive and can cause a life-threatening withdrawal syndrome.

Carbamates (e.g., meprobamate) are nowadays very rarely used as they are less effective than the benzodiazepines. They are hazardous in overdose and can produce dependence as well as withdrawal symptoms.

Use of antipsychotics or neuroleptics is incompatible with performing safety-sensitive tasks. Moreover, the underlying condition for which these medications are used will almost certainly mean that the mental state of a pilot or ATCO is not compatible with performing aviation safety related duties.

3.1.7 Nitrous oxide (N2O, Laughing gas)

Nitrous oxide (N_2O) is clinically used as a safe anaesthetic (dentistry, ambulance, childbirth) and appreciated for its anti-anxiety effect. It is also used in the food industry as a mixing and foaming agent for the production of whipped cream and as fuel booster in the motor industry. Since five years, recreational use of N_2O is rapidly increasing and is particularly popular among clubbers and ravers in the dance and festival scene where use of other substances is also common. It is cheap and in many countries nitrous oxide is freely available from catering outlets, street vendors, and via home-delivery service through the Internet or mobile vans advertising nitrous oxide for sale. For recreational use, nitrous oxide is commonly sold in prefilled balloons (at point of use) or small pressurized metal canisters designed for the food industry (Kaar et al., 2016).

Following one inhalation, in most cases from a balloon, a euphoric, pleasant, joyful, empathogenic and sometimes hallucinogenic effect is induced within 10 seconds and disappears within some minutes. It has no hangover effect and it is undetectable on routine drug screens. Recreational nitrous oxide use is generally moderate with most users taking less than 10 balloons of N_2O per episode and about 80% of the users having less than 10 episodes per year (van Amsterdam et al., 2015). Side effects of N_2O include transient dizziness, dissociation, disorientation, loss of balance, fainting, impaired memory and cognition, and weakness in the legs. Vomiting in patients who are obtunded by co-ingestion of other drugs carries an aspiration risk, and the disorientation and loss of motor control caused by nitrous oxide can result in trauma, particularly if used while driving or operating machinery. Some fatal accidents have been reported caused by hypoxia due to inhaling from a balloon. A few hours of exposure can cause megaloblastic changes in the bone marrow, and days of exposure can cause agranulocytosis.

Incidental use of nitrous oxide is hardly, or not at all, associated with major damage to health. However, the health damage of nitrous oxide, including its dependence risk, increases rapidly with daily use in higher daily doses. It is reported that some users inhale occasionally hundreds of cartridges per day. Especially after the emergence of larger nitrous oxide tanks, the number of serious neurological complaints increased (Nabben et al., 2021; van Riel et al., 2022). An increasing proportion of patients reported problematic heavy or frequent use, accompanied by chronic toxicity which is characterised by damage to the nervous system through interference with vitamin B12 metabolism, leading to megaloblastic anaemia and subacute degeneration of the spinal cord and peripheral neuropathy which can be invalidating and can be irreversible (Keddie et al., 2018).

Relevance for the aviation workplace

Occasional use of a single dose of nitrous oxide is leads to a very short effect and has no residual effects which would impair performance for aviation related tasks. However, it should be realised that nitrous oxide is often related to raves and dance parties where many balloons will be inhaled often in combination with other drugs such as MDMA (ecstasy) and alcohol. When there is any suspicion that a pilot or ATCO sometimes uses nitrous oxide, further assessment of the use of other drugs is indicated. Furthermore, pilots and ATCOs should be warned of nitrous oxide's dependence risk and chronic toxicity causing subacute degeneration of the spinal

cord and peripheral neuropathy. Nitrous oxide is eliminated and excreted essentially unchanged via the lungs. Because the elimination is very rapid (<5 minutes) and nearly complete, it is difficult to detect N_2O in hair or urine and impossible to detect with routine drug screening panels.

3.1.8 Dimethyltryptamine (DMT) and Ayahuasca

DMT is a powerful psychedelic drug, with serotonergic effects on the human brain, which can induce a rapid and intense psychedelic experience, often referred to as a 'DMT trip'. The DMT experience is usually characterised by visual hallucinations, frequently involving powerful entities, and is often associated with deeper meaning. This meaningful experience is sometimes called a 'DMT breakthrough'. When used as a recreational drug, DMT can be smoked, snorted, or injected in its crystal form. It is often used in the form of Ayahuasca of which it is the psychedelic constituent.

Ayahuasca is a hallucinogenic tea, which is considered an important element of shamanic tradition in the Upper and Lower Amazon. Ayahuasca contains the psychedelic compound DMT and monoamine oxidase inhibitors that prevent DMT from being broken down in the gut and liver. This combination allows DMT to have psychoactive effects when taken orally, and prolongs the intense psychedelic experience (https://www.drugscience.org.uk/drug-information/ayahuasca/). In the recent decennium the psychedelic properties and therapeutic potential of Ayahuasca have attracted significant attention in the wealthy Western countries, with a rapidly-emerging tourism sector centred around offering the ayahuasca ceremony to international visitors at ayahuasca retreats. (Frecska et al., 2016)

DMT is rapidly acting and effects are observed around 2-5 minutes after consumption and last approximately 15-20 minutes. Despite its short-lived effects, DMT is known as one of the most powerful psychedelic drugs. The subjective include:

- Eliciting intense visual alterations and hallucinations, specifically colourful and geometric forms
- Profound spiritual or mystical experiences
- Varying alternations in mood and emotion, including experiences of euphoria, calm, fear and anxiety
- Perceived encounters with external entities, which are often described as elf-like.
- Altered sense of time and place
- A sense of depersonalisation or out of body experiences
- Potential auditory hallucinations
- Evocation of powerful memories

DMT is considered as a powerful tool for self-discovery and understanding consciousness, which is assumed to have increased the interest in recreational use of DMT (Carbonaro & Gatch, 2016).

DMT is easily metabolised and is believed to have a low toxicity (Carbonaro & Gatch, 2016). However, it should be considered that it might elevate blood pressure and increase heart rate and, at high doses, seizures, respiratory effects and comas have been reported. The impaired cognitive and motor function poses a safety risk. There is some evidence that DMT may play a role in psychotic symptoms (Carbonaro & Gatch, 2016). Oral dosing of DMT via ayahuasca produces both behavioural and neurochemical effects, such as decreases in motor activity and impairment of cognitive function. Ayahuasca decreased markers of sleep quality and sleep disturbances are common on the night following administration.

DMT is not addictive. However, tolerance can develop with frequent use, whereby a higher dose is required to achieve the same effect. (Drug Science UK, 2022).

DMT may play a role in important adaptive mechanisms that can also serve as a promising tool in the development of future medical therapies (Frecska et al., 2013). There have been proposals that DMT might be a useful treatment of anxiety, substance abuse, inflammation, or for cancer. Experimental studies have been few and it is premature to conclude that DMT may have clinically relevant uses ((Carbonaro & Gatch, 2016).

Relevance for the aviation workplace

DMT and DMT-containing ayahuasca tea are in most cases used in spiritual self-discovery séances. Occasional or regular use of these drugs should alert the aeromedical examiner who, in that case, should explore the possible presence of psychological or psychiatric problems which could have been the reason for the pilot or ATCO to participate in such séances and use these drugs. Although rare, induction of psychosis has been described after ritual and recreational/non-controlled ayahuasca use (Dos Santos et al., 2017). Most tourists participating in an ayahuasca ceremony perceive this to be harmless. It should, however, be considered that in some cases psychosis can be triggered. Moreover, sleep disturbances after use of ayahuasca are common and therefore it is recommended to observe 24 hours “drug-to-aviation duty time” for pilots and ATCOs.

It should be considered that pilots and ATCOs, who use or have used DMT, might also use other recreative drugs in their search for psychedelic, stimulating, or sedating effects.

3.1.9 Volatile solvents

Volatile solvents include a wide variety of inhalable substances that produce mind-altering effects. Examples of volatile solvents include toluene, plastic cement, paint, gasoline, paint thinners, hair sprays, and various anaesthetic gases.

Volatile substance abuse (VSA) (glue sniffing, inhalant abuse, solvent abuse) and the deliberate inhalation of volatile substances in order to achieve intoxication, has been reported globally, mainly among adolescents, individuals living in remote communities and those whose occupations give ready access to abusable substances. Solvents from contact adhesives, notably toluene, petrol (gasoline), halogenated solvents, and volatile hydrocarbons such as those found in cigarette lighter refills, aerosol propellants, halocarbon fire extinguishers, and inhalational anaesthetics may be abused. VSA gives rise to dose-related effects similar to those of other hypnosedatives. The intoxication induced by inhalation of volatile substances produces some behavioural effects similar to those due to alcohol. Minutes after inhalation, dizziness, disorientation, and a short period of excitation with euphoria are observed, followed by a feeling of light-headedness and a longer period of depression of consciousness (EMCDDA, 2022-b). Higher doses may produce life-threatening effects such as convulsions and coma. Death may be caused indirectly by inhalation of vomit, or from direct cardiac or central nervous system toxicity. Chronic abuse of toluene-containing products and of chlorinated solvents such as 1,1,1-trichloroethane, can produce severe organ damage of the liver, kidneys, and brain. Drunken behaviour, unexplained listlessness, anorexia and moodiness may result from VSA.

The use of volatile substances is unlike most other forms of drug use in that it involves various compounds contained in readily accessible domestic or commercial products. These compounds, that are safe when used for their intended purposes, may cause intoxication and in some cases death when their vapours are deliberately concentrated and inhaled.

The mode of use depends upon the volatile compound and the nature of the product. Gases may be inhaled directly from containers, such as cigarette lighter refills. Aerosols may be sprayed through fabric (e.g., a towel or socks) to further remove the non-volatile components of the product. Solvents, such as toluene, may be poured onto a handkerchief or into a bag and the vapour inhaled. Glue is usually poured into a plastic bag which is palpated as the vapour is inhaled. Helium, often from disposable cylinders purchased from shops selling party balloons can also be fed into a plastic bag covering the head (EMCDDA, 2022-b).

A specific subgroup of volatile substances — alkyl nitrites — are used on the dance club scene because they cause relaxation of vascular smooth muscle and produce a 'rush', or to enhance a sexual experience. They are generally known as 'poppers' and can be found on the 'street' market in bars and clubs. The nitrite-containing products usually contain butyl or isobutyl nitrite and are often impure.

Marked changes in mental state are induced in people who misuse toluene and other solvents. Most users report elevation of mood and hallucinations. Potentially dangerous delusions can occur, thoughts are likely to be slowed, time appears to pass more quickly, and tactile hallucinations are common. These behavioural effects are accompanied by visual disturbances, nystagmus, incoordination and unsteady gait, slurred speech, abdominal pain and flushing of the skin.

Chronic exposure to solvents such as toluene damages the protective sheath around certain nerve fibres in the brain and peripheral nervous system. This extensive destruction of nerve fibres may be similar to that seen with neurological diseases such as multiple sclerosis. Trichloroethylene may cause cirrhosis of the liver, reproductive complications, hearing and vision damage.

Most deaths are assumed to be caused by a 'sudden sniffing death syndrome' (SSDS): an irregular and rapid heart rhythm brought on by the use of volatile substances and anoxia or hypercapnia and a sudden stimulus that produces an epinephrine (adrenaline) release. Deaths also may result from asphyxiation, particularly if a plastic bag is used to inhale the compound (e.g., when inhaling glue).

Relevance for the aviation workplace

The prevalence of volatile substance abuse (VSA) in pilots, ATCOs, or the general population is not known. Effects of misuse of volatile substances are not compatible with aviation safety.

For identification urine analysis is generally of little value except for the less volatile and more extensively metabolised compounds, such as toluene. Other volatile substances can be detected using hair analysis when there is a strong suspicion of VSA. However, it is often difficult for an AME to find suspicion because these substances can be found in readily accessible domestic or commercial products and the user considers the use of these substances as harmless until dependency has appeared.

3.1.10 Conclusion

Similar to other members of the European working population, aircrew and ATC personnel may encounter occasions to use popular psychoactive drugs in the 'party/festival circuit', viz. cannabis, ecstasy, cocaine, amphetamine, and to a lesser extent GHB (gamma-hydroxybutyrate), 'magic mush rooms' (psilocybin), and ketamine. All drugs mentioned in the present report have acute, prolonged, or residual effects, and/or withdrawal symptoms that are incompatible with flying or ATC duties. The prevalence of risky substance use by aircrew and ATCOs is unknown due to a lack of representative data. It is, however, reasonable to assume that aircrew and ATCOs have a similar prevalence of drug use as a European working population aged 18-67 years, which risk is estimated at around 5% during their professional career. It should, however, be considered that there are substantial differences between the EU countries in prevalence and types of drugs used. Therefore, it is recommended to take relevant national patterns of psychoactive drug use into account for NAAs determining the scope of their screening requirements.

4. Review of available methods of screening for use/misuse of psychoactive substances

4.1 Introduction

Recommendation 3 (b) of the Germanwings Task Force is: "The Task Force recommends mandating drugs and alcohol testing in the initial Class 1 medical assessment".

The background and reasoning of the Task Force is that the use/abuse of drugs and alcohol is one of the few disorders that has the potential to affect the mental health of pilots, for which screening by means of biochemical tests is available. The recommendation is intended to preclude problematic substance users from working within the safety-sensitive areas of aviation and aimed at deterring safety-sensitive aviation personnel from engaging in problematic substance use. In the present report it is recommended that this preventive measure should at the same time be utilized as a method to educate aircrew about the safety consequences of substance use and/or mental health problems and to stimulate their awareness of these issues during their pilot career (see section 5.3.3). This recommendation is in agreement with the current ICAO initiatives on upgrading of application of safety management principles in medical assessment process and the implementation of 'health promotion' Standard for States (Jordaan, 2015).

Current EASA requirements for **Class 1 pilots** as mentioned in MED.B.055 Mental Health (Annex IV Part-MED) state that (EASA, 2022):

- MED.B.055(b) Drugs and alcohol screening shall form part of the initial class 1 aero-medical examination.
- MED.B.055(c) Applicants with a mental or behavioural disorder due to use or misuse of alcohol or other psychoactive substances shall be assessed as unfit pending recovery and freedom from psychoactive substance use or misuse and subject to satisfactory psychiatric evaluation after successful treatment.
- AMC1 MED.B.055 (d) Psychoactive substance testing

  (1) Drug tests should screen for opioids, cannabinoids, amphetamines, cocaine, hallucinogens and sedative hypnotics. Following a risk assessment performed by the competent authority on the target population, screening tests may include additional drugs.

  (2) For renewal/revalidation, random psychoactive substance screening tests may be performed.[…]

  (3) In the case of a positive psychoactive substance screening result, confirmation should be required in accordance with national standards and procedures for psychoactive substance testing.

  (4) In case of a positive confirmation test, a psychiatric evaluation should be undertaken before a fit assessment may be considered by the medical assessor of the licensing authority.
- GM2 MED.B.055 (a) Drugs and alcohol screening tests used should:

  (1) provide information regarding medium-term consumption

  (2) be accepted on national level by the competent authority based on the availability and suitability for the scope mentioned in point (a) (1) above.

In addition to above mentioned requirements, EASA further requires for **ATCOs** that (EASA, 2019):

- the ATC service provider shall develop and implement an objective, transparent and non-discriminatory procedure for the detection of cases of problematic use of psychoactive substances by

ATCOs. The procedure shall be consistent with provision ATCO.A.015 of Reg. 2015/340 concerning "ATCO provisional inability" (https://www.easa.europa.eu/en/document-library/easy-access-rules/easy-access-rules-air-traffic-managementair-navigation-services).

The current EASA requirements for **ATCOs** as mentioned in ATCO.MED.B.055 Psychiatry (Regulation (EU) 2015/340) state that:

- Applicants with a mental or behavioural disorder due to alcohol or other use or misuse of psychoactive substances, including recreational substances with or without dependency, shall be assessed as unfit until after a period of documented sobriety or freedom from psychoactive substance use or misuse and subject to satisfactory psychiatric evaluation after successful treatment. Applicants shall be referred to the licensing authority.

For the AME the drugs and alcohol screening as mandated by the EASA requirements for the initial Class 1 examination is quite straightforward because these requirements necessitate testing as part of the initial aeromedical examination whether or not the AME has found any evidence of risky drugs or alcohol use. In the context of mandatory initial screening methods of screening for use/misuse of psychoactive substances will be reviewed in chapter 4.2 in which also tests to identify risky use of drugs and alcohol during the aero-medical examinations for renewal of class 1 medical license and initial/renewal class 2 and class 3 (ATCOs) medical licenses will be discussed. The methods described in chapter 4.2 will also be applicable for the testing procedure of the ATC service provider.

In chapter 4.3 recommendations will be made for detection of use of drugs and alcohol during initial Class 1 examinations as well as for the identification of risky use of psychoactive substances during the examinations for renewal of class 1 medical license and initial/renewal class 2 and class 3 (ATCOs) medical licenses.

Random testing in the framework of the Ramp Inspection Programme

Although random testing in the framework of the Ramp Inspection Programme is not a tool for the AME, and therefore not mentioned in the aeromedical requirements in Part MED, with ARO.RAMP.105 and ARO.RAMP.106 EASA mandated random testing of aircrew as an additional measure to reduce misuse of psychoactive substances and enhance flight safety. In the context of the present report random testing ("RAMP testing") will be discussed in chapter 4.4.

4.2 Screening tests for alcohol and drugs misuse

Drug and alcohol (D&A) testing –particularly the mandatory testing at the initial Class 1 examination- is considered to be useful to show the applicants the seriousness of regulations concerning use of drugs and/or alcohol by personnel in safety sensitive jobs. In addition, the D&A testing requirement provides an opportunity to educate pilots and ATCOs on the safety risks of illicit drugs, medication, and alcohol.

General considerations

- The psychoactive substances to be tested.

  By the national authorities of several countries zero tolerance testing is applied to five illicit drug groups – cocaine, marijuana, opiates, amphetamines and phencyclidine (e.g. CASA, 2006). In many countries authorities approve using a standard screen including cannabis, amphetamines, methamphetamines, cocaine, opiates, and benzodiazepines. The selection of psychoactive substances to be tested should be determined by each national authority in consultation with their aeromedical assessor or advisor and in line with specific national risks of consumption of specific psychoactive substances. The selection will be influenced by the location of the safety critical workers, by employment and residence, and local

factors including the availability of particular substances, accepted regional practices and availability of medicines, and certain types of food and drugs. Cultural practices and the diversity of the workforce and sectors flown should also be taken into account. In this context, it should be considered that modern societal norms tend to accept and even stimulate use of smart drugs and cognitive-enhancing drugs, such as methylphenidate, modafinil, and piracetam (Greely et al., 2008). Younger pilots might have used these drugs at school or university to improve their performance and might be unaware of the risks these drugs may have for aviation safety, such as boosting self-confidence and taking risks. Testing for specific prescription or OTC medications is not feasible in a standardized setting, because each medication or drug needs a specific test in a dedicated laboratory. In general, applicants will have no reserve to mention prescription and OTC medication to the AME. However, for use of anti-depressants this might not always be the case, because an applicant might try to hide a depressive illness. Therefore, screening for anti-depressants might be considered by the authorities. Guidance on drugs to be tested may need frequent updates taking into account national patterns of drug use and developments in test technology.

- Who undertakes testing

  Testing should be carried out in complete independence from the applicant. This should not be done by the AME or AeMC and is best guaranteed by an external accredited company. Trained staff should carry out screening tests usually by mouth swab (saliva), breath, blood, hair, or urine sample. The sample collection and testing process should be designed to ensure that the result is reliable. If a positive result is found further confirmatory testing should be undertaken. A confirmed positive result should be reported to the relevant regulatory authority.

- The samples to be taken

  The samples that are taken can be breath (for alcohol), urine, saliva, fingernails, or hair, while blood can be taken as evidential confirmation in case of a positive test. Several psychoactive substances can also be tested in sweat. However, taking sweat samples is considered impractical in an aeromedical setting and will therefore not be further discussed in the present report. Just like goes for breath and blood, the other methods have their advantages, disadvantages, and risks of false positives. Because the methods are very sensitive, occurrence of false positives is inevitable when a sensitive test is used in a population where the addiction rate is considered to be low, as is the case in the pilot and ATCO population.
- The following applies to all test methods (ASAM, 2013):
  - a negative result is not proof of abstinence, just the lack of evidence.
  - drug tests provide information about use of drugs, but drug tests do not identify substance use disorders or physical dependence.
  - a positive drug or alcohol test is no proof of impaired cognitive performance. It is an important risk factor for impairment of safe functioning.

- The decision what sample method to use depends on which drugs are to be identified and on logistical/financial considerations. For testing of hair, oral fluid, or urine it is important to follow the European Guidelines for Workplace Drug and Alcohol Testing. For cut-off values for a positive test, the guidelines of the European Workplace Drug Testing Society or from the testing analytic laboratory should be followed (www.ewdts.org ; Taskinen et al., 2017; Brcak et al., 2018; Salomone et al., 2016).

- Timing of test: before or after, or in conjunction with aeromedical assessment? It might be logistically easiest to perform the test in conjunction with the medical assessment. In case hair or finger nail testing is used, the applicant has the opportunity to prove sobriety of drugs and alcohol during the 90 days preceding the medical assessment.

- Testing can take place at the facility where the medical assessment takes place, or in a specialized laboratory.
- Handling of results. It is recommended having this done by impartial, trained Medical Review Officers (MRO) who are independent from the applicant, ensure a proper process, and determine the true positives. A MRO could be a member of the AeMC staff, but not the AME assessing Class 1 fitness of the applicant.
- Safeguards for the process should be laid down in rules which are transparent to the applicant e.g. chain of custody, legally secure, robust process, confidentiality.
- Quality standards including the accreditation of the service and ISO standard. Initial screening and confirmation methods should be based on different principles of analytical chemistry or different chromatic separations: e.g. first test immunoassay, confirmation test gas chromatography. Tests should be carried out by an accredited laboratory using accepted guidelines for procedures.
- Define procedure to be followed in the event of a positive test; consider impact on stakeholders (confidentiality, employment, loss of license, cost, litigation etc. Individual rights vs. public safety).
- Consider data collection with ongoing risk and trend analysis to drive policy and process development.
- Define policy on health promotion and safety management, with focus on prevention and support. For a pilot or ATCO who has a drug or alcohol problem, whether it is identified by a positive test, via self-report, or peer report, there should be a drug or alcohol intervention programme that includes assessment, treatment, education, counselling, and consultation with health care professionals, residential or non-residential treatment programs, monitoring and follow up action. Such programmes can best be run and coordinated by a Peer Support Programme (or 'Peer Intervention Programme') which is an independent body/foundation – in practice usually the professional pilot community led by a Mental Health expert that runs a programme into which pilots can report concerns about their colleagues and/or where pilots can turn to for advice and help with a specific problem, such as problematic substance use.

4.2.1 Overview of available test methods

For all of the testing types, which are discussed below, the AME should discuss positive results with the applicant and take further steps for evaluation and/or treatment.

Alcohol biomarkers are generally classified as direct and indirect alcohol biomarkers. Direct biomarkers are alcohol metabolites such as ethyl-sulphate (EtS) and ethyl-glucuronide (EtG) as well as acetaldehyde, the first alcohol metabolite, aldehyde-protein adduct, phosphatidyl-ethanol, and fatty acid ethyl esters. Indirect biomarkers are various liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) which are formed due to toxic effects of alcohol to the liver in heavy drinkers. Carbohydrate-deficient transferrin (CDT), beta-hexosaminidase, total serum sialic acid, and 5-hydroxtryptophaol are also indirect alcohol biomarkers.

Urine and whole blood are the traditional specimen types used to probe for recent ethanol ingestion or exposure. Non-traditional matrix types such as hair, nail, and dried blood spots (DBS) currently provide valid alternatives that offer advantages such as longer detection windows and ease of specimen collection.

4.2.1.1 Blood tests

Psychoactive substances are generally longer demonstrable in urine, hair, and nails than in blood. Blood testing is therefore mainly used for confirmation analysis testing when 1) an evidential breath test is positive for

alcohol; 2) a saliva test is positive for a drug; and 3) is used in forensic toxicology (e.g. Driving While Intoxicated testing).

4.2.1.2 Breath tests

"Evidential Breath Test" (EBT) is recommended for alcohol testing as it is non-invasive, provide immediate results and is scientifically and legally acceptable for workplace testing. Test devices should be compliant with the standard NEN 15964 (See https://www.transportation.gov/odapc/Approved-Evidential-Breath-Measurement-Devices for approved EBT devices).

When the EBT breath test is positive for alcohol, a confirmation analysis has to be performed using a different analytical technique. In the case positive breath alcohol, the confirmation analysis is in most cases done using blood taken by venipuncture.

A breath alcohol test determines the alcohol level the blood by measuring the amount of alcohol in the air the subject exhales. There are three main types of testing devices used to determine the blood alcohol concentration (BAC):

Breathalyzer - Uses a chemical reaction involving alcohol that produces a color change

Intoxilyzer - Detects alcohol by infrared (IR) spectroscopy

Alcosensor III or IV - Detects a chemical reaction of alcohol in a fuel cell

Each type is given by means of a device that has a mouthpiece, a tube through which the suspect blows air, and a sample chamber where the air goes. The advantage of breath tests is that they are easy to apply and give instantaneous results.

In the context of alcohol testing at the initial Class I medical assessment the most important disadvantage of breath tests is that it only detects use of alcohol within a limited time frame (up to 4-6 hrs) before the assessment. Therefore, breath testing is useful for Driving While Intoxicated testing or on-the-spot testing of pilots (Ramp testing) or ATCOs, but it is not recommended for alcohol testing at the initial or renewal aeromedical assessments because, as required by EASA, drugs and alcohol screening tests used should provide information regarding medium-term consumption (EASA, 2022). In the very odd case that an AME smells alcohol in an applicant's breath, it might be useful to use a breath test for on the spot confrontation. Such case should of course be further evaluated by confirmation tests and mental health expert consultation.

4.2.1.3 Urine tests

Because metabolites of drugs are excreted in urine, drugs are generally longer demonstrable in urine than in blood.

A urine test, or urinalysis, is the most common and economic test used for identification of drugs. Collection facilities should be used for convenience and a team should be hired to focus only on the results.

There are two types of urinalysis: the urine drug screen (UDS) and the urine drug analysis test or confirmation test. There is a huge difference between a drug screen and a urine drug analysis test. The urine drug screen (UDS; Enzyme Multiple Immunoassay Test = EMIT) comes first and is -in case of a positive result- followed by a urine drug analysis test for confirmation.

Drugs commonly tested and detection times in urine samples are alcohol (7-12 hours), amphetamines (1 - 2 days), methamphetamines (2 - 10 days), MDMA (ecstasy)(1-4 days), cannabinoids (THC 2 - 4 days), cocaine (2 - 4 days), phencyclidine (14 - 30 days), opiates (2 days), barbiturates (1 day - 3 weeks; short or long acting), benzodiazepines (3 days - 6 weeks; longer for chronic users), GHB (12 hours), ketamine (2 days), DMT (3 days), psilocybin (1-2 days), and methadone (3 days). Nitrous oxide (laughing gas) is not detectable in urine. Accuracy in urinalysis demands both the screen and the urine analysis test for those with positive results. The urine

analysis confirmation test should be done by gas chromatography-mass spectrometry or high-performance liquid-chromatography.

A drug screen (UDS) is very sensitive, and occurrence of false positives is inevitable in a population where the addiction rate is low, such as Aircrew and ATCOs. False positives have been reported for some painkillers, antibiotics, antihistamines, proton-pump inhibitors, poppy seeds, and some herbal teas (Table 4). However, a drug screen is faster and cheaper than a urine drug analysis test as it can be done with dipstick technology. A urine drug screen should be followed by a urine drug analysis test in case of positive results.

A major disadvantage of urine tests is that there are many methods for cheating published on the internet. The pH of human urine is usually near neutral (pH 7), although some biomedical conditions affect urine pH. The physiological range of the cut-offs for pH is based on a physiological range of approximately 4.5 to 9. Specimens with pH results outside this range should be reported as invalid. An extremely low pH (i.e., less than 3) or an extremely high pH (i.e., at or above 11) is evidence of an adulterated specimen. Research has shown that a specimen's pH may increase up to 9.5 in vitro when the specimen is subjected to high temperatures for an extended time. Therefore, conditions during specimen transport and storage may cause pH to be within the invalid range. Deliberate dilution of the urine specimen may occur by consuming large volumes of liquid, often in conjunction with a diuretic, or by adding water or another liquid. Donors also have been known to substitute urine specimens with drug-free urine or other liquid during specimen collection. Due to donor privacy considerations prevailing in many countries, collection for drug testing programmes is commonly unobserved.

Table 4 - Selected False Positives reported in Urine Drug Screen (UDS) (adapted from Markway & Baker, 2011)

SUBSTANCE	FALSE POSITIVES
Alcohol	Isopropyl alcohol
Amphetamine/Methamphetamine	amantadine, bupropion, chlorpromazine, labetalol, methylphenidate,phentermine, phenylpropanololamine, promethazine, pseudoephedrine, ranitidine, selegiline, thioridazine, trazodone, trimipramine
Barbiturates	fenoprofen, ibuprofen, naproxen
Benzodiazepines	oxaprozin, sertraline
Cannabinoids	efavirenz,fenoprofen,ibuprofen, naproxen, pantoprazole
Opates	dextrometorphan, diphenhydramine, gatifloxacin, ofloxacin, rifampicin, verapamil
Methadone	clomipramine, chlorpromazine, diphenhydramine, doxylamine, quetiapine, thioridazine, verapamil
Phencyclidine	dextrometorphan,diphenhydramine, doxylamine, ibuprofen, imipramine, ketamine, meperidine, thioridazine, tramadol, venlafaxine

Alcohol (ethanol) can be detected by direct markers such as Ethyl glucuronide (EtG) or ethyl-sulfate (EtS) testing, which are minor, non-oxidative ethanol metabolites that can be detected in several matrices (e.g. blood, urine, hair) for variable periods of time. In most cases EtG will be used to identify alcohol metabolites in the urine. When measured in urine after having more than 5 drinks in the preceding 24 hours, the sensitivity was 83% and the specificity 66%. The sensitivity decreased significantly to 39% (specificity 63%) when measured after 73 hours with drinking more than 5 drinks per day during the preceding 3 days. Wojcik & Hawthorne (2007) found that all urine samples collected beyond 26 hours after drinking 1.4, 2.9, and 4.3 standard doses of alcohol had false negative results. The authors concluded that to use a detection period as long as 80 hrs, which is a common idiom of the alcohol testing community, would result in low to moderate level drinking episodes going completely undetected. EtG in urine might be a useful test to identify alcohol use up to 24 hours after the last ingestion of alcohol.

The use of EtG analysis in hair to detect alcohol consumption over longer time periods will be discussed in section 4.2.1.6.

Phosphatidylethanol (PEth) is a specific metabolite of ethanol and is used as direct marker of ethanol consumption. PEth in whole blood as well as in a dry blood spot (DBS) is generally considered as specific for binge drinking during the past 2–4 weeks, while EtG in hair and fingernails is specific for repeated binge drinking in the last 1–3 months.

Fatty Acid Ethyl Esters (FAEE) are breakdown products of non-oxidative pathway of alcohol metabolism, formed by esterification of endogenous free fatty acids and ethanol by specific and non-specific enzymes in blood and several tissues. FAEEs in hair have been considered as a marker for chronic alcohol use. However, the Society of Hair Testing consensus states that use of ethanol-containing hair care products may lead to false-positive results.

The serotonin metabolite 5-hydroxytryptophol, known as 5-HTOL, is a normal, minor constituent of urine and is excreted mainly in conjugated form with glucuronic acid. The formation of 5-HTOL increases significantly after alcohol intake and the elevated urinary excretion remains for some time (>5-15 hours depending on dose) after ethanol has been eliminated from the blood. This biochemical effect can be used for detection of recent alcohol intake (Beck & Helander, 2003). The ratio of the serotonin metabolite 5-hydroxytryptophol (5-HTOL) to creatinine or to 5-hydroxyindol-3-ylacetic acid (5-HIAA) in urine has been proposed as a specific marker for short-term alcohol consumption. If no alcohol is used, the ratio 5-HTOL/5-HIAA is very low. The ratio identified circa 73% of all drinking occasions exceeding 7 g alcohol the previous evening or late afternoon, as compared with 22% by alcohol blood analysis. False-positive results have been reported in patients using drugs inhibiting the enzyme aldehyde dehydrogenase (Beck et al., 1995).

The measurements for the urine confirmatory analysis test are based on gas chromatography-mass spectrometry (GC-MS) or high-performance liquid chromatography with electrochemical detection. Although the advantage of this method is its high reliability, the GC-MS technique is time consuming, costly, and therefore these methods are only used for confirmation and are less suitable for primary screening purposes.

Conclusion

A urine drug screen (UDS) using dipsticks is useful to demonstrate the use of the most commonly used drugs in a period covering approximately 2 to 4 days before the test is taken. Due to its high sensitivity, false positives can occur. A laboratory urine analysis based on gas chromatography-mass spectrometry (GC-MS) or high-performance liquid chromatography enables to detect more types of drugs and alcohol (by EtG; reliable up to 24 hours afters ingestion; or PEth in a dry blood spot (DBS) for binge drinking during the past 2–4 weeks). If use of drugs and/or medication is to be identified over a longer time period before the initial aeromedical examination, hair (covering 30-90 days) or finger nails testing (covering 3-6 months) are to be preferred (see chapters 4.2.1.6 and 4.2.1.7). For the evaluation of drug use in the week prior to the aeromedical examination, a urine drug screen or urine EtG may be used because hair and fingernail testing do not cover this period.

4.2.1.4 Transdermal alcohol testing (TAC)

Approximately 1% of ethanol consumed is excreted through sweat. There are a range of wearable transdermal alcohol sensors that are available and are being developed. As ankle or wrist monitors, these devices have the potential to monitor alcohol consumption continuously over extended periods in an objective manner, overcoming some of the limitations of other alcohol measurement methods (blood, breath, and urine).The monitors can potentially be worn for long periods of time (e.g., months), passively collecting transdermal alcohol concentration (TAC) data for continuous alcohol consumption monitoring. They were developed to monitor alcohol abstinence rather than provide quantitative measurements of blood alcohol concentration (BAC). There is currently a lack of research investigating the accuracy of transdermal alcohol sensors as a tool for monitoring alcohol consumption in clinical populations and use over extended periods (Brobbin (a) et al., 2022; Brobbin (b) et al., 2022).

4.2.1.5 Oral fluid tests (saliva)

Swab drug tests are slightly less invasive than urine tests and can be randomly administered at any time and at any place. These tests are commonly used to determine if one has recently used drugs and focus on drugs such as opiates, marijuana, cocaine, and phencyclidine. The disadvantage is that only those drugs that are taken 1 to 48 hours prior to the test can be detected. Oral fluid tests are therefore not suited to use at the initial Class 1 screening where the authorities would like to cover substance use over a medium long time period. It is, however, the most rapid method for on-site drug screening and oral fluid (saliva) testing is the recommended method for Ramp drug testing. The test takes approximately 15-20 minutes and provides instantaneous results. In some countries saliva drug testing is therefore used for Driving While Intoxicated testing by the police. An advantage of oral fluid tests is that, in contrast to urine testing, it is very difficult to tamper with the sample. A disadvantage is that sample collection may be hindered by lack of available oral fluid (dry mouth syndrome). Dry mouth syndrome is relatively common and can be caused by the anxiety of the collection procedure, or lack of proper hydration of the individual. Or anticholinergic effects due drug or medication use itself (e.g. amphetamine, ecstasy, cannabis, anticholinergic drugs, and antidepressants) (Drummer, 2006).

Conclusion

Oral fluid testing is considered less suited for drug testing in the context an initial or renewal aeromedical examination because only those drugs that are taken 1 to 48 hours prior to the test can be detected. For the odd case that evaluation of drug use in the two days prior to the aeromedical examination is indicated, an oral fluid test might be used because hair and finger nail testing do not cover this period. When the aim is to detect and remove drug impaired persons from the aviation safety sensitive activities, oral fluid testing is recommended. It should be emphasised that positive results of oral fluid tests should always be confirmed by a confirmation test based on mass spectrometry (Liquid Chromatography-Mass Spectrometry) to provide legal evidence.

4.2.1.6 Hair testing

Hair testing is also known as “hair follicle screen” although the hair follicles are not used for the tests. Hair testing is an increasingly common method of assessment in substance misuse, particularly in legal and regulatory proceedings. Hair testing is usually twice to three times as expensive as urine testing, depending on the number of analyses that is required. Another drawback is that the availability of testing facilities is still very limited in some of the Member States.Tampering with the sample is much more difficult than with urine testing. If the applicant has no hair on their head, hair from the nape of the neck can be used as well. Hair analysis has the virtue of showing a 'history' of drug use due to hair's slow growth. The standard hair follicle screen covers a period of 30-90 days with hair growing at around 1cm per month; each centimetre can usually identify drugs consumed in 30 days, although certain cosmetic treatments (e.g. dyeing or bleaching hair) can interfere with this. A disadvantage is that after a drug is used, it takes about 7-10 days for the hair containing the drug to grow out of the scalp enough to be cut. Therefore, the hair test will not include drugs used in the week prior to the

test, which may be a disadvantage. Over 30 drugs including alcohol (as metabolite ethylglucuronide = EtG) are able to be identified in hair. The cut-off value of EtG in hair is set at 30 pg/mg. However no standardized protocols are yet available for the analysis of EtG levels in hair samples, and the current protocols vary in sample preparation and extraction procedures. Variables such as hair length, cosmetic treatment, gender, and pathophysiological conditions influence the final results and should be taken into account when interpreting the results (Crunelle et al., 2014; Biondi et al., 2019).

Considerations concerning hair testing:

- Timing of test: before or after, or in conjunction with aeromedical assessment? It might be logistically easiest to perform the test in conjunction with the medical assessment. In case hair or fingernail testing is used, the applicant has the opportunity to prove sobriety of drugs and alcohol during the 90 days preceding the medical assessment. If hair analysis will be used for alcohol and drugs testing in the context of initial Class I medical assessments, applicants should receive the information and education material at least 30, 60, or 90 days before the assessment date depending on the time period that should be covered by the analysis (AeMC to decide).
- Testing can take place at the facility where the medical assessment takes place, or in a specialized laboratory. If hair is taken from the head at least 3.5 to 4 cm containing 90 to 120 strands of hair (in practice: a pencil thick lock of hair) from the backside of the head should be taken to cover a 90-days drug history. In cases of baldness, hair from the nape of the neck can be used as well. If hair is taken from the chest, legs, underarms, or pubic region, then the collector has to shave and collect a cotton ball size of hair (approximately 0.5 grams).
- Handling of results. It is recommended have this done by impartial, trained Medical Review Officers (MRO) who are independent from the applicant, ensure a proper process, and determine the true positives. An MRO could be a member of the AeMC staff, but not the AME assessing Class 1 fitness of the applicant.
- Safeguards for the process should be laid down in rules which are transparent to the applicant e.g. chain of custody, legally secure, robust process, confidentiality.
- Quality standards including the accreditation of the service and ISO standard. Initial screening and confirmation methods must be based on different principles of analytical chemistry or different chromatic separations (first test immunoassay, confirmation gas chromatography). Tests should be carried out by an accredited laboratory using accepted guidelines for procedures.
- Define procedure to be followed in the event of a positive test; consider impact on stakeholders (confidentiality, employment, loss of license, cost, litigation etc. Individual rights vs. public safety).
- Consider data collection with ongoing risk and trend analysis to drive policy and process development.
- Define policy on health promotion and safety management, with focus on prevention and support. For a pilot who has a drug or alcohol problem, whether it is identified by a positive test, via self-report, or peer report, there should be a drug or alcohol intervention programme that includes assessment, treatment, education, counselling, consultation with health care professionals, residential or non-residential treatment programs, monitoring and follow up action. Such programmes can best be run and coordinated by a Peer Support Programme (or 'Peer Intervention Programme') which is an independent body/foundation – in practice usually the professional pilot association in cooperation with the regulator and the airline – that runs a programme into which pilots can report concerns about their colleagues and/or where pilots can turn to for advice and help with a specific problem, such as problematic substance use.

Advantages of hair testing

- Hair analysis shows a 'history' of drug use covering a period of 30-90 days; each centimetre can usually identify drugs consumed in 30 days.
- Tampering with the sample is much more difficult than with urine.
- Over 30 drugs + alcohol (EtG) can be identified. Up to now the screening and quantification methods have been validated for the analysis of drugs from different groups: opiates, amphetamines, hallucinogens, benzodiazepines, antihistamines, antidepressants, antipsychotics, barbiturates and other sedatives, and muscle relaxants (Montesano et al., 2014).

Disadvantages of hair testing

- Hair testing is more expensive than urine or saliva testing. Prices are from 100 to 200 € depending on the laboratory and on the number and the type of drugs/medication that are to be analysed. EtG (alcohol) analysis is often quite expensive: around 250 €.
- Hair testing will not detect drugs used 7-10 days prior to the test.
- Certain cosmetic treatments (i.e. dyeing or bleaching hair, use of hemp oil) and swimming in a chlorinated pool can interfere with the analysis.
- Finding cannabinoids in hair does not prove cannabis consumption. All three cannabinoids can be present in hair of non-consuming individuals because of transfer through cannabis consumers, via their hands, their sebum/sweat, or cannabis smoke (Moosmann et al., 2015). This may be considered in cases in which hair analysis is positive for cannabis, while the person concerned denies to have used it (such case would need further evaluation). However, most analytical laboratories currently state that they apply decontamination techniques that adequately remove environmental contaminants like sweat, sebum, dust, cosmetics and hair colours in order to avoid the risk of false positives.
- The availability of testing facilities is still very limited in some of the Member States.
- Turnaround times for results of hair analyses are often quite long (4-6 weeks) which can impact on the management of the initial Class I assessment.

Conclusion

It is considered that hair testing is suited for initial pilot/ATCO, or pre-employment, or (if indicated) renewal drug testing because it provides a 30-90 days drugs/medication history of the applicant (i.e. antidepressants and tranquillizers can also be detected in addition to drugs). It should be taken into account that hair testing will not detect drugs or alcohol used 7-10 days prior to the test.

4.2.1.7 Fingernails testing

Fingernails grow at an average rate of 3.47 millimetres (mm) per month, or about a tenth of a mm per day. Drugs are incorporated into nails by a double mechanism: (i) deposition into the root of the growing nail via the blood flow in the nail matrix; and (ii) incorporation via the nail bed during growth from the lunula to the beginning of the free margin (Palmeri et al., 2000). Drugs can be identified in nail clippings 2-4 weeks following ingestion and can be detected up to 3-6 months after last usage. Fingernail samples are highly stable, simple to collect, and easy to ship and store. Fingernails are, like hair, made up of keratin. As the nail grows, substances can pass from the blood vessels below the nail into the keratin fibres where they become trapped. Fingernails are four times thicker than the typical strand of hair and often capture more of a substance than hair can. Biomarkers become locked in keratin fibres along the entire length of the nail. The time period during which drug or alcohol ingestion can be detected depends on the substance used, the amount used, and personal metabolism. Fingernail samples are clipped and collected by the donor in front of a trained collection staff member. A clipping of 2-3 mm long (about the width of a quarter) from all ten fingernails will give about 100 mg of sample, which is the ideal amount for screening and confirmation. The advantage is that drugs and alcohol use can be traced over a very long period before the assessment. A major disadvantage is that recent

use up to 4 weeks from the assessment date may be missed. If fingernail analysis will be used for alcohol and drugs testing in the context of initial Class I medical assessments, applicant should receive the information and education material at least 6 months before the assessment date, which may be a disadvantage of using this method. The same substances that can be analysed in hair, can also analysed in nail clippings and methods are reliable and validated (Shu et al., 2015). Scientific data indicate that EtG cut-off levels in nails should be set significantly higher compared to the established 30 pg/mg EtG cut-off in hair representing heavy drinking. EtG may disappear faster from nail than expected from nail growth physiology (Fosen et al., 2017).

Conclusion

Fingernails testing provides a 3-6 months drugs/medication history of the applicant. The detection period is longer than for hair testing, which might be an advantage. However, the non-detection period of nail testing is also longer than for hair testing (2-4 weeks following last ingestion) which might be a disadvantage in comparison to hair testing. Applicants should receive information at least 6 months before the assessment date, while in the case of hair testing this period would be 3 months (90 days).

Apart from the above-mentioned differences between hair testing and nails testing, both methods seem to be suited for initial pilot/ATCO, or pre-employment, or (if indicated) renewal drug testing.

4.2.1.8 Indirect biomarkers

There are currently no indirect markers that are used to identify drugs use. Indirect biomarkers for alcohol use are various liver enzymes such as alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), and gamma-glutamyl transferase (GGT) which are formed due to toxic effects of alcohol to the liver in heavy drinkers. In addition, mean corpuscular volume (MCV), carbohydrate-deficient transferrin (CDT), beta-hexosaminidase, total serum sialic acid, and 5-hydroxtryptophaol are indirect alcohol biomarkers. In the context of aeromedical examinations beta-hexosaminidase, total serum sialic acid, and 5-hydroxtryptophaol will not be discussed because their analysis is expensive and has to be done by specialised laboratories which may not be available in all EASA member states.

The most frequently used indirect biomarkers for alcohol misuse are GGT and CDT. Table 1 shows that scientific data about their sensitivity and specificity provide very diverse values depending on how stringent the screening test was and the prevalence of alcohol (mis)use in the sample of people used in the analysis (e.g. alcohol addicts, general population). Predictive values are more relevant than are sensitivity and specificity when people are being screened (Trevethan, 2017) and Negative Predictive Value (NPV), Positive Predictive Value (PPV), and accuracy are affected by prevalence (Ray et al., 2010). However, PPV and NPV are in most cases not reported in articles.

Table 5 - Sensitivity and specificity of indirect alcohol markers in heterogeneous populations and the direct alcohol marker EtG. GGT = gamma-glutamyl transferase; MCV = Mean Corpuscular Volume; CDT = carbohydrate-deficient transferrin; uEtG = ethyl glucuronide in urine. (Sillanaukee, 1996; Schmitt et al., 1997; Grodin et al., 2020]

MARKER	SENSITIVITY %	SPECIFICITY %	T½ ELIMINATION
GGT	37-95	18-93	2-3 weeks
MCV	40-89	80-90	3 months
CDT	39-94	82-100	2 weeks

uEtG	83	66	<24 hrs after >5 drinks
uEtG	39	63	After 73 hrs >5 drinks/day

The range of values reported for the sensitivity and specificity in different studies of any biomarker are often very wide. The cut-off point has a direct effect on sensitivity and specificity. When a cut-off point is set for a high sensitivity, the specificity will decrease and this may lead to a high false positives rate in populations with a low prevalence of alcohol misuse. The appropriate marker or combination of markers should be chosen in each case according to the particular question that is to be answered by laboratory analysis. E.g. in acute cases where alcohol abstinence has to be demonstrated in forensic cases, such as driving while intoxicated, direct biomarkers (such as urine EtG, breath alcohol, etc.) are more useful than indirect markers (such as GGT and CDT) which in turn may be used for screening of chronic excessive drinking.

For aeromedical screening of pilots and ATCOs, populations in which the prevalence is likely to be low, it is considered useful to have a high sensitivity in order to find possible red flags (suspicion) for alcohol misuse at the cost of a higher false positive rate. The false positive cases may then be identified during a further detailed evaluation. With regards to aeromedical screening it should be considered that the analysis of the indirect biomarkers beta-hexosaminidase, total serum sialic acid, and 5-hydroxtryptophaol has to be done in specialised laboratories and is much more expensive than GGT and CDT analysis. Therefore, analysis of these biomarkers is currently not relevant nor suited for use in the aeromedical examination practice.

The sensitivity of ALAT, ASAT, and MCV to identify chronic excessive drinking is rather low (respectively 15-40%, 25-60%, and 40-50%; Schmitt et al., 1997). For aeromedical screening of pilots and ATCOs, GGT and CDT are recommended as indirect biomarkers for alcohol misuse. This recommendation is based on the fact that GGT has a high sensitivity when screening on a population level, but has a low specificity and CDT has a low sensitivity when screening on a population level, but has a high specificity. These biomarkers have the advantage that they can be measured as part of inexpensive routine testing in clinical-chemistry laboratories.

GGT

The rise in serum levels of GGT in response to alcohol consumption varies between individuals and within individuals according to their drinking patterns and history. A positive correlation between ethanol intake and serum GGT activity have been established in many studies. The minimal alcohol consumption required for having an elevated GGT is about 74 g/week for men and 60 g/week for women (Sillanaukee et al., 2000). GGT levels increase after excessive alcohol intake that has continued for several weeks, rather than episodic heavy drinking. The level of GGT generally returns to normal reference range in 2-6 weeks after abstinence (half-life of GGT is 2-3 weeks; table 1). Therefore, GGT levels are used as an indicator of chronic consumption of alcohol (Niemelä, 2016). GGT never increases with a single dose of alcohol unless the person has previously been an excessive drinker.

The low specificity of GGT is caused by the fact that GGT levels can also be increased due to non-alcoholic liver diseases such as biliary cirrhosis, obesity, pancreatitis, prostate-related diseases, diabetes, hypertension, hypertriglyceridemia, smoking, and use of medications (hormones and anticonvulsants).

CDT

Excessive alcohol intake of >50–60 g ethanol per day over a period of at least 1 to 2 weeks results in the loss of carbohydrate side chains of transferrin. Carbohydrate-deficient transferrin (CDT) is a specific, but not very

sensitive biomarker (table 1). In unselected populations the sensitivity of CDT is lower and the specificity is higher than that of GGT. CDT is therefore less suitable for screening of a population with a low prevalence of alcohol abuse and GGT is more suitable for such screening. CDT is useful to indicate chronic excessive drinking and for monitoring during treatment of alcohol addiction. Biological factors, such as genetic variants, female hormones, end-stage liver disease, and an elevated BMI (Body Mass Index) can increase CDT levels, resulting in false-positives. In these cases caution should be applied when interpreting %CDT results. Moreover, a small percentage of the population is CDT insensitive. Heavy alcohol consumption does not raise the level of CDT in these cases which can lead to false negativity (Zühlsdorf et al. 2016). Therefore it is generally recommended to use CDT in combination with another alcohol biomarker, such as GGT. Allen et al. (1994) showed that, in largely unselected populations, combining GGT with CDT, tended to substantially raise sensitivity, whereas specificity was minimally reduced. Although it has a low sensitivity, MCV remains longer elevated after chronic excessive alcohol consumption than GGT/CDT (3 months vs. 2-3 weeks). Therefore, MCV might be a useful addition if identification of chronic excessive alcohol consumption should cover a period of 2-3 months. The combination of GGT, MCV, and CDT was found to have a sensitivity of 88% and a specificity of 95% (Mundle et al., 1999; Helander, 2003). The period of abstinence before the blood test had a strong influence: the longer the period of abstinence prior to the test, the lower the sensitivity was.

CDT is reported as the percentage of CDT of the total transferrin concentration in blood: %CDT – Cut-off 1.5-2.5% (laboratory specific). A combination of GGT and %CDT, based on the formula [0.8×ln(GGT)]+[1.3×ln(%CDT)] is superior to %CDT as an alcohol biomarker (Anttila et al., 2003). With a cut-off value of 4.18 (for men) and 3.81 (for women) this combined GGT-CDT biomarker reached a sensitivity of 90% and a specificity of 98% in a study comparing 165 documented heavy drinkers with 86 healthy volunteers who were either abstainers or moderate drinkers (daily alcohol consumption between 1 and 40 g) (Hietala et al., 2006).

It is important to emphasize that alcohol biomarker test results should never be interpreted in isolation, but always in the context of medical history, clinical findings and the patient's mental and physical state of health.

4.3 Conclusions and recommendations

4.3.1 Tests suitable for testing use of psychoactive substance in the initial Class 1 medical examination and future initial Class 3 ATCO medical examinations

For an initial aeromedical examination it is useful to have objective information about an applicant's history of possible psychoactive substance use. Therefore, psychoactive drug tests should provide information regarding medium-term consumption and for that purpose analysis of hair samples or nail clippings offer the best opportunities. Hair analysis is considered best suited for initial Class 1 pilot/Class 3 ATCO, or pre-employment psychoactive substance testing because it provides a 30-90 days drugs/medication history of the applicant (i.e. antidepressants and tranquillizers can also be detected in addition to drugs). For hair analysis, screening and quantification methods have been validated for the analysis of drugs from different groups: opiates, amphetamines, hallucinogens, benzodiazepines, antihistamines, anti-depressants, antipsychotics, barbiturates and other sedatives. However, it should be considered that no standardized protocols are currently available for the analysis of EtG levels (alcohol) in hair samples and that EtG analysis in hair is expensive and availability of laboratory facilities may be limited. If it is decided not to request an EtG analysis in hair, it can be considered to perform a Phosphatidylethanol (PEth) test in whole blood or using a dry blood spot (DBS). This test is generally considered as specific for binge drinking during the past 2–4 weeks. The available laboratory facilities for PEth analysis might, however, be limited. Because laboratory facilities in all member states will allow for GGT/CDT analysis, GGT in combination with CDT is recommended to identify chronic excessive drinking, although the GGT/CDT combination only covers the period of 2-3 weeks prior to the examination. To extend

this period to 2-3 months, it can be considered to add determination of MCV in the combination with GGT and CDT.

Similar to analysis of hair samples, analysis of nail clippings can also provide the longer-term psychoactive substance history of the applicant. The detection period is longer than for hair testing (up to 6 months for fingernails – toenails up to 12 months), which might be an advantage. However, the non-detection period of nail testing is also longer than for hair testing (2-4 weeks following last ingestion) which might be a disadvantage in comparison to hair testing. It should also be considered that applicants should receive information at least 6 months before the assessment date when a 6 month detection period is preferred and this might be logistically difficult. The cost of nail testing and hair testing are similar. Analysis of nail clippings may be a useful back-up for hair analysis when hair is unavailable.

4.3.2 Tests suitable for screening of psychoactive substance use in the context of the examinations for renewal of Class 1 medical license and initial/renewal Class 2 and renewal Class 3 (ATCO) medical licenses.

A urine drug screen (UDS) using dipsticks is best suited to demonstrate the use of opioids, cannabinoids, amphetamines, cocaine, hallucinogens and sedative hypnotics over a time period covering approximately 2 to 4 days before the test is taken. Due to its high sensitivity, false positives can occur. A positive result of an UDS should be followed by a urine drug confirmation test using gas chromatography-mass spectrometry or high-performance liquid-chromatography. When the AME has indications that psychoactive substance use has to be excluded over a longer time period, hair analysis is best suited for that purpose. The AME can consider ordering such analysis when evidence is found that an applicant might have been using (a) psychoactive substance(s) and a UDS is negative.

Because misuse of alcohol cannot be identified by a UDS, analysis of EtG in urine is suitable to demonstrate excessive alcohol use within 72 hours prior to the examination. However, many harmful alcohol users will try to abstain from alcohol in the days prior to the examination. Depending on the available laboratory facilities, it can be considered to perform a Phosphatidylethanol (PEth) test in whole blood or using a dry blood spot (DBS). This test is generally considered as specific for binge drinking during the past 2–4 weeks. If evidence has to be found for chronic excessive alcohol use, the combination of serum levels of GGT and CDT - using the formula [0.8×ln(GGT)]+[1.3×ln(%CDT)]- is the most suitable method to be used in these examinations.

4.3.3 Maximizing the usefulness of drugs and alcohol testing in the initial Class 1 medical assessment by education on medication, alcohol and drugs, and mental health problems

The yield of drugs and alcohol testing at the initial Class I medical assessment is anticipated to be comparably low to the yield of pre-employment testing of pilots. Statistical evidence from US data demonstrates that pre-employment testing is effective in excluding people with identified illicit drug usage from employment in safety sensitive roles. In the period 1990 – 2002 this type of testing produced 20,827 positive results for drug use among persons seeking to enter employment in the US aviation industry (CASA, 2006). However, these statistics do not indicate which categories of personnel were tested, or the total number of tests done.

The significance and usefulness of a negative drugs and alcohol test at the initial aeromedical assessment are very limited in the context of flight safety because among the aircrew members, that have passed the initial test, dependency on alcohol/drugs and mental problems –as in most cases- may evolve during their professional career (Simons & Valk, 2003).

Testing of drugs and alcohol at the initial Class I medical assessment is useful to enforce the regulations – viz. show the applicants the seriousness of all regulations concerning use of drug and/or alcohol by aircrew. At the same time this testing requirement provides a 'golden' opportunity to educate aircrew on the safety risks of illicit drugs, medication, and alcohol and to stimulate their awareness of the safety consequences of mental health problems and life stress. A prerequisite of drugs and alcohol testing during the initial Class I assessment is that publicly available information should enable the applicants to inform themselves well in advance about:

1) that there will be a mandatory drugs and alcohol testing during the medical assessment, including method of testing and legal aspects;

2) the rationale of testing: what are the risks of drugs and alcohol in terms of flight safety and personal well-being;

3) information concerning the use of over-the-counter (OTC) and prescription drugs: tell your physician that you are/intend to become a pilot or an ATCO and that use of medication may be subject to restrictions; always inform the AME about the use of medication; be aware that some medication can cause a false positive drugs test;

4) information about life stresses which can emerge during the pilot career and how these can become mental health problems affecting performance, flight safety, and personal well-being;

5) information about Peer Support Systems: how the system works and how to access the system in case of problematic drugs and alcohol use or mental health problems of yourself or a colleague.

The applicant should be enabled to study above information well before the date of the medical assessment. During the medical assessment, the AME should take the time to discuss all the above issues in order to provide the applicant with sufficient knowledge to guarantee a basic awareness on the flight safety consequences of drugs, alcohol, medication, and mental health problems at the start of her/his commercial pilot career.

Applicants should know that self-reporting of addiction or mental health problems will improve flight safety; that one can recover from addiction and/or mental health problems; and that self-reporting can be the start of regaining a healthy and safe pilot or ATCO career.

Prerequisites for the above approach are sufficiently trained and dedicated AMEs, the existence/availability of Peer Support Programmes and a (no blame) Just Culture.

4.4 Random testing of Aircrew

There are two forms of random testing: 1) random testing within a group of individuals (individuals to test are randomly selected), and 2) random testing of an individual (time points of testing are randomly selected).

The first form (1) concerns 'No-notice' testing of individuals who are randomly selected from a group (e.g. crew members of flights departing on a certain calendar day). In most cases, regulators mean this form of testing when they refer to 'random testing'. Authorities or employers must use a truly random selection process and each individual must have an equal chance to be selected and tested.

The second form (2) concerns 'No-notice' testing of an individual at randomly selected times during his/her employment. This form of random testing is used to check for abstinence from alcohol or drugs of individuals who have been treated for problematic use of alcohol or drugs or for individuals who are suspected to use, or have used drugs or alcohol. This form of testing also applies to the RAMP alcohol testing programme (discussed in section 4.4.1) as well as operator or national random testing programmes (which could include both alcohol and drugs) or the testing during the period of suspension in the context of an alcohol or drugs rehabilitation programme.

The rationale of random testing is one of deterrence: individuals who are aware that they could be subject to random, unannounced searches for evidence of prohibited conduct will choose not to engage in such conduct if they perceive a likelihood of the use being detected and that adverse consequences will apply if detection occurs.

The PROs of Random Testing are:

- One of the primary benefits of random testing is that it has a pro-active deterrent effect on the decision to ingest performance impairing substances.
- Random testing has minimal selection bias and uses an objective method.
- Another benefit may be public trust. Even if it may be doubtful that random testing of aircrew will mitigate all risks related to the misuse of psychoactive substances, it will increase the trust of the general public and decision makers in the aviation system. This is demonstrated by the political and public call for random drug and alcohol testing after the German Wings catastrophe.
- In addition to its purported deterrent effect, random testing may provide data for answering important research questions. Analysis of random testing data can help to estimate the point prevalence rates of alcohol violations among airline employees with safety-sensitive functions by occupation and over time. The results of the study are valuable for monitoring alcohol violations in aviation employees and for program evaluation and policy reform (Li et al. 2007).
- Random testing is a valuable tool in the context of alcohol and drug treatment and rehabilitation programmes. In such programme random testing will be implemented when an individual has been treated for problematic use of alcohol or drugs. There is convincing evidence that this form of random testing is essential to maintain this person's abstinence from alcohol or drugs.

The effects of random testing on deterrence are difficult to substantiate and there is little robust evidence on the deterrent effects of random drug testing for either illicit drugs or alcohol in the workplace (Australian Safety and Compensation Council, 2007). Data from random drug testing programs show a low yield for alcohol testing. FAA random alcohol testing data showed an annual violation rate of 0.148% in 2020 which was not significantly deviant compared to the years before 2020 (https://www.govinfo.gov/content/pkg/FR-2021-11-23/pdf/2021-25511.pdf). For drug testing the yield appears to be somewhat higher: from 2006 to 2014 the mean annual random drug test positive rate was 0.524% and in 2020 it was 0.771% in the FAA programme, which covers flight crew, flight attendants, flight instructors, aircraft dispatchers, maintenance personnel, aviation screeners, ground security coordinators, and air traffic controllers. Violation rates for drugs were highest for maintenance personnel (1.00%) and aircraft screeners (1.16%) and lowest for flight crew (0.05%) (Li et al., 2011).

Whether there is a causal relation between the low yield of random testing of aircrew and the deterrence effect is difficult to study because it is likely that aircrew, who refrained from alcohol or drugs use because they feared detection by a random screening, are not likely to disclose their position.

It should be considered that hangover effects of alcohol will be missed by random testing (ramp or crew centre). Use of alcohol by pilots shortly prior to their flight is probably very rare in commercial air transport. However, harmful use of alcohol in the evening prior to a next-day flight is probably far more common practice (e.g. Modell & Mountz, 1990; Cook, 1997; Maxwell & Harris, 1999; ICAO, 1995; Simons & Valk, 2003). Pilots with residual effects of alcohol ("hangover") form an insidious danger for flight safety as these effects may cause subtle incapacitation which may not be noticed by other crewmembers. Alcohol will also disturb pre-flight sleep which presents an additional hazard to flight safety. Significant residual effects (also called "hangover", "carry-over" effects) on piloting skills which have been evidenced in several studies (Morrow et al., 1990; Taylor et al., 1994; Simons & Valk, 2003). These pilots will not be detected with random breathalyzer testing, because on

"the morning after the night before" they will have no alcohol in their blood or breath (BAC will be 0.0%; Simons &Valk, 2003).

Deterrence, to the extent it occurs, may occur within a group of occasional users and not in dependents or addicts (ICAO, 1995). Special consideration should be given to random testing for alcohol, which may be less useful to deter alcohol dependents than occasional users because there is only a narrow time window during which the BAC would be detectable. Once an individual escapes detection, the deterrence value of a random programme is diminished for that person and anyone who knows of the escape.

It should also be considered that urine drug testing has significant false positive rates caused by use of approved prescription and OTC medication, food (e.g. bread with poppy seed!), environmental contamination (e.g. THC), and methodological limitations (see section 4.2.1.3 urine drug tests). There is a concern with false positives where valuable flying time may be lost while a second test is conducted to confirm that it was a false initial positive. Should blood testing be required for confirmation of an initial test, results from these can take longer than 32 days (CASA, 2006). Random drug testing also has significant false negative rates. Point of Care (POC) testing in addiction treatment settings found high rates of clinically false negatives, that is, samples tested by POC were reported negative but laboratory gas chromatography-mass spectrometry or high-performance liquid-chromatography results were positive. Twenty-nine percent of opioids, 28% methadone, 43% amphetamines, 35% benzodiazepines, 40% cocaine, and 20% marijuana identified by gas chromatography-mass spectrometry or high-performance liquid-chromatography were missed by POC tests (ASAM, 2013).

It should be considered that there is a massive production and use of products to defraud or 'beat' random testing, and in particular urine drug tests. Some 400 products are marketed on the Internet and in drug-culture magazines with the objective of producing drug-free results.

4.4.1 EU Ramp Inspection Programme

The EU Ramp Inspection Programme as implemented by EASA concerns 27 EU Member States and 3 States of the EFTA Agreement. Since 2021 these States perform alcohol testing, while some of these also perform drug testing. Alcohol tests are carried out by Ramp Inspectors -in some States supported by the police- on flight crew and cabin crew in accordance with the Ramp Inspection Programme as defined in Commission Regulation (EU) No 965/2012 Part ARO.RAMP. In addition to the implementation of this random testing programme it is recommended that all Air Operator Certificate (AOC) holders and Air Navigation Service Providers (ANSPs) should have a drug and alcohol policy as part of their Safety Management System which should include a training and education programme, briefing on self-awareness and facilitation of self-referral for help with an alcohol or drug problem, procedures for monitoring the efficacy of the alcohol and drugs policy (this includes a drug and alcohol testing programme 'with cause', post incident/accident and random), and monitoring and support for return to work after rehabilitation for an alcohol or drug problem. EASA mentions that nothing should prevent operators and ANSPs to implement a random testing programme in accordance with national requirements on testing of individuals.

Alcohol tests must be performed with an approved breath alcohol analyser compliant with the standard EN 15964 (see section 4.2.1.2). The breath alcohol concentration should not exceed a level equivalent to 0.2 grams of blood alcohol concentration (BAC) per litre of blood (0.2‰). Every confirmed positively tested crew member will be prohibited to perform his/her duty and will be handed over to the legal enforcement body as appropriate, reported to competent aviation authorities, the licensing authority, and the state of the operator. Any refusal or lack of cooperation during an alcohol test will lead a prohibition of the aircrew member to perform his/her further duties.

In some member states the random test programme is performed by the ramp inspectors, or by the police in collaboration with the inspectors/authorities. Who is testing (ramp inspectors, police, authority, independent testing service, or combination of those) is depending on national laws, capacities, and experience.

Testing Procedure

Authorities that perform or require alcohol or - in some cases- drug testing have defined the following preconditions with regards to the testing procedure:

- Handling of results. It is recommended have this done by impartial, trained Medical Review

  Officers (MRO) who are independent from the applicant, ensure a proper process, and determine the true positives.

- Safeguards for the process should be laid down in rules which are transparent to the applicant e.g. chain of custody, legally secure, robust process, confidentiality.

- Quality standards including the accreditation of the service and ISO standard. Initial screening and confirmation methods must be based on different principles of analytical chemistry or different chromatic separations (first test immunoassay, confirmation gas chromatography).

- Tests should be carried out by an accredited laboratory using accepted guidelines for procedures.

- Define procedure to be followed in the event of a positive test; consider impact on stakeholders (confidentiality, employment, loss of license, cost, litigation etc. Individual rights vs. public safety).

What is tested?

All existing random testing programmes test for alcohol using EBT breathalyzers. Some programmes also test for drugs. Several States require a standard screen including cannabis, amphetamines, methamphetamines, cocaine, opiates, and benzodiazepines. Because the use of so-called 'party drugs' is presently widespread among the general population and young adults in particular, it is emphasised that, in addition to alcohol testing, random drug testing should be pursued in all States in order to extend the deterrence effect also to the use of drugs.

Deciding which drugs and medicines to test for should be determined by the individual national competent authority in conjunction with their aeromedical advisor. The selection will be influenced by the location of the safety critical workers, by employment and residence, and local factors including the availability of particular substances, accepted regional practices and availability of medicines, and certain types of food and drugs. Cultural practices and the diversity of the workforce and sectors flown should also be taken into account. Testing for specific prescription or OTC (over-the-counter) medications is not feasible in a standard random test setting, because each medication needs a specific test in a dedicated laboratory. Guidance on drugs to be tested may need frequent updates.

Test method

The decision which sample method to take depends on which drugs are to be identified and on logistical/ financial considerations. On-Site Testing (POCT) means testing in the crew centre before a flight or in the aircraft (on the ramp). The purpose is to do a quick screening test, which can be followed by a confirmatory test in positive cases. For this purpose breath testing (alcohol only), urine testing, and oral fluid testing are suitable, while hair testing is not suitable for quick screening as the hair has to be analysed in a specialized laboratory which will take a considerable time period before the results will be known. Moreover, recent drug use may be missed in hair samples because it takes one week after use before a drug or alcohol appears in hair in a measurable quantity.

A breath alcohol test determines how much alcohol is in the blood by measuring the amount of alcohol in the air one exhales. See section 4.2.1.2 for a discussion of the three main types of testing devices used to determine the breath alcohol concentration. The advantage of breath screening tests is that they are easy to apply and give instantaneous results. A disadvantage is that it only detects use of alcohol within a limited time frame (up

to 4-6 hrs) before the assessment, but the advantage is that it detects alcohol use within 6 hours before a flight and therefore enables the decision to ban a positive crew member from the flight.

A urine test, or urinalysis, is the most common test used for identification of drugs. Collection facilities should be used for convenience and a team should be hired to focus only on the results. See section 4.2.1.3 for a discussion of the urine drug screen and the drug test for confirmation.

Oral fluid (saliva) can provide a quick and non-invasive specimen for drug testing. However, its collection may be hindered by lack of available oral fluid due to a range of physiological factors, including drug use itself

(e.g., amphetamine, ecstasy, cannabis, anticholinergic drugs, and antidepressants). Dry mouth syndrome is relatively common and can –apart from above-mentioned drugs- be caused by the anxiety of the collection procedure, or lack of proper hydration of the individual. Dry mouths require much longer collection times; often several minutes to collect 1 mL. Food and techniques designed to stimulate production of oral fluid (e.g. citric acid candy, chewing gum) can also affect the concentration of drugs. Oral fluid concentrations of basic drugs such as amphetamines, cocaine and some opioids are similar or higher than those in plasma. Tetrahydrocannabinol (THC), the major species present from cannabis use, displays similar concentrations in oral fluid compared to blood in the elimination phase.

Oral fluid has been seen as a non-invasive alternative to blood but also as an alternative to urine when substitution or adulteration is suspected. The present generation of saliva testers operates on the basis of antibodies. This means that the substances similar to the body's own substances cannot be detected. The popular party drug GHB is such a substance and can therefore not be traced with a saliva tester.

The advantage of oral fluid drug tests is that they are less invasive than urine tests and can be randomly administered at any time and at any place. Since the collection of oral fluid specimen can be viewed by a second person without infringing privacy it does not suffer from the same issues regarding possible adulteration or substitution as for urine. In oral tests it is very difficult to tamper with the sample and detection is instantaneous. These tests are generally used to determine if one has recently used drugs and focus on drugs such as opiates, marijuana, cocaine, and phencyclidine.

Both oral fluid and urine testing have advantages and disadvantages. Whilst urine testing has a longer track record it is also more intrusive and logistically complex, and in an aviation setting, urine drug testing would pose challenging and costly issues around access to toilet facilities.

Oral fluid testing is more aligned with recency of use and therefore, by extrapolation, impairment. This is important when the aim of the testing programme is to detect and remove impaired persons from the aviation safety sensitive activities, and not to identify persons who may have used a substance at some time in the recent past. However, urine testing may be preferred by employers who aim to detect 'drug users' rather than impaired persons so that they can actively manage those who are at risk. Some oral fluid testers have a lower sensitivity for THC than most urine tests, although oral fluid has higher sensitivities than urine for some other drugs. CASA Australia uses preferably oral fluid testing (CASA, 2008), while urine testing is still commonly used for random tests under the requirements of the FAA. However, the US Department of Transport (DOT) has recently proposed to use oral fluid testing.

When using oral fluid drug testing the European Guidelines for Workplace in Oral Fluid of the European Workplace Drug Testing Society should be followed (http://www.ewdts.org/data/uploads/documents/ewdts-oral-fluid-2015-05-29-v02.pdf).

Minimum annual testing rate

For an effective deterrence effect it is important to realise a sufficiently high minimum annual testing rate. Therefore the minimum testing rate should be determined and evaluated by the Competent Authorities under supervision of EASA. E.g. the FAA/DOT has set the testing rate for drug testing in 2022 at 25% and at 10% for

alcohol testing. The rates can be defined by the FAA/DOT for each year based on the violation rate detected through random drugs and alcohol testing in the past year for the entire aviation industry (https://www.govinfo.gov/content/pkg/FR-2021-11-23/pdf/2021-25511.pdf).

Furthermore, it is important to exclude any possibility for prediction of test dates, or locations (aerodromes). That is the dates/flights and locations should be selected randomly using accepted methodologies.

Timing of test: Is Ramp testing possible?

With regard to random testing, the detail and under what circumstances a random test will be carried out needs to be considered carefully i.e. the location and timing of such tests.

The procedure of screening for alcohol using a breathalyzer will take no more than 1-2 minutes and can easily be performed on-site. Therefore, breath alcohol screening is suitable for ramp testing.

The most rapid method for on-site drug screening would be oral fluid (saliva) testing. Although the test itself can be done in a few minutes, it can take up to 20 minutes in case the mouth has to be washed because of contamination with food and other debris, or the screened person has a dry mouth syndrome. Therefore, when drug testing would be included in the ramp testing programme, it should be considered that in some cases this may lead to a delay of the flight.

Conclusion

It is concluded that for ramp testing alcohol can best be detected by a breath test, while the use of drugs can best be tested by collecting an oral fluid sample because this has clear logistical advantages over the collection of a urine sample. Taking the increase of recreative drug use in Europe into account, it is recommendable to pursue drug testing addition to alcohol testing, in all States involved in the EU Ramp Inspection Programme in order to extend the deterrence effect also to the use of drugs.

4.5 Testing sobriety of pilots and ATCOs in the suspension period after treatment of alcohol addiction

Alcohol and drugs testing is also used to demonstrate sobriety for pilots and ATCOs during the suspension period following treatment of alcohol or drug addiction. The EASA requirements state that:

“A fit assessment may be considered after a period of two years of documented sobriety or freedom from psychoactive substance use or misuse. At revalidation or renewal, a fit assessment may be considered earlier with an OML”. The goal of these requirements is to return the pilots or ATCOs to duty after successful treatment as soon as long-term sobriety can be guaranteed.

In this context, breath and urine analysis (e.g. by EtG and EtS), is limited by the short half-life of ethanol. There are technical methods to mandate candidates to perform and report a breath test at random times (determined by the computer software). However, this method cannot prevent fraud because any sober individual can replace the candidate to perform the breath test. Indirect blood markers of heavy alcohol consumption (e.g. GGT, liver enzymes, MCV, CDT) may have some limitations in terms of sensitivity or specificity, but a combination of GGT and %CDT, based on the formula [0.8×ln(GGT)]+[1.3×ln(%CDT)] can be useful and accurate to screen candidates on sobriety. An advange of testing GGT in combination with CDT is that the candidate has to show up in person at defined time intervals (e.g. 2-3 weeks) to have a venapuncture, thus preventing fraud.

In contrast to needing venapunctures, transdermal devices (TAS; see section 4.2.1.4), measuring alcohol in sweat, are non-invasive, objective, and easy-to-use allowing for the screening of alcohol in real-world contexts for weeks or months. The various types of TAS are worn on the ankle (similar to a house arrest monitor), or worn exclusively on the wrist and have approximately the same size as a watch. The transdermal alcohol monitors currently available are most commonly used by some countries in the criminal justice system to monitor offenders who have been ordered to abstain from alcohol. Because the aim of testing sobriety of pilots or ATCOs engaged in an alcohol rehabilitation programme is also to demonstrate that a candidate is abstaining from alcohol, use of transdermal devices for this purpose in the aeromedical practice should be considered.

The newer TAS devices have the potential to communicate wirelessly through a sim card or with a smartphone. Using this as a method of data collection could reduce the time and resources required for data capture.

Most TAS devices contain temperature sensors, which can detect if the device has been removed from the skin. The ability to see this allows for discussion with patients (why was it removed?). Fraud is still possible by removing the device and placing it on another (sobre) individual. How to identify or prevent this and other forms of tampering are issues that are currently studied by the various manufacturers and it is likely that these problems will be solved in the very near future. Current research also addresses longer-term accuracy and reliability, as well as wearing-comfort problems in real world situations. It is recommendable to evaluate the various new devices that will be developed in the coming years for their suitability to test sobriety of pilots and ATCOs in the suspension period after treatment of alcohol addiction (Brobbin (a), 2022).

5. How can the Aeromedical Examiner identify problematic use of substances?

5.1 The AME interview

Preambles

- As is stated in EASA AMC1 MED.B.055 Mental health, as part of the initial class 1 aero-medical examination the AME should conduct and record a comprehensive mental health assessment taking into account social, environmental and cultural contexts. The applicant's history and symptoms of disorders that might pose a threat to flight safety should be identified and recorded.
- Pilots and ATCOs are reluctant to report mental and/or emotional Issues to AMEs due to fears to lose their job and due to a widespread social stigma associated with mental health issues, such as alcohol and drugs misuse or dependency.
- Pilots and ATCOs are reluctant to seek treatment for mental health issues, or tell colleagues about their problems.
- According to the World Health Organisation, the General Practitioner's detection rate of mental health issues is low (33%; WHO, 2018; Haavet et al., 2021).
- Pilots and ATCOs are often unaware about the impact of their problems on professional performance and health.
- The decision to take the first step in opening up about mental health issues will always be a voluntary choice by the pilot.
- 27% of the adult EU population (aged 18–65) had at least one mental disorder in the past year: substance use, psychoses, depression, anxiety (Wittchen et al., 2011).
- As they are adult members of the European population, estimated prevalences of mental disorders might also apply to pilots and ATCOs, albeit that there can be slight differences related to their specific job characteristics, personality, or their selection criteria.
- Like members of the general population, pilots and ATCOs might be affected by stresses of life, such as work-related problems, financial worries, health concerns, bereavement issues, relationship / family difficulties, separation from family, and social demands. This may lead to impaired performance and to significant mental health problems in some cases (Hammen, 2005; Young, 2008).

History taking of the examinee is the most important part of the aeromedical examination and is the most important means of identifying suspicion ("red flags") of psychoactive substance misuse and mental health problems. Most clinical interviews by AMEs will be structured interviews. The advantage of structures interviews is that these are standardised which avoids missing important aeromedical questions. The disadvantage is that it may hinder an open and informative communication with the interviewees due to the fixed questions and the rigid structure. A rigid structure may also prevent interviewees to open up about emotional problems. As proposed by Bor et al., (2017), "a reasonable compromise is to divide a mental health assessment interview into a loosely structured first half followed by a more structured and systematic second half". The loosely structured start of the interview is to provide the AME with a "picture" of the pilot's or ATCO's life, family, and occupational environment. In this context, recommended subjects of questions and conversation are:

For initial, revalidation, renewal Class 1 and 2, and Class 3 ATCO (Hudson & Herbert, 2017; EASA, 2022):

- The Job: type of flying (pilots) or ATC work; employer details; length of service in current employment; full-time/part-time; total flying hours; hours flown since last medical; roster pattern: long-, medium-, short-haul; number of sectors flown in a duty period; Also for ATCOs: are rosters fair or reasonable?;

fatigue; job satisfaction/; attitude towards job; aspirations for future career development; difficulties with operational crew resource management (CRM); any difficulties with employer and/or other colleagues and managers; company peer support?
- Commuting: distance to work; commuting time; ease of commuting; mode of travel; return journey home.
- The applicant's role and attitude in accidents or incidents, problems in training or proficiency checks, behaviour or knowledge relevant to the safe exercise of aviation tasks relevant for their class of licence.
- Coping strategies under periods of psychological stress or pressure in the past, including seeking advice from others;
- Family arrangements: married, co-habiting, or single; relationship; ages of children; child care; family life; health issues family; partner employment;
- Interpersonal and relationship issues, including difficulties with relatives, friends, and work colleagues
- Security: (for pilots) airport security checks; fear of terrorism, unruly passengers?
- Finance: concerns about money; debts; overtime; second job?
- Hobbies: other interests, hobbies; what do you do in your spare time?
- Holidays: how many times/year; where do you go?; does the family join?

Followed by a structured medical history taking on:

- Health, illness, symptoms, organ systems (functioning, complaints)
- Sleep: quality and amount (at home and on stopovers); jet lag / shift work; rest arrangements prior to duty; sleep medication? Snoring?
- Exercise/diet: activities; diet; food during work.
- Medication: prescribed; over-the- counter; via internet
- Drugs/alcohol/smoking habits: alcohol type/amount/binge drinking; suggested bottle to throttle time; social / party drugs; legal highs; driving license offences (Driving While Intoxicated)?

In addition to the above and specifically for initial Class 1 examination (EASA, 2022):

- general attitudes to mental health, including understanding possible indications of reduced mental health in themselves and others;
- childhood behavioural problems;

Analysing driving-while-intoxicated (DWI) convictions in the context of flight safety

It is considered that pilots or ATCOs who have been convicted for driving-while-intoxicated have shown irresponsible behaviour associated with use of alcohol. Such pilots and ATCOs may be considered prone to violating rules also in other fields than aviation safety and may likely do this also when it comes to job-related safety requirements, including but not limited to the (mis)use of alcohol and/or drugs. Therefore, DWI convictions should be taken into account when considering alcohol-related risk profiles of individual pilots (Simons & Valk, 2003). This view is supported by a study by McFadden (1997), who analysed FAA data on flying performance of 70164 airline pilots to correlate with either DWI convictions or positive random alcohol testing results. DWI convictions were found to be associated with a significantly greater risk of pilot-error accident. In contrast, no evidence was found to validate the assumption that a random testing program could have prevented accidents. These results provide background for implementing a DWI background check program for pilots. In analogy with FAA's Federal Aviation Regulation 14 CFR 61, It is recommended that the regulator requires a pilot or ATCO to report any DWI conviction. It should be considered that each DWI-convicted pilot or ATCO should have an aeromedical expert examination to judge the flight safety consequences of this fact.

All information that gives clues to potential problems should be followed by a dedicated in-depth interview. When there is an indication for mental problems, including misuse of psychoactive substances, pilots/ATCOs should be referred to a mental health expert.

As required by EASA in AMC1 MED.B.055 Mental health (EASA, 2022), the following aspects should be taken into consideration when conducting the mental health examination: Appearance; Attitude; Behaviour; Mood; Speech; Thoughts process and content; Perception; Cognition; Insight; and Judgement.

In order to find suspicion or red flags for misuse of psychoactive substances, the AME should give particular attention to behavioural, social, or medical signs that may be associated with substance misuse.

Red flag signs of alcohol misuse:

- Mood disorders and mood swings.
- Anxiety disorder, depression, ADHD, and PTSS are known for a higher risk of alcohol misuse (e.g., Shivani et al., 2002).
- Gastro-intestinal problems, reflux symptoms, gastritis, diarrhea, pancreatitis, hepatitis.
- Cardiac arrhythmia (unexplained by cardiac conduction disorders).
- Uncontrolled hypertension (unexplained by other causes)
- Insomnia and hypnotic use.
- Chronic headache (unexplained by other causes)
- Psychosocial problems (at work or at home),particularly in combination with Syncope, black-outs, frequent accidents or fractures.
- Hangovers including headaches and nausea and vomiting.
- Spider-naevi, facial plethora.
- Hand tremor.
- Sexual problems.
- Evidence of family violence
- DWI conviction
- Aggressive, antisocial behaviour.
- Family history of addiction

Red flags for drugs misuse (e.g., NIDA, 2020):

- Behavioural changes
- Mood swings
- Anxiety disorder, depression (or vice versa?)
- Increased need for privacy
- Decreased anger control
- Increased risk-taking
- Sleep problems
- Loss of interest in hobbies, sport, or other activities
- Loss of interest in family members, friends
- Reduced personal hygiene
- Snotty or running nose, nose bleeds, lost sense of smell (cocaine)

5.2 Questions and Questionnaires to identify misuse of psychoactive substances

There are many questionnaires developed to identify alcohol misuse or to identify use of drugs. Their suitability for screening purposes varies with the target group for whom the questionnaire was developed, the aim of the questionnaire (e.g., to identify alcohol dependence, hazardous drinking, or follow-up during treatment), the cut-off points used, and the classification of alcohol misuse that is used. There is a multitude of questionnaires that use essentially the same basic questions. Many questionnaires contain additional detailed questions of which the specificity depends on the purpose and target population. In the context of reviewing questionnaires

that potentially qualify to be used for aeromedical screening of pilots and ATCOs, only the most commonly used questionnaires will be discussed in the present report. In general, it is recommendable that AMEs use the essential basic questions to identify a suspicion or "red flag" concerning use of psychoactive substances. In case suspicion is raised more detailed questions can be asked and/or the applicant will be referred to a peer support programme or mental health specialist.

When considering to use questionnaires for alcohol or drug screening of pilots or ATCOs in the context of a mandatory initial or renewal medical examination, it should be realised that:

- All available questionnaires are designed and validated for clinical use among patients who visit a health care facility to seek help, or for studies to assess the prevalence of psychoactive substance use in a specified population/cohort. Patients generally seek help for their health problem and tend to be cooperative to diagnose and treat their problem and, although they might be reluctant to admit psychoactive substance use, they are motivated by their wish to rehabilitate to give honest answers to most questions. Subjects participating in prevalence studies are assumed to answer honestly because anonymized data analysis will be guaranteed in such studies.
- In contrast with patients who visit a health care facility, or anonymous study participants, pilots and ATCOs do not seek help when they visit the AME for their mandatory medical screening. They are highly intelligent individuals highly motivated to be declared fit for the job and to obtain or renew their medical certificate. For aeromedical screening purposes paper/pencil and electronic versions of the available questionnaires are considered not suitable for the purpose, because pilots and ATCOs will easily recognise what they should answer to make sure that their answers have no consequences for their professional career. Therefore, AMEs are advised to try and build a trustful relation with the applicant and to use selected questions from the available questionnaires and "wave them in" into the medical history taking.

Single Question Alcohol Screen

A single screening question about whether a patient has recently consumed more than 5 drinks (more than 4 drinks for females) in one day has been found to be effective in identifying at-risk drinking among primary care patients. In a sample of 394 adult English-speaking patients recruited from primary care waiting rooms, the single-question screen was 81.8% sensitive and 79.3% specific for the detection of unhealthy alcohol use. It was slightly more sensitive (87.9%) but was less specific (66.8%)for the detection of a current alcohol use disorder. Test results were similar to that of a commonly used three-item AUDIT screen, and were affected very little by subject demographic characteristics (Smith et al., 2009).

The Single Question Alcohol Screen is suited to be asked orally as part of the aeromedical history taking.

Aviation personnel who report having exceeded the defined number of drinks 1 or more times within the past year are considered positive and further evaluation using more detailed questions and biochemical methods is needed.

Alcohol Use Disorders Identification Test: AUDIT

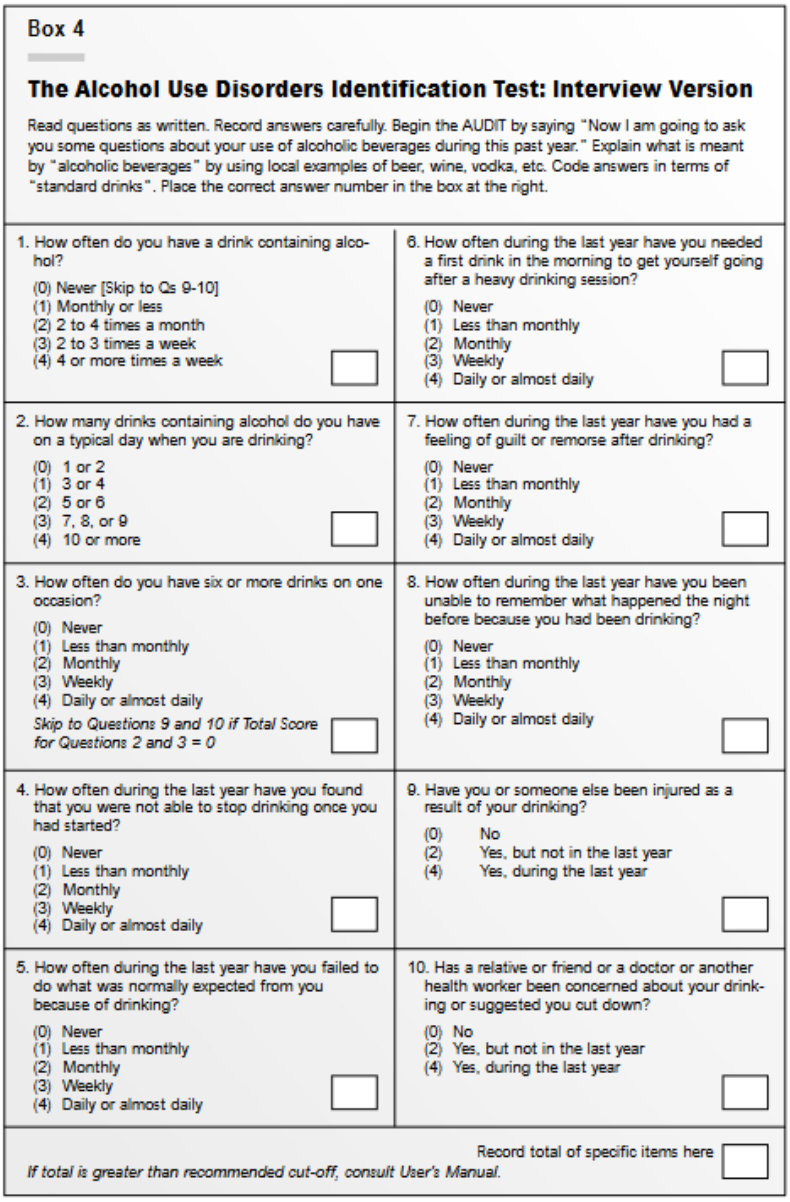
The original AUDIT questionnaire has been developed and validated by the WHO (Babor et al,. 2001). It can be used as an oral interview (or questions woven in the medical interview) or a written questionnaire in the context of an intake. Whether it is used in an interview or as a paper questionnaire, it is recommended that an explanation be given to the candidates of the content of the questions, the purpose for asking them, and the need for accurate answers. The original WHO version is shown in Box 1 (Source Babor et al., 2001).

In the AUDIT, Questions 2 and 3 assume that a standard drink equivalent is 10 grams of alcohol. For many candidates it is not necessary to administer the complete AUDIT because they drink infrequently, moderately, or abstain entirely from alcohol. The interview version of the AUDIT (Box 4) provides two opportunities to skip questions for such cases. If the candidate answers in response to Question 1 that no drinking has occurred

during the last year, the interviewer may skip to Questions 9-10. A second opportunity to shorten AUDIT screening occurs after Question 3 has been answered. If the candidate scored 0 on Questions 2 and 3, the interviewer may skip to Questions 9-10 because the candidate's drinking has not exceeded the low risk drinking limits.

Interpretation of scores (text cited from Babor et al., 2001)

Total scores of 8 or more are recommended as indicators of hazardous and harmful alcohol use, as well as possible alcohol dependence. Selection of the cut-off point should be influenced by national and cultural standards and by clinician judgment, which also determine recommended maximum consumption allowances. Technically speaking, higher scores simply indicate greater likelihood of hazardous and harmful drinking. In general, a score of 1 or more on Question 2 or Question 3 indicates consumption at a hazardous level. Even in the absence of current hazardous drinking, positive responses on these items should be used to discuss the need for vigilance by this candidate. Points scored above 0 on questions 4-6 (especially weekly or daily symptoms) imply the presence or incipience of alcohol dependence. Points scored on questions 7-10 indicate that alcohol-related harm is already being experienced. According to Babor et al. (2001) the cut-off scores for AUDIT-10 are 0 - 7 indicates low risk, 8 - 15 increasing risk, 16 - 19 indicates higher risk, and 20 or more indicates possible dependence.



Box 4

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?
(0) Never [Skip to Qs 9-10]
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8, or 9
(4) 10 or more

3. How often do you have six or more drinks on one occasion?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily
Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4. How often during the last year have you found that you were not able to stop drinking once you had started?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?
(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?
(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

Record total of specific items here

If total is greater than recommended cut-off, consult User's Manual.

Figure 2 - The 10-item Alcohol Use Disorders Identification Test: AUDIT-10 (Babor et al., 2001)

AUDIT-3

Since the publication of the AUDIT guidelines for use in primary care, many adapted and/or shortened versions of the 10-point AUDIT have been developed and validated for clinical use. Adaptations were made based on cultural differences and differences of characteristics of the target groups. One of frequently used shortened versions is the AUDIT-3 (also called AUDIT-C), which uses the first 3 questions of the AUDIT-10 questionnaire as shown in below table. These first 3 questions of the AUDIT-10 cover the domain of hazardous alcohol drinking, questions 4-6 cover dependence symptoms, and questions 7-10 cover the domain of harmful alcohol use (Babor et al., 2001). The stage of hazardous drinking, covered by questions 1-3, is the early and risky stage of alcohol misuse. Because the alcohol screening of pilots and ATCOs should be focused at identifying risky cases as early as possible, the hazardous stage is essentially what the AME/AeMC should try to identify. Therefore, the AUDIT-3 questionnaire could be suited for use in the aeromedical screening practice as part of the medical history interview. The three questions should therefore be woven in into the

medical history interview. The questionnaire can also be administered on paper or electronically, but in that case pilots and ATCOs will easily recognise what they should answer to make sure that their answers have no consequences for their professional career and, therefore, most of them will answer NO to all questions.

The AUDIT-3 has the advantage that it identifies both excessive regular drinking and excessive occasional (binge) drinking in only three questions.

Table 6 - The 3-item Alcohol Use Disorders Identification Test: AUDIT-3 (Babor et al., 2001)

QUESTIONS	SCORING SYSTEM					
	0	**1**	**2**	**3**	**4**	**Score**
How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times per month	2 to 3 times per week	4 times or more per week	
How many units of alcohol do you drink on a typical day when you are drinking?	0 to 2	3 to 4	5 to 6	7 to 9	10 or more	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	

AUDIT-3 performed similarly to AUDIT-10 in detecting risky drinking and had equivalent receiver operating characteristics (ROC) curves and their areas under the curve when used to identify risky drinking in patients visiting primary health care centres in Spain for randomly varied reasons. For men and women AUROCs were 0.913 and 0.957 respectively (compared to 0.920 for AUDIT-10). The term “drink” in questions 2 and 3 encompasses amounts of alcohol ranging from 8 grams to 13 grams. Where a standard drink is defined as an amount outside this range (e.g. 20 grams), it is recommended that the response categories are modified accordingly. Some studies use positivity cut-off scores of ≥7 for females and ≥8 for <65 males. However, for screening of a population of pilots and ATCOs it is recommendable to use a prudent approach in which sensitivity is high. This would enable to “catch” every case, while accepting a risk of false positives. With a cut-off score of 5 for men the AUDIT-3 had a sensitivity of 92.4% and specificity of 74.3% (Gual et al., 2002). When using higher cut-off scores the sensitivity will decrease and the specificity will increase. For screening purposes cut-off scores of 5 for men and 4 for women are advisable.

The questions of the AUDIT-3 are suited to be used in aeromedical history taking. It is recommended that if a score of ≥5 among men and ≥4 among women is observed, a more in-depth assessment of drinking pattern and alcohol-related problems should be carried out. For this purpose, question 4 -10 of the AUDIT-10 can be used in combination with biochemical tests.

The CAGE questionnaire

This questionnaire consists of four questions (abbreviation CAGE explained by the bald words):

Table 7 - The CAGE questionnaire. The name is an acronym composed of the bald printed words in its four questions (Ewing, 1984)

1. Have you ever felt you needed to **Cut** down on your drinking?	**NO = 0**	**YES = +1**
2. Have people **Annoyed** you by criticizing your drinking?	**NO = 0**	**YES = +1**
3. Have you ever found **Guilty** about drinking?	**NO = 0**	**YES = +1**
4. Have you ever felt you needed a drink first thing in the morning (**Eye** opener) to steady your nerves or to get rid of a hangover?	**NO = 0**	**YES = +1**

The CAGE's brevity may make it a useful screening and case-finding tool for the busy primary care physician. In the primary care setting, Aertgeerts et al. (2001) found a high Negative Predictive Value of 93% and a low Positive Predictive Value of 34% using a cut-point of ≥1. They found that the CAGE questionnaire performed poorer than several variations of the AUDIT questionnaire. The CAGE questionnaire is commonly considered a valid tool for detecting alcohol abuse and dependence in medical and surgical inpatients, ambulatory medical patients, and psychiatric inpatients (average sensitivity 0.71, specificity 0.90), however, its performance in primary care patients is varied (Dhalla & Kopec, 2007).

For aeromedical screening purposes the separate questions of the CAGE questionnaire can best be "woven-in" into the medical history taking. Standard administration of a paper/pencil or electronic version is not recommended, because in that case pilots and ATCOs will easily recognise what they should answer to hide their alcohol problems and answer NO to all four questions.

The NIDA Quick Screen for alcohol and drug misuse

The NIDA Quick Screen (NIDA, 2020) combines a single alcohol screen and single drug screen. On a scale of Never / Once or Twice / Monthly / Weekly / Daily or almost daily, applicants have to answer the question: In the past year, how often have you used

- 5 or more drinks a day (for men) / 4 or more drinks a day (women)?
- Prescription drugs for non-medical reasons?
- Illegal drugs?

If the applicant answers "Never" to all questions the screening is complete. Answers that raise suspicion (e.g. weekly 5 or more drinks per day, or weekly use of prescription drugs for non-medical reasons or illegal drugs) a more in-depth assessment of alcohol- or drug-related problems should be carried out and biochemical testing should be considered.

In analogy with the considerations of the above CAGE questionnaire, for aeromedical screening purposes the separate questions of the NIDA questionnaire can best be "woven-in" into the medical history taking. Standard administration of a paper/pencil or electronic version is not recommended, because in that case pilots and ATCOs will easily recognise what they should answer to hide their alcohol or drug problems and give "certification friendly" answers to all three questions.

Drug screening questionnaires

There are many questionnaires designed to screen for drugs and most of these are designed to screen in a clinical and social health care populations. Commonly used examples are the Drug Abuse Screening Test (DAST),

the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), and the Drug Use Disorders Identification Test (DUDIT). The NIDA Quick Screen has been discussed above (under alcohol screening questionnaires) and together with the Single-Question Sceening Test for Drug Use, both DAST and ASSIST will be briefly discussed in the present report. The DUDIT will not be discussed because this questionnaire has only been validated in criminal justice and detoxification settings and is therefore not considered for use in the aeromedical screening practice.

Single-Question Screening Test for Drug Use

Like the single alcohol screening question, this instrument allows easy screening for illicit drugs and the misuse of prescription medications by asking: “How many times in the past year have you used an illegal drug or used a prescription medication for non-medical reasons (for example, because of the experience or feeling it caused)?” A response of ≥1 is considered positive.

Sensitivity and specificity of the test have been assessed by Smith et al. (2010) in 394 primary care patients randomly recruited from the waiting room. The single screening question was 100% sensitive (95% CI 90.6% to 100%) and 73.5% specific (95% CI 67.7% to 78.6%) for the detection of a drug use disorder. It was less sensitive for the detection of self-reported current drug use (92.9%, 95% CI 86.1% to 96.5%) and drug use detected by oral fluid testing or self-report (81.8%, 95% CI 72.5% to 88.5%). Test results were similar to that of the 10-question DAST (see below), and were affected very little by subject demographic characteristics. The authors conclude that as a screening test (as opposed to an assessment of severity or a diagnostic tool) the single-question screen performed almost as well as the longer DAST-10 in the primary care population that we studied.

It is concluded that the Single Question Screening Test for Drug Use is suited to be asked orally as part of the aeromedical history taking.

Aviation personnel with a response of ≥1 is considered at risk and further evaluation using more detailed questions and biochemical methods is needed.

DAST - Drug Abuse Screening Test

Originally The Drug Abuse Screening Test (DAST) is a 28-item questionnaire used as a screening instrument for the abuse of drugs other than alcohol. There are several versions of the DAST questionnaire which differ in number and selection of questions. The present report only discusses the most commonly applied version DAST-10 which has 10 items and assesses drug use, not including alcohol or tobacco use, in the past 12 months (Skinner, 1982).

Table 8 - The 10-item version of the Drug Abuse Screening Test (DAST-10; Skinner, 1982)

THESE QUESTIONS REFER TO THE PAST 12 MONTHS	NO	YES
1. Have you used drugs other than those required for medical reasons?	0	1
2. Do you abuse more than one drug at a time?	0	1
3. Are you always able to stop using drugs when you want to? If never use drugs, answer “Yes.”	1	0
4. Have you had "blackouts" or "flashbacks" as a result of drug use?	0	1

5. Do you ever feel bad or guilty about your drug use? If never use drugs, choose “No.”	0	1
6. Does your spouse (or parents) ever complain about your involvement with drugs?	0	1
7. Have you neglected your family because of your use of drugs?	0	1
8. Have you engaged in illegal activities in order to obtain drugs?	0	1
9. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?	0	1
10. Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)?	0	1

Information for the applicant:

Each question needs a YES or NO response. “drug abuse” means the use of prescribed or over-the-counter medications/drugs in excess of the directions and any non-medical use of drugs.

The various classes of drugs may include: cannabis (e.g., marijuana, hash), solvents, tranquilizers (e.g., Valium), barbiturates, cocaine, stimulants (e.g., speed), hallucinogens (e.g., LSD) or narcotics (e.g., heroin).

Remember that the questions do not include alcohol or tobacco.

Individuals receive 1 point for every "yes" answer except question #3, for which a "no" answer receives 1 point. For aeromedical screening purposes scores of 1 or more should lead to further investigation.

Standard administration of a paper/pencil or electronic version the DAST test is not recommended, because pilots and ATCOs will easily recognise what they should answer to hide their drug problems and give “certification friendly” answers to all ten questions.

ASSIST - Alcohol, Smoking and Substance Involvement Screening Test (WHO, 2010)

This questionnaire is designed for health care workers and any human services worker who may come into contact with people who use substances in a harmful or hazardous way in their line of work, or who work with people whose substance use may place them at increased risk of harms compared with the rest of the community. The questionnaire has eight main questions and each question has sub-questions referring to the different types of substances: tobacco products, alcohol, cannabis, cocaine, amphetamine-type stimulants (ATS), sedatives and sleeping pills (benzodiazepines), hallucinogens, inhalants, opioids, and ‘other’ drugs. The ASSIST has never been designed for screening pilots and ATCOs who do not seek help for their problems but, instead, have to undergo a mandatory medical examination to obtain or renew their license. The ASSIST questionnaire is, therefore, not suited for aeromedical screening. It can be used to find out what the consequences of the applicant’s drugs use are/were in cases where the applicant has admitted to use drugs.

Questionnaires currently used by AMEs/AeMCs

Several mental health screening questionnaires used by AMEs/AeMCs contain the following questions about use of alcohol and drugs:

- Sometimes I feel guilty after drinking alcohol – Yes/No?
- I rather like to relax after work, having a drink – Yes/No?
- Sometimes I use medications or substances to keep me better – Yes/No?

- I think that use of alcohol and mood altering substances do not affect my work capacity – Yes/No

These health screening questionnaires are not harmonized between member states and are not validated for use in the framework of a mandatory aeromedical examination. The questions regarding alcohol and drugs use (see e.g.: Rios Tejada, 2018) seem useful for AMEs to be used as mnemonic and to be "woven-in" into the face-to-face medical history taking, but have very limited value when asked as part of a paper/pencil or electronic mental health questionnaire because pilots and ATCOs will know what they should answer to be declared fit. The fact that some competent authorities necessitate these questionnaires to be signed by the pilots may provide (false) security to AMEs as well as mistrust of pilots which may lead them to tick only favourable answers.

Conclusion

Paper/pencil or electronically administered questionnaires of alcohol and drugs misuse may be useful in clinical and penitentiary settings, but pilots and ATCOs will be very aware of the consequences of an unfavourable evaluation of their fitness status. For most aware pilots and ATCOs it is easy to recognise and tick the most favourable answers. For aeromedical examinations it is recommended to use some of the questions from these questionnaires in the oral medical history taking. It should also be considered that addicts are champions in misleading their doctors! Therefore, use of biochemical testing methods is often necessary in cases where the AME suspect alcohol and/or drugs misuse.

If the AME at the time of the medical check observes signs or symptoms or medical problems which may be related to, or induced by, alcohol or drugs misuse, s/he should consider to perform biochemical screening tests on alcohol or drug use.

5.3 Conclusions and recommendations

Initial Class 1 and initial Class 3 ATCO examination

For the mandatory drugs screening on opioids, cannabinoids, amphetamines, cocaine, hallucinogens and sedative hypnotics providing information regarding medium-term consumption, hair analysis is the most suitable and informative method. For screening of medium term alcohol consumption analysis of EtG can be included in the hair analysis. Applicants should be informed well in time before the examination that they should take care to have a suitable hair sample available (sufficient, not bleached, not dyed hair). If no hair is available, analysis of nail clippings is equally suitable. It should be taken into account that the non-detection periods of hair testing and nail testing are respectively 7-10 days and 2-4 weeks following last consumption. In case there are indications that consumption only occurred in these non-detection periods, it is recommended to perform urine EtG analysis + GGT/CDT (for excessive alcohol consumption) and a urine drug screen (UDS).

It is emphasised that the initial Class 1 and ATCO examination should include physical examination and extensive history taking by the AME in which several dedicated questions concerning psychoactive substance use should be included. This is important to enable the AME building a complete picture of the applicant and finding clues that might need further evaluation. If there are clues that indicate consumption of other psychoactive substances than opioids, cannabinoids, amphetamines, cocaine, hallucinogens and sedative hypnotics (e.g., antipsychotics, antidepressants), the AME/AeMC can include these in the request of the hair analysis. If history and physical examination are "clean" a hair analysis should be performed of the standard list of drugs: opioids, cannabinoids, amphetamines, cocaine, hallucinogens and sedative hypnotics. When this analysis is done without EtG (alcohol), analysis of GGT in combination with CDT and MCV can be considered to identify chronic excessive alcohol consumption.

Renewal Class 1, initial/renewal Class 2 and renewal Class 3 medical licences

Taking an extensive history, including dedicated questions on psychoactive substance use woven into interview is the mainstay of each aero-medical examination. When applicants admit misuse of psychoactive substances –which is not likely in most cases- they can be directly referred to specialised evaluation and care. When reasonable suspicion emerges, confirmation tests can be performed. In this case, suitable tests are urine EtG analysis + GGT/CDT (for excessive alcohol consumption) and a urine drug screen (UDS). Depending on the available laboratory facilities, it can be considered to perform a Phosphatidylethanol (PEth) test in whole blood or using a dry blood spot (DBS). This test is generally considered as specific for binge drinking during the past 2–4 weeks.

If these tests are negative and reasonable suspicion remains, a hair analysis can be done to exclude psychoactive substance use.

If very recent alcohol use prior to the examination is suspected, an Evidential Breath Test (up to 3-4 hrs after consumption), or 5-HTOL in urine (5-15 hrs after consumption), or urine EtG (up to 2-3 days) are suitable identification methods depending on the estimated period of alcohol consumption prior to the examination.

It is questioned whether it would be effective to perform a routine urine drug screen at each initial and renewal examination. Although an UDS is inexpensive and easy to perform, it should consider that the yield is likely to be low (low prevalence and drugs-using applicants will at least refrain from drug use in the days prior to an examination) and that false-positives will occur in the low prevalence population of pilots and ATCOs.

Simons and Valk (2003) suggested that early identification of chronic excessive alcohol consumption can be enhanced through re-introduction of GGT blood tests at each aeromedical examination. Being a sensitive but non-specific marker for chronic excessive alcohol use, the measure would add to the AME's limited tools to decide whether there is a suspicion of chronic excessive alcohol consumption. However, the effectiveness and practicality of routine GGT analysis in the aeromedical examination practice is considered questionable by many AMEs and AeMCs (venepuncture needed, time before result is known, false-positives).

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European Union Aviation Safety Agency

Konrad-Adenauer-Ufer 3
50668 Cologne
Germany

Mail EASA.research@easa.europa.eu
Web www.easa.europa.eu

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