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Commentary

Alcohol Hand Sanitizers, Ethylglucuronide (EtG) and Ethylsulfate (EtS) Tests in the COVID-19 Pandemic Era - Interpret with Caution!

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Alcohol (ethanol) is the most abused psychoactive drug in the world. The National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) has estimated that excessive alcohol use is responsible for 95,000 deaths in the United States, including 1 in 10 total death among working-age adults [1]. This agency has also estimated that excessive alcohol use since 2010 has cost the United States economy in excess of $249 billion per year with about 40% of the costs being paid by federal, state and local governments. One of such costs could be borne by the justice system, either through incarceration of the offenders of drunk driving, or through the work of the Child Protective Services having to fund foster homes for children of alcoholic parents. Child Protective Services (CPS) is the name of a governmental agency in many states in the United States charged with providing protection children from abusive and negligent parents. In the justice system, drug testing is used to monitor abstinence and compliance and is designed to serve as a deterrent to people on probation.

On March 11, 2020, the World Health organization (WHO) SARS-CoV-2 (COVID-19) as a global pandemic. The spread of the virus is very effectively controlled with social distancing (6 ft, at the peak of the pandemic), the wearing of masks and the regular washing of hands. The use of ethanol hand sanitizers has been found to be an effective surrogate for washing of hands and all governments have endorsed it. For those who are required to abstain from alcohol, it seems clear that the use of alcohol-based hand sanitizers may expose them to legal jeopardy because of dermal absorption and the use of a common test called ethylglucuronide (EtG), commonly called the 80-hour test [2].

Upon ethanol ingestion, it is believed that less than 5% remains unchanged and can be detected in saliva, urine and breath. Breath ethanol analysis is commonly performed by the traffic law enforcement officers using a Breathalyzer® which uses a conversion ratio of 1:2100, (blood to breath volume) to display a blood alcohol concentration (BAC) [3]. Disposition of ethanol, like any drug does, goes through the four stages of disposal: absorption, distribution, metabolism and excretion. The amount of ethanol absorbed depends on the mode of exposure - including intravenous, inhalation, and dermal but the most common route is by mouth (*per os*), entering gastrointestinal system, where absorption begins in the stomach (~20%) and mainly via the duodenum and the small intestines (80%). All the blood from the gastrointestinal track travel via the hepatic portal vein to the liver. Ethanol is metabolized predominantly via oxidative and non-oxidative pathways [4]. Oxidative metabolism is catalyzed predominantly (> 95%) by hepatic alcohol dehydrogenase (ADH), which leads to the production of acetaldehyde and acetate.

Acetaldehyde is believed to be responsible for the undesirable and uncomfortable symptoms associated with alcohol intoxication. Catalase and the cytochrome enzyme CYP2E1 also catalyze ethanol via the oxidative pathway conferring different sensitivities to the central nervous system [5]. In the non-oxidative pathway ethanol metabolism uses several enzymes including uridine diphospho-glucuronosyltransferase, (UDT) to produce a minor ethanol metabolite ethylglucuronide (EtG) and sulfotransferase enzyme (SULT) to produce of ethylsulfate (EtS) (Figure 1). It is estimated that less than 0.2% of an ingested ethanol is actually converted into EtG and EtS. The tests EtG

and EtS are now extensively used by the justice system as biomarkers of alcohol use or exposure to monitor abstinence from alcoholic beverages and compliance to legal requirements. The extended window of detection for these ethanol metabolites in urine specimens (about 130 hours for EtG and 110 hours for EtS) has made them very attractive test for forensic purposes. For routine use, EtG/EtS is commonly referred to as the 80-hour urine alcohol test but is also detectable in hair specimens [6-8].

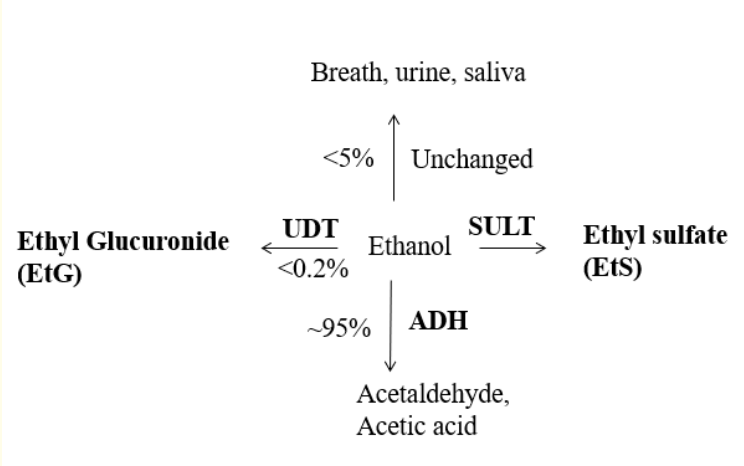

Figure 1: *Ethanol disposal pathways.*

There are several challenges to the proper interpretation of EtG results. Although the EtG was discovered in humans in the mid-1960s and is sensitive for detecting alcohol consumption, several studies have also shown that several conditions can lead to false positive results. In August 2006, Kevin Helliker published an article in the Wall Street Journal entitled "A Test for Alcohol - And Its Flaws" in which he told the story of a recovering addict, whose nursing license was suspended on suspicion of alcohol use, a violation of her agreement. The nurse denied any alcohol use, with the exception of using alcohol hand sanitizers in the course of her duties as a nurse. To prove her innocence, she agreed to be sequestered in an observation facility and used alcohol hand sanitizers as she would at work. It was shown that indeed the use of alcohol hand sanitizers can produce positive EtG results. Dermal ethanol absorption may lead to "Very Low" positive (100 - 500 ng/mL) or "Low" positive EtG tests as defined by the Substance Abuse and Mental Health Health Services Administration (SAMHSA) [9], an agency of the United States Department of Health and Human Services (Table 1). The Covid-19 pandemic has affected all segments of the global population and in the United States where the Justice System uses EtG tests to monitor the use of alcohol in clients for Family Law/Child custody and Child Protective Services, it is very important for people who request the test to remember that alcohol hand sanitizers can produce false positive especially as the alcoholic content of the hand sanitizers may range from 60% to 80%, and people have unlimited access to them at their places of work and at home. Additionally, the frequency of use of the hand sanitizers could not only potentially increase the risk of testing positive but in alcoholics who are best served to avoid any exposure to alcohol, dermal absorption could potentially lead to a relapse. Other well-documented causes of false positive EtG results include the consumption of non-alcoholic beverages, which typically contains less than 0.4% ethanol, storage of urine specimen with high glucose (as would be expected for example, in an uncontrolled diabetic person) and urines contaminated with yeast infection (*Candida* spp) could lead to the production of EtG [10,11]. One very important change that could improve the interpretation of EtG is to normalize its concentration. Presently EtG is commonly reported in ng/ml and normalizing this by the urine creatinine would be very helpful.

"High Positive" (> 1000 ng/mL) may indicate:
• Heavy drinking on the same day or previous day or two
• Light drinking the same day
"Low" positive (e.g. 500 - 1000 ng/mL) may indicate:
• Previous heavy drinking (previous 1-3 days)
• Recent light drinking (e.g. past 24 hours)
• Recent intense "extraneous exposure" (within 24 hours or less)
"Very Low" Positive (100 - 500 ng/mL) may indicate:
• Previous heavy drinking (1 - 3 days)
• Previous light drinking (12 - 36 hours)
• Recent "extraneous" exposure

Table 1: *Urine EtG cutoffs and interpretation.*
Derived from Substance Abuse and Mental Health Services Administration (SAMHSA) Guidelines, USA.

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