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Rapid Communication

# Is Alcohol in Hand Sanitizers Absorbed Through the Skin or Lungs? Implications for Disulfiram Treatment

Colin Brewer<sup>1</sup> and Emmanuel Streeel<sup>2,\*</sup>

<sup>1</sup>Retired Psychiatrist and addiction Physician, London, SE1, London, UK, and <sup>2</sup>CHU Brugmann, Free University of Brussels, 1020, Brussels, Belgium

\*Corresponding author: CHU-Brugmann, Place Van Gehuchten, 1020, Brussels, Belgium. Tel.: +3224772111;  
E-mail: manu.streeel@hotmail.com

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## Abstract

**Aim:** In view of the increase in the use of ethanol-containing hand sanitizers throughout the world due to the current COVID-19 pandemic, we wished to review the possible risks to patients treated with disulfiram, following a case report in which an apparent DER (disulfiram–ethanol reaction) was attributed to the cutaneous absorption of alcohol from hand sanitizers as well as by inhalation of vapour.

**Method:** Simple experiments to assess the levels of absorption by each route separately.

**Results:** Our results strongly suggest that while amounts of alcohol sufficient to cause a DER may be inhaled when hand sanitizers are used in confined spaces, absorption can be avoided by dispersal of the fumes, and absorption from the skin alone does not occur in pharmacologically significant quantities.

**Conclusion:** Warnings about absorption of alcohol through the skin from hand sanitizers and products such as perfumes, deodorants and after-shave (whose use is often warned against when disulfiram is prescribed) should be modified accordingly.

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## INTRODUCTION

The editor of *Alcohol and Alcoholism* invited us to comment on a submission (De Sousa, 2020) that in its original draft suggested that disulfiram (DSF) may cause a typical disulfiram–ethanol reaction (DER) when ethyl alcohol (ethanol) is absorbed through the skin after the use of ethanol-containing hand sanitizers. Textbooks of alcoholism treatment and product information sheets often claim that as well as avoiding alcohol in food or drink, patients taking DSF should not apply ethanol-containing perfumes or after-shave lotions to the skin because this may cause a DER (Joint Formulary Committee, 2020). However, on physicochemical grounds, we doubted whether enough alcohol could be absorbed through the skin to cause a DER. Drugs suitable for transdermal administration using skin patches are typically very potent with 24-hour absorption levels at milligram or microgram levels. They are in contact with

the skin throughout that time, and their liquid-containing excipients are protected from evaporation. In contrast, to cause a DER, several grams of alcohol would have to be absorbed in the space of the minute or two before hand sanitizer evaporates in normal use. We therefore surmised that inadvertent inhalation of alcohol vapour was a more likely mechanism, assuming that the reaction was indeed a genuine DER rather than some other condition or reaction that just happened to coincide with the use of hand sanitizer—something that cannot be completely excluded. Relevant published studies did not seem to have measured absorption by cutaneous and inhalation routes separately but rather than speculate about the nature and mechanism of the reported reaction, we decided to follow the eighteenth-century British surgeon John Hunter's famous advice to William Jenner: 'Why think? Why not try the experiment?'

## MATERIALS AND METHODS

From a local pharmacy, we obtained an ordinary commercial hand sanitizer gel containing 70% of ethanol. Ethanol absorption was measured using a Lion Alcolmeter 500 which measures alcohol concentration in exhaled breath in the range 2mcg/100 ml to 200mcg/100 ml (0.02–2.00 mg/l). (BrAC reliably indicates blood alcohol level under Henry's Law.) We give breath alcohol concentration (BrAC) results as mcg/100 ml breath. Three subjects (A, B and C) participated but not in all of the experiments. We repeated some experiments using 40% alcohol-by-volume vodka in place of the gel.

We tested the following:

- absorption exclusively through the skin;
- absorption after rubbing the hands with gel at a point about 6 inches (15 cm) from the mouth and inhaling the vapour (or inhaling at the same distance above a broad-rimmed vessel containing vodka) while remaining stationary as one usually would at a hand-sanitizing location;
- absorption by breathing normally while rubbing the hands with gel at waist level and
- absorption by breathing normally while rubbing the hands with gel at waist level and walking briskly round a room to prevent the local accumulation of ethanol vapour.

## RESULTS

On the day in question, no subject consumed alcohol before any experiments, and all pre-experimental BrAC readings were zero.

### Experiment 1

A generous quantity of the gel—more than we would normally use—was applied to one hand, which was then placed in a transparent plastic food bag, secured and occluded with an elastic band at wrist level, thus preventing the inhalation of ethanol vapour. After 20 minutes, the BrAC of subject A remained at zero.

Subject B repeated the procedure after placing in the bag 50 ml of vodka warmed to approximately body temperature, with identical results.

Since these results clearly indicated that ethanol was not absorbed from the skin (or absorbed only in negligible amounts) even after prolonged application, we proceeded to:

### Experiment 2

Both hands were rubbed with a normal amount of gel until dry (around 20 seconds) at about 6 inches (15 cm) from the mouth while breathing deeply but not rapidly. Breath samples were then analysed in an adjacent room 1, 3 and 5 minutes later. BrACs for subject A were 7, 2 and 0.

The experiment was modified by inhaling vodka, warmed to approximately body temperature, for 90 seconds above the rim of a small saucepan. At 2, 4, 8 and 10 minutes, the readings for subject A were 15, 6, 2 and 0, respectively.

### Experiment 3

Hands were rubbed with a normal amount of gel at waist level until dry while breathing deeply but not rapidly and remaining in the same place. Breath samples were then analysed in an adjacent room. For subject B, readings were 4, 0 and 0 at 1, 3 and 5 minutes; readings for subject C were 3 and 0 at 1 and 5 minutes.

### Experiment 4

A normal amount of gel was applied to the hands of subject A, who then immediately moved to an adjacent room and rubbed his hands at waist level until dry while walking briskly around the room. Breath samples were analysed in the same room. The readings at 1 and 3 minutes were 0 and 0.

## DISCUSSION

Our results add to existing knowledge because unlike other studies, our methodology aimed to distinguish between cutaneous and pulmonary (and possibly oropharyngeal) ethanol absorption and apparently succeeded in doing so.

Brown *et al.* (2007) measured serum and blood ethanol levels in health-care workers after intensive and repeated use of ethanol-based sanitizer and confirmed that although in a small minority of subjects ethanol could be detected in blood and breath samples, the breath levels were too low to register on the screening breathalysers used by Australian police. However, they specifically noted that their methodology could not indicate whether alcohol was absorbed cutaneously or by inhalation. Experiment 1, which isolated the hand from the ambient atmosphere, demonstrates that if cutaneous absorption of ethanol does occur and reaches the circulating blood (as opposed to dermal capillaries), the amount must be extremely small and thus extremely unlikely to cause a generalised DER. A Japanese study in patients taking the aldehyde dehydrogenase (ALDH) inhibitor cyanamide instead of DSF showed that the brief application of alcohol to the skin could cause a mild and localized erythema but no generalized DER-type manifestations (Yamauchi *et al.*, 2000).

As ethyl glucuronide in urine and hair in the last decade began to be used as a specific biomarker for ethanol ingestion, the possibility of unintended absorption of ethanol from use of hand sanitizers was considered. The conclusion reached was the same as our conclusion: that lungs but not skin could be a potential route (Arndt *et al.*, 2014).

Halothane (a widely used volatile anaesthetic) boils at 50.2°C. Ethanol boils at 78.2°C, but the amount inhaled in Experiment 2, using both gel and warmed vodka, was enough in each case to make the subject feel slightly intoxicated for a few minutes. This did not happen with either gel or vodka in Experiment 1 using an atmospherically isolated hand. Isopropyl alcohol (propanol), which is often used as an alternative to ethanol in hand-gels, boils at 82.6°C and was apparently used in the past as a volatile anaesthetic agent in veterinary procedures, though it is rather toxic. It is therefore not surprising that inhaled ethanol vapour can reach the blood in measurable and pharmacologically significant quantities (Maclean *et al.*, 2017). In the case of isopropyl alcohol metabolized in the body to propionaldehyde, it would be helpful to know whether propionaldehyde's metabolism to propionic acid by ALDH is inhibited by DSF to the same extent as acetaldehyde's metabolism to acetic acid (as seems likely) and whether elevated propionaldehyde levels can cause a DER-like reaction (as seems possible). The greater toxicity of isopropyl alcohol, compared with ethanol, decided us against inhaling, it but it may be absorbed more readily from the skin than ethyl alcohol. Leeper *et al.* (2000) report the case of a woman who had 'been soaking towels with isopropyl alcohol and applying them to her skin overnight to ease arm pain she was experiencing'. She experienced cardiac symptoms, and propyl alcohol was detected in blood and urine, but that report too appears not to have excluded inhalation as the route of absorption. The symptoms disappeared when she stopped using the towels.

A notable feature of our breathalyser measurements was the rapidity with which they returned to zero. As a clinical rule of thumb, BrAC falls at a rate of around 7mcg/100 ml per hour, though the rate may be higher in heavy drinkers. We would not, therefore, expect BrACs of 15 and 7 to fall to zero within less than 10 minutes, and we wonder whether breathalysers, which measure ethanol that reaches the alveolae via the pulmonary artery and is then excreted in breath, may not accurately reflect the true blood alcohol concentration, via Henry's law, when the process is reversed and ethanol reaches the pulmonary circulation from the alveoli. It can then pass directly via the pulmonary vein into the left ventricle and from there to the brain (without first-pass metabolism) in quantities clearly sufficient to cause subjective effects. Brown *et al.* also found that the low levels of alcohol that they recorded disappeared from breath within 2 minutes and from blood within 7 minutes. We therefore hypothesize that inhaled ethanol may pass more slowly from the alveoli into the pulmonary circulation than vice versa, possibly due to transient accumulation in lung tissues and that ethanol levels in blood reaching the brain via the large carotid arteries may be significantly higher than in organs supplied by smaller arteries branching from the more distal parts of the aorta. Since proving this hypothesis with current techniques would require the simultaneous collection of samples from both a carotid and a femoral artery, it is likely to remain a hypothesis.

We also hypothesize that the apparent DER described by De Sousa (2020) may not have reflected an increase in acetaldehyde throughout the body but a more localized increase occurring mainly in the lungs, rapidly causing both unpleasant subjective symptoms and a visible flush over the upper body that is also supplied from the most proximal part of the aorta. It has been shown that in many patients, no objective or subjective DER occurred when they were challenged with half a unit of alcohol (12.5 ml of 40% spirits) several days after taking 200 mg of DSF daily (or its thrice weekly equivalent) under supervision—often in the context of a probation order (Brewer, 1984). Some, but not all, had a DER when the challenge dose was increased to a whole unit. Others only responded when the DSF dose was progressively increased and a very small number had no response on doses as high as 1500 mg (Brewer and Streele, 2018). This has led us to recommend, as have others (Newton-Howes, *et al.*, 2016), that when patients taking standard 200–250 mg doses of DSF do not get a DER if, despite warnings, they drink alcohol, DSF treatment should not be abandoned. Instead, the dose of DSF should be increased until a medically supervised or spontaneous ethanol challenge is positive, or until the patient is consistently deterred from drinking on the higher dose without an ethanol challenge, or until further dose increases (and/or generally uncooperative behaviour) show that DSF is not going to be a useful intervention for that patient.

Conversely, food containing very small amounts of alcohol—sauces, for example—does not usually cause a DER. One of us recalls an alcoholic sauce chef treated with supervised DSF after a positive half-unit challenge dose of alcohol, whose continued employment required the repeated tasting of sauces that sometimes contained alcohol. He reported that he could taste occasional alcoholic sauces without discomfort but experienced a mild DER if he had to taste several in quick succession.

## LIMITATIONS OF OUR STUDY

For reasons that included doing the study during the COVID-19 lockdown period, we were unable to calibrate the Alcolmeter, especially for its accuracy at low alcohol levels. It would be useful to repeat the study using blood as well as breath samples and forensic-quality apparatus.

## CONCLUSION

Despite the small number of subjects and measurements, this anecdotal study strongly indicates that contrary to repeated claims, significant cutaneous absorption of ethanol from even frequent use of hand sanitizers or other ethanol-containing liquids does not occur. However, especially in confined spaces and at close quarters, the inadvertent (or, *a fortiori*, deliberate) inhalation of ethanol vapour from sanitizers or other sources may transiently produce levels of ethanol absorption that are high enough to cause a mild DER. Even without further and more detailed studies, the traditional warnings in textbooks, papers, formularies and product information sheets should probably be modified accordingly.

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