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Safety evaluation of ethanol based products and its influence on humans

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ABSTRACT

Ethanol is almost used in all kinds of products which has direct contact to the human skin like hand disinfectants, cosmetics like hairsprays or mouthwashes, pharmaceutical preparations, and many household products.The first and foremost concerns of topical ethanol applications for public health are its carcinogenic effects, as there is uncertain evidence for the carcinogenicity of ethanol orally consumed in the form of alcoholic beverages. So far there is a lack of evidence to associate topical ethanol use with an increased risk of skin cancer. Limited evidence is available on the link between the use of ethanol in the oral cavity in the form of mouthwashes or mouth rinses and oral cancer. Some studies pointed to an increased risk of oral cancer due to locally produced acetaldehyde, operating via a similar mechanism to that found after alcoholic beverage ingestion.In addition, topically applied ethanol acts as a skin penetration enhancer and may facilitate the transdermal absorption of xenobiotics (e.g. carcinogenic contaminants in cosmetic formulations). Ethanol use is associated with skin irritation or contact dermatitis, especially in humans with an aldehyde dehydrogenase (ALDH) deficiency.After regular application of ethanol on the skin (e.g. in the form of hand disinfectants) relatively low but measurable blood concentrations of ethanol and its metabolite acetaldehyde may occur, which are, however, below acute toxic levels. Only in children, especially through lacerated skin, can percutaneous toxicity occur.

Keywords: Ethanol ,Carcinogen ,Alcohol absorption ,erythema ,skin irritation ,chronic and acute.

INTRODUCTION

Ethanol is widely used solvent both in the home and in industry . Consumers may be exposed to ethanol from its application as a constituent of many household and personal products, such as cosmetics, hairsprays, window cleaners, de-icers .The safety of topical applications of ethanol is still a unconcluded area for final conclusion but then we cannot also totally neglect its adverse effects , although the deleterious effects of ethanol exposure on the skin may pale into insignificance compared to its effects on the liver, central nervous system, and other body systems after ingestion.

However, there appears to be at least some evidence, including epidemiological data, about mouthwash use, and data from animal experiments showing that ethanol on the skin or inside the oral cavity may cause harm if used chronically.

METHODS

Data on the safety of topical ethanol was obtained by a computer-assisted literature search using the key words “topical ethanol”, “topical alcohol”, mouthwash, mouth rinse, “hand disinfectant”, “alcohol based disinfectant” “alcohol/ethanol & melanoma”, “alcohol/ethanol & skin” “alcohol/ethanol & penetration”, “alcohol permeation”, “acetaldehyde & skin”. Searches were also made from the available articles based on the ethanol and its effects and also from the books available on the alcohol.

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REVIEW

Our discussion will be carried on the mechanisms of toxicity on application of the ethanol and its carcinogenicity effects on local application on the human skin and also the effects of ethanol as a skin penetration enhancer will be discussed. Finally, certain groups of products are discussed in detail (cosmetics, mouthwashes, and hand disinfectants), and an overall risk assessment is provided.

EFFECTS OF ETHANOL ON THE SKIN

Besides skin cancer, alcohol abuse has been associated with the development of several skin disorders including psoriasis, discoid eczema and superficial infections. Chronic alcohol abuse is also a predisposing factor for necrotizing wound infections and delayed wound healing. There are several theories about the causes for such skin diseases including immune suppression, mal-nutrition, liver disease or the influence of alcohol on lipid metabolism. As acute and chronic alcohol abuse modulate immunity, this mechanism can explain dermatological diseases, which have an immune pathogenetic mechanism .Topical application of 10% ethanol stimulates the proliferation of peritoneal tissue explants – a semi in-vivo wound model – which can be interpreted as positive influence for stimulation of wound healing by ethanol .

An interesting patch test was conducted by Haddock et al.. 1.5-cm patches moistened with 0.1 ml of 100% ethanol or 10% acetaldehyde were applied to a group of patients. No erythema were observed from patch tests with ethanol on non-hydrated skin, while all applications of acetaldehyde resulted in notable erythema. Using the same test on hydrated skin (i.e. immersion of the test site in water for 10 min before

application of the patches), localized erythema were also caused by ethanol. The reactions were judged to represent a direct pharmacologic action of topical alcohols on the cutaneous microvasculature, and that erythemogenesis is enhanced after hydration because of an increase in cutaneous permeability to alcohol.

ETHANOL AS A PENETRATION ENHANCER

Systematic *in vitro* and *in vivo* studies have elucidated the mechanism of percutaneous alcohol absorption. It is now generally accepted that the "barrier" function of the skin resides almost entirely in the stratum corneum. Most water-soluble, low-molecular weight non-electrolytes – among them ethanol – applied to the skin surface can diffuse much faster into the blood-stream if the epidermis is diseased, damaged or removed .

Ethanol is also well known as a topical penetration enhancer and may be used in transdermal delivery systems . Bommannan et al. found *in vivo* in humans that ethanol enters the skin and removes measurable quantities of the lipid barrier material from the stratum corneum. This lipid extraction may lower the skin barrier function and render the membrane more permeable, which is the most likely explanation for the effect of ethanol as a skin penetration enhancer.

Animal studies demonstrated that both chronic and acute ethanol consumption increase transdermal penetration, resulting in higher exposure of several xenobiotics, e.g. herbicides or the tobacco carcinogen nitrosonornicotine .The transdermal absorption of xenobiotics may be facilitated by ethanol induced changes in lipid peroxidation and transepidermal water loss .

BLOOD ALCOHOL LEVEL AFTER ETHANOL PENETRATION THROUGH THE SKIN

The studies about ethanol as a penetration enhancer for pharmaceutical preparations show that ethanol is absorbed into the normal, intact skin, and may reach the blood stream to be systemically distributed in the human body.

Bowers et al. reported a controlled study to assess the likelihood of ethanol being absorbed through intact skin and producing measurable blood-ethanol concentrations in experiments involving four children (7–9 years of age) and one adult. The legs of the subjects were wrapped in cotton from above the knees to the feet, and the wrappings were subsequently soaked with 200 ml of 95% (v/v) ethanol. Although the ethanol-soaked cotton was kept covering the skin with rubber sheeting and adhesive tapes for 4–9 hours, no ethanol was measurable in the blood.

ETHANOL THROUGH LACERATED SKIN AND ITS CAUSES TO THE CHILDREN

The possibility of alcohol absorption across the injured skin is generally accepted .In 1950, Paulus conclusively showed in animal experiments that alcohol is absorbed relatively rapidly through areas of wounded skin. A human case relating to the absorption of ethanol through abraised and lacerated skin was reported by Jones et al. The damaged skin (33% of total body surface) of a victim of a traffic accident was washed in the operating theatre with surgical spirit (70% (v/v) ethanol). A blood ethanol concentration of 0.046 g/100 ml was determined, which corresponded to an absorption of approx. 30 ml of the ethanol solution. The authors concluded that there is a risk of ethanol being absorbed into the bloodstream if damaged skin is washed with surgical spirits.

Alcohol is an agent that poses a risk of percutaneous toxicity in the newborn. Exposure of immature skin (especially under occlusion) may lead to significant local reactions and systemic toxicity. Percutaneous absorption of ethanol through damaged skin resulting in clinical manifestations of intoxication has been reported in a 1-month-old infant and in a 2-year-old child . Giménez et al. reported ethanol poisoning in 28 children, aged one to 33 months, after application of alcohol-soaked cloths to relieve abdominal pain (which was a common practice in Argentina). Two of the children with ethanol poisoning died.

ETHANOL AS MOUTHWASHES

Ethanol is still a component of a significant number of oral-care products. When adults use such ethanol-containing mouthwashes, oral rinses, and similar products as they are intended to be used, an acute-toxic effect in the sense of typically intoxication occurring after alcoholic beverage consumption caused by an increased blood-alcohol level is not likely .

The absence of acute-toxic effects in adults has previously been interpreted to indicate that such mouth-rinsing cosmetics are safe in every respect. However, the risk arising from this product group does not result primarily from systemic blood alcohol concentrations. Further adverse effects of the use of mouthwash were reviewed by Gagari et al. For adults, these are predominantly local and systemic allergic effects, which were postulated to be caused by the combination of a high content of alcohol, an acidic pH, and other ingredients that act individually or synergistically. Furthermore, it was shown that the *in vitro* toxicity of ethanol-containing mouthwashes may exceed that of pure-ethanol solutions. Other studies also reported the opposite effect that ethanol containing mouthwashes may be less toxic than formulations without ethanol in tissue cultues of explants of neonatal rat peritoneum.

However, another recent study showed that the genotoxicity of mouthwashes is caused by ethanol and not by any other ingredient. This is in line with mechanistic evidence that ethanol causes sister chromatid exchange in both lower organisms and mammalian cells, including human cells, and that the data from studies in animals suggest that ethanol causes DNA damage in target tissues .

Mechanistic evidence especially points to detrimental effects of ethanol in the upper gastrointestinal tract (i.e. the oral cavity, pharynx, larynx/hypopharynx). The mucosa may be damaged by ethanol, which leads to the stimulation of cell regeneration. Genetic changes may then cause the development of dysplasia or leukoplakia and, finally, cancer. The possibility of damage to the oral mucosa also exists with the use of mouthwashes .

ETHANOL AS HAND DISINFECTANTS

Ethanol-based hand disinfectants are widely used in occupational settings mostly in hospitals. The antimicrobial effects of alcohols (except methanol) are based on protein denaturation. Alcohols have excellent, and the most rapid bactericidal and fungicidal activity of all agents used in hand disinfection. Ethanol was described to be preferred because the smell of this alcohol is tolerable when compared to other alcohols . While alcohol-based hand rubs generally have a broad and relatively rapid activity against vegetative bacteria, they are often limited in their ability to inactivate non-enveloped viruses .

Alcohols were described as non-toxic in their application as a hand

disinfectant and they were judged to lack any allergenic potential. It was also concluded that alcohol-based hand rubs have a less deleterious effect on the skin than other physical irritants, which enhance skin reactivity. The repetitive use of different alcohol-based hand rubs was shown to not significantly change transepidermal water loss, dermal water content or the sebum content of the skin. The potential of ethanol-containing hand rubs to cause skin irritation was tested using single and repetitive patch tests and wash tests. No significant change in skin barrier or erythema was induced, whereas skin hydration decreased significantly. The wash tests demonstrated that alcohol application caused significantly less skin irritation than washing with a detergent. Even on previously irritated skin, ethanol did not enhance irritation. Alcohol-based hand rubs cause less skin irritation than hand washing, and are therefore preferred for hand hygiene from the dermatological point of view .

CONCLUSION

The facts that ethanol is widely used in topical applications and that its adverse effects were seldom reported should not be dismissed. The studies reviewed in this article, shows the possibility exists that on the point of impact, very high concentrations of ethanol and acetaldehyde may cause chronic toxic effects. The effects may be more pronounced in ALDH-deficient humans, but this association demands further research.

Due to the conflicting evidence in many cases, the precautionary toxicological principle should be currently favoured in the evaluation of ethanol for topical uses. Until unambiguous evidence about the safety of ethanol in topical preparations exists, the necessity of its use should be critically evaluated. In certain product groups (e.g. mouthwashes), ethanol can be easily substituted for other compounds. In other product groups - especially hand disinfectants in hospital hygiene -, the advantages for the patients may outweigh the potential risks for the users. However, in this case, the formulations should be critically evaluated if ethanol cannot be at least partially substituted with e.g. other alcohols with a more favourable toxicological profile.

Finally, an advancement in testing strategies for genotoxicity and mutagenicity appears to be necessary, with a refocus on testing the final formulation rather than the isolated constituents. The effect of ethanol as penetration enhancer for other constituents of the formulations must especially be considered in such a safety evaluation of cosmetics.

SUMMARY OF OUTCOMES OF USAGE OF ETHANOL

1. Topically applied ethanol (e.g. in the form of cosmetics or hand disinfectants) on un-lacerated human skin will not cause acute or systemic toxic effects, which can only occur if applied on damaged skin especially in children.

2. Adverse effects of topically applied ethanol may include skin irritations or allergic contact dermatitis.

3. Ethanol and its metabolite, acetaldehyde, are potentially carcinogenic for humans, however, only limited evidence supports the carcinogenicity of mouthwashes, and a complete lack of data about the carcinogenicity of all other groups of products (e.g. cosmetics, hand disinfectants) was detected.

4. Further concerns include the permeation-enhancing capabilities of ethanol, which could lead to an increased absorption of other components of topically applied formulations (e.g. nitrosamines from cosmetics).

5. Safety assessments of ethanol in any form of application must include the carcinogenic and genotoxic properties of ethanol and its metabolite acetaldehyde.

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