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Safety assessment for ethanol-based topical antiseptic use by health care workers: Evaluation of developmental toxicity potential

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ABSTRACT

Ethanol-based topical antiseptic hand rubs, commonly referred to as alcohol-based hand sanitizers (ABHS), are routinely used as the standard of care to reduce the presence of viable bacteria on the skin and are an important element of infection control procedures in the healthcare industry. There are no reported indications of safety concerns associated with the use of these products in the workplace. However, the prevalence of such alcohol-based products in healthcare facilities and safety questions raised by the U.S. FDA led us to assess the potential for developmental toxicity under relevant product-use scenarios. Estimates from a physiologically based pharmacokinetic modeling approach suggest that occupational use of alcohol-based topical antiseptics in the healthcare industry can generate low, detectable concentrations of ethanol in blood. This unintended systemic dose probably reflects contributions from both dermal absorption and inhalation of volatilized product. The resulting internal dose is low, even under hypothetical, worst case intensive use assumptions. A significant margin of exposure (MOE) exists compared to demonstrated effect levels for developmental toxicity under worst case use scenarios, and the MOE is even more significant for typical anticipated occupational use patterns. The estimated internal doses of ethanol from topical application of alcohol-based hand sanitizers are also in the range of those associated with consumption of non-alcoholic beverages (i.e., non-alcoholic beer, flavored water, and orange juice), which are considered safe for consumers. Additionally, the estimated internal doses associated with expected exposure scenarios are below or in the range of the expected internal doses associated with the current occupational exposure limit for ethanol set by the Occupational Safety and Health Administration. These results support the conclusion that there is no significant risk of developmental or reproductive toxicity from repeated occupational exposures and high frequency use of ABHSs or surgical scrubs. Overall, the data support the conclusion that alcohol-based hand sanitizer products are safe for their intended use in hand hygiene as a critical infection prevention strategy in healthcare settings.

1. Introduction

Topical antiseptics used by healthcare professionals in hospitals, clinics, doctor's offices, outpatient settings, and nursing homes include several categories of products: healthcare personnel hand washes and rubs, surgical hand scrubs and rubs, and patient pre-operative and pre-injection skin preparations. These antiseptics may contain any of a variety of active ingredients, including ethanol, and are intended to reduce the presence of viable bacteria on the skin (Boyce and Pittet, 2002; Guilhermetti et al., 2001; Rotter, 2011, 2001, 1995). The routine use of such products is a major aspect of modern infection control procedures in the healthcare industry (Boyce and Pittet, 2002; Johnson et al., 2014).

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In the U.S., the Food and Drug Administration (U.S. FDA) regulates all categories of antiseptics used on humans as drug products. Healthcare antiseptics may be marketed via the Over The Counter (OTC) drug monograph process or the New Drug Approval (NDA) process. In the 2015 Proposed Amendment of the 1994 Tentative Final Monograph for over-the-counter (OTC) antiseptic drug products,[1] FDA indicated that their administrative record for the safety of alcohol is incomplete with respect to the following:

- Human pharmacokinetic studies under maximal use conditions when applied topically (MUsT) and
- Data to help define the effect of formulation on dermal absorption

Questions of particular interest surround the potential for dermal uptake and any resulting unintended developmental and reproductive toxicity (DART) risks arising from dermal application of topical antiseptics containing ethanol, generally referred to as alcohol-based hand sanitizers (ABHSs). While there is no indication of safety signals associated with this exposure scenario, no comprehensive studies of DART associated with occupational use of ABHSs are available to verify the absence of adverse effects among healthcare workers. The possibility of such effects has been hypothesized based on several open questions.

- Does occupational use of ABHS have the potential to generate sufficiently high internal ethanol doses to cause reproductive or developmental effects? This question reflects the observation that a measurable fraction of the alcohol dose applied on skin can be detected in the blood following simulated high topical use scenarios (U.S. FDA, 2014a; Kramer et al., 2007).
- Can a dose threshold be determined for the onset of reproductive and developmental effects of systemic ethanol exposure? The association of ethanol with developmental effects, when ingested in alcoholic beverages at high levels during pregnancy, is well accepted. However, identification of an effect threshold for developmental effects following low amounts of ethanol ingestion in humans remains elusive (Fig. 1) and major medical organizations and the U.S. Surgeon General have published precautionary statements that there is no known safe intake level for alcoholic beverages during pregnancy (Table 1).

The lack of clarity about the fetal dose–response at low doses of ethanol suggests there is value in conducting a systematic assessment using methods of health risk assessment (National Research Council, 2009). We evaluated the internal doses of ethanol associated with topical exposures to alcohol-based antiseptics using an updated physiologically-based pharmacokinetic (PBPK) model, including an updated assessment of dermal uptake (Supplement A). The dose–response characteristics related to reproductive and developmental effects of systemic ethanol exposure were assessed after considering the epidemiology and animal toxicology data. Although ethanol exposures can affect reproductive endpoints, the toxicology data show that adverse effects on developmental outcomes are more sensitive (i.e., occur at lower doses) (Supplement B Tables SB3a–d)). Thus, this paper focuses on the more relevant question of developmental toxicity potential. The data were arrayed to estimate the ratio of known toxicity effect levels or other typical non-work related ethanol exposures to the internal doses from normal-use, high-use, and intensive-use (maximum-use) occupational scenarios. These ratios represent margin of exposure (MOE) estimates that support decisions regarding the safety of alcohol-based topical antiseptic products when used as intended.

2. Characterization of effects and dose response behavior for ethanol

2.1. Pharmacokinetic considerations

An in-depth consideration of the pharmacokinetics of ethanol is an important component of the safety assessment of ABHS use by healthcare workers. The pharmacokinetic profile of ethanol is well characterized and supports several important aspects of the assessment of exposures arising from occupational use of alcohol-based topical antiseptics. Ethanol can be readily absorbed via the inhalation and oral routes, but dermal absorption is markedly lower than these two other routes. Ethanol distributes completely in body fluids and readily crosses membrane barriers, is extensively metabolized, and is cleared via metabolism and excretion with no significant bioaccumulation. Studies that describe the general characteristics of ethanol are complemented by additional studies evaluating pharmacokinetic properties that are of particular relevance to assessing developmental outcomes. Thus, the pharmacokinetics database for ethanol is extensive and sufficiently robust to support a risk assessment of the use of alcohol-based sanitizers in the healthcare industry.

The primary routes of exposure for occupational uses of alcohol-based topical antiseptics such as hand sanitizers is by direct dermal application and inhalation of small amounts of volatilized product. Epidemiology studies that assess developmental outcomes following occupationally-relevant exposure routes were not identified and only limited numbers of animal toxicology studies with inhalation dosing were identified. In contrast, the epidemiology and toxicology literature regarding developmental effects of ingested ethanol (in alcoholic beverages) is vast. This portfolio of studies on ethanol intake and developmental effects is useful to assess the developmental toxicity risks from dermal occupational exposure after considering route-specific pharmacokinetics. Since developmental effects of concern arise primarily from in utero exposures, the systemic dose represented by maternal blood ethanol levels is an appropriate metric for exposure. Thus, oral studies that provide blood level data are directly useful for assessing dose–response issues for all routes. However, the consideration of equivalent occupational exposures among healthcare workers must account for route-specific bioavailability differences. In general, dermal absorption of ethanol is limited; primarily due to loss from the skin via evaporation (Pendlington et al., 2001). Dermal penetration models (Gajjar and Kasting, 2014) and PBPK models used to simulate occupational exposures to alcohol-based products (Supplement A) are consistent with human controlled exposure studies (Ahmed-Lecheheb et al., 2012; Brown et al., 2007; Kirschner et al., 2009; Kramer et al., 2007). These human studies suggest that the total extent of systemic absorption of ethanol in alcohol-based sanitizers applied to skin is in the range of 1–3% for normal healthy skin. Application of such models allows for direct comparisons of blood alcohol (ethanol) concentration (BAC) data from oral studies in relation to internal doses predicted from topical use of alcohol-based products in the workplace.

2.1.1. Maternal peak BAC as a surrogate dose metric

The use of maternal BAC as a surrogate dose metric for the purpose of this safety assessment is supported by in vivo distribution characteristics, including exposure of the developing fetus in utero and post-natal lactational exposures. Ethanol is not stored or accumulated in body tissues and it penetrates cell membranes by simple diffusion, readily crossing physiological barriers, including the placenta. The placenta is only capable of minute amounts of

[1] Federal Register/Vol. 80, No. 84/Friday, May 1, 2015/Proposed Rules (FDA, 2015a).