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

Andrew Maier [a, *], Jerald L. Ovesen [a], Casey L. Allen [a], Raymond G. York [b], Bernard K. Gadagbui [c], Christopher R. Kirman [d], Torka Poet [e], Antonio Quiñones-Rivera [f]

[a] Department Environmental Health, University Cincinnati College of Medicine, Cincinnati, OH, USA
[b] RG York and Associates LLC, Manlius, NY, USA
[c] Toxicology Excellence For Risk Assessment, Cincinnati, OH, USA
[d] Summit Toxicology LLP, Cleveland, OH, USA
[e] Summit Toxicology, LLP, Richland, WA, USA
[f] GOJO Industries, Inc., Akron, OH, USA

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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.

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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).

* Corresponding author. University of Cincinnati College of Medicine, 160 Panzeca Way, Cincinnati, OH 45267, USA.
E-mail address: maierma@ucmail.uc.edu (A. Maier).

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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).

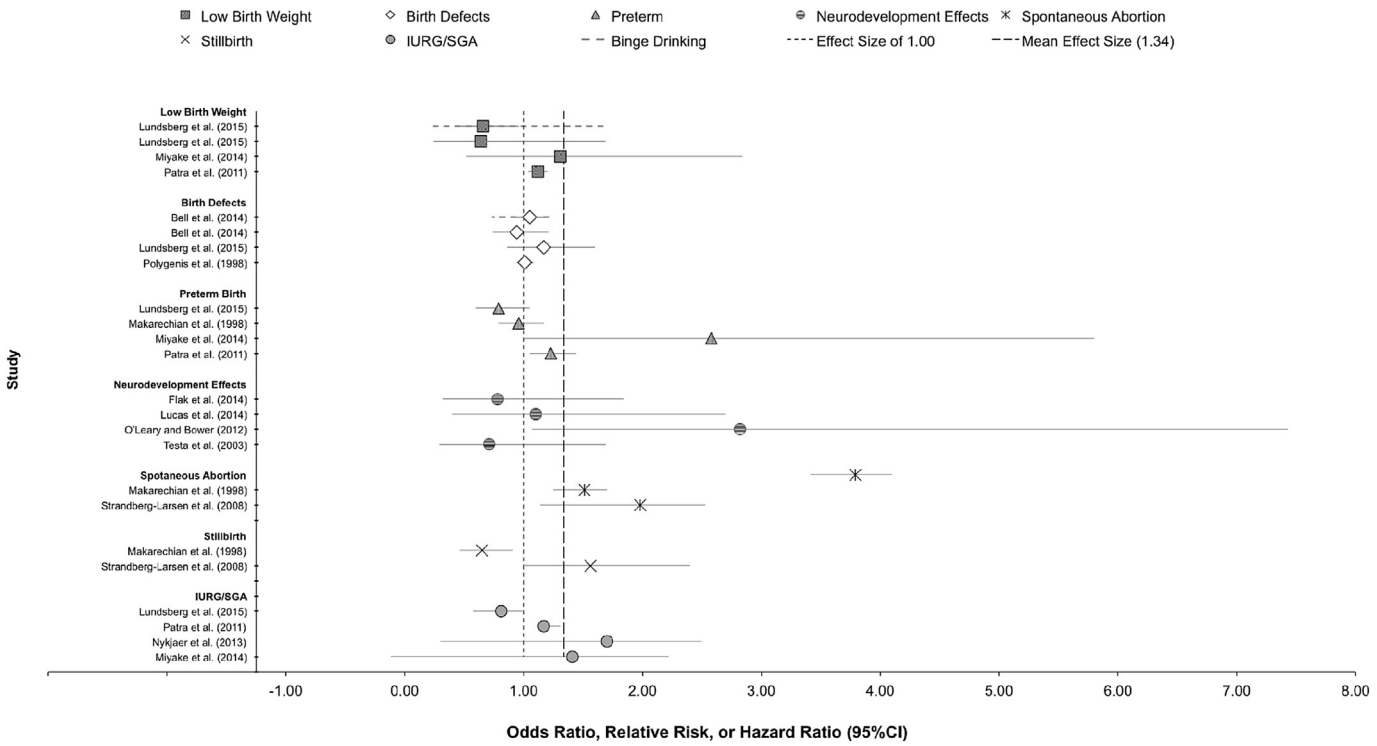

Fig. 1. Forest plot (Odds Ratio, Relative Risk, or Hazard Ratio 95% CI) of key studies for effects of fetal alcohol exposure.

Table 1
Statements and recommendations regarding alcohol drinking during pregnancy by region and organization.

United States: Mass of ethanol per drink = 14 g	
American Congress of Obstetricians and Gynecologists (2014)	"Women should avoid alcohol entirely while pregnant or trying to conceive …"
Centers for Disease Control and Prevention (2014)	"There is no known safe amount of alcohol use during pregnancy or while trying to get pregnant. There is also no safe time during pregnancy to drink."
U.S. Surgeon General (2005)	"No amount of alcohol consumption can be considered safe during pregnancy."
American Academy of Pediatrics (2014)	"There is no known safe amount of alcohol consumption during pregnancy. For that reason, the American Academy of Pediatrics recommends that women who are pregnant, or who are planning to become pregnant, abstain from drinking alcoholic beverages of any kind."
United Kingdom Mass of ethanol per drink = 8 g	
National Institute for Health and Care Excellence (2008)	"Pregnant women and women planning a pregnancy should be advised to avoid drinking alcohol in the first 3 months of pregnancy if possible because it may be associated with an increased risk of miscarriage." "If women choose to drink alcohol during pregnancy they should be advised to drink no more than 1 to 2 UK units once or twice a week (1 unit equals half a pint of ordinary strength lager or beer, or one shot [25 ml] of spirits."
U.K. Department of Health (International Center for Alcohol Policies, 2009)	"Pregnant women or women trying to conceive should avoid drinking alcohol. If they do choose to drink, to minimize the risk to the baby, they should not drink more than 1–2 units of alcohol once or twice a week and should not get drunk."
Royal College of Obstetricians and Gynaecologists (2014)	"The safest approach in pregnancy is to choose not to drink at all. Small amounts of alcohol during pregnancy (not more than one to two units, not more than once or twice a week) have not been shown to be harmful. Regular binge drinking, around conception and in early pregnancy, is particularly harmful to a woman and her baby."
Australia: Mass of ethanol per drink = 10 g	
Australian National Health and Medical Research Council (2009)	"For women who are pregnant or planning a pregnancy, or breastfeeding not drinking is the safest option."
Canada: Mass of ethanol per drink = 14 g	
Center for Addiction and Mental Health (2014)	"If you are pregnant, planning to become pregnant, or before breastfeeding, the safest choice is to drink no alcohol at all."

ethanol metabolism and does not appreciably reduce the amount of ethanol reaching the fetus (Paintner et al., 2012). The metabolic capacity of the fetus is very limited, functioning at a rate of 5–10% of adult hepatic activity (Pikkarainen, 1971). The observations of the ready diffusion and limited placental and fetal metabolism of ethanol support the conclusion that maternal blood concentrations appropriately represent in utero exposures (Hayashi, 1991). Ethanol also is readily distributed into mammary glands from maternal blood to breast milk; ethanol in breast milk is slightly higher in concentration than in the mother's blood due to the higher water content of breast milk (Lawton, 1985).

Although the available epidemiological studies do not provide definitive information on internal ethanol doses and the associated risks of developmental and reproductive effects (Fig. 1), the similarity in overall pharmacokinetic profile among species (Supplement B Table SB1a–g and Table SB2) supports the direct consideration of animal toxicity studies to develop conclusions regarding the spectrum of effects associated with ethanol doses in

humans. Based on the overall qualitative interspecies concordance in the pharmacokinetic and pharmacodynamic profiles of ethanol, information on the spectrum of effects observed in animals likely also applies to human exposures. This concordance is of particular importance because it supports inferences about the dose–response behavior for ethanol toxicity, including: 1) the existence of a dose (BAC) below which effects are unlikely, as identified in available animal toxicity studies; 2) the relative effect levels for the spectrum of effects that support neurological effects being the most sensitive effects; and 3) the identification of peak BAC (i.e., C_{max}), and not total cumulative exposure (area-under-the curve, AUC), as the primary basis for all the demonstrated developmental effects.

2.1.2. Critical effect windows

Fig. 3 identifies approximate windows of time, or "critical periods", for pregnant humans following exposure to ethanol that lead to adverse developmental effects. In general, there is a constellation of effects for each organ system that is usually more severe (major anomalies) in the embryonic period (first trimester). Teratogen exposures that occur later, during continued growth and differentiation in the second and third trimesters of the fetal period, result in less severe (minor) anomalies. The wide varieties of adverse congenital and functional malformations that can manifest over the entire gestational period indicate there are probably multiple teratogenic pathways.

When evaluating adverse pregnancy outcomes in humans, it is important to identify the timeframe for the reported gestational age. Determining the gestational week of exposure based on the date of the last menstrual period versus the date of conception can produce a two-week difference in time that can be critical when evaluating an association between a birth defect and ethanol exposure. In this report, when gestational age is given, it refers to time since conception. During the first two weeks after conception, the developing embryo is not very susceptible to teratogenesis. Ethanol exposures during this time period are not known to cause congenital anomalies in humans; however, such exposures may interfere with cleavage of the zygote or implantation of the blastocyst and cause fetal loss in the form of early death and spontaneous abortion (see Fig. 3).

2.2. Epidemiological studies

Adverse human reproductive and developmental outcomes are associated with high BACs that result from the deliberate ingestion of ethanol. Since the 1980s, several warnings have communicated

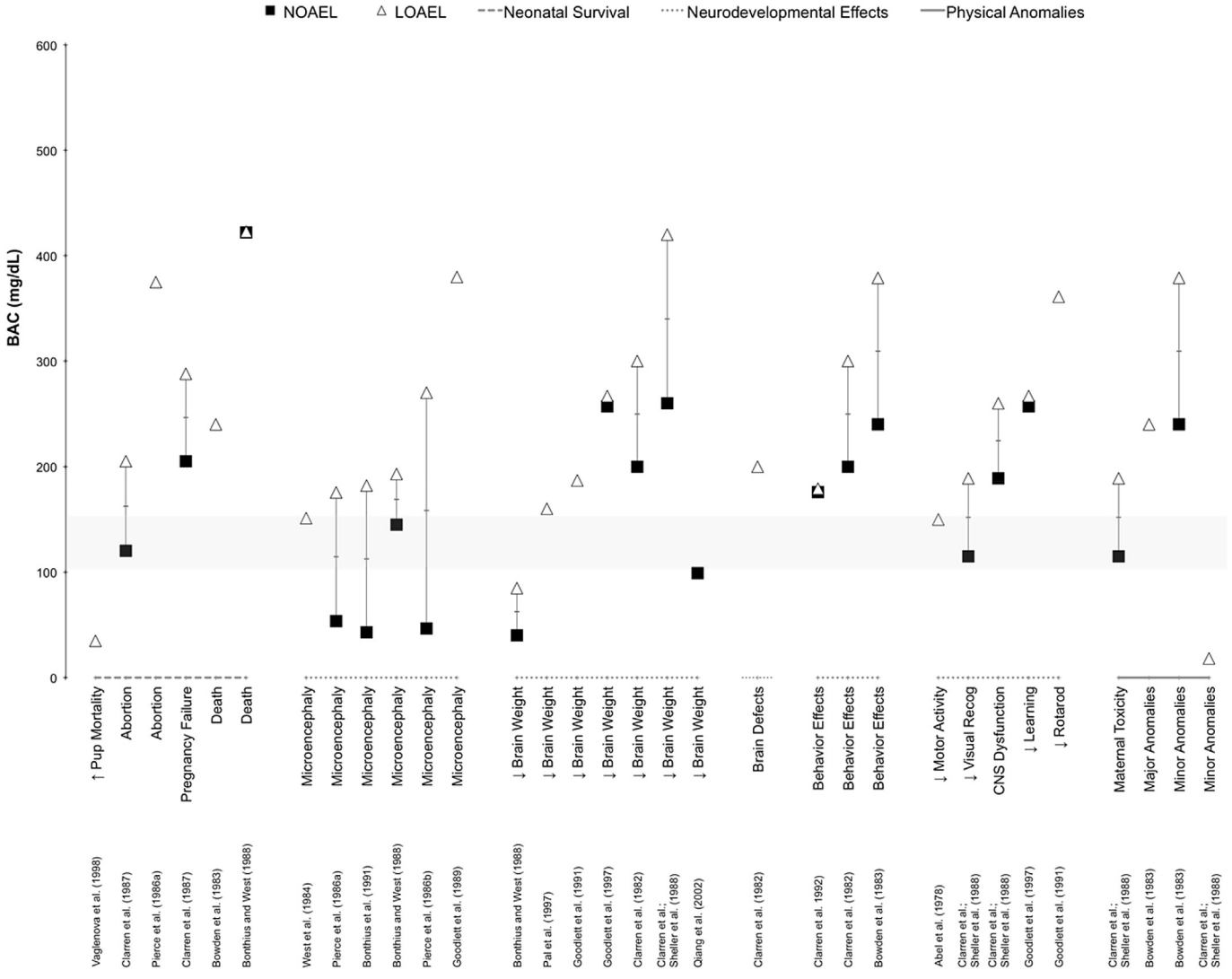

Fig. 2. Effect levels for various examined critical study effects (Sant'Anna and Tosello (2006)).

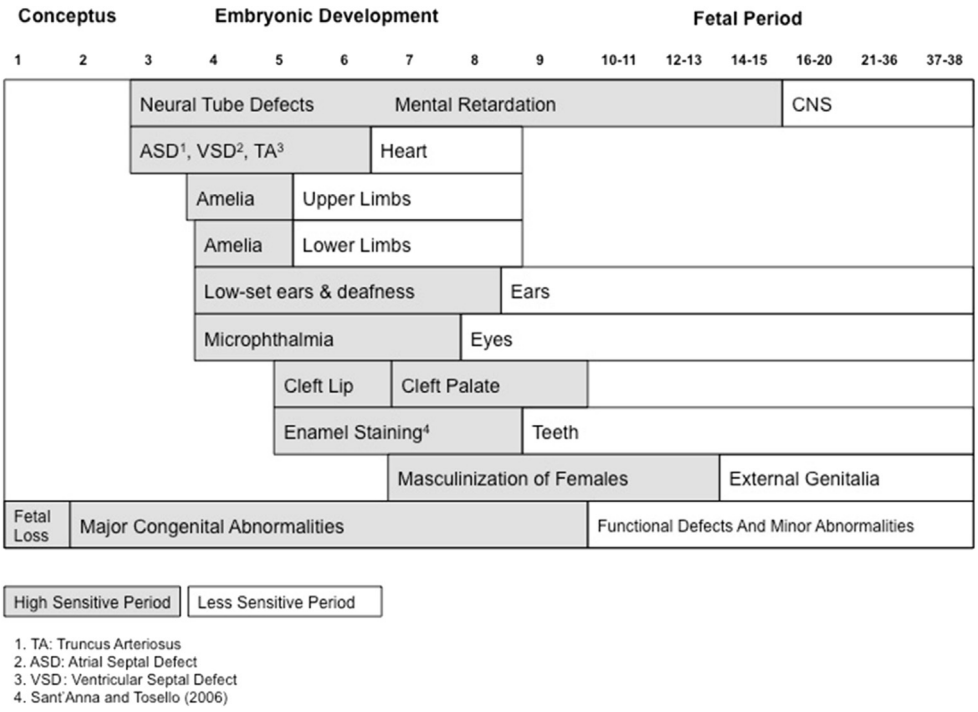

Fig. 3. Critical windows or stages (in weeks) of human development associated with prenatal ethanol exposure.

this association to the public (American Congress of Obstetricians and Gynecologists (2011); U.S. Government, 1988; Warren and Bast, 1988). The developmental effects of prenatal ingestion of alcohol can be recognized clinically (Jones et al., 1973; Jones and Smith, 1973). In general, human studies suggest that high doses of ethanol cause adverse developmental effects, with many studies providing data that implicate a role of alcohol in affecting various aspects of development (Bay and Kesmodel, 2011; Forrest et al., 1991; Gray and Henderson, 2006; Henderson et al., 2007a, 2007b; Jacobson and Jacobson, 1999; Lundsberg et al., 2015; O'Leary and Bower, 2012; Patra et al., 2011; Polygenis et al., 1998). Fetal Alcohol Spectrum Disorders (FASD) is the term now used to describe a group of conditions that can occur in children of mothers who consume alcoholic beverages, generally at high levels, during pregnancy. FASD can include any of several symptoms in the physical, cognitive, and behavioral domains (Centers for Disease Control and Prevention (CDC), 2015). Evaluations of individuals with this diagnosis, who have by now reached adulthood, provide unique information about the long-term developmental effects of prenatal alcohol exposure (Brown et al., 1991; Church and Gerkin, 1988; Streissguth et al., 1991). These authors concluded that FASD was more prevalent in the younger school children populations than previously estimated, estimated at 2–5% versus the 1% (9.9/1000) previously estimated by Sampson et al. (1994).

Systematic reviews of observational studies, meta-analyses, and more recent prospective cohort studies were identified that investigated the effects of fetal alcohol exposure in humans. These outcomes include low birth weight, preterm delivery/birth or premature birth, intrauterine growth restriction (IUGR), small for gestational age at birth (SGA) or fetal growth, spontaneous abortion or miscarriage, stillbirth, fetal or infant death, neurodevelopmental outcomes and fetal malformations. Supplement B Table 1 shows the identified studies and the critical information of each while Fig. 1 and Table 2 summarizes their key findings.

The results from these studies indicate that prenatal ethanol consumption at high levels or binge drinking can cause adverse developmental effects. While some of the studies identified no-observed-adverse-effect-levels (NOAELs)[2] or lowest-observed-adverse-effect-levels (LOAELs),[3] no apparent threshold could be identified for some effects. The available studies indicate that consumption of 7–12 g of pure ethanol/day or binge drinking (defined as 5 or more drinks on an occasion) is not likely to result in low birth weight (Lundsberg et al., 2015; Nykjaer et al., 2014) or IUGR, SGA or fetal growth (Miyake et al., 2014; Nykjaer et al., 2014). An alcohol intake of 2.9–20 g/day during pregnancy was reported to cause spontaneous abortion or miscarriage (Makarechian et al., 1998). With the exception of one study (Nykjaer et al., 2014) that reported alcohol intake of 0.9 g/week to cause preterm delivery or premature birth, intake of up to 20 g/day in other studies (Makarechian et al., 1998; Patra et al., 2011) did not result in preterm delivery. The meta-analysis by Flak et al. (2014) suggests that any binge prenatal ethanol exposure (defined by the authors as 4 or more drinks on one occasion) can adversely affect child cognition; moderate prenatal ethanol exposure (82.2 g/week or 12 g/day) can adversely affect child behavior; and mild-to-moderate prenatal ethanol exposure (41–82 g/week) can affect child cognition. Studies on FASD in children have highlighted the sensitivity in changes in morphology of the central nervous system (CNS) due to fetal alcohol exposure (Clarren et al., 1978; Hanson et al., 1978; Mattson et al., 1992).

In addition to changes in morphology of the CNS, effects of fetal alcohol exposure also manifest as altered cognitive and physical

[2] Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure (Duffus et al., 2007).

[3] Lowest concentration or amount of a substance (dose), found by experiment or observation, which causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure (Duffus et al., 2007).

Table 2
Study dose and standard drink definitions key studies used in Fig. 1 [a].

Effect	Study	Ethanol exposure	Ethanol intake (g/day)	Exposure period
Low birth weight	Lundsberg et al. (2015)	0–3.5 d/wk	7	1st Trimester
	Lundsberg et al. (2015)	4 + d/occ (Binge)	56	1st Trimester
	Miyake et al. (2014)	≥1.0 g/day	1	Pregnancy
	Patra et al. (2011)	1 d/day	10	Pregnancy
Birth defects	Bell et al. (2014)	1 − 9 d/wk	10	Pregnancy
	Bell et al. (2014)	5 − 7 d/occ (Binge)	50	Pregnancy
	Lundsberg et al. (2015)	0–3.5 d/wk	1	1st Trimester
	Polygenis et al. (1998)	3 − 14 d/wk	6	1st Trimester
Preterm birth	Lundsberg et al. (2015)	0–3.5 d/wk	7	1st Trimester
	Makarechian et al. (1998)	3 + d/wk	20	Pregnancy
	Miyake et al. (2014)	≥1.0 g/day	1	Pregnancy
	Patra et al. (2011)	3 d/day	36	Pregnancy
Neurodevelopment Deficits	Flak et al. (2014)	3 − 6 d/wk	6	Pregnancy
	Lucas et al. (2014)	2 − 28 d/wk	4	Pregnancy
	O'Leary and Bower (2010)	0 - 60; 61–70 g; ≥ 60 g/wk	1	1st Trimester
	Testa et al. (2003)	<1 d/day	11	Pregnancy
Spontaneous abortion	Makarechian et al. (1998)	3 + d/wk	3	Pregnancy
	Strandberg-Larsen et al. (2008)	5 + drinks	180	1st Trimester
Stillbirth	Makarechian et al. (1998)	3 + d/wk	3	Pregnancy
	Strandberg-Larsen et al. (2008)	5 + drinks	180	1st Trimester
IURG/SGA	Lundsberg et al. (2015)	0–3.5 d/wk	7	1st Trimester
	Miyake et al. (2014)	≥1.0 g/day	1	Pregnancy
	Nykjaer et al. (2014)	<2 units/wk	2	1st Trimester
	Patra et al. (2011)	1 d/day	10	Pregnancy

[a] Abbreviations Used:g = grams; d = drinks, wk = week, occ = occasion.

functions and behavior. While others suggest that reduced birth weight is the most sensitive developmental endpoint associated with ethanol exposure (Allebeck and Olsen, 1998), Sampson et al. (1994) suggested adverse behavioral effects are the most sensitive. Heavy maternal drinking during pregnancy has been linked to deficits in motor function and IQ measures while cognitive disorders have been linked with moderate levels of consumption (Streissguth et al., 1991, 1990). Impaired motor function and hearing have been associated with FASD (Church and Gerkin, 1988). Prenatal exposure to sufficiently high levels of alcohol can lead to persistent cognitive deficits (Streissguth et al., 1991) and learning deficits but prenatal exposures to low-to-moderate intakes were not associated with neurodevelopmental effects (Brown et al., 1991; Falgreen-Eriksen et al., 2012; Kesmodel et al., 2012; Underbjerg et al., 2012).

While it is clearly understood that high, daily alcohol consumption appears to be consistently associated with birth defects and subsequent neurodevelopmental problems (Bay and Kesmodel, 2011; Henderson et al., 2007b) there is considerable doubt as to whether infrequent and low levels of alcohol consumption during pregnancy result in any long-term harm, in particular after the first trimester (Royal College of Obstetricians and Gynaecologists (2006)). Some studies evaluating neurobehavioral outcomes have reported significant detrimental association between moderate prenatal alcohol exposure and child behavior (Flak et al., 2014), with binge drinking in pregnancy also reported to be associated with poor neurodevelopmental outcomes (Flak et al., 2014; Henderson et al., 2007b). While a dose–response relationship may be expected between alcohol consumption and neurodevelopmental effects, studies that measured neurodevelopmental effects at multiple dose levels (Falgreen-Eriksen et al., 2012; Flak et al., 2014; Humphriss et al., 2010; Testa et al., 2003) do not show a clear dose–response relationship.

The methodological limitations of the available epidemiological studies of oral consumption of alcohol in alcoholic beverages might explain the apparent absence of a true dose–response relationship and the inability to identify a NOAEL or threshold for neurodevelopmental effects. These limitations include, among others, the imprecise measure of amounts and concentrations of ethanol consumed in the human observational studies, differences in drinking patterns, timing and duration of consumption, underreporting alcohol intake in pregnancy by women (recall bias), ill-defined gestational timing of exposure, genetic differences, variation in the extent to which studies adjusted for potential confounders, and publication bias (in which studies reporting adverse effect of alcohol exposure are more likely to be submitted and published). The effect of recall bias in epidemiological studies could lead to a systematic overestimation of risk. For instance, it has been shown that, when reporting alcohol consumption after delivery, women with adverse outcomes tended to report significantly less consumption than the amount initially reported by them (Feldman et al., 1989). Despite the large number of epidemiological studies, confounding variables (e.g., amount and timing of ethanol intake, metabolism, concurrent use of other drugs, socioeconomic status) also contribute to the difficulty of establishing a safe dose estimate (West et al., 1994). Thus, while the association between high BAC levels from alcohol consumption and adverse developmental effects has been established, a safe level of consumption has not been identified from the limited dose–response data available in current epidemiology studies.

Although the body of epidemiology literature is vast, it does not specifically address the reproductive or developmental risk among healthcare workers that use ABHSs. Nonetheless, a variety of other sources of information on human effects and surveillance efforts are available and should be considered in order to more fully address concerns with ABHS safety.

To date, no reports or observations have been made to suggest there exists a risk of adverse developmental outcomes associated with the use of ABHSs or surgical scrubs. For instance, since 1976, the Nurses ' Health Studies have followed several cohorts of nurses and conducted large investigations into risk factors for major chronic diseases in women (Speizer et al., 2015). A children's follow-up study, Growing Up Today Study (GUTS), was designed to evaluate health outcomes, including developmental, reproductive, and endocrine related effects. It is important to note that nurses were selected as a study population “because of their broad health

knowledge, which increased the accuracy of self-reported information" (Colditz and Hankinson, 2005). It is reasonable to conclude that if a significant occurrence of developmental effects could be attributable to the use of ABHSs by nurses, an association would have been observed and reported.

In addition, the U.S. FDA can track significant safety issues related to prescription and over-the-counter (OTC) drugs, such as hand disinfectants using:

- The Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) which is used by the Office of New Drug (OND) and Office of Surveillance and Epidemiology (OSE) and focuses primarily on significant safety issues.
- The U.S. FDA Adverse Event Reporting System (FAERS), which is a database, that contains information on adverse event and medication error reports submitted to U.S. FDA (FDA, U.S. 2014b).
- MedWatch, which is the U.S. FDA Safety Information and Adverse Event Reporting Program, is the public's gateway for clinically important safety information and reporting serious problems with human medical products (FDA, 2015b).

None of these U.S. FDA surveillance programs have identified developmental safety issues for healthcare using ABHSs.

In conclusion, ABHSs and alcohol-based surgical scrubs have a long history of broad and extensive safe use in the healthcare industry and there is no evidence of adverse effects from chronic use from human effects data.

2.3. Toxicology findings (animal studies)

Experiments in laboratory animal models have been employed to determine the developmental effects of ethanol under controlled conditions. Such toxicology data add significantly to the understanding of dose–response and address some of the limitations of the current epidemiology studies (Cudd, 2005). The animal toxicology database on ethanol includes a variety of laboratory animal models, several routes of exposure, and a variety of endpoints and ethanol exposure levels (Supplement B Table SB2).

Most of the developmental toxicity studies conducted in animals were designed to compare the reproductive and developmental effects of relatively high doses of ethanol in animals with those observed in children of alcoholic mothers. The challenge in these studies is measuring reliable internal doses, such as peak BAC, in some species.

To improve the interpretation of animal studies for human health risk assessment, it is useful to evaluate the effects on the basis of a measure of internal dose. This presents a challenge for the oral dosing studies because measuring reliable peak BACs can be difficult in such studies. Adding ethanol to the drinking water or feed (liquid) is problematic with some species, such as rats, that tend to eat and drink at night, or small rodents (mice) that have limited blood supplies for multiple collection samplings. Pair-feeding studies, where groups of animals receive feed rations based on the feed consumption of the high ethanol group, often result in the pair-fed group eating their entire ration at once, compared to the common 'grazing' with *ad libitum* feeding. It also takes some days for animals to adjust to a liquid diet containing ethanol. In a study with exposure of pregnant rats, Gavin et al. (1994) reported that dams fed liquid diet containing ethanol, initially rejected it, dropping their mean intake from 1123 mL to 36 mL. With continued exposure, they consumed more of the ethanol diet, averaging 70 mL by the last day of exposure. This reduction in nutrition during a critical period of gestation will have confounding effects. Many rodent studies use a 5% ethanol liquid diet that provides 35–36% ethanol-derived calories because, as Lieber and De Carli (1989) noted, with lesser amounts of ethanol, intake falls below a critical level and the BAC becomes negligible. OECD (2004) estimated that the use of a 5% ethanol liquid diet is approximately 10–12 g/kg-day to a pregnant rat. It should be noted that this is 10 or more times greater than the Limit Test Dose of 1000 mg/kg body weight in current standard OECD 414 Prenatal Developmental Toxicity Study testing guidelines (OECD, 2001) and might affect interpretation of the corresponding effects at low doses in humans as anticipated from occupational scenarios.

A second challenge related to direct use of the animal toxicology studies for dose–response assessment, relates to translation of specific effects from the animal model to humans. The phenotype associated with ethanol-induced toxicity can vary among species based on exposure timing compared to species-specific windows of susceptibility (Fig. 3). Thus, this as well as other species-specific factors must be taken into account. For example, there is no single animal model that shows all the diagnostic criteria of FASD. Mice are very useful to investigate facial dysmorphologic features of FASD (Sulik et al., 1981; Sulik and Johnston, 1983) and offer more opportunities for genetic manipulation with the available transgenic, knock-in, and knock-out strains (Cudd, 2005).

A large body of literature is available on the anatomy, physiology, reproduction, and teratology of rats and mice. However, unlike humans, in whom the greatest brain growth occurs in the third trimester, in rats and mice the greatest brain growth occurs postpartum. Behaviorally, there are a multitude of tests for rodents, such as eye-blink for learning (Green et al., 2000), Morris maze for spatial learning and memory (Hamilton et al., 2003), and rotarod for motor coordination. Both rodent models have relatively short gestations (19–22 days) and are relatively inexpensive to acquire and maintain. The guinea pig (also a rodent) has a longer gestation (68 days), has fetal and behavioral effects similar to humans, and rapid brain growth early during gestation (Abdollah et al., 1993). Sheep fetal physiology and pharmacokinetics have been studied extensively during the past 50 years and rapid brain growth occurs in utero, similar to the human. As study animals, pigs (full, mini-, micro-) present the distinct advantage that they have a preference for ethanol and will voluntarily drink it. They also have rapid brain growth profile most similar to humans; are highly intelligent, and have a good behavioral dataset. Non-human primates are the most intelligent laboratory species and display similar behaviors as observed in humans; however, their rapid brain growth occurs earlier than that of humans. Because of the complexity of using neurodevelopmental changes as an endpoint we used a weight-of-evidence approach considering the merits of individual animal studies that included various species and dosing regimens. Together the body of diverse studies provides a cohesive pattern suggestive of an identifiable onset threshold for neurodevelopmental effects.

The animal studies with well-defined dosing strategies show a general trend of increased severity with increased internal dose as measured by BAC (Supplement B, Table SB3a–d). The BAC measure represents a peak concentration, not a metric for cumulative dose. It is clear from the animal studies that the most reliable and sensitive effects of alcohol exposure during development are those related to neurodevelopment, most notably, decreased brain weight and microencephaly, where the brain itself is abnormally small (Fig. 2 and Table 3).

The animal toxicology data demonstrate the existence of a NOAEL for developmental toxicity. This conclusion is consistent with the U.S. EPA's Registration Eligibility Document (2006) which highlighted the findings of the OECD (OECD, 2004) regarding ethanol DART as follows: "collective evidence is that the NOAEL for developmental effects in animals is high, typically = or > 6400 mg/

Table 3
Critical animal studies and events.

Study	Species	Treatment	Effect	NOAEL		LOAEL	
				External dose (g/kg/day)	BAC (internal dose) (mg/dL)	External dose (g/kg/day)	BAC (internal dose) (mg/dL)
Pierce and West (1986a)	Rat	Gastrostomy, PND 4–10	Microcephaly	6.6	53.7	7.4	175.3
Pierce and West (1986b)	Rat	Gastrostomy, PND 4–10, 12 doses over 24 h	No Effect	6.6	46.6	–	–
		Gastrostomy, PND 4–10, 6 doses over 12 h	Microcephaly	–	–	6.6	270.2
Kelly et al. (1987)	Rat	Gastrostomy, PND 4–10, continuous over 24 h	No Effect	6.6	56.8	–	–
		Gastrostomy, PND 4–10, continuous over 8 h	Microcephaly and hyper activity	–	–	6.6	415.7
Goodlett et al. (1989)	Rat	Gastrostomy, PND 4	Microcephaly	–	–	7.5	380
		Gastrostomy, PND 5	Microcephaly	–	–	7.5	439
		Gastrostomy, PND 6	Microcephaly	–	–	7.5	460
Bonthius and West (1990)	Rat	Gastrostomy, PND 4–10, 12 doses	No Effect	6.6	43	–	–
		Gastrostomy, PND 4–10, 4 doses (5.1% solution)	Microcephaly	–	–	4.5	182
		Gastrostomy, PND 4–10, 2 doses (10.1% solution)	Microcephaly	–	–	4.5	318
		Gastrostomy, PND 4–10, 12 doses (2.5% solution)	No microcephaly	6.6	39.23	–	–
West et al. (1984)	Rat	Gastrostomy, PND 4–10, 8 doses over 24 h	Microcephaly	–	–	7.2	151
Bonthius and West al. (1988)	Rat	Gastrostomy, PND 4–10, 12 doses over 8 h	Deceased brain weight	2.5	40	3.3	85
Goodlett et al. (1991)	Rat	Gastrostomy, PND 4–10, 4 doses	Decreased brain weight	–	–	4.5	187
		Gastrostomy, PND 4–10, 2 doses	Decreased brain weight, decreased Rotarod test score	–	–	4.5	361
Goodlett and Johnson (1997)	Rat	Gavage, 2 doses per day PND 7–9	Decreased placement learning	4.5	218	5.25	276
Abel and Dintcheff (1978)	Rat	Gavage dams GD1-birth	Decreased motor activity, decreased litter weight	–	–	4	150
Altshuler and Shippenberg (1980)	Rhesus Monkeys	Continuous	Spontaneous abortion	–	100	–	150
Clarren and Bowden (1982)	Macaque Monkeys	Once weekly through pregnancy	Brain defects	–	–	0.36	200
Clarren et al. (1987)	Macaque Monkeys	Once weekly PND7-21	Spontaneous abortion	0.17	120	0.26	200
Clarren et al. (1988); Sheller et al. (1988)	Macaque Monkeys	Once weekly PND7–21	Single minor anomaly/ developmental anomalies	–	–	0.04	24–26
Clarren and Astley (1992)	Macaque Monkeys	First 3 weeks of gestation	No effect	0.26	176	–	–
		Second 3 weeks of gestation	Abnormal behavior	–	–	0.26	179
		Last 3 weeks of gestation	Abnormal behavior			0.26	189
Bowden et al. (1983)	Macaque Monkeys	Weekly GD 1 - GD40	Minor anomalies	–	–	0.26	240

kg bw, compared to maternally toxic effects at 3600 mg/kg bw." Based on the totality of the available animal studies, the NOAEL-to-LOAEL boundary for neurodevelopmental effects is in the BAC range of 150 mg/dL. The key studies and effects are shown in Fig. 2 and described in Table 3. In a study of alcohol-related microencephaly, Bonthius and West (1988) reported a NOAEL for microencephaly at a BAC of 145 mg/dL, while West et al. (1984) observed microencephaly in rats with a measured BAC of 151 mg/dL. In primates, neurodevelopmental changes, as evidenced by behavioral changes, brain defects, and reported CNS dysfunction, appear to manifest in response to alcohol exposure at a BAC range of 180–200 mg/dL. Thus, microencephaly in rats seems to be the sensitive critical effect when considering the risk of alcohol exposure during development. Reliance on this endpoint for safety assessment is supported by its close relationship to the most sensitive effects in non-human primate studies as well as the neurobehavioral effects observed in epidemiological studies. An appropriate point of departure (POD) from the effects in these studies is in the range of 150 mg/dL. It should be noted that the BAC levels reported in Bonthius and West (1988) may have been measured at a time that would not have given a true peak BAC (and provide a low estimate of the effect level). These authors also showed a LOAEL for decreased brain weight at 85 mg/dL, but the magnitude of the changes were not significant at this level; no significant decrease in brain weight was reached unless animals had a peak BAC of 195 mg/dL which also resulted in microencephaly. As the measured BAC increases, effects become more severe. In monkeys, behavioral changes were reported at BACs in the 180–200 range; at BACs above 200, the incidence of major physical morphological differences and fetal mortality increased, including spontaneous abortions and pregnancy failures. Once maternal BAC levels are above 200 mg/dL in monkeys and 375 mg/dL in rats, there seems to be increased risk of fetal mortality (Bonthius and West, 1988; Bowden et al., 1983; Clarren et al., 1987; Pierce and West, 1986a; Vaglenova and Petkov, 1998).

The small number of studies that have reported developmental effects at BACs below 150 mg/dL (Fig. 2) have been shown to have significant design flaws that reduce their utility in identifying the peak BAC associated with the onset of developmental effects. For instance, Bonthius and West (1988) reported post-natal day (PND)

10 decreased brain weight at BACs below 150 mg/dL. In this study blood samples were collected 75 min post exposure, while in other studies of microencephaly and decreased brain weight, blood samples are typically collected 90 or 120 min after alcohol exposure (Bonthius and West, 1991; Pierce and West, 1986a, 1986b). Pierce and West (1986a) showed that the peak BAC occurred at 120 min after the exposure, suggesting the BAC measurement in Bonthius and West (1988) was too early to represent the actual peak BAC (i.e., the true peak was higher than reported). Despite the fact that these BAC samples were most likely taken at a less than true peak time in Bonthius and West (1988) the reported decrease in brain weights were not significantly different except in pregnant dams who had peak BACs of 195 mg/dL Qiang et al. (2002) reported that all levels of exposure in their prenatal alcohol exposure investigation into corpus callosum development of the rat, including their lowest exposure level that produced a BAC of 1–99 mg/dL, caused changes in neuronal development in the corpus callosum. However, this study did not evaluate any functional effects on neurodevelopment. In addition, the lowest BAC group (0–99 mg/dL) rarely showed any significant difference ($p = .01–0.98$) in increased dendritic length or more branches in the corpus callosum. No significant correlations were obtained between brain weight (a hallmark of adverse brain development) and number and length of apical and basilar dendritic branches in the deep or superficial cortical layers at the lowest exposure level. Clarren et al. (1988) reported "minor anomalies" at BACs of 23–25 mg/dL (Fig. 2). These effects were attributed to only slight delays for two animals on the Wisconsin General Testing Apparatus and one animal with a slight delay in motor development. Moreover, all three results were of questionable significance (Clarren et al., 1988). Finally, Vaglenova and Petkov (1998) reported a low BAC associated with increased pup mortality, but this value was described by the authors as being related not to developmental issues but due to dam aggression and pup cannibalism (Vaglenova and Petkov, 1998). Despite some of the reported effects at low BAC values, an earlier review by Irvine et al. (2003) recognized a NOAEL peak BAC of 100 mg/dL, suggesting a threshold above this value. Thus, a critical review of the available studies supports a BAC of up to 150 mg/dL representing the approximate threshold range for the onset of neurodevelopmental effects.

The data also are consistent in showing that the primary driver for developmental concern with regards to ethanol exposure is the peak BAC, not the total daily ethanol intake or cumulative exposure (such as the area under the time concentration curve, AUC). Four key studies with rats were identified that tested the effects of dose-rate on neurodevelopmental effects of ethanol. In a study using rat pups, Pierce and West (1986b) administered a dose of 6.6 g/kg/day of ethanol, delivered in 12 equally-spaced fractions each 24 h, or 6 fractions over 12 h (with 6 ethanol-free fractions the remaining 12 h) during PND 4–10. In the group that received their dose in 12 fractions, the mean peak BAC was 46.6 mg/dL (range 12.1–98.3 mg/dL) and showed no effect on brain growth, while the group that received their daily ethanol in 6 fractions showed a peak BAC of 270.2 mg/dL (range 195.2–345.0 mg/dL). The group that received the ethanol in high concentration events (6 fractions/24 h with a peak BAC of 270 mg/dL) showed significant brain weight reductions while the other group did not, suggesting that peak BAC, and not the cumulative ethanol dose, is the important contributor to the development of microencephaly (Pierce and West, 1986a). This dose–response pattern was confirmed by Kelly et al. (1987), who administered a daily dose of ethanol of 6.6 g/kg over either 8 h or 24 h during PND 4–10. The group that had continuous alcohol exposure had daily average BACs of 79.1 mg/dL and 87.4 mg/dL at the morning and evening collections, respectively. The group that received their dose in just 8 h averaged 415.7 mg/dL in the evening after 8 h of ethanol exposure and 56.8 mg/dL in the morning after 16 h of being alcohol free. In the 8-h group there was increased incidence on microencephaly and hyperactivity at PND 90 while the continuous exposure group showed no adverse developmental effects (Kelly et al., 1987). Similarly, in a third study, ethanol was administered during PND 4–9 at 6.6 g/kg/day to one group of rats in 12 doses while two other groups received 4.5 g/kg/day in either 2 or 4 doses per day (Bonthius and West, 1990). The group that received 4.5 g of ethanol/kg/day in 2 feedings/day had a peak BAC of 318.2 mg/dL, the group that received the same amount in 4 feedings had a peak BAC of 182 mg/dL. The group that had the highest daily alcohol exposure of 6.6 mg/kg/day but divided over 12 feedings only had a peak BAC of 43.8 mg/dL. While the group that received the 6.6 mg/kg/day had no reported adverse developmental outcomes, both groups of pups receiving the lower total dose, but with a higher peak BAC, displayed increased incidence of microencephaly and neuronal loss at PND 90. Goodlett et al. (1991) used a similar gastrostomy dosing pattern – with two groups of rats receiving 4.5 g/kg/day either in 2 or 4 equal fractions – and reported similar increased effects. Both groups had decreased brain weights, and rats that received their daily dosage in just 2 fractions, with a higher peak BAC, also performed worse in a rotarod test at 405 days of age (Goodlett et al., 1991). While other toxicology studies did not include specific dosing strategies to evaluate peak versus cumulative dose effects, these studies do show that the observed increase in the incidence and severity of effects correlates to increasing peak BAC and not total alcohol dose alone (Table 3).

3. Exposure assessment

3.1. Product use scenarios

In this exposure assessment for alcohol-based topical antiseptics, we considered two different application scenarios: a hand-hygiene application, where relatively small amounts of product are applied repeatedly throughout the day, and a surgical application, where a somewhat larger amount of product is applied but at a lower application frequency. The internal doses associated with ABHS use were simulated using an updated PBPK model (Supplement A).

The simulation of the hand-hygiene scenario was based on three different hand-hygiene scenarios and one surgical use scenario. For the hand-hygiene use scenarios we modeled patterns: 1) a hypothetical, intensive use scenario, modeled after descriptions made by the U.S. FDA (Bashaw, 2014), 2) a high use, and 3) an average use rate scenario. The high and average use patterns are based on data available in the open, peer-reviewed literature or based on published studies (Table 4). The average use hygiene scenario was defined to consist of 1.3 mL of hand sanitizer (14.4 mg/kg/dose, assuming a 64 kg body weight), applied to the front and back of hands, at a frequency of 7 times per hour over a 12-h work shift (Fig. 4A). Not all topical antiseptic products contain the same percentage of ethanol. Although alcohol-based products currently in the marketplace can contain ethanol concentrations as low as 61%, as a worst-case assumption, we modeled products as if they contained 90% alcohol for all three hygiene use scenarios.

For the surgical scrub scenario we modeled intensive use conditions based on the experiments of (Kramer et al., 2007) and one alternative typical product use scenario. The typical use surgical scenario was defined to consist of 6 mL of hand sanitizer (61% ethanol) every 4 h over a 12-h work shift (Fig. 4B), applied to hands and forearms. For the intensive use surgical scenario, 20 mL of hand sanitizer (90% ethanol) was assumed to be applied to hands and forearms every 4 h over a 12-h work shift (Fig. 4B).

Table 4
Alcohol-based hand sanitizer use rates.

Use rate scenario	Use rate (Events/Hour)	Basis	Reference
Hypothetical intensive (Maximal) use rate	30 handrubbing events/hour, for 12 h per day	Statement in WHO (2009) guidance document	World Health Organization (2009)
100% compliance scenario	22 handrubbing events/hour	- 25 opportunities/hr - 100% compliance rate - 87.6% fraction of opportunities using alcohol handrubs	
Intensive care unit	**22 events per hour, for 6–8 h per day**	**Observational studies**	Pittet (2014)
Surgical wards	17 times per hour, for 6–8 h per day	Observational studies	Pittet (2014)
Real-world practice	13.3 handrubbing events/hour	- 25 opportunities/hr - 60.8% compliance rate - 87.6% fraction of opportunities using alcohol handrubs	Girou et al. (2006)
Internal medicine ward	15 times per hour, for 6–8 h per day	Observational studies	Pittet (2014)
Pediatric unit	8 times per hour, for 6–8 h per day	Observational studies	Pittet (2014)
Intensive care unit (Night shift)	**Mean: 7.1 for 8 h per day** **Max: 12.3 times/hour**	**Observational studies**	(Monsalve et al., 2014; Polgreen, 2014)
Intensive care unit (Day Shift)	Mean: 6.5 times/hour Max: 11.13 times/hour	Observational studies	Polgreen (2014)

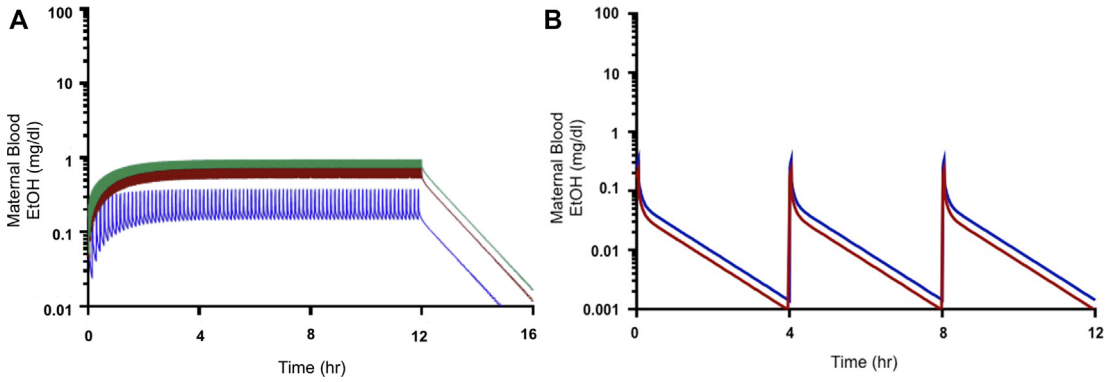

Fig. 4. PBPK model simulation results for hand hygiene (A) and surgical exposure scenarios (B). A. Hand Hygiene Use Scenarios: Blue = Average use; Red = High use; Green = Intensive (Maximum) use. B. Surgical Exposure Scenarios: Red = Typical use; Blue = Intensive (Maximum) use. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Model selection

A number of PBPK models have been published for ethanol (Dumas-Campagna et al., 2014; Huynh-Delerme et al., 2012; Goldsmith et al., 2010; Loizou and Spendiff, 2004; Martin et al., 2015, 2014, 2012; Pastino et al., 1997; Ramachandani et al., 2009; Umulis et al., 2005). These models describe the pharmacokinetics of ethanol in pregnant and non-pregnant mice, rats, neonatal rats, and humans, and have been published in respected peer-reviewed journals. In addition, generic models have been extended to ethanol, some of which include a dermal pathway of exposure (Jongeneelen and Berge, 2011; Leveitt, 2009). For this assessment, the PBPK model of Martin et al. was selected due to its complete treatment of multiple species and extensive development (Martin et al., 2015, 2014, 2012; Pastino et al., 1997) and because it was developed for the purposes of supporting risk assessment and regulatory decisions. To support a human health risk assessment, the published PBPK model of (Martin et al., 2015, 2014, 2012) was modified to include a skin compartment to allow for simulation of complex dermal exposures consistent with ABHS use (Supplement A). In addition, the model was expanded to include the hepatic formation and urinary excretion of ethyl glucuronide, since this metabolite is frequently used as a biomarker for ethanol exposures. Data sets from the published literature were used to parameterize and validate the updated PBPK model. In recognition of the potential contributions of inadvertent inhalation exposures, apparent dermal permeability coefficient (Kp) values were derived to describe the biomarker data (blood ethanol, urinary ethyl glucuronide) measured following hand sanitizer use. For the exposure assessment, blood alcohol levels were estimated for several exposure scenarios, including hypothetical, intensive use scenarios. For the risk characterization, comparative risk scenarios (e.g., consumption of fruit juices, non-alcoholic beverages) were also evaluated.

The PBPK model predictions in this assessment are generally expected to be precautionary. The apparent Kp value used to characterize exposure (5 cm/h) is expected to overestimate the true contribution of the dermal pathway by more than an order of magnitude. Because contributions of the inhalation pathway were implicitly included in the dermal pathway characterized with an apparent Kp, exposures for the inhalation pathway were modeled to be more episodic (i.e., uptake of ethanol forced to occur during the short time period prior to volatilization from skin, in terms of seconds) rather than prolonged (e.g., remaining in room air for an

extended period of time, in terms of minutes to hours). Because of this assumption, the peak concentrations of ethanol in blood predicted by the PBPK model may overestimate the actual peaks. In addition, the magnitude of the inhalation component of exposure depends on the number of individuals present in a room who are using hand sanitizer at a given time. The number of hand sanitizer users per room tested under experimental conditions may not accurately reflect the number of users anticipated under actual use conditions. For example, Ali et al. (2013) assessed hand sanitizer use in groups of 25 individuals. For this reason, any future quantification of the inhalation pathway needs to consider to what degree experimental conditions might result in an overestimation of this pathway under actual use conditions due to experimental design.

4. Margin of exposure analysis

The margin of exposure (MOE) is a risk characterization tool. The MOE is calculated as the ratio of an exposure (or dose) associated with a predetermined effect level or comparator scenario to the estimated exposure (or dose) associated with the scenario under evaluation (International Program on Chemical Safety (IPCS), 2004). The MOE approach is often used when a safe dose (e.g., a tolerable intake or reference dose) has not been derived for a specific exposure scenario being evaluated. The larger the MOE, the less likely a significant concern for health risk exists.

In the absence of a published "safe dose" of ethanol during pregnancy, we evaluated the MOE on an internal dose basis for each of two product use categories: hand-hygiene use by healthcare personnel (i.e., the hand hygiene scenario) and surgical hand rubs (i.e., the surgical scenario). The internal ethanol doses (C_{max} and AUC) for variants of each product use scenario were estimated using the revised PBPK modeling in Supplement A.

Internal doses for the exposure assessment were compared to the internal doses corresponding to NOAEL and LOAEL ranges from the animal toxicology studies, internal doses expected for various beverage intakes, and current occupational exposure guidelines (Table 4). The MOE was approximately 160 for the peak BACs at or near the NOAEL-to-LOAEL boundary of 150 mg/dL for developmental effects from the available animal toxicology studies (Fig. 2). The designs of the current epidemiological studies do not adequately quantify the doses at which effects begin to occur. Thus, a clear NOAEL-to-LOAEL boundary is not identifiable from the available epidemiology studies.

In the absence of a known human effect threshold, we modeled the internal doses expected for consumption of one U.S. standard drink containing 14 g of ethanol. Based on the alcoholic beverage intakes and associated odds-ratios or relative risks, this dose appears to approximate a range where no clear neurobehavioral effects are observed (Fig. 1). The MOE for this one-drink scenario ranged from a value of 23–100 for the peak concentration estimates. We also compared internal doses from our occupational scenarios to those expected from consumption of a variety of "non-alcoholic" beverages. In all cases the peak dose, even the one associated with the intensive/maximum-use occupational use scenarios, was within 10-fold of the levels associated with consumption of a variety of non-alcoholic beverages.

For each of the evaluated scenarios, the MOE determinations based on the AUCs were generally lower (i.e., the peak exposures provided a greater MOE than the AUC for each scenario) (Table 5). However, as was shown previously, there are numerous studies that support the conclusion that the developmental effects of alcohol are related to peak blood alcohol levels (i.e., C_{max}) and not cumulative doses (i.e., AUC). We also compared the internal dose predicted from occupational exposure scenarios to the level of current OEL recommendations and found that the anticipated exposures from topical antiseptic use are near or below current workplace recommendations as shown in Table 5.

5. Discussion

A safety assessment using a weight-of-evidence (WOE) approach was used to assess the potential for adverse developmental effects related to the use of ABHSs by healthcare workers. To our knowledge a comprehensive risk assessment of this topic using a formal health risk assessment methodology has not been published.

We weighed four separate lines of evidence to conduct our assessment using information on exposures and resulting systemic doses (in terms of peak BACs). To that end, we:

1. Evaluated what is known about developmental effects of alcohol from the epidemiology literature,
2. Compared occupational exposures to NOAEL-to-LOAEL boundaries from laboratory toxicology studies conducted in multiple animal species,
3. Compared exposures from ABHS use to routine background exposures arising from ingestion of common-place, non-alcoholic beverages generally deemed to be safe, and
4. Compared internal doses from occupational topical uses of hand sanitizers to the internal dose associated with current OSHA occupational exposure limits.

All four lines of evidence support the conclusion that the use of alcohol-based hand sanitizers by healthcare workers is safe even under hypothetical, worst-case conditions and that the risk of developmental or reproductive effects under such exposure conditions is negligibly small.

Our results show a substantial MOE from available NOAELs and LOAELs. While there is no predetermined or established minimum MOE that is required to reach a conclusion of safe use for all scenarios, the estimated MOEs represent a substantial level of safety. This reflects, in part, our understanding of variability and uncertainty in extrapolating from known effect levels based on high exposures to alcoholic beverages ingested orally to the range of low exposures to alcohol administered dermally.

Working from this perspective, the traditional areas of uncertainty used in occupational risk assessments (Dankovic et al., 2015) can inform the conclusion. For a MOE estimated from animal toxicology data, information suggesting commonality with human effects supports applying a lower MOE. The opposite would be true if humans were known to be more sensitive than animals. For MOE calculations based on human data this consideration does not apply. A framework for organizing such data has been developed that considers relative species sensitivity in terms of pharmacokinetics and pharmacodynamics (IPCS, 2005). The MOE results presented here already address pharmacokinetic issues because comparisons were done on the basis of internal doses. In terms of toxicodynamics (responses at a given target tissue dose) the appearance of a predictable spectrum of effects among all species tested suggests overall comparability of susceptibility. Moreover, the available data are not inconsistent regarding the identified effect levels between rodents, non-human primates, and humans.

Considerations of variability in susceptibility are addressed to some degree by the nature of the endpoint, which considers a susceptible life-stage. We did not specifically evaluate variability in blood concentrations of alcohol for humans. However, the involvement of genetics as one of the risk factors in fetal alcohol spectrum disorder (FASD) has been suggested by animal models and by molecular epidemiological studies on different populations

Table 5
PBPK model predicted internal doses and margin of exposure (MOE) estimates.

Predicted internal doses	ABHS hand hygiene			Surgical scrub	
	Average use[1]	High use[2]	Hypothetical intensive (maximal) use[3]	Typical use	Intensive use[4]
Peak (mg/dL)	0.39	0.75	0.94	0.22	0.33
AUC (mg/dL*hr)	2.3	7.4	10.1	0.17	0.24
MOEs for various reference: Peak dose values (mg/dL)					
Animal NOAEL (Peak = 150 mg/dL)	380	200	160	680	450
Alcoholic beverage (Peak = 22 mg/dL)	56	29	23	100	67
One Non Alcoholic Beverage (Peak = 1.2 mg/dL)	3.1	1.6	1.3	5.5	3.6
Flavored water (Peak = 0.5 mg/dL)	1.2	0.6	0.5	2.1	1.4
Orange juice (Peak = 0.10 mg/dL)	0.3	0.1	0.1	0.5	0.3
OSHA Permissible exposure limit (PEL) [1] (Peak = 0.89 mg/dL)	2.3	1.2	0.9	4.0	2.7
MOEs for various reference: Cumulative Dose (AUC) Values (mg/dL*hr)					
Alcoholic beverage (AUC = 44 mg/dL*hr)	19	6	4	260	180
Non alcoholic beverage (AUC = 1.8 mg/dL*hr)	0.8	0.2	0.2	11	7.5
Flavored water (AUC = 0.16 mg/dL*hr)	0.1	0.0	0.0	0.9	0.7
Orange juice (AUC = 0.73 mg/dL*hr)	0.3	0.1	0.1	4.3	3.0
OSHA PEL (AUC = 8.0 mg/dL*hr)[5]	3	1.1	0.8	47	33

[1]7 events/hour for 12 h. See Table 4.
[2]22 events per hour for 12 h. See Table 4.
[3]Hypothetical Intensive (Maximal) use of 30 events/hour for 12 h. See Table 4.
[4]Based on Kramer et al. (2007).
[5]PELs are regulatory limits on the amount or concentration of a substance in the air.

bearing allelic variants for those enzymes, such as alcohol dehydrogenase (ADH) and CYP2E1, involved in ethanol metabolism. In our calculation of MOEs, we did not consider the potential of decreased metabolic clearance of ethanol in some individuals. Considerations of such polymorphisms do not appear to be important for predicting peak blood concentrations. Sultatos et al. (2004) conducted a Monte Carlo evaluation for ethanol using the PBPK model of Pastino et al. (2000), from which the Martin et al., models are derived. In this Monte Carlo evaluation, organ and body weights, blood flows, and ventilation rates were allowed to vary as either normal or lognormal distributions. In addition, polymorphisms in ethanol metabolizing enzymes were considered, with specific evaluations of 18 phenotype combinations. The mean predicted peak blood concentration of ethanol across all phenotypes following an oral dose of 525 mg/kg was approximately 75 mg/dL, while the 95th percentile values were less than 150 mg/dL (<2-fold higher) in all cases. Due to the small impact of pharmacokinetic variation reported by Sultatos et al. (2004), it was not considered necessary to repeat this exercise using the modified PBPK model used here. Martin et al. (2014a) conducted a sensitivity analysis for the human model. Peak blood ethanol concentrations were reported to be very sensitive to oral dose, and moderately sensitive to the partition coefficient for the slowly perfused compartment, cardiac output, and the oral absorption rate constant (Martin et al., 2014a).

Variation in parameter values for the dermal component added to the model for this work here are not expected to have a meaningful impact on variation in predicted blood values. For example, the dermal permeation constant (Kp) value of 5 mg/cm^2 conservatively corresponds to a maximum flux rate for ethanol across human skin, and therefore increases in Kp value are not expected to result in corresponding increases in predicted blood concentrations. The modeling conducted for our assessment did not explicitly account for variability in dermal permeation associated with differences in skin condition. Some studies demonstrate that damaged skin allows for increased ethanol absorption (Lachenmeier, 2008; McKenzie et al., 2011; Jones and Rajs, 1997; Püschel, 1981; Paulus, 1950). It is also expected that there would be some avoidance of use by those that have broken damaged skin due to the burning sensation of alcohol when applied to the affected areas (Lachenmeier, 2008).

Because of the inherent limitations in the current suite of epidemiology studies of alcohol consumption, we did not attempt to estimate a threshold "safe dose" for effects of ethanol on pregnancy. Some studies do show effects at high doses (intake of alcoholic beverages), but most studies do not show a clear dose–response, and none of the available human effect studies was adequate to support estimation of a NOAEL. It is important to note that the absence of human data to accurately estimate a threshold does not support the conclusion that a threshold does not exist. The animal toxicology data are convincing that the dose–response curve for the onset of systemic effects of alcohol is very steep. This suggests that when extrapolating from a no effect level to low dose ranges a smaller margin would be adequate to protect from adverse effects because a small decrease in dose yields a large decrease in response, and thus a large decrease in risk.

The nature of the observed effects also impact assessment of the margin. We arrayed dose–response data for many different developmental effects, including neurobehavioral effects based on this approach. It is unlikely that other, more sensitive effects will be identified. However, the evaluation of neurobehavioral effects is complex (Abel, 1982). While there is residual uncertainty regarding the possibility of neurobehavioral effects that have not been fully elucidated, the extant data overall show effects are limited until high alcohol levels in blood are reached. This reduces the likelihood of identifying new subtle effects that manifest following low levels of exposure associated with topical applications in the workplace.

The MOE is a ratio of exposure estimates and, thus, the interpretation of this measure needs to consider assumptions applied for the scenarios being compared. We modeled three alternative scenarios for use of ABHS products. Even under hypothetical, intensive use conditions (i.e., maximal application rates and high ethanol concentrations in the product) a significant MOE exists. The margin is larger for the more likely use patterns. The exposure assessment could benefit from high confidence empirical field data to provide clarity on actual likely ranges of product use. Two scenarios for the surgical scrub product were explored and, as with the hand sanitizer scenarios, a significant MOE was observed even under intensive (maximum) use assumptions.

A protective MOE exists despite several additional assumptions that likely overestimate the actual exposures in the workplace. These assumptions include:

- Hypothetical, intensive (maximum) use scenarios for product use volume, frequency, and ethanol content.
- The PBPK modeled peak estimates likely overestimate actual peak blood concentrations because the total doses are assumed to occur via a dermal pathway, whereas the amount of doses contributed via the inhalation pathway would take longer to reach steady state.
- The internal doses from our PBPK modeled use scenarios were validated against existing internal dose data for humans simulating occupational use (Kramer et al., 2007). Reliance on these data may overestimate the actual internal doses because those studies did not distinguish dermal and inhalation intake. As a result, our analysis is based on "apparent dermal uptake" that likely reflects contributions from both pathways (Supplement A). The actual degree of safety from the dermal route alone would be higher than reflected by our MOE estimates.
- The experimental studies used for validation (Kramer et al., 2007) did not make clear if the subjects simulated typical movement from room to room after application of the product as is common in healthcare work. The potential contributions of inhalation exposures from reentry into the same room and thus total measured blood alcohol levels may have been higher in the controlled simulation studies reported by Kramer et al. (2007) than would occur under real workplace conditions where a worker would move from room to room.

Overall, we report MOEs of approximately 160 for comparison to the range of the NOAEL for most sensitive reproductive and developmental in animal studies. This margin is in excess of a factor of 100 often considered adequate for comparison to a NOAEL identified in a well-conducted animal toxicology data set, and well in excess of a factor of 30 generally used when toxicokinetic differences are accounted for using a PBPK model, (U.S. Environmental Protection Agency (U.S. EPA), 2012; Scientific Committee on Toxicity, Ecotoxicity and the Environment, 2001). Margins ranging from 23 to 100 were determined on a peak dose basis when occupational exposures are compared to intakes of a standard alcoholic beverage (i.e., 14 g of ethanol as a bolus dose). Whether such an intake represents a human NOAEL is not certain based on the current epidemiology data. However, an MOE in this range is adequate to account for key areas of uncertainty in extrapolating from a minimal LOAEL in humans.

The MOEs that we present in this analysis are significant and expected to be protective given that:

- We conducted comparisons using sensitive effects for the relevant windows of susceptibility,
- The impact of pharmacokinetic variability on peak blood concentrations for a given exposure to ethanol is expected to be relatively small for this assessment (i.e., less than 2-fold difference between PBPK-predicted 95th percentiles and means for ethanol in blood (Sultatos et al. (2004)),
- The appearance of a predictable spectrum of effects among all species tested suggests overall comparability in terms of responses at a given target tissue dose (pharmacodynamics),
- The dose–response appears steep and we extrapolated from a NOAEL and
- Our exposure scenarios represented intensive (maximal) product use conditions and other precautionary assumptions.

Our conclusion is also supported by the observation that the levels of exposure from the use of ABHSs are in the approximate range of exposure that result from the intake of a variety of common non-alcoholic beverages. The ethanol doses associated with workplace use scenarios are likely to be in the range of those associated with the safe consumption of many items that contain ethanol, including flavored water, soft drinks, fruits, juices (Logan and Distefano, 1998; Musshoff et al., 2010; Obenland et al., 2008). The internal doses on a peak and AUC basis are in the range of or below current OSHA occupational exposure guidelines.

One of the current challenges in communicating developmental risks of occupational exposures to ethanol arises from lack of clarity in statements made by medical and government agencies regarding the risk of alcoholic beverage consumption during pregnancy. Nearly all health organizations advise to avoid consuming alcohol during pregnancy (Table 1). A precautionary statement that no safe level of alcohol exposure has been determined in the scientific literature usually accompanies this advisory. Most organizations do not provide a technical rationale document exploring such statements or explicitly distinguish between the statements that "there is no safe level" or that "no level has been shown to be safe."

Some national research and public health organizations have recognized the limitations of epidemiological studies of alcohol consumption during pregnancy and have acknowledged that the risk of developmental effects may be low at low alcohol intakes (doses). For example, Australia's National Health and Medical Research Council states that:

> "A 'no-effect' level has not been established, and limitations in the available evidence make it impossible to set a 'safe' or 'no-risk' drinking level for women to avoid harm to their unborn children, although the risks to the fetus from low-level drinking (such as one or two drinks per week) during pregnancy are likely to be low. A conservative, public health approach has therefore been taken in recommending that 'not drinking alcohol is the safest option' for pregnant women and women planning a pregnancy. This decision was not based on the fact that substantial new evidence had emerged since the previous guidelines were published, but on limitations of the existing evidence," (Australian National Health and Medical Research Council, 2009)

Similar types of statements are provided in the documentation accompanying such policies on drinking and pregnancy by Canadian (Center for Addiction and Mental Health, 2014) and United Kingdom (Royal College of Obstetricians and Gynaecologists, 2015) authorities.

The adoption of precautionary approaches might reflect consideration of risk benefit trade-offs. Such arguments would suggest that, in the case of alcoholic beverage consumption during pregnancy, any additional risk (even if extremely low) is not balanced by a known health risk reduction for expecting mothers or their children. This weighing of risks and benefits differs for consideration of occupational uses of alcohol-based topical antiseptics in the healthcare industry, where ABHSs are a critically important tool in the control of infectious diseases.

In viewing the assessment with this comparative risk lens, an obvious factor that impacts the overall risk of developmental outcomes is the potential for increased incidence of infectious illnesses. Viral and bacterial infections are not innocuous to the developing fetus. In fact, numerous studies have demonstrated increased risks of pre-term delivery, fetal stress, or congenital abnormalities associated with bacterial or viral infections (Graham et al., 1998; Luteijn et al., 2014; Mak et al., 2008; Organization of Teratology Information Specialists (2012); Stowell et al., 2014). The American Congress of Obstetricians and Gynecologists (ACOG) and the CDC acknowledge the importance of infection control for the health of pregnant women and to reduce the risk of birth-defects, miscarriage, and early labor (American Congress of Obstetricians and Gynecologists (2014); CDC, 2013). CDC suggests

in situations where hand washing with soap and water are not possible, that pregnant women use alcohol based hand-sanitizers to help reduce infection (CDC, 2013).

It could be argued that overall risk reduction could be achieved by substituting alcohol-based topical antiseptics with non-alcohol alternatives. The scientific basis for such an approach is challenging because the developmental risk profiles and efficacy of other chemical substitutes are not as well understood. In addition, adherence to hand hygiene in healthcare settings has historically been unacceptably low. The introduction of ABHSs and the adoption of their use as the primary means of hand hygiene in healthcare systems have led to significant improvements in hand hygiene compliance and reduction in healthcare associated infections. Ethanol is more effective and acts quickly against a wide spectrum of bacteria, fungi, and enveloped viruses than soap and water. Alcohol-based topical antiseptics have acceptable skin tolerability, quick and simple applications with high compliance, economical, and sinks are not required (Rotter, 2001).

Although challenging, there is significant value in communicating considerations of dose–response behavior to inform decision-making. Such an effort eliminates confusion arising from apparent inconsistencies in health policy. As noted above, daily consumption of many foods and beverages are considered "safe and healthy", with no exception made for pregnancy, despite the presence of low levels of ethanol. For example, "non-alcoholic" beers are known to contain small but detectable amounts of alcohol. In one study, repeated sampling of several lots of non-alcoholic beers yielded mean ethanol concentrations of 3.1 and 3.2 g/kg, equivalent to 0.41 and 0.42 vol% (Thierauf et al., 2010). Similarly, fruits, fruit juices, and soft drinks are known to contain small amounts of alcohol (Logan and Distefano, 1998).

The U.S. FDA acknowledges, and has an established policy, that non-alcoholic beverages that contain alcohol at concentrations below 0.5%, though not alcohol-free, do not warrant cautionary label warnings or treatment as if they were alcoholic beverages. According to the FDA:

> Beverages such as soft drinks, fruit juices, and certain other flavored beverages which are traditionally perceived by consumers to be "non-alcoholic" could actually contain traces of alcohol (less than 0.5 percent alcohol by volume) derived from the use of flavoring extracts or from natural fermentation. U.S. FDA also considers beverages containing such trace amounts of alcohol to be "non-alcoholic." (Office of Regulatory Affairs (2005))

These beverages are broadly consumed and do not require specific warnings related to intake during pregnancy.

In developing the assessment approach we considered the limitations in the dataset identified by U.S. FDA regarding the safety data for ethanol. These deficiencies in the U.S. FDA administrative record for the safety of alcohol and the gap filling results derived from analysis of this work include:

- The administrative record is incomplete regarding human pharmacokinetic studies under maximal use conditions when applied topically. In response to this concern we have applied and expanded extant PBPK models for ethanol to predict internal doses of ethanol, as BACs, in humans under intensive (maximal) use scenarios. These predictions were used to address systemic doses from relevant maximal use scenarios.
- The administrative record is incomplete regarding data to help define the effect of formulation on dermal absorption. The available studies do not suggest that differences in product formulation, other than alcohol concentration, result in appreciable differences in dermal absorption. Published studies are available where products with different alcohol concentrations are applied to the skin. The impact of variation in ethanol content on internal dose was evaluated in the revised PBPK model. Moreover these assessments include a hypothetical intensive (maximal) use application rate that is significantly higher that what would be expected to occur in actual product use in the health care industry. In addition, our revisions to the PBPK model were consistent with empirical data that used actual formulated product in a simulation of workplace activities.

6. Conclusions

A critical review of the literature and our modeling results support the conclusion that the use of alcohol-based hand sanitizers by healthcare workers is safe even under hypothetical, worst-case conditions and that the risk of developmental or reproductive effects under such exposure conditions is negligibly small. We used a WOE approach to evaluate the safety of alcohol-based topical antiseptics. Occupational use of ABHSs in the healthcare industry can generate low, detectable concentrations of ethanol in blood. This unintended systemic dose likely reflects contributions from both dermal absorption and inhalation of volatilized product. The resulting internal dose is low, even under hypothetical, worst-case intensive (maximum) use assumptions.

A critical evaluation of dose–response and exposure information supports the following conclusions:

- A significant MOE exists compared to demonstrated effect levels for developmental toxicity under worst case use scenarios, and the margin is even more significant for typical anticipated use patterns.
- Levels of exposure yield BACs that approximate those associated with consumption of non-alcoholic beverages.
- Estimated internal doses from expected topical application rates of alcohol-based hand sanitizers are in the range of or below occupational exposure limits.
- No significant risk of developmental or reproductive toxicity is expected from potential occupational exposures from alcohol-based hand sanitizers or surgical scrubs based on the exposure margins and the dose–response characteristics of ethanol.

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 and should continue to be available.

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Appendix A. Supplementary data

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Transparency document

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