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REVIEW ARTICLE

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Assessment of ethanol exposure from hand sanitizer use and potential for developmental toxicity in nursing infants

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Abstract

Ingestion of ethanol during pregnancy is known to have detrimental effects on the fetus. Although the potential developmental effects of maternal ethanol intake during lactation are less well characterized, public health guidelines recommend avoidance of alcohol or, if alcohol is consumed, to allow for 1–2 h to pass before nursing. A proposal to classify ethanol as potentially harmful to breast-fed children warrants an investigation of the potential adverse neurodevelopmental effects of low-dose ethanol exposure during lactation. There currently are no studies that have examined neurodevelopmental outcomes from lactational exposure to ethanol from the use of topical products that contain ethanol, such as alcohol-based hand sanitizers (ABHS). Furthermore, the epidemiological literature of lactational ethanol exposures from maternal alcohol consumption is limited in design, provides equivocal evidence of neurological effects in infants, and is insufficient to characterize a dose–response relationship for developmental effects. Toxicological studies that observed neurodevelopmental effects in pups from ethanol via lactation did so at exceedingly high doses that also caused maternal toxicity. In this investigation, blood ethanol concentrations (BECs) of breastfeeding women following typical-to-intense ABHS use were computationally predicted and compared to health benchmarks to quantify the risk for developmental outcomes. Margins of 2.2 to 1000 exist between BECs associated with ABHS use compared to BECs associated with neurotoxicity adverse effect levels in the toxicology literature or oral ethanol intake per public health guidelines. Neurodevelopmental effects are not likely to occur in infants due to ABHS use by breastfeeding women, even when ABHSs are used at intense frequencies.

KEYWORDS

alcohol-based hand sanitizer, developmental toxicity potential, ethanol, exposure assessment, exposure via breastfeeding, lactation exposure, lactation hazard, PBPK modeling, safety assessment

1 | INTRODUCTION

Systemic exposure to ethanol, especially resulting from high dose intakes from binge drinking, is a known neurological health risk to the fetus. Ethanol exposure during fetal development has been associated with brain damage and brain cell death, and may be modulated by alterations in neurotrophins and neurotransmitters (Carito et al., 2019; Climent et al., 2002; Manzo-Avalos & Saavedra-Molina, 2010). Alcohol intake during pregnancy has been associated with neuropsychological effects and fetal alcohol syndrome (Comasco et al., 2018; Manzo-Avalos & Saavedra-Molina, 2010; Pruett et al., 2013). The impacts of low to moderate ethanol intake (up to one standard drink or 14 g ethanol a day per United States Department of Agriculture) and the effects of ethanol intake during lactation on fetal neurodevelopment are less well characterized (Comasco et al., 2018; Giglia & Binns, 2006; Manzo-Avalos & Saavedra-Molina, 2010; Pruett et al., 2013; United States Department of Health and Human Services, 2020). The metabolism of ethanol in newborns is approximately half of that in adults, suggesting even small amounts of ethanol that may transfer from breastfeeding can lead to adverse neurological effects (Haastrup et al., 2014). Various international public health guidelines generally recommend avoidance of alcohol consumption during breastfeeding or waiting 1 to 2 h after ingestion of an occasional standard alcoholic drink before nursing (American Academy of Pediatrics, 2012; Canadian Centre on Substance Use and Addiction, 2018; Centers for Disease Control and Prevention, 2021; Gartner et al., 2005; *Institute of Medicine (US) Committee on Nutritional Status During Pregnancy and Lactation*, 1991; Bavarian Health and Food Safety Authority, 2013; Australian National Health and Medical Research Council, 2020; Royal College of Obstetricians & Gynaecologists, 2018).

Based on the potential adverse effects of ethanol exposure during lactation on the neurodevelopment of nursing infants, a "lactation hazard" classification has been proposed. On August 14, 2020, the European Chemicals Agency updated the Classification and Labelling Registry of Intentions to indicate that the Greek Competent Authority intended to submit a proposal for the reclassification of ethanol. In addition to the current, harmonized classification of Flam. Liq. 2, H225 (highly flammable liquid and vapor), the Greek proposal would add

- Eye Irrit. 2, H319 - causes serious eye irritation
- Repr. 2, H361d - suspected of damaging the unborn child
- Lact., H362 - may cause harm to breast-fed children
- STOT SE 3, H336 - may cause drowsiness or dizziness
- STOT RE 2, H373 - may cause damage to organs through prolonged or repeated exposure

In October 2020, the Greek authority indicated its intention to submit the dossier by December 13, 2020. As of September 13, 2021, the dossier had not been submitted and is currently "delayed until further notice" (European Chemicals Agency, 2021). To support the proposed classifications of ethanol, the Greek authority appears to be relying on a combination of data from studies of heavy drinking in humans and animal studies simulating excessive drinking. However, the studies that have evaluated other exposure scenarios, such as light to moderate drinking, and the use of products containing ethanol, as well as ethanol exposure via other routes (e.g., dermal), do not appear to be included in the Greek assessment. Therefore, applicability of the proposed hazard classifications to products containing alcohol, especially those applied dermally, remains unclear.

Ethanol is an approved common active ingredient in alcohol-based hand sanitizers (ABHS) and hand hygiene products. In practice, contact with ethanol can be frequent for high-use professions, such as health-care workers (HCWs). Further, ethanol has been demonstrated to be absorbed dermally and via inhalation of ethanol vapors, although dermal absorption may be limited due to high rates of evaporation (Kramer et al., 2007; Pendlington et al., 2001). Following ingestion of alcohol, ethanol can be detected in the blood and milk of lactating mothers (Haastrup et al., 2014; Kesaniemi, 1974; Lawton, 1985; Mennella & Beauchamp, 1993). Therefore, it is possible that dermal use of ABHS and unintentional inhalation of ethanol yields small amounts of ethanol in breast milk as well. This suggests the need to evaluate resulting systemic doses for ABHS use scenarios during lactation and potential implications for neurodevelopment among infants who are breastfeeding from women using ABHS. Prior work (Maier et al., 2015) assessed this consideration for gestational, but not lactation-specific, exposures. This represents a gap in the literature, whereby there is little evidence regarding the potential neurological effects of exposure to ethanol during breastfeeding. To our knowledge, there is no evidence regarding the potential for these neurological effects as a result of maternal ABHS use during lactation.

To date, we did not identify any integrated epidemiological and toxicological analysis in which maternal blood ethanol concentrations (BECs) and the likelihood of developmental effects in nursing infants are assessed following maternal ABHS use. Thus, with a focus on potential neurological effects, we evaluated the risk to infants that are breastfed by mothers that use ABHSs. To that end, we conducted a literature review to identify (1) guidelines for alcohol consumption limits during lactation and (2) relevant epidemiological and toxicological studies of maternal ethanol exposure during breastfeeding and associated outcomes, especially neurological, in infants or offspring. Multi-pathway physiologically based pharmacokinetic (PBPK) modeling was performed to estimate the maternal BEC following average-to-intensive use scenarios of ABHS, simulating a range of conditions for product users, such as HCWs. Predicted BECs from ABHS use scenarios were compared to estimated BECs according to recommended public health alcohol ingestion limits and to BECs from animal toxicological studies that elicited neurological effects in nursing offspring. This analysis provided an approach to evaluate the applicability of the proposed lactation hazard classification for certain ethanol-containing products, like ABHS, with respect to potential harm or developmental effects in breastfed children. We conclude our assessment with a thorough discussion of the margins between modeled internal BECs associated with typical and Food and Drug Administration (FDA)-proposed

ABHS "maximum use conditions" and various toxicological effect levels or guideline benchmarks; these margins have important implications for regulatory bodies considering the potential benefits and risks of ethanol-based sanitization products.

2 | METHODS

2.1 | Literature search methodology

A literature search was conducted in the PubMed online database to identify available studies that assessed the association between ethanol exposure during lactation and developmental outcomes in children. Key words used to identify studies with relevant exposure and timing of exposure included "alcohol consumption," "ethanol," "lactation," "breastfeeding," "breastfed," or "lactating". Key words used to capture the outcome of interest included "developmental toxicity," "development," "IQ," and "autism". This search identified 193 articles published prior to December 2020. We also performed an additional literature search specific to hand sanitizer and biological verification of blood ethanol. Key words included "hand sanitizer," "hand sanitizers," "hand rub," "ethanol," "alcohol-based," "alcohol based," "blood," or "plasma." This search identified 34 articles published prior to December 2020. The content and references of systematic reviews and meta-analyses identified in the search were reviewed but not included in the full qualitative synthesis. Letters to the editor, commentaries, or articles of similar scope were excluded. The references in Maier et al. (2015) were also reviewed, due to the similarities in scope and range with this assessment; two articles cited by Maier et al. (2015) were not identified in our literature search but were identified for inclusion (Lawton, 1985; Vaglenova & Petkov, 1998). The PubMed literature searches were crosschecked in the Google Scholar search engine to ensure that all relevant papers were captured. No additional references were identified. Ultimately, 46 articles were deemed appropriate for full text review, and 28 articles were included in the full qualitative synthesis.

2.1.1 | Criteria for confidence scoring

Nine epidemiological and fifteen toxicological studies were identified in the literature search that assessed maternal ethanol intake during lactation, or lactation and gestation, and measured subsequent neurodevelopmental outcomes. Four additional pharmacokinetic studies were reviewed that assessed alcohol intake in nursing or lactating mothers and measured the resulting blood and/or milk ethanol concentrations. These studies were evaluated for relevance and reliability according to criteria outlined in Data S1. Supporting Information, Tables S1–S6 and further categorized by confidence in the stated study conclusions (Data S1. Supporting Information, Table S7). Relevance, reliability, and overall confidence for each reviewed study are also summarized in supplementary tables (Data S2. Supporting Information).

2.1.2 | Literature review and data abstraction

To analyze and compare exposures and results across the reviewed studies, relevant data were abstracted and summarized (Data S2. Supporting Information). Data abstraction for epidemiological studies captured the cohort or population characteristics, exposure timing (during lactation or gestation or both) and measurement (self-report alcohol consumption or biologically verified ethanol levels), outcomes and validity of outcome measurement techniques, statistical methods, consideration for confounding variables, and significant findings described in each study. For toxicological studies, information regarding the study design (species, diets, treatment groups and duration, and exposure timing [during lactation or gestation or both]), measured internal ethanol concentrations and toxicological outcomes (in dams and pups, where data were available), developmental/neurodevelopmental outcomes in pups, and other significant findings were extracted. Data for pharmacokinetic studies regarding alcohol intake and measured outcomes (blood/milk ethanol concentration over time) were summarized.

2.2 | Exposure assessment

2.2.1 | Toxicological extrapolation of no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) in animals

In order to compare the exposure and outcomes of the reviewed studies, the reported doses were converted to g/kg-day exposures taking into account the animal weight and water consumption. In the absence of reported data for rodent weight, Environmental Protection Agency (EPA) reference values were substituted (United States Environmental Protection Agency, 1998). Additionally, for ethanol doses reported as percentages of water, when water consumption was not reported, the EPA water intake factor was used to calculate a daily water consumption, from which a daily ethanol dose was calculated (United States Environmental Protection Agency, 1998). A summary of the determined doses and values used for calculations is provided in Data S1. Supporting Information, Table S8.

2.2.2 | Margin of exposure versus benchmark estimates

Exposures from ethanol in ABHS were compared to toxicological or guideline benchmarks. Specifically, maternal BECs associated with a point of departure (POD) for offspring neurotoxicity reported in animal toxicological studies and predicted BECs corresponding to recommended intake limits for breastfeeding women were compared to estimated BECs corresponding to hand sanitizer use under different scenarios. The margin was calculated by dividing BECs from various toxicological studies and alcohol intake guidelines (toxicological exposures or oral consumption) by the estimated peak BECs resulting from

hand sanitizer use. The toxicological BEC was derived from Oyama et al. (2000) using a benchmark dose (BMD) modeling approach; a BMD and its 95% lower confidence limit (BMDL) were calculated using the maternal BEC (mg/dL) and pup brain weight (g). Of note, the ratio of the average maternal BEC (2.87 ± 1.06 mg/dL) and the corresponding lowest administered dose (5% ethanol in drinking water) was markedly lower than the ratios of average BECs (43.45 ± 11.50 and 100.66 ± 25.30 mg/dL) at the higher doses (10% and 20% ethanol in drinking water, respectively) (Oyama et al., 2000). Therefore, (1) the actual maternal BEC at the lowest dose may be higher than what was observed, (2) the administered dose was lower than the reported nominal dose, or (3) the BECs at the higher doses may be elevated due to metabolic saturation. Despite the uncertainties in the underlying dose, no other dose–response studies were available, and therefore, the results as reported in Oyama et al. (2000) were used for this analysis. BMD modeling was performed in the US EPA BMD Software (BMDS), Version 3.2. All frequentist, continuous models were used to calculate a BMD and BMDL associated with a change of one standard deviation (1 SD) in mean pup brain weight. Models assumed homogenous (constant) variance across dose groups. The BMD model fits were assessed according to the US EPA's BMDS guidance document (United States Environmental Protection Agency, 2011); this included evaluation of the goodness-of-fit *p* value, visual fit, scaled residuals, and the Akaike Information Criterion. The data utilized for BMD modeling and a summary of the results are presented in Tables S9 and S10, and Figure S1 in Data S1. Supporting Information. All BMD modeling results are provided in Data S4. Supporting Information. A BMDL of 9.45 mg/dL was selected as the BEC for derivation of the margin of exposure for toxicological endpoints.

2.3 | PBPK simulations

PBPK modeling was used to predict internal ethanol concentrations to provide exposure estimates appropriate for comparison to the available dose–response data. A detailed description and evaluation of the PBPK model, including the model code, physiological and ethanol-specific parameters used for the model, derivation of dermal and inhalation exposure estimates from the use of ABHS, and verification of the model, are provided in Data S1. Supporting Information. Briefly, previously published PBPK models developed by Maier et al. (2015) and More et al. (2020) were modified to address relevant exposure scenarios (dermal and inhalation) and estimate ethanol pharmacokinetics in exposed mothers. The PBPK models in Maier et al. (2015) and More et al. (2020) provided the general framework and physiological parameters to describe the disposition and metabolism of ethanol with a nine-compartment model (Data S1. Supporting Information, Figure S2). Maier et al. (2015) included a skin compartment and parameterized the model to simulate the absorption of ethanol through human skin via an apparent permeability value (Kp in cm/h) and partitioning from skin to blood; however, the Kp value was described to be an overestimate of the actual dermal exposure, accounting for concurrent inhalation of ethanol vapors. The current model was modified to allow independent inputs for dermal and inhalation exposures. Dermal ethanol absorption and ethanol evaporation rates were estimated using IH SkinPerm, the American Industrial Hygiene Associations excel-based software, with additional calibration to consider measured ethanol permeation rates. Various factors were considered, such as the physicochemical properties of ethanol, mode of deposition into skin, air thickness, and concentration of ethanol. Breathing zone ethanol concentrations were estimated using a two-zone (near-field/far-field) model representative of a generic-sized work room with relatively low air ventilation rates accounting for generation rate of ethanol vapor, air ventilation rates, volume of the space in which the exposure occurs, and the radius of the breathing zone hemisphere (see Data S1. Supporting Information for a complete description of the dermal and inhalation simulations). The model is also capable of simulating milk ethanol concentrations (MECs), but due to the lack of comparable MECs in toxicological studies, the model was only used for the estimation of BECs. The model simulates dermal absorption of ethanol in a healthy skin compartment and does not account for irritated or damaged skin, although injured skin with compromised barriers may cause an increase in ethanol absorption (Lachenmeier, 2008). The model was coded in R Studio 4.0.3: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria). The model code is available in Data S1. Supporting Information.

2.3.1 | Exposure simulations

To compare internal ethanol doses from ABHS use to toxicological and public health benchmarks, different scenarios of ABHS use were considered and the associated internal doses were predicted with the PBPK model. Hand hygiene, pre-surgical hand disinfection, and survey-based ABHS scenarios were assessed.

Three hand hygiene scenarios, average, high, and intensive ABHS use (in terms of exposure frequency and overall volume), were evaluated:

- Average: 3 mL of 90% ethanol hand sanitizer applied to the front and back of the hands for 1 min, 7 times per hour over a 12-h work shift
- High: 3 mL of 90% ethanol hand sanitizer applied to the front and back of the hands for 1 min, 22 times per hour over a 12-h work shift
- Intensive: 3 mL of 90% ethanol hand sanitizer applied to the front and back of the hands for 1 min, 30 times per hour over a 12-h work shift

Two pre-surgical hand disinfection scenarios were also assessed:

- Typical use scenario: 6 mL of 61% ethanol hand sanitizer applied to hands and forearms for 3 min, once every 4 h over a 12-h work shift

- Intensive scenario: 20 mL of 90% ethanol hand sanitizer applied to hands and forearms for 3 min, once every 4 h over a 12-h work shift

ABHS use simulations among health-care workers (HCWs) based on user survey data (Boyce et al., 2017) included:

- Average user: 3 mL of 90% ethanol hand sanitizer applied to the front and back of the hands for 1 min, 3 times per hour over a 12-h work shift
- 95th percentile user: 3 mL of 90% ethanol hand sanitizer applied to the front and back of the hands for 1 min, 12 times per hour over a 12-h work shift

Hand hygiene and pre-surgical hand disinfection ABHS use scenarios were based on observational studies as described in Maier et al. (2015), and reports in Brown et al. (2007) and by the World Health Organization (WHO) (2009). There is no agreed-upon definition for what is an "intensive use" scenario for ABHS. Brown et al. (2007) suggested that, in clinical settings, intensive use of ABHSs included applications of up to 30 times per hour. Similarly, in their introductory remarks to the 2014 Nonprescription Drugs Advisory Committee meeting, held on September 3, 2014, the FDA defined "maximal use conditions" for ABHS as 30 applications per hour for a full 8- or 12-h shift. Although the FDA cited the WHO Guidelines on Hand Hygiene in Health Care (World Health Organization, 2009), it appears that the WHO document was referring to total hand hygiene events per hour of patient care, not ABHS use rates per hour. To clarify the matter of maximal use rates of ABHS by HCWs, Boyce et al. (2017) conducted a systematic review of published hand hygiene studies that included data from two hand hygiene studies using electronic compliance monitoring systems. The analysis of the available studies indicated that in 95% of nursing shifts, individual nurses used ABHS 141 times or less per shift, and 15 times or less per hour. ABHS use frequencies as described in Boyce et al. (2017) were also simulated in this assessment to represent reasonably anticipated and realistic use conditions reported in surveys among HCWs. Therefore, the intensive as well as the high ABHS use conditions in this current assessment represent exaggerated use frequencies that are intended to capture the upper extreme of exposure for HCWs. These exposure assumptions also represent conditions that are expected to be higher than exposures for the general public.

A 3-mL application of hand sanitizer is a typical amount reported in other studies (Bessonneau et al., 2010; Bessonneau & Thomas, 2012; Dumas-Campagna et al., 2014; Hautemaniere et al., 2013) and is a recommended amount needed to fully cover the surface area of adult hands (Zingg et al., 2016). Additionally, hand sanitizer containing 90% ethanol is considered to be a concentration on the high end compared to other available products on the market that may contain considerably lower concentrations (at least 60% recommended by Centers for Disease Control and Prevention) (Maier et al., 2015). The "typical" pre-surgical hand disinfection scenario is described in Maier et al. (2015). The pre-surgical hand disinfection scenario described as "intensive" by Maier et al. (2015) was defined based on a study conducted by Kramer et al. (2007) in which a standard surgical disinfection protocol was used according to the European Committee for Standardization. Collectively, these exposure scenarios characterize appropriate to conservative exposure estimates.

Parameter selections used in the PBPK simulation of these ABHS use scenarios are provided in Data S1. Supporting Information, Tables S11 and S12. These scenarios varied in exposure frequency, volume, or ethanol concentration of hand sanitizer, while holding other considerations (e.g., duration of hand rubbing) constant.

2.3.2 | BEC estimations in lactating women

The PBPK model was used to estimate peak BECs (mg/dL) as reference points to allow comparison between expected ethanol concentrations from various exposures to ethanol (ingested or via hand sanitizer) and BECs associated with developmental (neurotoxicity) endpoints or according to recommended guidelines by various public health organizations (Table 1). In Table 1, predicted BEC ranges from ethanol consumption are summarized, where the lower value represents the peak blood ethanol concentration (mg/dL) in women after 1 h or 2 h post-drink consumption (as guidelines recommend waiting 1 h to 2 h before breastfeeding) and is therefore the maximum BEC associated with those that comply with the guidelines. Values in parenthesis in Table 1 are overall peak BECs, which occur approximately 30 min after ingestion; this value represents the highest concentration, in the event the mother breastfeeds before the 1 to 2 h recommended wait time. Peak BEC estimates for various hand sanitizing use conditions and inhalation exposures are summarized in Table 3.

3 | RESULTS

3.1 | Alcohol consumption during breastfeeding guidelines

The relationship between ethanol exposure during pregnancy and developmental outcomes is well established in the epidemiologic literature. However, the relationship between ethanol exposure during breastfeeding and developmental outcomes is not as clear. Most clinical bodies and health organizations have released conservative guidelines for alcohol consumption during breastfeeding that state that avoiding alcohol consumption is the safest option (Table 1). These guidelines are based on the body of evidence surrounding adverse fetal development outcomes, including the wide range of symptoms and morphologies captured under fetal alcohol spectrum disorders (FASD) observed following oral alcohol consumption during pregnancy. Following alcohol consumption, ethanol can be detected in

TABLE 1 Recommended public health guidelines for breastfeeding mothers and estimated BECs

Organization	Guideline year	Recommendation	PBPK modeled estimated BECs[a,b]
United States mass of ethanol per drink = 14 g			
Centers for Disease Control and Prevention (CDC)	2021	"Not drinking alcohol is the safest option for breastfeeding mothers. However, moderate alcohol consumption (up to 1 drink/day) is not known to be harmful to the infant, especially if the mother waits at least 2 hours after a single drink before nursing."	*6.1 (20.6) mg/dL*
American Academy of Pediatrics	2012	"Ingestion of alcoholic beverages should be minimized and limited to an occasional intake but no more than 0.5 g alcohol per kg body weight, which for a 60 kg mother is approximately 2 oz liquor, 8 oz wine, or 2 beers. Nursing should take place 2 hours or longer after the alcohol intake to minimize its concentration in the ingested milk."	*46.0 (74.2) mg/dL*
American Academy of Pediatrics	2005	"Breastfeeding mothers should avoid the use of alcoholic beverages, because alcohol is concentrated in breast milk and its use can inhibit milk production. An occasional celebratory single, small alcoholic drink is acceptable, but breastfeeding should be avoided for 2 hours after the drink."	*6.1 (20.6) mg/dL*
National Academy of Sciences—Institute of Medicine	1991	"There is no scientific evidence that consumption of alcoholic beverages has a beneficial impact on any aspect of lactation performance. If alcohol is used, advise the lactating woman to limit her intake to no more than 0.5 g of alcohol per kg of maternal body weight per day."	*46.0 (74.2) mg/dL*
Canada mass of ethanol per drink = 14 g			
Canadian Centre on Substance Use and Addiction	2018	"If you are pregnant or planning to become pregnant, or about to breastfeed, the safest choice is to drink no alcohol at all."	*0 mg/dL*[c]
United Kingdom mass of ethanol per drink = 8 g			
Royal College of Obstetricians & Gynaecologists	2018	"The safest option is to avoid alcohol during breastfeeding … if you do choose to drink, it is safest not to drink more than 14 units per week[d] and best to spread your drinks evenly during the week."	*8.0 (24.8) mg/dL*
Australia mass of ethanol per drink = 10 g			
Australian National Health and Medical Research Council	2020	"For women who are breastfeeding, not drinking alcohol is safest for their baby."	*0 mg/dL*[c]
Germany mass of ethanol per drink = 10 g			
Bavarian Health and Food Safety Authority	2013	"It is safest for the health of the mother and child if no alcoholic drinks of any kind are consumed during the nursing period. … if, as an exception, you drink a glass of wine, champagne or the like during the nursing period, you should … [p]lan at least one to two hours between the consumption of an alcoholic drink and the next breastfeeding to allow the alcohol in your blood and in the milk to degrade to the greatest possible extent."	*7.6 (12.7) mg/dL*

References: American Academy of Pediatrics, 2012; Canadian Centre on Substance Use and Addiction, 2018; Centers for Disease Control and Prevention, 2021; Gartner et al., 2005; Institute of Medicine, 1991; Bavarian Health and Food Safety Authority, 2013; Australian National Health and Medical Research Council, 2020; Royal College of Obstetricians & Gynaecologists, 2018

[a]Blood ethanol concentrations (BECs) were estimated with PBPK modeling. It was assumed that the drink was consumed in a short period of time (a single dose to the gut). Values are BECs (mg/dL) of mothers after 1 or 2 h post-drink (depending on guideline recommendations, assumed 2 h if no recommendation given); therefore, it is the maximum concentration associated with those that comply with the recommendations. Values inside the parenthesis are peak BECs, which occurs approximately 30 min after ingestion; this value represents the highest concentration, in the event the mother breastfeeds before the 1 to 2 h recommended wait time.

[b]Values assume a mother's body weight of 74.15 kg (post-delivery); this weight was estimated using a pre-pregnancy weight of 64 kg (Maier et al., 2015), a pregnancy weight gain of 15 kg (Abebe et al., 2015), and weight loss during delivery estimation to account for weight of the infant, placenta, and amniotic fluid (Haiek et al., 2001).

[c]Estimated BEC is 0 mg/L as the guideline recommends no drinking during breastfeeding. Note that numerous other countries recommend entirely avoiding alcohol during breastfeeding. A list of guidelines from additional countries can be found here: http://iardwebprod.azurewebsites.net/science-resources/detail/Drinking-Guidelines-for-Pregnancy-and-Breastfeedin

[d]14 units per week was assumed to be two drinks per day.

breast milk; the ethanol concentration in breast milk approximates, or may be slightly higher than, the mother's blood ethanol concentration, due largely to ethanol's water-soluble properties and the high water content of breast milk (Lawton, 1985). Several guidelines factor in this approximation and state that breastfeeding following alcoholic beverage consumption is permissible as long as intake is limited and breastfeeding is avoided for 2 h following ingestion of a standard drink, which would allow the mother's blood and milk ethanol concentrations to return to below-effect levels. However, it is of note that guidelines from several public health organizations in countries included in this table (i.e., Canada and Australia) and beyond (Netherlands, France, Belgium, Bulgaria, China, Japan, and others) state that the safest option is to abstain completely from alcohol consumption during breastfeeding (International Alliance for Responsible Drinking, 2019).

For guidelines that allow limited alcohol consumption, peak BECs of breastfeeding women adhering to the guidelines (waiting 1–2 h to breastfeed after consuming alcoholic beverage) and overall peak BECs (in the event recommended wait time is not considered) were estimated with PBPK modeling, as described in section 2.3.2 (results are in Table 1). The estimated BECs vary based on guidelines and on the mother's weight; however, among guidelines that provided recommendations for "safe" alcohol consumption, estimated average BECs ranged from 6.1 mg/dL to 46 mg/dL (Table 1). These values are comparable to the values observed in the literature (Kesaniemi, 1974; Lawton, 1985). However, these values are based on the oral intake of alcohol and result in higher BECs compared to those predicted to occur as a result of various ABHS use scenarios, for which peak BECs range from 0.044 mg/dL for typical pre-surgical hand disinfection to 2.80 mg/dL for intensive hand hygiene scenarios.

3.2 | Epidemiological findings for ethanol consumption and breastfeeding

The majority of studies were unable to identify a statistically significant relationship between alcohol consumption during breastfeeding and developmental health outcomes. The major findings of the nine relevant studies are described in Data S2. Supporting Information and summarized in Figures 1 and 2. Among the few studies that provided outcome data by multiple exposure levels, findings were mixed. Two studies (Gibson & Porter, 2020; Little et al., 1989) identified significant decrements in psychomotor development, numeracy, and spelling scores. In a study of 400 women and children from the Group Health Cooperative of the Puget Sound in Seattle, Washington, infants were assigned an infant absolute alcohol (AA) score for which mother's average daily ethanol intake was multiplied by infant's breastfeeding experience score (value of 1 for totally breastfed, 0.55 for partially breastfed, and 0 for formula fed) (Little et al., 1989). Infants were tested on the mental and psychomotor indexes of the Bayley Scales of Infant Development around their first birthday. In this study, there was a statistically significant negative linear trend between infant AA score and psychomotor development score ($p = 0.006$), but there was no significant relationship between AA score and mental development score. Additionally, significant decrements in mean psychomotor development were statistically significant only among women who drank more heavily, based on AA score, and

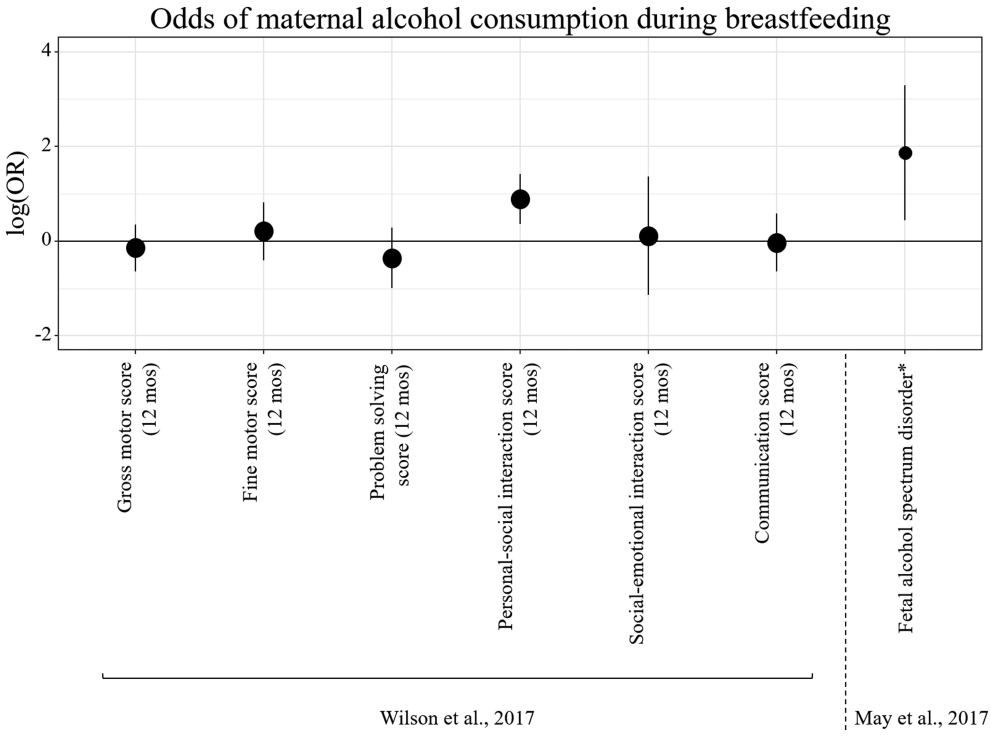

FIGURE 1 Odds of maternal alcohol consumption during breastfeeding associated with infant and adolescent physical, cognitive, and social development outcomes identified in the epidemiological literature. Sizes of the circles correspond to the confidence scoring of the study (weak, limited, and strong); larger circles denote higher confidence *Fetal alcohol spectrum disorder is a term used to describe the range of physical, cognitive, and behavioral effects observed in relation to infant alcohol exposure

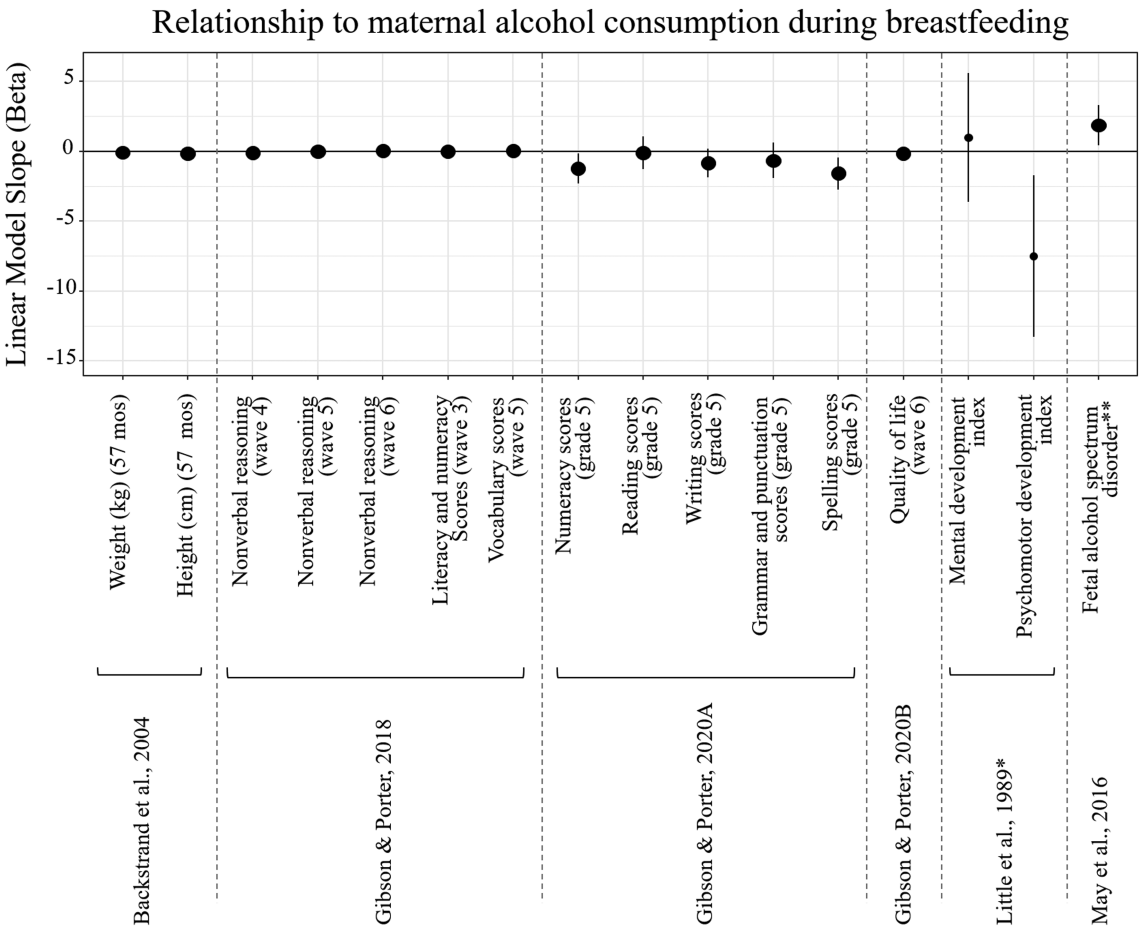

FIGURE 2 Beta coefficients from linear regression models estimating the relationship between maternal alcohol consumption during breastfeeding associated with infant and adolescent physical, cognitive, and social development outcomes in the epidemiological literature. Sizes of the circles correspond to the confidence scoring of the study (weak, limited, and strong); larger circles denote higher confidence.
*In Little et al. (1989), alcohol consumption scores were only statistically significantly associated with mean psychomotor development index scores at heavier drinking (AA score > = 1.0 or the occurrrence of binge drinking, defined as drinking 74 mL or greater of alcohol on one occasion) levels and were not significantly associated with lighter drinking scores.
**Upper and lower bounds estimated based on reported SE from May et al. (2016)

may be confounded by exposure during pregnancy. Gibson and Porter (2020) identified significant trends between maternal alcohol consumption during breastfeeding and academic scores, including numeracy and spelling scores; however, the identified relationship is small and the authors postulate that it "may have little clinical significance unless mothers consume large quantities of alcohol or regularly binge drink." May et al. (2016) also identified increased odds that a mother who consumed alcohol while breastfeeding had a child with a FASD; however, the number of participants that did not consume alcohol during pregnancy is small ($n = 26$) and the studied population is specific to a region in South Africa with a low socioeconomic status and poor food quality, therefore limiting the generalizability of this study. After adjustment for multiple comparisons, there was no statistically significant difference in verbal intelligence quotient, dysmorphology scores, or other cognitive and behavioral outcomes between children exposed to ethanol via breastmilk but not during pregnancy.

3.3 | Ethanol exposures and measured internal concentrations in animals

A summary of the exposures and measured ethanol concentrations from review of relevant toxicological studies is provided in Table 2. The maternal dose ranged from 5.0 to 136.0 g/kg/day, and ethanol was delivered via drinking water, liquid diet, or intubation. Maternal BECs were measured in eight of the reviewed studies, and the time of blood sampling occurred at different time points (relative to stage of gestation, post-natal days, or time post exposure); reported maternal BECs ranged from 2.87 to 157 mg/dL. Maternal milk concentrations were limited and reported in only two of the reviewed studies (information in Data S2. Supporting Information). Corresponding pup BECs were only measured in four studies, ranging from 0 to 37 mg/dL at various sampling time points. In the two studies (Gottesfeld & LeGrue, 1990; Lancaster et al., 1986) in which both maternal and pup BECs were available, the pup BECs

TABLE 2 Summary of ethanol exposures and measured internal concentrations in reviewed toxicological studies

Study	Maternal EtOH dose reported	Maternal EtOH dose (g/kg/day)[a]	Route	Maternal BEC (mg/dL)	Pup BEC (mg/dL)	Time of maternal BEC sampling	Time of pup BEC sampling
Brancato et al., 2016	20% in water	25.2	Drinking water	-	-	-	-
Detering et al., 1979	35% of calories	12.3	Liquid diet	61 ± 6	-	Not specified	-
Gonzalez-Burgos and Alejandre-Gomez, 2005	20% in water	24.0	Drinking water	67.94 ± 17.58	-	End of pre-gestation	-
Gottesfeld & LeGrue, 1990	7.3 g/kg/day	7.3	Liquid diet	42 ± 7	10 ± 3	PND 10 and 16	PND 10 and 16
Heil et al., 1999	3 g/kg/day	3.0	Intubation	126 ± 13	-	20 min post-exposure	-
				157 ± 14	-	40 min post-exposure	-
Hekmatpanah et al., 1994	5% in water	6.0	Drinking water	-	21	-	PND 13–15
	10% in water	12.0		-	37	-	
Lancaster et al., 1986	27% of calories	Unknown[b]	Liquid diet	65–120[c]	0–30[c]	2 h post-exposure	2 h post-exposure
Museridze and Gegenava, 2010	15% in water	18.7	Drinking water	-	-	-	-
Oyama et al., 2000	5% in water	10.9	Drinking water	2.87 ± 1.06	-	PND 12	-
	10% in water	15.3		43.45 ± 11.50	-		-
	20% in water	22.6		100.66 ± 25.30	-		-
Oyama & Oller Do Nascimento, 2003	4% in water	5.0	Liquid diet	-	-	-	-
Tavares do Carmo et al., 1999	20% in water	25.2	Drinking water	105.3 ± 4.5	-	PND12	-
Tavares-do-Carmo & Nascimento-Curi, 1990	20% in water	25.2	Drinking water	-	-	-	-
Vaglenova & Petkov, 1998	1 g/kg/day	1.0	Intubation	35.0 ± 5.78	-	GD14	-
Vilaro et al., 1987	25% in water	31.6	Drinking water	-	18.09 ± 5.3	-	PND15

Key – EtOH: ethanol; BEC: blood ethanol concentration; PND: postnatal day; GD: gestational day.

[a]Calculations shown in Data S1. Supporting Information, Table S8.

[b]Inadequate information to calculate maternal EtOH dose.

[c]Range; mean not provided.

Note 1: Assumed PND days to be equal to lactation days.

Note 2: Pauli et al. (1995) is not included in this table as ethanol exposure was not via lactation, but pups were directly exposed to ethanol.

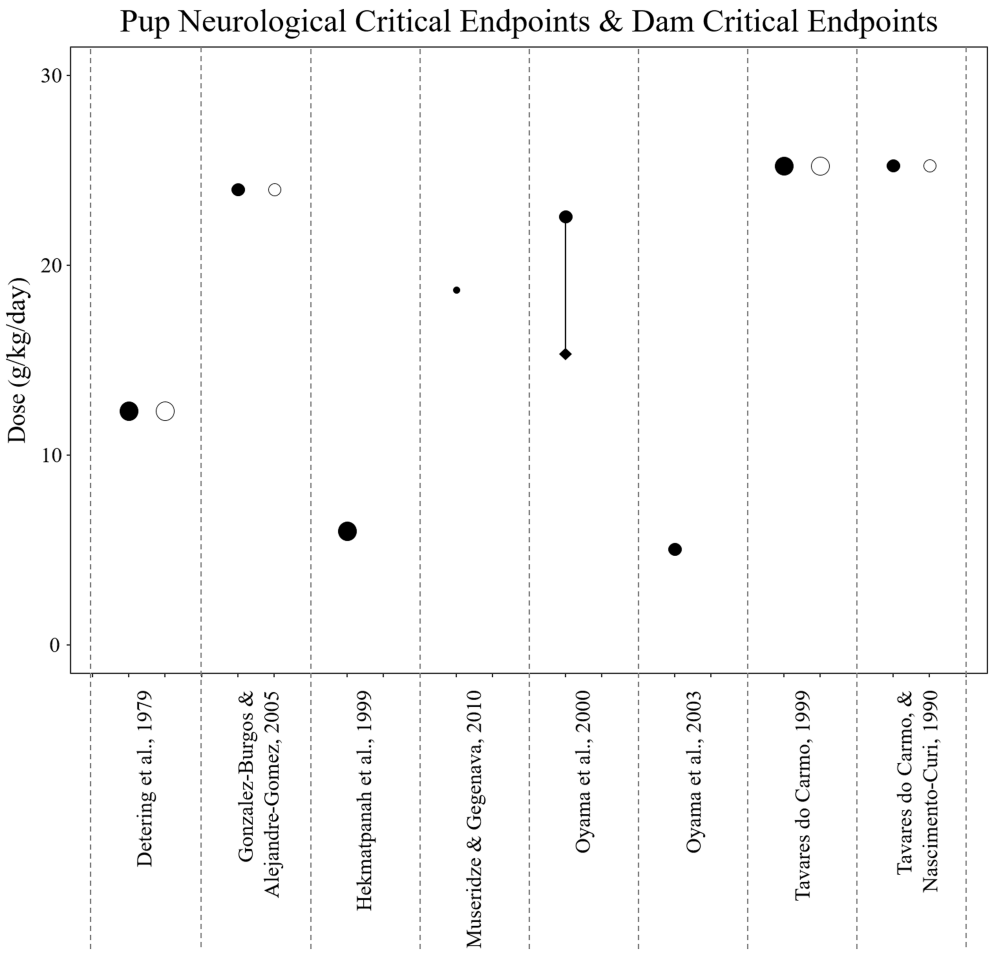

FIGURE 3 Neurological critical endpoints in pups and associated critical endpoints in dams that were exposed to ethanol. Circles represent LOAELs, diamonds represent NOAELs, filled shapes indicate pup critical endpoint values, and open shapes indicate dam critical endpoint values. Sizes of the shapes correspond to the confidence scoring of the study (weak, limited, and strong)

(0–30 mg/dL) were appreciably lower than the maternal BECs (42–120 mg/dL) (Table 2).

3.4 | Developmental outcomes in animals from ethanol exposure via lactation

Of the studies that administered ethanol to dams and examined toxicity endpoints in pups, the dam toxicity LOAELs ranged from 3.0 to 31.6 g/kg/day, the dam NOAELs from 1.0 to 136 g/kg/day, and the pup LOAELs ranged from 1.0 to 136 g/kg/day (see Data S3. Supporting Information). Due to the limited dosing regimens, no NOAELs were reported in pups for general toxicity. The basis for the maternal critical endpoints were general toxicity indicators, such as decreased body weight and altered biochemistry, as well as disrupted maternal behavior, mammary gland weight, milk yield, and biochemistry. The basis for the pup LOAELs were general toxicity indicators, such as decreased body weight and growth indices, altered biochemistry, and decreased organ weights. Additionally, eight LOAELs were identified in pups for adverse neurological effects (e.g., reduced brain weight, cellular effects in the brain, chemical effects in the brain, and increased escape latency). The range of neurological LOAELs was 5.0 to 25.2 g/kg/day (Figure 3). One neurological NOAEL was identified in a multi-dose study (Oyama et al., 2000). In this study, the neurological NOAEL was 12.6 g/kg/day, and the neurological LOAEL was 25.2 g/kg/day based on decreased brain weight; general toxicity was observed at doses lower than those that caused neurotoxicity (general toxicity LOAEL of 6.3 g/kg/day) based on altered biochemistry (Oyama et al., 2000).

3.5 | Blood ethanol concentration predictions and margin of exposure versus benchmark estimates

BECs of breastfeeding women (assumed maternal body weight is 74.15 kg, as described in Data S1. Supporting Information), using the hand hygiene scenarios and pre-surgical hand disinfection scenarios described previously, were predicted with PBPK modeling (Figure 5). Peak blood concentrations for the hand hygiene scenarios were 0.33 mg/dL, 1.8 mg/dL, and 2.8 mg/dL for the average, high, and intensive conditions, respectively. Peak blood concentrations for the pre-surgical hand disinfection scenarios were 0.044 and 0.28 mg/dL for the typical and intensive conditions, respectively. Peak BECs for HCWs based on survey data ranged from 0.14 to 0.73 mg/dL. BECs for all simulated conditions are summarized in Table 3. Modeled BECs corresponding to health guideline limits for breastfeeding women

TABLE 3 Predicted ABHS BECs and margin of exposure versus benchmark estimates

Exposure[a]	Peak BEC (mg/dL)[b]	Margin	
		Toxicological point of departure[c]	Recommended public health guideline[d]
Average hand hygiene 3 mL 90% ABHS, 7×/h over 12 h	0.33	29	18–140
High hand hygiene 3 mL 90% ABHS, 22×/h over 12 h	1.8	5.3	3.4–26
Intensive hand hygiene 3 mL 90% ABHS, 30×/h over 12 h	2.8	3.4	2.2–16
Typical pre-surgical hand disinfection 6 mL 61% ABHS, 1×/4 h over 12 h	0.044	210	140–1000
Intensive pre-surgical hand disinfection 20 mL 90% ABHS, 1×/4 h over 12 h	0.28	34	22–160
Average ABHS use among HCWs 3 mL 90% ABHS, 3×/h over 12 h	0.14	68	44–330
95th percentile ABHS use among HCWs 3 mL 90% ABHS, 12×/h over 12 h	0.73	13	8.4–63

[a]Hand hygiene and pre-surgical hand disinfection conditions were selected based on Maier et al. (2015) and FDA remarks (see section 2.3.1), which includes average to intensive use scenarios. BECs were also predicted based on user survey data among health-care workers (HCWs) reported in Boyce et al. (2017).
[b]PBPK simulations.
[c]Compared to maternal BEC of 9.45 mg/dL at the point of departure for pup neurotoxicity (decreased brain weight) reported in Oyama et al. (2000).
[d]Compared to predicted peak BEC range of 6.1–46 mg/dL of breastfeeding mothers per recommended consumption and 1 to 2 h wait time before nursing (see Table 1).

were also determined (Table 1). Margins >3 between the exposure and toxicological benchmarks in Table 3 demonstrated that the POD for pup neurotoxicity (BMDL of 9.45 mg/dL) was consistently higher than BECs associated with ABHS use. Additionally, the BECs from exposures associated with recommended health guideline limits for breastfeeding women were largely higher than all ABHS use conditions.

4 | DISCUSSION

4.1 | Epidemiological study review

Given that there is no epidemiologic evidence on infant or adolescent health outcomes related to maternal hand sanitizer use and lactational ethanol exposure, we examined developmental outcomes associated with maternal alcoholic beverage consumption during breastfeeding. Nine epidemiological studies were identified that assessed maternal ethanol intake during lactation, or lactation and gestation, and measured subsequent developmental outcomes in the children. These studies assessed a wide range of physical and cognitive developmental endpoints with varying sensitivities. These outcomes included height, weight, vocabulary scores, nonverbal reasoning, literacy, numeracy, psychomotor development, locomotor development, diagnosis of alcohol-related neurodevelopmental disorders or birth defects, feeding and sleeping behavior, and social and socioemotional development.

Our ability to interpret the findings of these studies was severely limited by the imprecision and limited reliability of the ethanol intake estimations and the depth of consideration for additional factors that might impact the relationship between ethanol exposure and developmental outcomes (Data S1. Supporting Information, Table S2 and Data S2. Supporting Information). Of the nine studies assessed, only one study provided biologically verified BECs (Flores-Huerta et al., 1992). The remaining studies relied on maternal reports of the frequency, duration, and volume of their alcohol beverage consumption during pregnancy and lactation. Under-reporting of alcohol consumption, due to recall and self-report biases, is well documented in the literature among both pregnant and non-pregnant populations (Ernhart et al., 1988; Livingston & Callinan, 2015; Morrow-Tlucak et al., 1989). Not only do individuals misremember, or purposefully under-report their alcohol consumption as a result of stigma, but people are also likely to pour drinks significantly larger than the standardized amount, which interferes with researcher's ability to ascertain the actual amount of alcohol consumed (Boniface et al., 2013; Morrow-Tlucak et al., 1989). Additional issues arise from the variation in type of beverage and methods of measurement. For example, Backstrand et al. (2004) evaluated 58 mother-infant pairs from 6 rural villages in Mexico and measured intake of Pulque, a Mexican alcoholic beverage, but did not consider alcohol consumption from other sources. Other studies measured general alcohol consumption with assessments ranging from the modified version of the alcohol use disorders identification test to self-reported number of alcoholic beverages per week or number of "binge" drinking episodes. Alcohol content per beverage

varies, and some studies estimated the amount of ethanol consumed, while others reported simply on number of drinks. Due to these variations in the ethanol exposure estimations, study outcomes cannot be directly compared and observed outcomes are not directly tied to a specific ethanol concentration in blood or breast milk.

Another major limitation of exposure ascertainment is the lack of information regarding timing of exposure. In order to fully understand any developmental health effects associated with ethanol exposure via lactation, the ideal analysis would include mothers who only consumed alcohol during lactation and did not consume alcohol during pregnancy. However, every study in this review included at least a portion of women who consumed alcohol during pregnancy and gestation. Adverse developmental outcomes resulting from prenatal alcohol exposure may be influencing any result observed attributed to post-natal alcohol exposure. For instance, mothers in Flores-Huerta et al. (1992) consumed alcohol during both gestation and lactation. The relative risk (RR) of a child born with a birth weight or head circumference below the third percentile was already statistically significant at birth (RR = 3.39, $p < 0.03$; RR = 4.25, $p < 0.01$, respectively), which hinders determination of causal relationships between any observed adverse developmental outcomes later on and exposure to alcohol during lactation.

Inadequate control of confounding factors also limits the ability to evaluate the causal relationship between ethanol exposure and developmental outcomes. There are numerous factors that affect both the likelihood and quantity of maternal alcohol consumption, and developmental outcomes in children. Some of the most influential characteristics include socioeconomic status, particularly maternal education or household income; child sex; child and maternal age; maternal BMI; nutrient intake; drug use; and caffeine intake. Control of these factors, especially socioeconomic factors, was evaluated and considered in the study quality evaluation (Data S1. Supporting Information, Tables S1 and S2). Among studies that do not adequately account for these factors, it is impossible to attribute any adverse developmental outcome specifically to maternal alcohol consumption during lactation, as noted in Data S2. Supporting Information.

Nonetheless, the majority of studies were unable to identify a statistically significant relationship between alcohol consumption during breastfeeding and developmental health outcomes. The major findings of the nine relevant studies are in Data S2. Supporting Information and summarized in Figures 1 and 2.

Within the scarce amount of epidemiologic evidence available to evaluate this relationship, observations regarding developmental outcomes were not concordant. Within and across the nine studies, most measurable developmental outcomes were not statistically significantly associated with maternal ethanol intake during lactation (Figures 1 and 2). Some statistically significant relationships were observed; however, negative effects were typically confounded by prenatal ethanol exposures (Little et al., 1989; May et al., 2016). Moreover, the studies with statistically significant findings were generally reported in studies with limited or weak confidence in their findings (Backstrand et al., 2004; Gibson & Porter, 2020; Little et al., 1989; May et al., 2016). Overall, conclusions from the epidemiological literature are mixed and do not provide conclusive evidence of a concentration-response relationship between ethanol exposure via breastmilk and developmental effects. While the range of findings may suggest there is not a relationship between maternal alcohol consumption during breastfeeding and subsequent child development, the variability in outcomes and exposure make it difficult to draw conclusions on this body of evidence alone. Further, alcoholic beverage consumption results in a significantly greater infant ethanol exposure than that expected to occur during maternal use of ABHSs during breastfeeding. Therefore, information from toxicology studies should be integrated, including mode of action (MOA) and metabolism information, to supplement our understanding of a possible causal relationship, as the findings are less subject to the variability of outside factors. Additionally, PBPK modeling, in which internal doses from exposures more similar to hand sanitizer use can be estimated, will provide quantitative and relevant estimates of exposure for consideration for this lactation hazard evaluation.

4.2 | Toxicological study review

Fifteen studies were identified that examined maternal and pup toxicity following ethanol consumption in rodents (summarized in Data S3. Supporting Information). Of these 15 studies, 13 examined the effects of maternal ethanol dosing on pups through lactation; one study reported effects in dams only (Brancato et al., 2016); and one dosed pups directly (Pauli et al., 1995). Generally, limitations identified in at least some of these studies included (a) a lack of an isocaloric/isoenergetic control, (b) use of only one dose of ethanol, (c) no reported or measured intake of ethanol (e.g., ethanol administered in drinking water ad libitum), (d) no measured maternal BEC, pup BEC, and/or milk ethanol concentration, and (e) a lack of toxicity outcomes observed in both pups and dams. Some studies only examined the effects of treated groups compared to a vehicle control group; however, due to the increased caloric intake from ethanol exposure, without an isocaloric/isoenergetic control, the findings cannot be attributed to ethanol alone but are confounded by different caloric intake and potential malnutrition. Additionally, all but two studies (Hekmatpanah et al., 1994; Oyama et al., 2000) exposed dams to only one dose of ethanol; therefore, elucidation of the NOAEL/LOAEL boundary or assessment of dose–response is not possible from most studies. While some ethanol treatments were reported as mass/kg bodyweight per day, or provided information regarding intake of the ethanol solution and dam body weight throughout the exposure duration, most studies did not provide or record this type of data. Therefore, the apparent exposures in dams for most of the studies were estimated using reference values or according to assumed daily food/water intake in rodents (Data S1. Supporting Information, Table S8). A major limitation in examining the effect of maternal ethanol exposure on pups through lactation is the inability to quantify the actual pup exposure due to the lack of reported maternal BEC, pup BEC, milk ethanol concentration, and milk volume consumed. As such, the dose

that elicits the adverse effects in the studies remains uncertain. Finally, although effects were observed in pups in all studies, maternal toxicity was not examined in all of these studies. Therefore, it cannot be determined whether the pup toxicity occurred with or without maternal toxicity in all cases. In the nine studies that examined neurological outcomes in pups, only four examined toxicity in dams as well. Of those four studies, dam toxicity was observed in three studies.

There are limitations in drawing conclusions about the relationship between the doses of ethanol received by the pups and associated general and neurological adverse effects for several reasons. First, as summarized in Table 2, review of the currently available studies demonstrates that there is variation in the delivery of ethanol, limited range of doses, mix of gestation and lactation exposures, and inconsistent sampling times of blood to measure BECs. Further, not all studies reported internal doses in dams and even fewer studies reported internal doses in pups. Additionally, milk ethanol concentrations were only reported in two studies, which was not sufficient to evaluate as a metric for potential exposure to the pup. Overall, there are constraints in evaluating a dose–response relationship due to inconsistencies among the available studies and lack of comparable data. Another major limitation is that the overall LOAELs for pup toxicity were observed at the lowest or single dose administered in all but one study; therefore, the NOAEL/LOAEL boundary remains uncertain. One study did identify a NOAEL and a LOAEL for neurological toxicity in pups, with values of 12.6 and 25.2 g/kg/day (Oyama et al., 2000). However, maternal toxicity or behavior were not examined in this study; therefore, the developmental toxicity potential of ethanol remains uncertain, and a true NOAEL/LOAEL boundary for neurological developmental toxicity remains unknown. Further, the study did not implement isocaloric controls, and thus, it cannot be discounted that the effects observed in pups are potentially caused by maternal toxicity or malnutrition. The NOAEL of 12.6 g/kg/day ethanol from this study is higher than LOAELs identified in other studies in which maternal animals were dosed—6 g/kg/day based on decreased brain weight and altered brain cell morphology and 5.0 g/kg/day based on decreased brain weight (Hekmatpanah et al., 1994; Oyama & Oller Do Nascimento, 2003). Additionally, in a study where pups were dosed directly, a LOAEL of 7.5 g/kg/day was identified based on increased escape latency (Pauli et al., 1995). Therefore, despite the identification of a NOAEL for neurotoxicity in pups whose mothers were administered with ethanol, this may not be the best POD for subsequent analyses.

4.3 | Proposed modes of action

The available studies demonstrate that pup exposure to ethanol through lactation results in general toxicity characterized by decreased body and organ weights and altered biochemistry, at maternal doses as low as 1.0 g/kg/day (measured maternal BEC of 35.0 ± 5.78 mg/dL) (Vaglenova & Petkov, 1998). Evidence for neurotoxicity in the pups is characterized by decreased body and brain weights, altered brain histology, and effects on neurobehavior (e.g., increased escape latency) at doses as low as 5.0 g/kg/day. Five hypotheses have emerged that may explain the MOA for ethanol toxicity in the pups arising from exposure during lactation (Figure 4).

No studies evaluated all of the following factors: maternal behavior, milk nutrient quality, pup milk intake, and ethanol in milk. In support for hypothesis 1, which poor maternal care leads to nervous system effects in pups, Brancato et al. (2016) noted a decrease in maternal response in dams treated with ethanol as well as disruptions in nursing, both of which could lead to adverse outcomes in pups; however, pups were not examined for toxicity in this study. One other study that noted decreased pup brain weight also demonstrated decreased maternal care of pups. Detering et al. (1979) also observed negative changes in maternal behavior, including poor nesting, lack of

	Maternal effect from ethanol exposure	Pup effect from maternal ethanol exposure	Observed developmental or neurodevelopmental outcome in pup	Relevance to MOA based on existing animal evidence
Hypothesis 1	Decreased maternal care	Decreased pup nutrition	Decreased body weight and brain weight	There is some evidence that decreased maternal care may lead to pup neurotoxicity.
Hypothesis 2	Decreased nutrient quality of milk	Decreased pup nutrition	Decreased body weight and brain weight	There is weak and limited evidence that decreased milk quality may lead to pup neurotoxicity.
Hypothesis 3	Ethanol in milk causes taste aversion	Less milk consumed; Decreased pup nutrition	Decreased body weight and brain weight	There is inadequate evidence to evaluate whether taste aversion may lead to pup neurotoxicity.
Hypothesis 4	Decreased milk production	Less milk consumed; Decreased pup nutrition	Decreased body weight and brain weight	There is support that decreased milk production may lead to pup neurotoxicity.
Hypothesis 5	Ethanol is distributed to milk	Pups directly consume ethanol in milk	Decreased body weight and brain weight caused by ethanol exposure	There is support that ethanol is distributed to milk, which may lead to pup neurotoxicity.

FIGURE 4 Five hypotheses to describe the mode of action (MOA) for ethanol developmental toxicity in pups exposed via lactation

interest in pups, lack of pup grooming, and loss of sensitivity to external stimuli. Therefore, there is some evidence that this hypothesis may explain neurotoxicity observed in pups born to dams exposed to high doses of ethanol.

Hypothesis 2 states that dams exposed to ethanol produce milk with poor quality. Evidence against hypothesis 2 is presented by Heil et al. (1999), in which milk from ethanol-treated rats did not differ in lipid or fatty acid content compared to control. A small, but significant, increase in phosphatidylserine was noted in the ethanol group compared to control; however, no neurological effects were observed in pups (Heil et al., 1999). Evidence for this hypothesis comes from Vilaro et al. (1987), in which milk composition and nutrient content were significantly different from controls, and the energy output in the milk of ethanol-treated dams was decreased compared to controls (Vilaro et al., 1987). However, neurotoxicity was not examined in this study. Therefore, the evidence for this hypothesis is limited.

No animal toxicity studies examined the palatability of milk to pups from dams administered ethanol (hypothesis 3); however, a study was conducted by Mennella and Beauchamp (1993) in which lactating women consumed alcoholic (0.3 g/kg alcohol) and non-alcoholic beer (<0.5% v/v) and provided milk samples over a 4 h period. Ethanol was not detected at or above the limit of detection (10 mg/dL) in the milk of subjects that consumed non-alcoholic beer at any time point; however, some samples were reported to have an alcohol odor. In the alcoholic beer group, peak milk ethanol levels were measured 1 h after ingesting alcoholic beer, and a noticeable alcohol odor was reported for all milk samples. Infants consumed significantly less milk from mothers that drank alcoholic beer, compared to mothers that drank non-alcoholic beer (149.5 ± 13.1 mL vs. 193.1 ± 18.4 mL). There were some uncertainties in the validity of the methods used to evaluate odors (blinded panelists were asked which milk samples smelled "more like alcohol") and the estimation of milk consumed (infants were weighed immediately before and after feeding). However, based on the odor and the decreased infant milk consumption from mothers who drank alcoholic beer, taste aversion cannot be eliminated as a hypothesis.

In regards to hypothesis 4, it is possible that dams have decreased milk production as a result of decreased body weight. Detering et al. (1979) reported that dams treated with ethanol had a decreased body weight of 30% compared to initial weight over the first three weeks post-partum, while controls had a 25% increase in body weight; this could indicate that fewer resources available for milk production contributed to decreased brain weight in pups. Tavares do Carmo et al. (1999) also observed decreased body weight in dams exposed to ethanol compared to control and the isocaloric group, which correlated with decreased brain protein and DNA levels in pups. Further, Lancaster et al. (1986) noted a decrease in diet consumption compared to control (but not the isocaloric control); however, this could be attributed to decrease palatability of the liquid diet containing ethanol. Further, no decrease in dam body weight was observed, and the LOAEL was not based on neurotoxicity outcomes (Lancaster et al., 1986). Dam body weight changes were also not observed by Vaglenova and Petkov (1998), and pup toxicity was only characterized by decreased body weight and not neurological endpoints. Despite the equivocal evidence for maternal body weight causing decreased milk production, evidence for hypothesis 4 includes altered mammary gland weight and milk production, regardless of dam weight. Evidence for this was provided by Tavares-do-Carmo and Nascimento-Curi (1990), who found that dams exposed to ethanol have significantly decreased mammary gland weight, which could indicate decreased milk production (although this was not measured). Pups fed by these mothers had decreased brain weights (Tavares-do-Carmo & Nascimento-Curi, 1990). As previously mentioned by Tavares do Carmo et al. (1999), decreased maternal body weight and decreased pup brain protein and DNA were associated with decreased milk yield in lactating Wistar rats exposed to ethanol compared to controls on days 4, 8, and 12 post-partum and to isocaloric controls on days 8 and 12. Finally, Vilaro et al. (1987), which noted the decreased nutrient quality of milk, also reported that dams exposed to ethanol had decreased mammary tissue weight and altered mammary gland composition compared to controls. Further, milk production was significantly reduced compared to controls (Vilaro et al., 1987). Therefore, there is support for hypothesis 4.

Finally, there is some, although limited, support that ethanol content in milk directly contributes to rat developmental neurotoxicity (hypothesis 5). Maternal BECs were measured in seven of the studies in which the range of maternal ethanol exposure was 1.0 to 136.0 g/kg/day, with average doses in the ethanol treated groups ranging from 2.9 to 157 mg/dL (Data S2. Supporting Information). Ethanol concentration in the milk (MEC) was measured in two of the studies at 25 and 630 mg/dL, in which dams were exposed to 7.3 and 31.6 g/kg/day, respectively. Pup BEC was measured in four studies in which the maternal animals were dosed with ethanol at doses of 6.0 to 136.0 g/mg/day, with BECs ranging from 10 to 37 mg/dL. Only two studies examined both maternal BEC and pup BEC, with maternal levels approximately 2 to 4 times higher than those in the pups (Gottesfeld & LeGrue, 1990; Lancaster et al., 1986). The ethanol concentration in milk measured in two studies at 25 and 630 mg/dL was approximately 2.5 and 35 times greater than the pup blood ethanol concentration, respectively (Gottesfeld & LeGrue, 1990; Vilaro et al., 1987). Only one study measured the ethanol concentration in maternal blood, milk, and pup blood, in which the levels were 42, 25, and 10 mg/dL, respectively (Gottesfeld & LeGrue, 1990). Of the five studies that measured BEC in pups, only two reported neurological effects in pups—decreased brain weight and increased escape latency (Hekmatpanah et al., 1994; Pauli et al., 1995). Despite the limited studies that examined BEC in pups and dams and milk, taken together, these studies suggest that ethanol is transferred to the pups through milk in measurable quantities.

The toxicological studies in rodents, despite their limitations, suggest that maternal ethanol concentration can lead to neurological effects in offspring. Of the proposed hypothesis, the data support pup neurotoxicity as a result of decreased milk production by dams and subsequent intake by pups and ethanol in milk directly leading to central nervous system effects in offspring. However, the dose at which these effects occur remains uncertain due to the limited doses

administered in each study and the gaps in maternal toxicity endpoints examined along with pup toxicity.

Based on the results of various ex vivo and in vitro studies, ethanol elicits direct cellular effects on the neurological system. However, the doses that elicit such effects in ex vivo and in vitro studies are relatively high compared to the toxicological POD selected for this ABHS scenario. The maternal BEC derived from BMD modeling of the Oyama et al. (2000) data was used as the POD; this was 9.45 mg/dL, which is equivalent to 0.53 mM. The range of doses in the in vitro and ex vivo studies ranges from 200 to approximately 1,800 mg/dL (equivalent to 11.1 to 100 mM), which are approximately 20 to 190 times higher than the toxicological POD. Doses of 50–75 mM ethanol for 24 h exposures, with or without carbachol, which induces neurite outgrowth, inhibited axon growth of rat hippocampal neurons harvested at 21-day old fetuses, mediated through inhibition of pKC and ERK1/2 activation (VanDemark et al., 2009). Following exposure to 50 mM ethanol for 24 h, neurite outgrowth of hippocampal pyramidal neurons from rats (PND 5) was inhibited, despite the presence of 1 mM carbachol (Giordano et al., 2011). Hippocampal-entorhinal cortical slices in rats (PND 7; cultured 2–2.5 weeks) treated with 100 mM ethanol experienced oxidative stress characterized by protein adducts altered phospholipase signaling (Moon et al., 2014). Ethanol treatment (average 57.3 mM) of rat cerebellar granule cells from 5- to 9-day old rats resulted in altered N-methyl-D-aspartate current, but no overt signs of cellular neurotoxicity or decreased cell viability (Nath et al., 2012). Additionally, ethanol has been found to contribute to cell death through mitochondrial disfunction and inhibition of neurite outgrowth at 400 mg/dL (Chen et al., 2009; Heaton et al., 2011). Doses of 200, 400, and 800 mg/dL ethanol reduced cerebellar granule neurons from mouse pups (PND 7), and 800 mg/dL only reduced neuronal numbers at certain time points (Li et al., 2015). High levels of exposure 20 to 190 times greater than the expected toxicological POD are associated with neurological effects. Further, there are no data to demonstrate that the neurological effects observed from ethanol exposure in these ex vivo and in vitro studies would occur at the lower doses associated with the ABHS use scenarios. Similar types of studies at these more relevant concentration ranges would be useful in assessing the potential for direct effects on nervous system targets for relevant exposure scenarios.

4.4 | Margin of exposure versus benchmark analysis

The margins determined for ethanol exposures in hand sanitizer also demonstrate that neurological effects in pups from maternal exposure to ethanol occur at BECs higher than BECs expected from hand sanitizer use (Table 3). BMD modeling was applied to the data from Oyama et al. (2000), using the maternal BEC (mg/dL) and pup brain weight (g) to determine a POD for this assessment. The BMD lower 95% confidence limit (BMDL) is an intended refinement of the POD based on the pup neurological effects, for which a maternal NOAEL was initially identified as 15.3 g/kg/day (43.45 mg/dL maternal BEC measured) (Oyama et al., 2000). However, other studies (Hekmatpanah et al., 1994; Oyama & Oller Do Nascimento, 2003) reported LOAELs at concentrations below the NOAEL identified by

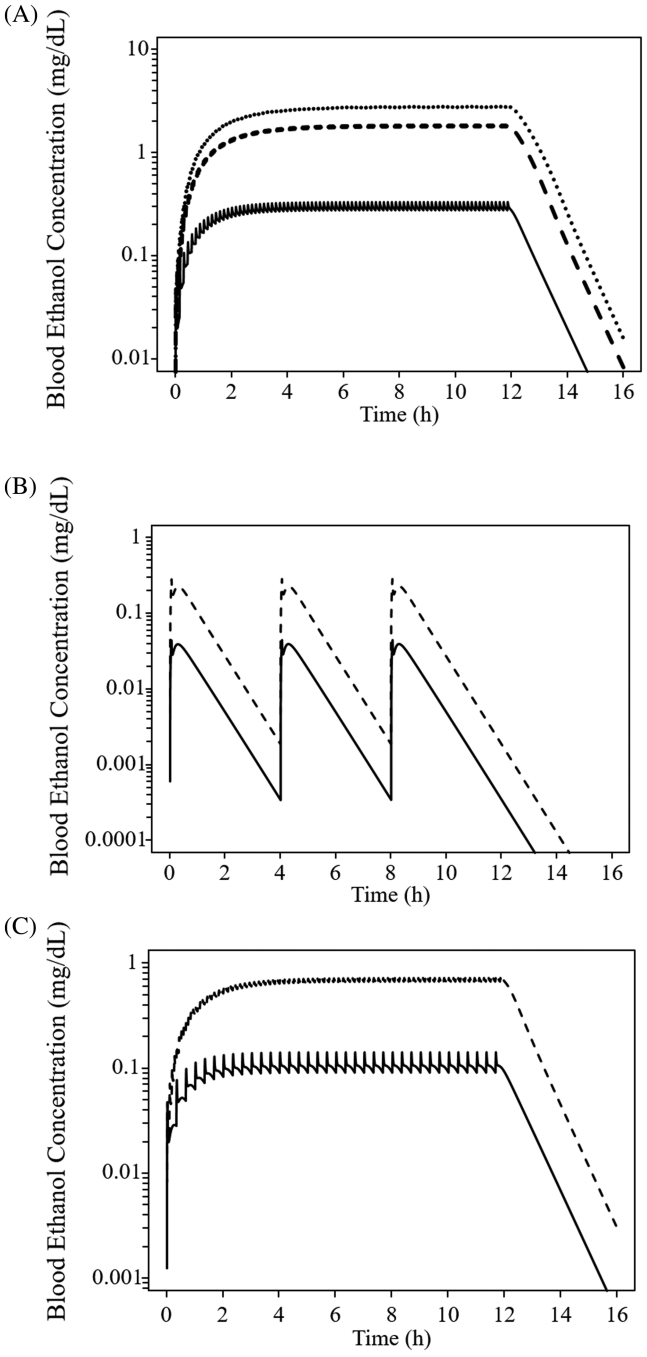

FIGURE 5 The PBPK model predicted BECs (mg/dL) following three hand hygiene use scenarios (A), two pre-surgical hand disinfection scenarios (B), and two ABHS use scenarios based on user data among HCWs (C). Solid, dashed, and dotted lines in 5 (A) represent BECs resulting from average, high, and intensive hand hygiene use, respectively. The solid and dashed lines in 5(B) represent BECs resulting from typical and intensive pre-surgical hand disinfection scenarios, respectively. The solid and dashed lines in 5 (C) represent BECs resulting from average and 95th percentile ABHS use frequencies among HCWs, respectively

Oyama et al. (2000). Therefore, the BMDL was selected as a more appropriate POD to account for uncertainty in the NOAEL to LOAEL range. In comparison of the toxicological POD to various ABHS use exposures (Figure 5), the margins (3.4–210) indicate hand sanitizer use is not likely to produce maternal BECs that correspond to neurotoxicity in nursing offspring. Note that for the most intensive ABHS use scenarios the margins calculated in this assessment are in the range of, but not above, those that would typically be considered adequate in extrapolating from an animal-based POD. A margin of at least 3–10 would be desired for the available toxicological database. This reflects that a factor of 3 is often used to address differences in toxicodynamics across species even when accounting for toxicokinetics differences using dosimetry approaches (as was done in this case via reliance on an internal dose metric of BEC). In addition, a factor of 10 is often used to account for human variability in susceptibility—but this factor could be reduced to a value of 1 up to 3 since the POD is from the sensitive group of interest (nursing offspring). The data regarding other elements of extrapolation would be a factor of unity, since the POD and study design account for the target endpoint of interest, period of exposure of interest, and extrapolation from a BMDL. Together, these two considerations suggest a desired target margin of threefold to tenfold. This margin was exceeded for most of the modeled use scenarios; however, for the most intense uses, margins fall in this target range (i.e., 3.4 for intensive hand hygiene uses and 5.3 for high hand hygiene use). Additionally, as noted below, the exposure estimates are also likely overestimates based on the assumptions included in the modeling. Thus, actual margins are likely higher than those calculated for this study.

BECs resulting from recommended intake limits for breastfeeding women (summarized in Table 1) were overall higher than BECs predicted for hand sanitizer use, resulting in margins ranging from 18 to 140 for average hand sanitizer use, 3.4 to 26 for high use, 2.2 to 16 for intensive use, and 22 to 1,000 for pre-surgical hand disinfection use conditions (Table 3). However, it is of note that several organizations, including those in Canada (Canadian Centre on Substance Use and Addiction) and Australia (Australian National Health and Medical Research Council) recommend no alcohol consumption during breastfeeding. These conservative guidelines are more so a reflection on the limitations within the existing scientific evidence that have hindered the establishment of a "no-effect" or "safe" drinking level, rather than explicit decision around the risk of ethanol exposure. As discussed in Maier et al. (2015), alcohol consumption presents an additional risk (even if low) that is not balanced by an established health risk reduction for breastfeeding mothers or their children. The risk benefit trade-off associated with alcohol consumption is not synonymous with that of alcohol-based hand sanitizer use. Alcohol-based hand sanitizers have become broadly accepted as the standard of care for hand hygiene in health care (Vermeil et al., 2019). The Centers for Disease Control and Prevention recommends the use of alcohol-based hand sanitizers that contain at least 60% alcohol when soap and water are not readily available (Centers for Disease Control and Prevention, 2020).

The ABHS use scenarios modeled for this evaluation includes extreme use conditions (Figure 5). The high and intensive hand hygiene conditions of 22 times per hour over 12 h and 30 times per hour over 12 h equate to 264 and 360 uses within the workday or once every 2 to 3 min. Additionally, a high content of ethanol (90%) was considered for all simulations, although hand sanitizers with ethanol levels as low as 61% are available on the market (Maier et al., 2015). Furthermore, ethanol concentrations for this analysis were predicted under the conditions that the hand sanitizer application occurs in a generic-sized work room with low air ventilation rate, and a breathing zone hemisphere with a radius of 0.3 m was selected to conservatively assume that the user is not moving, with hands positioned in front of the body and close to the face. Realistically, if hand sanitizer was used every 2 min, it is possible that one would shake or wave their hands to quickly dry, reducing the dermal amount absorbed. Additionally, in a health-care setting, the worker is likely to move around from patient to patient while applying hand sanitizer, potentially increasing air movement and leaving the space which contained most of the evaporated ethanol, therefore reducing the amount of ethanol inhaled. Boyce et al. (2017) also summarized that typical hand sanitizing frequencies among health-care workers can vary, but the highest use was reported at 166 times over a 12 h shift, which is considerably lower than the total amount of uses for the high and intense use scenarios modeled in our analysis (264 and 360, respectively). The authors further noted that if hand sanitizer was used 30 times an hour, there would be little time for patient care. Collectively, the average hand hygiene condition (7 times an hour over 12 h or 84 times a day or once every 8.5 min) and resulting BEC are more comparable to realistic use frequencies reported in user surveys among health-care workers and the associated BECs (Figure 5). The BECs predicted for high and intensive hand hygiene conditions are considered conservative overestimations compared to realistic use frequencies, but extreme cases were also considered to capture worst-case scenarios. While empirical use patterns of ABHS for non-health-care workers were not available in the literature, it is expected that the general population uses ABHS less frequently in the home, office/work, and public, and therefore, the margin of exposure compared to toxicity and health benchmarks is anticipated to be larger and the hazard potential is further reduced for the average breastfeeding mother, even during situations of increased use (e.g., during a pandemic).

In summary, a comprehensive review of epidemiological and toxicological literature coupled with PBPK modeling estimates demonstrated that use of ABHS by lactating women is not likely a developmental hazard to a nursing child. Epidemiological literature shows mixed conclusions and do not provide concrete evidence of a dose–response relationship between ethanol exposure via breastmilk and developmental effects. Further, the review of animal toxicological studies found maternal ethanol doses shown to elicit neurological or developmental effects in pups via lactation-based exposures were overall high and also caused maternal toxicity effects. However, the BEC associated with the POD for pup neurotoxicity was found to be

appreciably higher than the BECs expected from realistic ABHS use scenarios. The margin is also significant for average to intensive ABHS exposures, compared to the consumed dose of recommended standard alcoholic drink limits for breastfeeding mothers (i.e., the BEC resulting from ABHS use is lower than the BEC resulting from recommended guidelines for consumption of alcoholic beverages during breastfeeding).

Overall, the assessment demonstrates that BECs associated with various maternal ABHS use conditions are below BECs likely to create a developmental concern for nursing infants. Therefore, there is low potential for ethanol containing hand sanitizers to be a lactation hazard.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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