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Alcohol use in paediatric medication: potential impact on the brain and the current regulation

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Abstract: Alcohol is an organic solvent that can interfere with neurological function. It is frequently used as an excipient in liquid medication as a solubiliser, preservative, and odorant. The addition of alcohol to liquid medicines, especially for paediatrics, has potential risks as some alcohol metabolizing enzymes are not fully expressed in some subpopulations of paediatrics. Accumulation of alcohol in the blood interferes with normal brain function. Major medicine agencies such as the Food Drug Administration (FDA) and the European Medicine Agency (EMA) recommend the limitation of the alcohol content in paediatric drug formulations to prevent alcohol toxicity in children. However, this recommendation has been underappreciated. This review aims to explore the current regulations on alcohol restriction in paediatric medication and the application of these regulations across different countries. The halal aspect of alcohol content in the medication was also discussed. This review will improve the understanding of the potential risk of alcohol in children as well as support the safety of liquid formulations for infants and toddlers.

Keywords: Ethanol restriction; Paediatric; Liquid medication; Brain

1.0 INTRODUCTION

Alcohol, particularly ethyl alcohol or ethanol, is a semipolar and volatile liquid that is commonly used as a co-solvent in liquid drug formulation to improve drug solubility (Sajedi-Amin et al., 2017; Savjani et al., 2012; Vemula et al., 2010). It is also used in pharmaceutical preparation as a preservative and flavour enhancer. Almost 80% of medicines for children are in the form of syrup, emulsion, or solution. Among these liquid medications, some products contain alcohol as one of

their ingredients, ranging from 2.3% to 20% (Soremekun et al., 2019). The main concern regarding the presence of alcohol in medication is that it is also present in some over-the-counter medicines in addition to the prescribed medication (Batista & Antoniosi, 2020; Soremekun et al., 2019; Svirskis et al., 2013).

Ethanol is an organic solvent produced on a large scale via the hydration of ethylene from the petrochemical industries since there is a high demand for alcohol in the chemical, food, beverage, and pharmaceutical sectors (Pang et al., 2019). Traditionally, this substance is produced by fermentation of sugar-containing food or liquid with the aid of yeast. Ethanol is also commonly found in over-ripe fruits such as durian, banana, and black palm (Dudley, 2004). It is affordable and completely miscible in water. For these reasons, ethanol is the most commonly used co-solvent in pharmaceutical industries compared to other co-solvents such as propylene glycol and glycerine. Ethanol increases the solubility of the active pharmaceutical ingredients by altering the solubility parameter and allowing the less soluble drug to form a hydrogen bond with water (Sotomayor et al., 2013). In this review paper, the word alcohol is used when discussing drinking behaviour and the alcohol regulation in society. However, this is essentially addressed in relation to ethanol. The word ethanol in this review paper is used to explain the scientific findings of ethyl alcohol, a substance concerning alcoholic drinks or pharmaceutical preparations.

As a pharmaceutical excipient, alcohol cannot be considered as inert as the substance can cross the blood-brain barrier and act as a central nervous system (CNS) depressant (Reker et al., 2019; Wilson & Matschinsky, 2020). Furthermore, with an incomplete expression of alcohol metabolising enzymes such as alcohol dehydrogenase in infants and children under five years, there is a potential accumulation of alcohol in blood circulation (Marek & Kraft, 2014). Several studies have shown alteration in brain functions upon exposure to ethanol within 0-9 months postnatal. In animals, this developmental period is equal to the first 10 days in rat pups. Animal studies have shown that postnatal alcohol exposure (days 4 and 10, dose of 6.6 g/kg) is associated with a reduction of neuronal number in the cerebellum (Pierce et al., 1989). Although all lobules were examined, lobule 1 (frontal lobe) is the most significantly affected by this alcohol exposure.

A newer study also suggested that binge alcohol exposure to rats during the first 10 days postnatal is associated with a lower number of matured neurons in the hippocampus examined in adulthood (Klintsova et al., 2007). A separate study with a similar model of alcohol exposure resulting in a blood alcohol concentration (BAC) of 111 mg/dL was associated with a delay in spatial navigation skills (Goodlett et al., 1987). With a similar animal model, another study also suggested the reduction of dendritic network complexity in the prefrontal cortex (Whitcher & Klintsova, 2008). In addition to the brain, alcohol exposure at the perinatal correlates to muscle size reduction and nerve structure around the muscle (David & Subramaniam, 2005). Postnatal alcohol exposure also affects significant loss of the pyramidal, Purkinje, and mitral cells on the olfactory bulb (Bonthius et al., 1992). Although the blood alcohol concentration in the animal model used is considered a neurotoxic level that is above 100 mg/dL, the potential safety issue of alcohol exposure in newborns and infants, even in lower BAC, is concerning (summarised in **Figure 1**).

Apart from safety issues, the presence of alcohol in medications is associated with religious values, namely halal practice, where the use of alcohol in medicine should be avoided whenever possible (Afifi et al., 2014; Nurjannah et al., 2021). The presence of alcohol in medication has a different point of view among Islamic Scholars. Indonesian Religious leaders gave a fatwa (opinion) that, as long as the alcohol source came from the synthetic reaction from the petroleum industry and it is in a safe dose, it is categorised as halal. Alcohol status is different in terms of their presence in food and beverage. Alcohol from industrial synthesis or fermentation is considered non-halal when the concentration is above 0.5% v/v (Majelis Ulama Indonesia, 2018). This regulation is difficult to justify as more functional food, nutraceuticals, or food supplements are produced in a form resembling food and beverage.

Malaysian authorities also state that the threshold limit of alcohol in a product is 0.5% v/v. This threshold is slightly higher than the Research Association for the Inspection and Certification of Food and Supplies of Turkiye, which set a threshold of 0.3% v/v for being considered a halal product. Although official authorities have declared the limit and regulation, some Muslims believe that the addition of alcohol to the product is haram regardless of the levels (Nayeem et al., 2020). Due to alcohol potential threat, several medical authorities regulated the limit of alcohol that can be present in paediatric medication. Several health authorities, such as FDA and EMA, have set regulations

to reduce or eliminate alcohol use in paediatric formulations. In addition, labelling the product containing alcohol has been monitored by several countries to prevent the potential risk of alcohol (European Medicines Agency, 2010). However, this awareness is not a common practice globally and is more commonly applied in developed countries.

To date, a review paper that focused on dissecting the implementation of alcohol limits in paediatric medication is largely unavailable. This review aims to update alcohol use in pharmaceutical preparation, focusing on paediatric medicine. To begin with, a brief introduction to alcohol toxicity and pharmacokinetics in adults and children will be provided. The current practice of the presence of alcohol in paediatric preparation across different regions will be discussed. Finally, some regulations limit alcohol use in paediatric medication, and the recommendations are proposed to protect babies and toddlers from the potential toxicity of alcohol.

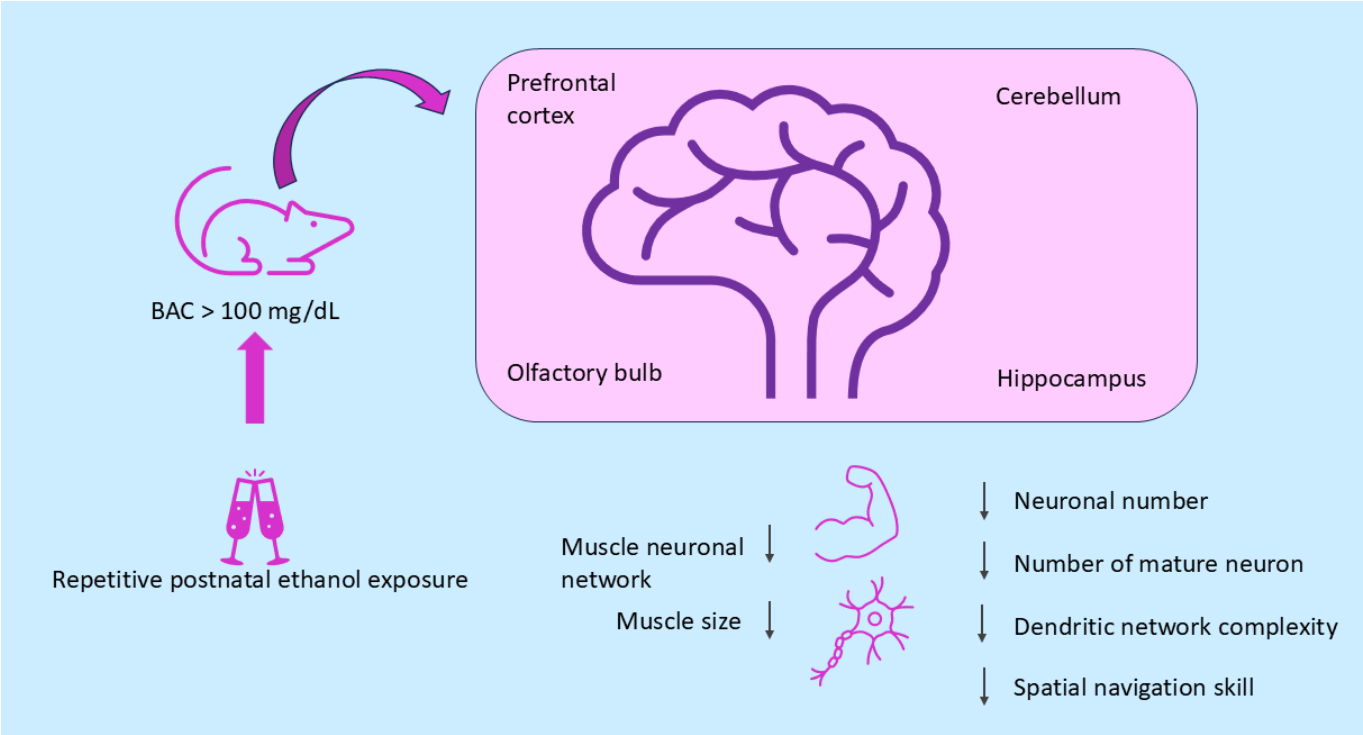

Figure 1: Alteration of brain and muscle structure upon ethanol exposure in newborn and infant. Due to its semipolar nature and small molecular weight, ethanol freely crosses the blood-brain barrier and contributes to the impairment of the brain structure during the developmental stage. Ethanol exposure in the first trimester at a concentration above 100 mg/dL is associated with fewer neuron numbers and decreased neuronal complexity in the different brain regions. This includes the cerebellum, hippocampus, olfactory bulb, and prefrontal cortex. In addition to the brain, ethanol exposure in postnatal life is associated with a reduced neuron network around the muscles and reduced muscle size.

2.0 METHODOLOGY

This literature review reviews original research published on the Scopus Database from 2010-2023. The literature search was performed from November 2022 to June 2023. The combination of search terms (in title or abstract fields) used are paediatric medication, alcohol or alcohol in food, alcohol or ethanol in medicine, blood alcohol concentration, alcohol or ethanol metabolism, alcohol or ethanol intoxication in children, and alcohol regulation, articles written in English and available in full text. The full texts were further examined to determine the detailed information about ethanol in the paediatric subpopulation. The reference lists of selected papers were also carefully searched to identify papers that fulfilled the eligibility criteria.

The title yield from the Scopus searches was screened for their relevance to the aim of this review. Relevant abstracts were then closely examined and selected if they met the inclusion criteria. For those categorised as appropriate, the full-text articles were then obtained and closely examined for appropriateness, and relevant articles were included in the review. The data from the

included papers were extracted into Excel sheets. Some of the data is further summarised and presented in tables and figures. Non-tabulated data or data summarised in figures were available as text in the review body. The review articles were also examined during the initial search to identify the original research for a particular topic.

3.0 INTRODUCTION TO ALCOHOL EXPOSURE IN CHILDREN

3.1 Ethanol ADME in adults

Like any other, ethanol's pharmacokinetics encompass four phases: absorption, distribution, metabolism, and excretion. Due to its small molecular weight, lipophilicity, and solubility, alcohol is easily absorbed by gastrointestinal cell lining via passive diffusion (Jones, 2019). Within the gastrointestinal segment, most ethanol is absorbed in the proximal part of the small intestine. About 20% of ethanol ingested is absorbed in the stomach, while the rest is absorbed in the mouth and oesophagus epithelial. The extent of ethanol absorption in the individual is determined by sex, body water content, food in the stomach, and gastric emptying time (Cederbaum, 2012). After the ingestion, ethanol is absorbed and distributed into the total body water. Females who are characterised by a lower total body water is expected to have higher ethanol absorption, resulting in a much higher BAC compared to men. In another topic, concomitant consumption of ethanol with any food is expected to delay the absorption of alcohol and also delay gastric emptying time, thus lowering BAC compared to alcohol consumption on an empty stomach.

Unlike psychoactive drugs, ethanol metabolism produces energy at 7.1 kcal per gram, higher than the 4 kcal per gram produced by proteins and carbohydrates. This value is less than the energy produced by fat, which is 9 kcal per gram (Jones, 2019). After intestinal absorption, most ethanol is metabolised to aldehyde, and less than 5% is excreted intact via the lungs, skin, and urine. Ethanol was metabolised through three different pathways (**Figure 2**): aldehyde dehydrogenase, CYP2E1, and catalases, all converting ethanol to acetaldehyde (Zakhari, 2006). The first enzyme is alcohol dehydrogenase (ADH). The ADH1 metabolises more than 80% of the ethanol intake. Most ADH1 responsible for this metabolism is expressed in the liver hepatocytes. In addition to those cells, alcohol dehydrogenase is also expressed in the stomach, oral cavity, oesophagus, and rectal to metabolise ethanol within the gastrointestinal cell lining. Since the stomach plays a significant role in ethanol metabolism, food and stomach emptying greatly influence ethanol absorption. Alcohol dehydrogenase is responsible for ethanol metabolism in low and moderate alcohol consumption (Jones, 2019).

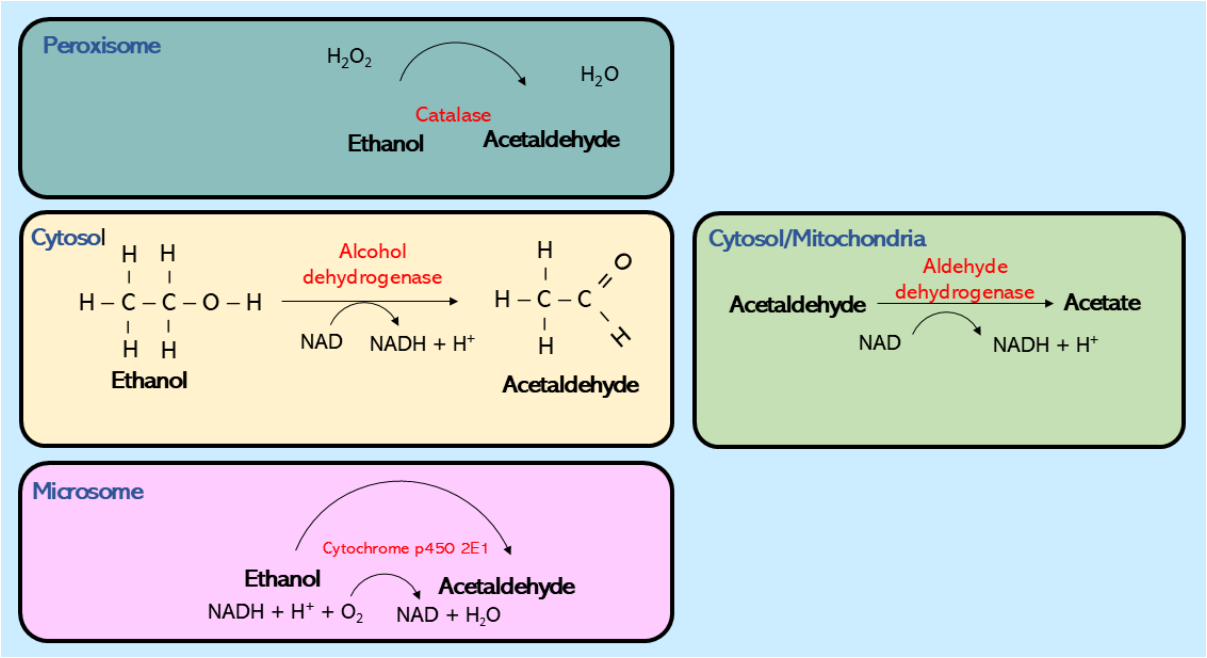

Figure 2: Ethanol metabolism in the cells. In adults, ethanol is metabolised through three pathways. All three pathways convert ethanol to acetaldehyde. The majority of ethanol intake was metabolised by alcohol dehydrogenase (ADH) in the cytosol. Secondly, CYP2E1 in the microsomes metabolised about 10% of the total ethanol intake. The reaction involved the conversion of NADH to NAD. The last route is catalase, which is present in peroxisome and consists of the conversion of peroxide to water molecules. Finally, aldehyde dehydrogenase (ALDH) converts the aldehyde to acetic acid.

The second enzyme involved in ethanol metabolism is CYP2E1, which is present in the microsomes of hepatocytes. This enzyme contributes to 10% of total ethanol metabolism, especially in chronic ethanol consumption or when an individual consumes high alcohol (binge drinking) (Cederbaum, 2012). Interestingly, this enzyme has been identified to contribute to the pathogenesis of alcohol-related diseases such as alcohol liver disease. Metabolism of ethanol by CYP2E1 produced reactive oxygen species, which increase oxidative stress in the liver (Jiang et al., 2020).

The third pathway for ethanol metabolism is the catalase enzyme present in the hepatocytes' peroxisomes. In the presence of H_2O_2, catalase metabolised ethanol to aldehyde and H_2O. This enzyme was minor in the whole ethanol metabolising process (Contreras-Zentella et al., 2022). Acetaldehyde produced by ADH, CYP2E1, and catalase was rapidly metabolised by ALDH in the mitochondria to produce acetic acid. The acetic acid was transported to blood circulation for further biochemical reactions to produce acetyl-CoA, which mitochondria and the brain used to synthesise lipids and cholesterol (Zakhari, 2006).

Unfortunately, the product of ethanol metabolism (acetaldehyde) is quite reactive and can form an adduct to many macromolecules such as proteins, DNA, enzymes, and microtubules. This process might change the protein conformation and function. Under chronic and heavy alcohol ingestion, CYP2E1 is induced to metabolise ethanol. In addition to acetaldehyde, CYP2E1 pathways produced reactive oxygen species such as hydroxyethyl, superoxide anion, and hydroxyl radicals that can attack different molecules and cause some tissue damage (Contreras-Zentella et al., 2022; Koken et al., 2010). The clinical manifestation of these processes in the human body can be observed in the chronic consumption of alcohol.

Alcohol intoxication in an individual can be divided into two significant symptoms. The first is maladaptive psychological behaviour, which includes violent and improper sexual behaviour, mood swings, poor judgment, and problems with social interaction. Furthermore, drinking alcohol can have a direct impact on the central nervous system (CNS), leading to symptoms like poor judgment, diminished cognitive function, decreased psychomotor performance, difficulty in solving problems, slurred speech, and an unsteady gait (Vonghia et al., 2008).

Alcohol/ethanol also affects the body's regular metabolism, which includes lowering the concentrations of albumin, phosphate, calcium, magnesium, kalium and glucose. Alcohol also causes lactic acidosis as it increases the activity of aldehyde and alcohol dehydrogenase, which lowers the amount of NAD and produces more NADH. The NADH/NAD ratio increases are linked to lactic acidosis and divert pyruvate's conversion to lactic acid (Yang et al., 2016).

3.2 Impacts of ethanol on the blood-brain barrier

Psychologically, in chronic consumption, alcohol might induce tolerance, withdrawal, sensitisation, and dependence (Becker, 2008). Furthermore, the effects of alcohol have a profound impact on the blood-brain barrier (Anand et al., 2022; Carrino et al., 2021; Laksitorini et al., 2021; Rubio-Araiz et al., 2017; Wei et al., 2019). The integrity of the blood-brain barrier is affected by immune-related signalling molecules and circulating cytokines, which are significantly influenced by alcohol use (Vore & Deak, 2021). The blood-brain barrier (BBB) is crucial in separating chemicals that enter the brain parenchyma from those that are safe (Daneman & Prat, 2015). Different biological components such as endothelial cells, are present and are sealed to one another by tight junction proteins, preventing the introduction of harmful chemicals that might change the brain function (Greene & Campbell, 2016; Laksitorini et al., 2014).

Oxidative stress, which can result from chronic binge alcohol drinking, might increase BBB permeability in both *in vitro* and *in vivo* models in response to various hazardous stimuli (Song et al., 2020; Vore et al., 2022). In general, not much is understood about the processes behind BBB alterations induced by binge drinking. An *in vitro* study using the rat brain endothelial line (RBE4) was conducted to assess whether ethanol alters the paracellular barrier of the BBB. The tight junction (TJ) protein ZO-1 distribution pattern was evaluated as a proxy for changes in BBB permeability. The research demonstrated the substantial impact of alcohol on the paracellular barrier. The distribution of the TJ protein ZO-1 changed after an hour of exposure to ethanol. These changes became more noticeable as the concentration and length of ethanol exposure increased. These changes could be related to oxidative stress, mitochondrial dysfunction, and ER stress, resulting in TJ dysregulation and increased brain endothelial cell permeability (Carrino, et al., 2021). On the other hand, prolonged alcohol drinking has been linked to decreased BBB permeability and integrity, as well as increased inflammation and oxidative stress,

cognitive decline, and pathological morphological alterations of the hippocampal regions. Long-term alcohol use has also been shown to increase BBB permeability and inhibit the expression of BBB structural and functional proteins (Wei et al., 2021).

Many scientists and government agencies have been interested in alcohol consumption behaviour to raise public awareness of the risks associated with it. Certain nations have enacted laws on the distribution and consumption of alcohol. Australia mandates that the number of standard drinks per container and the alcohol concentration of any beverage containing more than 0.5% v/v be disclosed (Tinawi et al., 2018). Due to its substantial increase in the likelihood of driving-related accidents, the BAC of 80 mg/dL was deemed prohibited. The United States Center for Substance Abuse Treatment (CSAT) states that BACs between 20 and 80 mg/dL might result in increased motor activity, mood swings, personality changes, and loss of coordination. A higher BAC of 80–200 mg/dL is linked to ataxia and slurred speech. Thus, the BAC of 80 mg/dL, or 8 grams in 10 L (0.08%) of blood, was considered illegal in the UK, USA, and Canada. This blood alcohol content can be attained by a male after five drinks (about 70 grams of alcohol) or by a woman after four drinks (about 56 grams of alcohol) in two hours. The legal limit for blood alcohol content for drivers in Germany is much lower, which is 50 mg/dL, or 0.05%. This regulation indicates the concern of legal authorities to limit the consumption of alcohol in adults (Vonghia et al., 2008).

4.0 ETHANOL EXPOSURE TO INFANT AND CHILDREN

4.1 Differential of infant and children physiology

Different from adults, infants and toddlers might accidentally consume ethanol through inhalation or via ethanol-containing food and medication. A small amount of ethanol may be present in foods with non-alcohol labels, such as breads, fruit juices, and fermented products, e.g., yoghurt and kefir (Gorgus et al., 2016). Furthermore, ethanol is occasionally present in pharmaceutical preparations as a cosolvent in liquid medication. In terms of herbal medicines, ethanol was used as a solvent to extract active moieties from herbal simplicia. It is important to note that due to the formation of an azeotrope mixture between ethanol and water, some ethanol residuals are present in crude extract (Srdjenovic et al., 2019). Additionally, several household products contain alcohol that may be accidentally consumed by the paediatric population, such as colognes, mouthwash, aftershave, hair tonics (Vonghia et al., 2008), fragrances, and antiseptics (Hon et al., 2018). These products, particularly those in liquid form, might be mistaken for common beverages due to their appearance and often vibrant colours, making them tempt to infants and toddlers. If consumed excessively, this can result in accidental ingestion and potential health risks.

As stated earlier, alcohol can be found in antiseptic products such as hand sanitiser. Hand sanitiser is a liquid, gel, or foam preparation that can be alcohol-based or alcohol-free. It is designed to quickly remove microorganisms from hands through rubbing (Jing et al., 2020; Saha et al., 2021). The formulation of alcohol-based hand sanitiser (ABHS) comprises active ingredients such as ethanol, isopropyl alcohol, and n-propanol. Other than that, ABHS can also feature excipients including hydrogen peroxide, gelling agent, humectant, fragrance, and colourants (Saha et al., 2021). The recommended ethanol concentration for optimum eradication of bacteria and viruses is 60% - 95% by volume (Jing et al., 2020). The main concern for hand sanitiser containing alcohol among paediatric populations is the potential of ingestion and inhalation since the appearance and the scent of hand sanitiser may be appealing to them. In a study located in the USA, data from 2011 – 2014 stated that 70,669 exposures to hand sanitisers were reported in children 12 years of age or younger, of which 65,293 (92%) were alcohol exposures. It is also found that 97% of children aged 0 – 5 years old are exposed to alcohol through oral ingestion. The most common adverse events were ocular irritation and vomiting (Santos et al., 2017).

Infant and toddler organs are not ready for ethanol metabolism (**Table 1**). Studies showed that the content of ADH in infants less than 8 months old is 10% of the adult ADH content. This corresponds to the ADH activities in the infant, which are found to be 3-4% of the ADH activities in adults. The ADH content and activities reach a similar level to adults when the toddler reaches 5 years old (Pikkarainen & Rälhä, 1967).

New studies using LC-MS/MS with liver cytosol samples suggested a more significant low ADH expression in newborns than in adults. Neonatal (0–27 days) showed ADH1A, ADH1B, ADH1C, and ALDH1A1 that were 3-, 8-, 146-, and 3-fold lower than the adult levels. The expression of this enzyme reaches 50% when the infant reaches 10-12 months. With the more sensitive technique (LC/MS/MS), this study confirmed the previous understanding that 6 years toddlers reach ADH expression to that of adults, but at the same time, provides new data that the expression of ADH1A, ADH1B, ADH1C, and ALDH1A1 is complete as early as 1

year old (Bhatt et al., 2017). This finding suggests that cautious needs to be taken during the formulation of liquid medication, especially for those that have indications for patients under 1 year old.

Like ADH, CYP2E1 expression in the infant is much lower than in the adult. Studies have shown that newborns express 5% of the CYP2E1 enzyme adult level (Ford et al., 2013). Apart from that, another study examining the expression of CYP2E1 in the liver microsomal sample using western blot, suggested that 1 to 3 months old newborns expressed 50% lower CYP2E1 than adults (Johnsrud et al., 2003). However, the data from 3 months to 18 years were combined, hence CYP2E1 expression levels between 1 to 6 years could not be evaluated. A recent study with LC/MS/MS provides more sensitive tools to assess the protein expression of CYP2E1 in a more detailed time frame. In this study, liver tissue samples were used; a newborn less than 1-month-old has 6-fold lower CYP2E1 expression compared to the adult. It reached 50% expression at the age of 0.6 years and reached similar expression to adults when reaching 1-6 years (Parvez et al., 2024). Unfortunately, distribution data of 1 to 6 years were not available to see the differences between 1 to 2 years.

Unlike ADH, the catalase level in an infant liver from 8 days to 32 weeks is similar or higher to that of the adult examined using the ELISA technique (Tran et al., 2007). Studies among seven newborns suggested that 4 of the samples had similar catalase expression compared to the adult. In contrast, the other three had a 2-3-fold abundance of catalase compared to adults. This catalase expression was thought to compensate for the low expression of ADH and CYP2EI in the newborn. More studies need to identify the level of catalase using the LC/MS/MS technique to illustrate the age-dependent expression of catalase across developmental stages.

Some premature babies require medication during their stay in the NICU, including antibiotics, antiepileptics, antihypertensives, and drugs to treat apnea of prematurity (Mfoafo et al., 2021). Medication for premature babies is normally prepared in liquid form and administered via intravenous administration. Thus, pharmaceutical companies should also develop products that are friendly for newborns and infants and meet this subpopulation's efficacy and safety requirements (Neville et al., 2014).

In addition to ethanol metabolising enzymes, infants have different total body water than adults. Usually, the total body water in adults is 65% (Marek & Kraft, 2014). A premature baby typically has total body water of 92%, while a full-term baby has total body water of 75%. Bigger total body water indicates a higher distribution volume, potentially affecting infant ethanol blood concentration. Although the total body water is higher, some other parameters, such as ADH level and CYP2E1 level, are significantly less than the adults. The ethanol pharmacokinetics in children remains inconclusive.

Table 1: Differences in physiology between baby and toddler as compared to adults regarding alcohol ADME

Age	Organ, Enzyme or Transporter	Comments	References
5 years	ADH	Start having similar activities to adult	(Ford et al., 2013)
2 months age	ADH activity	3-4% of adult ADH activity	(Pikkarainen & Rälhä, 1967)
5 years	ADH activity	Similar to adult	(Pikkarainen & Rälhä, 1967)
10 days – 32 weeks	ADH content	10% of the adult ADH content	(Tran et al., 2007)
10 days – 32 weeks	Catalase enzyme content	Not significantly different from adults	(Tran et al., 2007)
Birth – 1 year	CYP2E1	10-20% of the adult	(Vieira et al., 1996)
More than 1 year	CYP2E1	Similar to adult	(Vieira et al., 1996)
Neonatal	CYP1A2	5% of the adult	(Ford et al., 2013)
1 year age	CYP1A2	25% of the adult	(Ford et al., 2013)
10 – 32 weeks	Catalase	Similar or higher	(Tran et al., 2007)
Neonates	Gastric emptying time	Variable/prolonged	(Marek & Kraft, 2014)
Premature	Total body water	92% of the body weight	(Marek & Kraft, 2014)
Full term baby	Total body water	75% of the body weight	(Marek & Kraft, 2014)
1 year age	Total body water	60% of the body weight	(Marek & Kraft, 2014)
1 – 32 weeks	ADH	10% of the adult	(Tran et al., 2007)

4.2 Ethanol pharmacokinetics in children

Studies on the pharmacokinetics of ethanol in newborns, infants, and toddlers are limited due to ethical issues. The currently available study acquired data from the elimination rate of ethanol among intoxicated babies and toddlers accepted in the emergency department (Ford et al., 2013). Since the samples are scattered among different age groups and levels of intoxication, a systematic review is needed to conclude the pharmacokinetic profile of ethanol in newborns, infants, and toddlers.

The pharmacokinetic profile of alcohol in infants is interesting. Several studies have shown that the rate of serum alcohol clearance in acutely intoxicated paediatric patients is comparable to or even faster than that in adults (**Table 2**). This may be attributed to higher catalase activity, which becomes the major biotransformation route, while ADH and CYP2E1 are not fully expressed.

Depending on their age, children can have different alcohol elimination rates. A case study suggests that neonates have a slower elimination rate than adults (Ford et al., 2013). Studies on five-week-old infants who were admitted to the hospital unconscious showed BAC 270 mg/dL. Through several samplings, it was determined that the alcohol elimination rate in a five-week-old baby was 17.1-21.2 mg/dL/hour. This study's elimination rate is somehow comparable to adults as the alcohol elimination rate in normal adults is between 13-20 mg/dL/hour. Typically, adult males have an ethanol elimination rate of 18 mg/dL/hour, slightly higher than adult females, who have a rate of 16 mg/dL/hour. Studies among eight children between 18 and 156 months suggest that there the alcohol elimination rate in this sub-population is slightly higher than in adults at 28 mg/dL/hour (Ragan et al., 1979). Two other case reports about infants less than two months old tend to have an ethanol elimination rate that is less or similar to that of adults (Marek & Kraft, 2014). It is interesting to note that according to McCormick, the ethanol elimination in newborn babies followed first-order kinetic when BAC is lower than 225 mg/dL. Once the BAC exceeds 225 mg/dL, zero-order ethanol elimination is followed.

Table 2: Alcohol pharmacokinetics in infant and children

Patient Age	No. of Patients Analysed	Experimental Condition	Elimination Rate (mg/dL/hr)	References
5 weeks old infant	1	Initial blood ethanol level of 270 mg/dL and had no adverse events such as hypoglycemia, seizures, or apnea.	17.1 – 21.2	(Ford et al., 2013)
Adult	N/A	Malnourished individuals with low protein diets.	8 – 10	(Lands, 1998)
Adult	N/A	Healthy individuals after overnight (10 h) fasting and bolus ingestion of ethanol (<1 g/kg).	10 – 15	(Lands, 1998)
Adult	N/A	Regular drinkers after consumption of alcohol in the fed-state and with an appreciable starting BAC.	15 – 25	(Lands, 1998)
Adult	N/A	Alcoholics and binge drinkers during detoxification with very high blood-ethanol levels (>3.5 g/L). Hypermetabolic state, e.g., induced by drugs or burn trauma.	25 – 35	(Lands, 1998)
Adult	N/A		10 – 25	(Gaw & Osterhoudt, 2019)
1.5 – 3 years	4		32.2	(Leung, 1986)
7 months	1		49.7	(Chikwava et al., 2004)
9 months	1		28	(Edmunds et al., 2014)

The limited available data regarding ethanol elimination suggested that more systematic studies need to be done in the emergency department to plan and prepare protocols for handling emergency ethanol-intoxicated patients, especially paediatric patients. In addition, a robust and more sensitive analytical method to quantify the ethanol concentration in the body must be developed within hospitals. Currently, there is a gas chromatography-mass spectrophotometer that quantifies the level of ethanol in the blood as an alternative to a gas chromatography / flame ionization detector or the quantification of ethanol using an enzymatic assay (Xiao et al., 2014).

4.3 Ethanol intoxication in children

Although the elimination rate is comparable to that of adults, the clinical manifestation of alcohol intoxication in infants or children may be more significant in children. Negative impacts on the CNS in children typically manifest when the blood alcohol concentration ranges from 0.01 to 1.00 g/L (Srdjenovic et al., 2019). Due to some differences in the physiological features of the children, the BAC threshold that shows clinically significant and life-threatening alcohol intoxications for infants and toddlers is much lower compared to adults. The BAC 50 mg/dL is considered toxic for this age group (Gaw & Osterhoudt, 2019). Alcohol intoxication in children can be categorised as mild and severe intoxication. Mild alcohol intoxication is somehow non-specific. Infants can present with gastritis, abdominal distension, or fussiness at mild alcohol intoxication. Newborns and infants who experience alcohol intoxication tend to have lethargy, tremors, inattentiveness, weak crying, hypotonia, hypotension, and metabolic abnormalities. Young children and infants are more prone to the development of hypothermia, hypoglycemia, tachycardia, tachypnea, metabolic acidosis, and coma, even in cases with trace amounts of ethanol intake (Gaw & Osterhoudt, 2019).

Ethanol intoxication in a newborn was reported in Turkey, Japan and Taiwan. Case studies in Turkey reported a 19-day-old infant was exposed to 40 mL of alcohol (concentration of 96%) spilt to the facial area of the child after opening the umbilical care liquid for the child. The first hour after exposure, the BAC was 43 mg/dL, and there was no sign of metabolic acidosis. With this BAC, all the body function was normal except there is a hyperemia in the face that has contact with alcohol (Guleryuz, 2021). The second case was found in Japan that reported a 15-day-old baby girl experienced flushed skin, tachycardia, and low blood pressure, indicating circulatory failure, drowsiness, and metabolic acidosis without hypoglycemia and hypovolemia because of dehydration, indicating acute alcohol intoxication. The BAC level was 43.0 mg/dL three hours after alcohol ingestion from the accidental addition of sake into the baby formula (Zaitsu et al., 2013). The third case was reported from Taiwan; a three-day-old child had died due to being forced to drink 50 ml of rice wine by his father that drunk throughout the day. The baby was sent to the paediatric emergency room the day after with severe acidosis and could not survive. The BAC of the child a day after the incidence was 61 mg/dL, suggesting that the child's BAC was much higher at the time of the accident (Wu et al., 2017).

From the third case in Taiwan, the BAC observed may not be used as a standard to assess the severity of ethanol intoxication. Health practitioners need to gather information about when the accident happened since ethanol reaches its maximum concentration in the blood in the first 30-60 minutes after ingestion. A BAC of 61 mg/dL examined on the third day of intoxication suggested that an hour after the accident, the BAC was very high, which might be the cause of why this three-day-old baby died from ethanol intoxication.

Two case reports from Hong Kong showed that unsupervised children could accidentally consume alcohol. The first case reported a four-year-old girl who had stomach pain, vomiting, unsteady walking, and confusion while attending kindergarten due to licking and eating hand sanitiser jelly containing 75% ethanol after being left unsupervised. The BAC level was 224.7 mg/dL. She suffered cerebellar ataxia and evidence of disorientation. The second report mentioned a ten-year-old boy experienced vomiting, unsteady walking, and dizziness due to consuming a small amount from a bottle of spirit that contained 40% alcohol from his parents' wine cabinet. The test showed BAC level of 281 mg/dL (Hon et al., 2018). Unfortunately, the information on the time of the accident and time of BAC sampling were not available. This information will be essential to assess the correlation between initial alcohol consumption and the severity of alcohol intoxication.

Ethanol poisoning symptoms might differ, as seen in the instances mentioned above. The clinical course in the infant and toddler group differs significantly from that in the adolescent and adult groups. In newborns and early toddlers, symptoms of acute ethanol intoxication can result in hypoglycemia. Moreover, hypoxia and respiratory depression might result from the CNS depressive impact (Rayar & Ratnapalan, 2013). More severe symptoms due to increased blood alcohol, such

as deep coma, hypotension, bradycardia, and death from respiratory arrest, can occur. The lethal dose of ethanol for adults is 5 to 8 g/kg, whereas the lethal dose for children is 3 g/kg. As for newborns and infants, a dose of 0.6 g/kg can already lead to toxicity (Massey & Shulman, 2006).

The most typical symptoms of ethanol poisoning in children are hypoglycemia and hypoglycemic seizures, which are caused by insufficient liver glycogen reserves and are uncommon in older individuals. Several studies have reported this (Compton et al., 2022). two-year-old children with BAC 125 mg/dL experienced hypoglycemia with sugar levels as low as 40mg/dL. The average glucose level in infants and toddlers is 110-220 mg/dL before meals. Thus, children having a 40 mg/dL sugar level are considered low. Hypoglycemia in alcohol intoxication can cause seizures in severe cases. Additionally, alcohol use is more likely to cause hypoglycemia in children than in adults, which, if not treated carefully, can lead to brain injury and even death (Massey & Shulman, 2006).

5.0 ALCOHOL IN PAEDIATRIC MEDICATION

5.1 Alcohol-containing medication in infants and children

Due to different enzyme expressions, total body water, and gastric emptying time, infants and toddlers show potential variations in alcohol pharmacokinetics. Attention needed to be paid, especially to premature babies who sometimes require medication during their stays in the Neonatal Care Unit. Medication for premature babies is typically prepared in liquid form and administered via intravenous administration (Al-Shehri, 2019; Hitaka et al., 2023). Examination regarding the alcohol content in medication is required to prevent ethanol intoxication in newborns.

In addition to oral or intravenous medication, alcohol is present in the umbilical care products, hand sanitiser, and disinfectants used in the NICU room (Hakimi & Armstrong, 2020; McCulley et al., 2018). Among the 41 blood samples of the infant, it showed a median BAC of 7 mg/dL for those who used an incubator that had been disinfected with alcohol (Hitaka et al., 2023). Although this BAC is considered safe, this BAC value is significantly higher compared to a control group that was kept outside the incubator. Several studies have reported an elevation of BAC in newborns upon application of gauze that had been impregnated with alcohol-containing umbilical care products. Upon accidental spill of umbilical care products that contain alcohol to the face, there was a significant elevation of the BAC in newborns (Guleryuz, 2021).

Lopinavir/ritonavir oral solution (Kaletra®) is the first-line medication for HIV infection in children. Kaletra is an oral solution containing 42.2% alcohol (weight/volume) and 15.3% propylene glycol. This medication is contra-indicated for children under 14 days. Due to its ethanol content, the manufacturer recommended not to take more than 5 mL twice daily for children under 40 kg body weight. A case report from Lebanon from an Asian descent reported an 18-month-old baby girl receiving Kaletra on its recommended dose experiencing unstable gait where that patient seemed to be sleepy most of the time and holding the wall while she was walking, resembling as if she got drunk. (Yazbeck et al., 2020). This might be due to the presence of alcohol and propylene glycol, which they competitively use similar alcohol dehydrogenase enzymes for their metabolism. Unfortunately, the case did not report the BAC of the patients post Kaletra administration, so the unstable grid could not be identified whether it is because of the ethanol or propylene glycol toxicity. Some studies also reported using Kaletra pil for paediatrics as an alternative to the Kaletra oral solution. However, Kaletra tablets were crushed since the infants and children could not swallow pills. Studies showed that the area under the curve (AUC) of lopinavir and ritonavir declined by 45% and 47% when the tablets were crushed (Best et al., 2011).

Digoxin is a cardiotoxic that is commonly administrated in cardiac arrest. This drug is used not only for children but also for full-term and premature infants (Park, 1986). For paediatrics, the digoxin was prepared as an oral solution as an elixir with alcohol concentration varied from 10-11.4 % v/v ethanol (Marek & Kraft, 2014). When Marek and Kraft's study was performed in 2014, there were many paediatric medications marketed in the United States that contained ethanol more than 0.5% v/v including acetaminophen-containing codeine elixir (7%), cyproheptadine HCl syrup (5%), dexamethasone oral liquid (30%), diaxozide oral suspension (7.25%), phenobarbital elixir (15%) and furosemide oral solution (11.5%) (Marek & Kraft, 2014). Studies done within the Italian Medication Directory in 1999 showed that ethanol is present at a concentration of 0.015-31.5% v/v in different prescribed drugs for children and up to 60% of alcohol at the over the counter (OTC) drug, especially those in elixir dosage form (Fiocchi et al., 1999).

Although the use of chemotherapy among children and infants is less frequent than in adults, it is worth noting

that some chemotherapy agents use ethanol as a solvent, for example, paclitaxel, docetaxel, cabazitaxel, gemcitabine, and etoposide. Among 63,613 chemotherapy medications, 8.9% of them contain alcohol, and 4.9% of them contain alcohol at a level of >3 grams per infusion, which is above the EMA recommendation (Hiver et al., 2024). This study identified a case where gemcitabine and paclitaxel injection contained 20 grams of ethanol, while an etoposide infusion contained up to 50 grams. Chemotherapy drugs are naturally lipid soluble and often require organic solvents such as ethanol to improve their solubility and enhance physical stability. Chemotherapeutic agents are administered intravenously which make ethanol available in the blood circulation and accessible from the alcohol first-pass effect in the liver. As a result, alcohol can easily access the CNS in its unchanged form.

Cancer patients received chemotherapy containing alcohol at different levels. Studies on 451 cancer patients who received 1.28-3.50 grams of alcohol in the administration of Doxetacel suggested that 44.3% experience ethanol-induced syndromes such as facial flushing, nausea, and dizziness (Won et al., 2023). Studies on paclitaxel reported the ethanol content in paclitaxel chemotherapy is 49.7% v/v. The administration of chemotherapy in a shorter time frame will consequently raise the BAC significantly. FDA-recommended paclitaxel is administered at 135 mg/m^2 over 24 hours. Studies have reported a patient received paclitaxel at a dose of 348 mg/m^2 over a 3-hour IV infusion. With a shorter infusion time, the ethanol blood concentration in this patient was recorded to reach 98 mg/dL, which is illegal to drive in some states in the USA (Wilson et al., 1997).

Several studies also reported that cancer patients receive docetaxel. Thus, the research to develop chemotherapy that is alcohol-free, is imperative. Depending on the cancer therapy algorithm, physicians could explore chemotherapy options that do not require alcohol for their formulation, such as nab-paclitaxel, 5-fluorouracil, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, pemetrexed and topotecan (Fries et al., 2019). More studies are necessary to replace alcohol in the liquid dosage form, such as using non-alcohol cosolvent to improve drug solubility (Laksitorini & Purnomo, 2023). The extended Hildebrand equation can explore a cosolvent with a solubility power similar to a particular ethanol concentration. In addition, attention needs to be paid to children with cancer. Pharmaceutical formulations such as solid dispersion and liposome can be used as an alternative to increase the solubility of the drug instead of simply dissolving the drug using ethanol as a cosolvent (Budiman et al., 2023; Suryani et al., 2024).

Hemopathy is likely to include alcohol (Chirumbolo & Bjørklund, 2018). Because it works well as a solvent for extracting herbal medicines and helps to keep them stable, it is frequently used to extract the active components from dried herbs. Research indicates that while ethanol is present in trace levels when utilising herbal therapeutic goods, it can surpass 50% in homoeopathic plants and products (Kelber et al., 2017). Although studies suggest that homoeopathy's efficacy among the paediatric population is inconclusive, certain customers believe that it is safer than conventional drugs.

Homeopathy medicine presents a greater danger of unintentional ethanol intake than pharmaceutical formulations. Since there are no standards governing safety levels of ethanol, the ethanol content of herbal remedies is not as strictly regulated. To date, a limited study has examined the presence of ethanol in herbal medicine. Traditional herbal preparations in elixir and tincture may contain significant ethanol concentrations and pose a higher risk of ethanol syndrome when not properly consumed (Svirskis et al., 2013). This is due to the nature of the herbal products being readily available on the market without a prescription or advice from a health professional. Not only that, but a patient may also unnecessarily use traditional herbal medicines for an extended period and may even consume more than one herbal product containing ethanol simultaneously (Suseno & Qomariyah, 2021).

Traditional herbal remedies are more likely to include chronic ethanol exposure than non-traditional medications. Rules requiring the addition of warning signs that apply to dosages within the range or even below the level deemed safe for children are imperative. A label indicating the alcohol content of herbal medical goods should be prominently placed on product packaging or leaflets, according to guidelines established by the European Medicine Agency (EMA) on using these medicines in young patients. However, many herbal medications still come with labels that do not disclose how much alcohol is in them (Neo et al., 2014; Suseno & Qomariyah, 2021).

Alcohol concentration in paediatric medicine varies across different countries, as summarised in **Table 3**. This data is subject to change at times when the

pharmaceutical company changes its drug formula. However, this data shows that many paediatric oral medications have alcohol concentrations above 10%, including in the USA, Israel, Nigeria, Serbia, and New Zealand (Berlin et al., 2017; Biggs et al., 2018; Soremekun et al., 2019; Svirskis et al., 2013). According to available reports, some countries, such as the USA, Israel, and Brazil, provide paediatric medication with a concentration of alcohol below 0.5% v/v . Unfortunately, some countries still approve oral medication for children with an alcohol concentration above 50%, such as Israel, Nigeria, Brazil, and New Zealand. Together, these data suggested a lack of awareness among pharmaceutical industries regarding ingredient safety for newborns, infants, and children. At the same time, some health authorities have not regulated the limit of ethanol in paediatric medication.

Table 3: Alcohol content in paediatric formulations across the globe.

Country	Type of product evaluated	Number of product evaluated	Number of paediatric formulations with alcohol content			Alcohol Range (% v/v)	References
			< 0.5 (% v/v)	0.5-10 (% v/v)	>10 (% v/v)		
Indonesia	Syrup (in general)	106	N/A	6	1	3.72 – 10	(Rahem, 2019)
Malaysia	Herbal cough syrup (in general)	5	2	3	N/A	0.1 – 2.0	(Neo et al., 2014)
USA	Paediatric oral liquid medication	31	11	13	7	0 – 43	(Biggs et al., 2018)
Israel	Paediatric oral liquid medication	39	8	20	11	<1 – 66.4	(Berlin et al., 2017)
Nigeria	Paediatric oral medication	42	1	20	5	1 – 90	(Soremekun et al., 2019)
Brazil	Oral liquid formulation (in general)	17	11	6	N/A	0 – 8.83	(Batista & Antoniosi, 2020)
New Zealand	Paediatric oral Liquid medication	35	-	21	14	0.6 – 67.5	(Svirskis et al., 2013)
India	Asava and Aristha (Ayurvedic medicine)	20	0	20	0	3.22 – 11	(Maithani et al., 2019)

5.2 Health authorities' recommendation on ethanol restriction within paediatric medication

Although not all medications contain alcohol, many paediatric drug products include ethanol as their ingredient. This has raised a concern that some medications did not meet the international recommendation regarding the permissible amount of ethanol in paediatric medicines. The regulations related to ethanol in paediatric formulation were divided into several approaches. First, the maximum alcohol concentration percentage in each product for each age category is stated. For example, the Food Drug Administration recommends that children under 6 years should not consume medication with an ethanol concentration of more than 0.5% v/v (Food Drug Administration, 1995). Children between 6-12 years should not consume medication with ethanol concentration above 5%. Meanwhile, the maximum ethanol content in medication consumed by children over 12 years should be less than 10% v/v (**Table 4**).

The second approach used by the health authorities is to state the maximum BAC that infants and children can achieve after single-dose administration. This limit is different from one health authority to another. French Medicine Agency states that the BAC post-single dose

should be less than 12.5 mg/dL. At the same time, the European Medical Agency set a tighter limit where children should not achieve the BAC of 1 mg/dL post single administration. Lastly, the health authority also regulates the maximum amount of alcohol in the bottle. If there is any accidental intake by a baby or toddler, it should not be more than a particular amount. French Medicinal Agency and the European Medical Agency regulate that the amount of alcohol in the entire bottle should not reach ≤3 g/kg and ≤1.8 g/kg, respectively (European Medicines Agency, 2010). An alternative approach used by the agencies is to mention the maximum intake of alcohol within a day per body weight. For example, the EMA suggested that the maximum intake is 6 mg/kg/day for patients between 2-6 years.

Regulation on ethanol limitation in paediatric formulations has been implemented in the United States and some European countries. However, the regulation on the ethanol threshold for paediatrics has not yet been implemented in developing countries such as Indonesia, Nigeria, and Brazil (Batista & Antoniosi, 2020; Soremekun et al., 2013). In Indonesia, the National Agency for Drug and Food Control (NADFC) governs all pharmaceutical companies should mention the percentage of alcohol in the product labelling if alcohol is part of the ingredients. The regulation did not specify the maximum amount of ethanol in the paediatric formulation. For traditional medicine in Indonesia, it is mentioned in the regulation from the NADFC number 3, enacted in 2019, that the amount of ethanol in conventional medicine should not be more than 1% v/v, which is almost close to the limit set by the FDA and American Paediatric Association (0.5% v/v). More effort should be made to increase awareness among health practitioners and consumers to initiate the draft of regulations that limit the amount of ethanol in paediatric medications.

Table 4: Alcohol regulation across different institutions

Authority/Organization	Alcohol Restriction in Paediatric Medicine	References
Food Drug Administration (21 CFR P328 2013),	– Under 6 years: ≤ 0.5% v/v – 6-12 years: ≤ 5% v/v – Above 12 years: ≤ 10% v/v	(Marek & Kraft, 2014)
American Association of Pediatric	BAC ≤ 25 mg/dL after single administration	(Marek & Kraft, 2014)
European Medicine Agency	– BAC ≤ 12.5 mg/dL after single administration – The max dose for children under 6 years is 6 mg/kg.	(European Medicines Agency, 2022)

6.0 CONCLUSIONS

Alcohol inclusion in paediatric medication should be minimised and avoided whenever possible, especially for newborns and infants younger than two years old. Research and development efforts concerning the substitution of alcohol in herbal liquid medicines meant for paediatric use need to be intensified. This can be done by developing deep eutectic solvent extraction that avoids using ethanol during the extraction of active moieties from herbal medicine. When evaluating the benefit/risk ratio of the use of alcohol in paediatric formulations, one should consider the target population. To prevent alcohol accumulation in paediatric patients, the use of other medications that contain alcohol concurrently should be avoided.

In addition, it is advisable to arrange the dosage intervals to be kept as long as possible and at least 4 hours apart to prevent alcohol accumulation. It is recommended that countries establish and enforce regulations aimed at restricting the exposure of infants and young children to alcohol-containing products. We agree that it should be recommended that medicine for children under five years should not use alcohol more than 0.5% v/v. This value is also similar to the maximum level of ethanol in the product that can be considered halal. Enacting the 0.5% v/v ethanol limit in medication not only provides safe medicines for children and adults but also, at the same time, adheres to halal criteria. In preventing intoxication upon incidental consumption, the total volume in individual bottles should not reach 1.8 grams of ethanol per kg body weight of the patient. To raise awareness about the potential negative impact of

alcohol in medicine, more work needs to be done to disseminate the findings of neuroscience research, particularly those on alcohol, to interested parties like the pharmaceutical industry, medical professionals, government, and consumers.

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