Science for Communities

HEALTH RISK ASSESSMENT: HAND SANITISER

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ACRONYMS AND ABBREVIATIONS

BAC	Blood alcohol concentration
bw	Body weight
CDC	US Centers for Disease Control and Prevention
EDTA	Ethylene diamine tetra acetic acid
ESR	Institute of Environmental Science and Research Limited
EPA	Environmental Protection Authority
EtG	Ethyl glucuronide
EtS	Ethyl sulphate
GABA	Gamma aminobutyric acid
GP	General practitioner
HSDIRT	Hazardous Substances Disease and Injury Reporting Tool
HSNO	Hazardous Substances and New Organisms
IPCS	International Programme on Chemical Safety
NPC	New Zealand National Poisons Centre
NPDS	National Poison Data System (USA)
PEG	Polyethylene glycol
PPG	Polypropylene glycol
RfD	Reference dose
TBW	Total body water
WHO	World Health Organization

EXECUTIVE SUMMARY

The purpose of this report is to develop a generic health risk assessment for ingestion and dermal exposure to hand sanitiser. This report will only consider domestic, non-occupational, routine and incidental exposure to the components of these solutions.

Hand sanitisers are used for hand hygiene, particularly in locations where access to water for handwashing may be limited. Hand sanitisers are predominantly composed of alcohol, either ethanol or isopropanol. Although instances of methanol-based products have been reported this is likely to be due to ignorance or negligence on the part of the manufacturer and correctly formulated products will contain only trace amounts of methanol. The alcohol content of hand sanitisers is typically about 60%, although WHO suggest higher concentrations; 80% for ethanol and 75% for isopropanol.

For ethanol and isopropanol, toxicity is associated with the parent compound, while for methanol toxicity is primarily due to the major metabolite, formic acid. The severe acute effects of ethanol and isopropanol are due to depression of the central nervous system. The severity of effects due to ethanol and isopropanol are associated with the blood alcohol concentration (BAC). For ethanol, BAC in the range 50-150 mg/dL are associated with mild intoxication, characterised by impaired concentration and motor coordination. BAC greater than 400 mg/dL are potentially life-threatening in the absence of supportive treatment. Less information is available on the dose-response relationship for isopropanol, however, it appears likely that BAC greater than 300 mg/dL may be associated with severe effects.

Unintentional exposure to alcohols in hand sanitisers is most likely to be due to exploratory behaviour by young children. This is consistent with available surveillance data. Information from a US study suggests that incidents will typically involve ingestion of volumes up to 60 mL of hand sanitiser (median 15.4 mL).

There is insufficient information to determine the extent of dermal absorption of alcohols from use of hand sanitisers.

Surveillance suggests that serious health effects from ingestion of alcohol-based hand sanitisers are rare, but not unknown. This supports the assertion that most exposure events do not progress past a taste. However, exposure estimates for plausible exposure scenarios (up to 60 mL of products containing 80% ethanol or 75% isopropanol) for young children (1-2 years) indicate that BACs associated with severe central nervous system depression could occur through exploratory ingestion of alcohol-based hand sanitisers.

While exposure estimates were not derived for methanol in hand sanitisers, surveillance data suggests that methanol is an inappropriate ingredient for hand sanitisers and this conclusion is generally shared across international authorities.

1 INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for ingestion and dermal exposure to the hand sanitisers. This report will only consider domestic, non-occupational, incidental exposure to hand sanitiser contents. Exposure scenarios will be developed for the most common or likely exposure events.

1.1 CONSUMER PRODUCTS DESCRIPTION – HAND SANITISERS

Hand sanitisers are alcohol-based preparations applied for rapidly and effectively inactivating a wide array of potentially harmful microorganisms on hands. The World Health Organization (WHO) (2010) recommends alcohol-based hand sanitisers due to:

- Evidence-based, intrinsic advantages of fast-acting and broad-spectrum microbicidal activity with a minimal risk of generating resistance to antimicrobial agents;
- Suitability for use in resource-limited or remote areas with lack of accessibility to sinks or other facilities for hand hygiene (including clean water, towels, etc.);
- Capacity to promote improved compliance with hand hygiene by making the process faster, more convenient and immediately accessible at the point of patient care;
- Economic benefit by reducing annual costs for hand hygiene, representing approximately 1% of extra costs generated by health care-associated infection, and
- Minimisation of risks from adverse events because of increased safety associated with better acceptability and tolerance than other products.

Although commercial products may differ in some ingredients, WHO guidelines for local production of hand sanitisers include (WHO 2010):

- Alcohol to final concentration of 80% v/v ethanol or 75% v/v isopropanol
- Hydrogen peroxide (H_2O_2) to final concentration of 0.125% v/v. The low concentration of hydrogen peroxide is intended to help eliminate contaminating spores in the bulk solutions and is not an active substance for hand antisepsis. It is recommended that hydrogen peroxide is added as a 3% solution to minimise the corrosion hazards from this powerful oxidant.
- Glycerol to final concentration of 1.45%. Glycerol increases the viscosity of the hand sanitiser, to make it ‘stick’ to the skin. It also acts as a moisturiser, to maintain the condition of the skin.
- Water.

The active ingredient antimicrobial agent in commercial hand sanitisers is usually ethanol, propanol (propan-1-ol), isopropanol (propan-2-ol) or a combination of these, to a final concentration of 60-95% (Ahmed-Lecheheb et al 2012). While there are some reports of methanol being present as an undeclared ingredient or contaminant in hand sanitisers (Chan and Chan 2018; Dear et al 2020; Holzman et al 2021; Overbeek et al 2021; Welle et al 2021; Yip et al 2020), other studies did not detect methanol in commercial products (Berardi et al 2020) or detected methanol only at very low concentrations (Tse et al 2021). Acetaldehyde has also been reported as a common contaminant of alcohol-based hand sanitisers (Tse et al 2021).

A survey of the ethanol content of seven hand sanitisers available in Italy found contents ranging from 37.1 to 66.1% (Berardi et al 2020). The ethanol content was generally higher in products that stated the alcohol content, although the measured alcohol contents were 4-8% lower than the stated content.

Following easing of manufacturing requirements for hand sanitisers, due to the COVID-19 pandemic, products available in Canada (*n* = 42, 26 liquid and 16 gelled) were collected and analysed for a range of potential ingredients (Tse et al 2021). Health Canada adopted interim limits for methanol (200 ppm), benzene (2 ppm), acetaldehyde (75 ppm) and the sum of all other impurities (300 ppm) in manufactured hand sanitisers. Of the 42 products, 31 (74%) complied with the Health Canada requirements. Non-compliance was mainly due to concentrations of acetaldehyde, with concentrations ranging from not detected to 250 ppm. Levels of methanol were compliant in all samples, with concentrations in the range not detected to 47 ppm. Liquid products were all ethanol-based, with all but one product having ethanol concentrations in an acceptable range (63-90%). The remaining liquid product contained 50% ethanol. The alcohol content of the gelled products was not reported.

The US Food and Drug Administration (USFDA) issued similar interim guidelines in response to the COVID-19 pandemic and maintained a list of products found to contain unacceptable levels of methanol, 1-propanol, benzene, acetaldehyde or acetal (USFDA 2021).

Most other ingredients appear to be added to create suitable physicochemical properties and may include (Ahmed-Lecheheb et al 2012; Berardi et al 2020):

- Triglycerides
- Polyethylene glycols (PEGs)
- Acrylates
- Hydroxypropyl methyl cellulose
- Methylpropanediol
- Aminomethylpropanol

Ingredients reported in products available in New Zealand are summarised in Table 1.

Table 1. Ingredient reported in hand sanitisers available in New Zealand

Product	Ingredient type			
	Biocides	**Preservatives/ antioxidants**	**Humectants/emollients/sufactants**	**Other**
A	Alcohol (62%)	Tocopheryl acetate	Glycerol, propylene glycol, glyceryl polymethacrylate, triethanolamine	Fragrance, plant extract
B	Alcohol denatured*	Tocopheryl acetate	Polyacrylic acid, PEG-30 glyceryl cocoate, sodium EDTA, cellulose, hydroxypropyl methyl cellulose, retinyl palmitate	Fragrance, mannitol
C	Alcohol denatured (62%)	Tocopherol, BHT	Glycerol, propylheptyl caprylate, polyquaternium-37, dicaprylyl carbonate, ethylene glycol polymers, styrene/acrylate copolymer, hydroxypropyl methyl cellulose, lauryl glucoside, sodium lauryl sulphate	Fragrance, silica, limonene
D	Alcohol denatured	Tocopheryl acetate	PEG/PPG-17/6 copolymer, propylene glycol, acrylates, alkyl acrylate crosspolymer, tetrahydroxypropyl ethylenediamine	Fragrance, limonene

NS: not stated

* Denatured alcohol is ethanol that has additives to make it poisonous, bad-tasting, foul-smelling, or nauseating to discourage its recreational consumption.

It should be noted that a much wider range of products marketed as hand sanitisers are available to New Zealanders. However, for many of these products it was not possible to establish what the ingredients were.

1.2 REGULATION OF HAND SANITISERS IN NEW ZEALAND

The importation of hand sanitiser into New Zealand or the production of hand sanitisers in New Zealand is regulated under the Hazardous Substances and New Organisms Act 1996 (HSNO Act), administered by the Environmental Protection Authority (EPA). Hand sanitisers may be approved by inclusion in the existing Cosmetic Products Group Standard 2020 and associated Schedules (NZEPA 2020). Under the Group Standard there are many substances that cannot be added to cosmetic products. Of relevance to the current assessment, methanol is only permitted for the denaturation of ethanol and isopropanol and must not be present at a concentration greater than 5% in the finished product (Schedule 5).

2 HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health impact assessments for hand sanitisers were found for New Zealand.

2.2 HEALTH EFFECTS – HAND SANITISERS

2.2.1 Observations In humans

2.2.1.1 Incident surveillance - New Zealand

The HSDIRT tool (Hazardous Substances Disease and Injury Reporting Tool) is a GP-based system for reporting hazardous substance injuries and diseases.[1] During the 2019 year, of 98 notifications none related to exposure to hand sanitisers (Environmental Health Indicators 2019).

During the period 2017-2019, the New Zealand National Poisons Centre (NPC) advised on the management of 427 patients aged 0-14 years exposed to sanitisers out of a total of 14,077 unintentional exposures (3.0%) (Environmental Health Intelligence 2021). Of the exposures to sanitisers, 58 (13.6%) were referred for medical examination. These data do not include the COVID-19 timeframe, which would be expected to be influenced by pandemic response behaviours.

2.2.1.2 Incident surveillance – International

The impact of the COVID-19 pandemic on reported disinfectant and sanitizer exposures to the Croatian Poison Control Centre was assessed (Babić et al 2020). The most common type of sanitisers related to calls were ethanol and isopropanol-based. Reports of exposure to sanitisers increased about 9-fold compared to pre-pandemic; 46 cases compared to 5 in 2019. Of the 46 exposures, 32 (70%) related to young children (0-5 years), 43 (93%) related to ingestion as the route of exposure and 45 (98%) involved accidental exposure. The majority of cases (32, 70%) had no symptoms at the time the poisons centre was contacted, while the remainder (14, 30%) experienced mild symptoms.

A review of the American Association of Poison Control Centers' National Poison Data System (NPDS) was carried out for the period 2005-2009 (Gormley et al 2012). A total of 68,712 cases of hand sanitiser exposure were reported during this period, with 55,323 (80.5%) occurring in children less than 6 years (median age 2.0 years). Almost all (99.9%) of exposures in this age group were unintentional. There were 8,020 exposures reported for the age range 6 to 19 years (median age 10 years), with 77% unintentional, 16% intentional and 7% intention not specified. Amongst adults 20 years or older (median age 47 years) there were 5,369 exposures, with 78% unintentional, 13% intentional and 9% intention not specified. Across the period 2005 to 2009, exposures increased by an average of 1894 cases per year. The major of hand sanitiser exposures had a favourable outcome, although 288 moderate and 12 major medical complications were reported across the 5-year period. No deaths were reported.

The US Centers for Disease Control and Prevention (CDC) analysed data in the NPDS for cases of childhood (≤12 years) exposure to hand sanitisers during the period 2011-2014 (Santos et al 2017). A total of 70,669 exposures met the study criteria for this time period, with 92% classified as alcohol exposures. Exposures were predominantly for children ≤5 years (91%). Ingestion accounted for 95% of total exposures and 97% for children ≤5 years,

[1] https://www.ehinz.ac.nz/our-projects/hazardous-substances/hsdirt-notification-tool/ Accessed 18 August 2020

with virtually all (99.9%) exposures being unintentional. At least one symptom was reported for 12% of cases, with the most common symptoms being ocular irritation and vomiting. Most cases were associated with no effect or minor outcomes, while 158 cases (0.2%) were associated with moderate outcomes and 5 cases (<0.01%) with major outcomes, predominantly coma.

A further review of paediatric cases reported to the NPDS during the period January 2018 to May 2020 was carried out, to see if there had been any increase due to the COVID-19 pandemic (Hakimi and Armstrong 2020). The number of daily calls to poison control centres concerning paediatric hand sanitiser exposure was significantly higher in March 2020 (78.6 calls/day) compared to March 2019 (47.4 calls/day) or March 2018 (57.3 calls/day).

A similar comparison was carried out by the Arizona Poison and Drug Information Center (Holzman et al 2021). Reported exposures to hand sanitiser were compared between a 5-month period in 2019 and the equivalent period in 2020. Reported exposures increased by 124%. Of the reported cases, 28% involved hand sanitisers contaminated with methanol and five of these cases died.

NPDS data were reviewed for the period January to April 2020 (McCulley et al 2021). A total of 4,451 hand sanitiser exposures were identified for children ≤5 years. The majority of exposures (98.7%) related to ethanolic hand sanitiser, with products based on isopropanol making up the remaining 1.3%. Ingestion was the primary exposure route (94%), followed by ocular exposure (5.5%). Exposures were overwhelmingly unintentional (99.8%). Of 81 children referred for medical evaluation, five were hospitalised. For cases with information reported on the amount of hand sanitiser ingested, volumes ingested were generally small. However, two children (aged 1 and 4 years) were reported to have ingested 60 mL of hand sanitiser.

A retrospective analysis of exposures to alcohol-based hand sanitisers reported to the Texas Poison Center Network was carried out for the 2006 and 2007 years, with particular reference to exposures of children under 6 years of age (Miller et al 2008). In 2006 and 2007, there were a total of 826 and 1022 total exposures related to hand sanitisers. Of these exposures, 685 (83%) and 792 (77%) were in children under 6 years of age, and 621 (75%) and 737 (72%) exposures were ingestions. Of the entire study population, 55 and 62 sustained a minor effect, and 9 and 11 experienced moderate effects. It was concluded that, as with many paediatric exposures, the exposures in children under 6 almost invariably occurred as a brief taste or accidental ocular or dermal exposure, resulting in little or no toxicity.

A retrospective review of all exposures to hand sanitisers in children younger than 6 years reported to a US regional poison information centre from 1 January 2000 to 30 March 2007 was performed (Mrvos and Krenzelok 2009). A total of 647 cases were identified, ranging from 1 month to 5 years (mean age = 1.89 years, median age = 2 years). No cases were reported as having moderate or major outcomes and there were no fatalities.

The US Centers for Disease Control and Prevention (CDC) reviewed poison centre data for the period 1 May to 30 June 2020 and identified 15 cases of methanol poisoning from ingestion of hand sanitiser (Yip et al 2020). The mean age of cases was 43 years (range = 21–65 years); 13 were male. All patients had a history of ingesting alcohol-based hand sanitiser products. All cases had evidence of metabolic acidosis. Earliest measures of blood methanol were in the range 21->500 mg/dL. Six cases developed seizures. Nine cases received haemodialysis or continuous renal replacement therapy. Seven cases were discharged from hospital, with four experiencing no sequelae and the remaining three with visual impairment. Four cases died and the other four cases remained in hospital at the time

the report was published. The methanol content of the hand sanitiser products and the amount of hand sanitiser ingested were not reported.

2.2.1.3 Case reports

Gormley et al. (2012) reviewed 14 cases of intentional alcohol-based hand sanitiser ingestion reported in the scientific literature. Ingestions occurred in hospitals, correctional facilities and psychiatric wards and involved ingestion of ethanol and isopropanol-based products. For those ingesting ethanol-based products, blood ethanol concentrations were in the range 180 to 700 mg/dL A range of treatments were given, with intubated being most common (7 of 14). One case died, but all remaining cases recovered. Four cases reported suicidal intentions, four reported intoxication as their intention and no intention was reported for the other eight cases.

In a case report from Hong Kong, a 29-year-old Chinese man was admitted to hospital after drinking 500 mL of hand sanitiser (Chan et al 2017). The man was in a deep coma at admission and was intubated. Serum toxicology detected isopropanol (55 mmol/L) and methanol (72 mmol/L). The case was treated by haemodialysis, folinic acid and ethanol infusion. Serum methanol concentrations dropped within 12 hours. The man regained consciousness and was extubated after 2 days. No retinal damage was detected. The hand sanitiser was analysed and contained 36% isopropanol, 22% methanol and 3.5% ethanol.

Health Canada (2013) reported two deaths following ingestion of a hand sanitiser containing methanol, rather than ethanol.

Holzman et al. (2021) reported details of five cases who had died after ingesting methanol-contaminated hand sanitiser. Cases were aged 36 to 53 years old and all ingested the hand sanitiser intentionally, for its alcoholic content or with suicidal intentions. All cases had severe metabolic acidosis, suggesting significant metabolism of methanol to formic acid. Blood methanol concentrations were available for three cases, with concentrations in the range 165 to 309 mg/dL. Concentrations in the range 40-50 mg/dL have been reported to produce serious toxicity.

A 27-year-old man presented to an emergency department with vomiting and altered mental status (Overbeek et al 2021). He had ingested hand sanitiser at least twice over the previous two days. Shortly after presentation the case became unresponsive, had multiple seizures and developed cardiac arrest. He was resuscitated but remained in profound shock. A serum methanol concentration of 240 mg/dL was determined on the day of presentation, decreasing to an undetectable level by day 4. The case was treated for severe metabolic acidosis, but was pronounced dead on day 9. There was evidence that he may have ingested more than 1 L of hand sanitiser. The brand was subsequently recalled due to methanol contamination.

A 36-year-old man with a history of schizophrenia and alcohol abuse presented to an emergency department with ethanol intoxication (Schneir and Clark 2013). The case had a breath alcohol reading of 278 mg/dL. Four hours later the case was calm and cooperative and was discharged 30 minutes later. Thirty minutes later the case was found unresponsive and without a pulse in the bathroom of the emergency department waiting room. An empty 354 mL container of hand sanitiser (62% ethanol, <5% isopropanol) was found next to him. The case was resuscitated but never regained consciousness. He was found to have a serum ethanol concentration of 526 mg/dL. Care was withdrawn 7 days later and the patient died.

A 40-year old patient in a US psychiatric facility was found minimally responsive with two empty 1 L bags of hand sanitiser (Darracq et al 2013). The patient was intubated and

transferred to the emergency department. On arrival, vital signs were within normal limits. The blood ethanol content was 382 mg/dL. The patient was given supportive care and extubated after approximately 24 hours.

A 4-year-old girl, weighing 14 kg, was brought to an emergency department with altered mental status after consuming alcohol-based hand sanitiser (62% ethanol, <10% isopropanol, amount ingested not reported) (Engel and Spiller 2010). Upon arrival, the case was stuporous and would periodically hypoventilate, resulting in oxygen saturation falling to 90%. When stimulated the case became combative. The case was tachycardic (139 beats/minute). Serum ethanol levels was 243 mg/dL. The case was intubated and given intravenous fluids. The following day she was extubated and discharged without sequelae.

A 17-year-old male with immunodeficiency, weighing 37 kg, was hospitalised for pneumonia (Gormley et al 2012). On his sixth day in hospital he complained of dizziness and was found to be tachycardic (133 beats/minute) and with depressed oxygen saturation (92%). After a period of somnolent, but responsive, behaviour, the case ceased spontaneous movement and was intubated. A nurse found an empty 500 mL bottle of hand sanitiser (61% ethanol) and the cases serum ethanol was found to be 720 mg/dL almost six hours after the onset of symptoms. The case underwent haemodialysis. He awoke after three hours and was extubated the following morning. He admitted infusing the hand sanitiser into gastronomy tube but denied any suicidal intent.

A 43-year-old alcoholic man was admitted to hospital with chest pains, but subsequently became hypotensive and delirious (Emadi and Coberly 2007). Laboratory analyses were normal except for a trace of acetone in the urine. The following day, the patient was haemodynamically stable, but his mental status did not improve. Because of a sweet, ketotic odour in the room, analysis for serum isopropanol and acetone levels were conducted. His serum isopropanol level was 13.6 mg/dL, and his acetone level was 269.4 mg/dL (normal range, 0 to 1.9 for both). The case admitted ingesting hand sanitiser (63% isopropanol) for the purpose of intoxication. Unlike ethanol and methanol, isopropanol is more toxic than its metabolite, acetone. In this case, the isopropanol had been largely metabolised and the case was given supportive treatment only. He recovered fully.

Two cases of ocular harm from hand sanitisers have also been reported (Yangzes et al 2021). A 4-year-old girl experienced unintentional exposure to the right eye when attempting to dispense hand sanitiser from a stand-mounted container. At presentation, the child reported severe photophobia and the right eyelid was swollen. There was conjunctival chemosis (swelling of the membrane covering the eye) and ischaemia (reduced blood flow) to part of the eye and a large epithelial defect in the central cornea. Oral and topical medication was initiated. The epithelial defect healed completely and the ischaemia resolved within two weeks. A 5-year-old boy presented with recent ocular exposure to hand sanitiser. The right eye had conjunctival congestion (red eye) with superficial punctate keratopathy (death of cells on corneal surface, resulting in the eye becoming red, watery and sensitive to light). A thorough saline wash was followed by topical medications. The condition resolved within five days.

2.3 TOXICITY OF HAND SANITISERS

There is no evidence that the toxicity of hand sanitisers is related to any ingredient other than the predominant alcohol ingredients (ethanol and isopropanol) or methanol, present as a contaminant or an illegal alternative ingredient.

For ethanol and isopropanol, the alcohol is the primary toxicant, with metabolites being of lower toxicity. For methanol, the reverse is the case.

Ethanol undergoes oxidative phase I metabolism by the enzyme alcohol dehydrogenase to produce acetaldehyde (Le Dare et al 2019). Acetaldehyde is then oxidised by the enzyme aldehyde dehydrogenase to form acetate. About 10% of ingested ethanol is metabolised by cytochrome P450 (CYP) enzymes, giving the same metabolic products (Le Dare et al 2019). In some populations, activity of the aldehyde dehydrogenase enzyme can be low, resulting in ethanol intolerance. Some of the symptoms of this intolerance (nausea, dysphagia, headache, and the vasodilation responsible for facial flush in particular) are thought to be due to accumulation of acetaldehyde (Le Dare et al 2019). However, in most individuals the acute toxic effects of ethanol ingestion are due to ethanol itself and its interaction with receptors, such as the gamma-aminobutyric acid (GABA) receptors, contributing to depression of the central nervous system (Le Dare et al 2019).

Isopropanol is also oxidised by alcohol dehydrogenase to form acetone (Kraut and Mullins 2018). While details of isopropanol toxicity have not been fully established, like ethanol, isopropanol toxicity mainly results in depression of the central nervous system (Slaughter et al 2014). This is considered to be predominantly due to the action of the parent alcohol, although acetone may have a contributory role (Slaughter et al 2014).

While methanol follows the same metabolic steps as the other alcohols, being oxidised to formaldehyde and then to formic acid, it is the metabolite formic acid/formate that is responsible for the acute toxicity of methanol (Medinsky and Dorman 1995). The primary adverse effects of formic acid in humans are a severe metabolic acidosis and effects on the retina that may result in vision impairment or even blindness. Due to the differences in the mode of toxicity of ethanol and methanol, ethanol is sometimes used as a treatment for methanol poisoning as it preferentially binds to the alcohol dehydrogenase enzyme.

For all alcohols, blood concentrations of the parent alcohol are used as a measure of exposure.

3 DOSE-RESPONSE INFORMATION

In the current context, concerns associated with oral exposure to hand sanitiser fluid will be related to single exposure (acute) events. While chronic abuse of alcohol-based hand sanitisers may occur, this is outside the scope of the current assessment. While a wide range of compounds may be present in hand sanitisers, most of these are likely to be toxicologically insignificant, due to their low level of inclusion and/or their low inherent toxicity. The following sections will consider dose-response information for the alcohols, ethanol and isopropanol, and methanol as a potential contaminant.

3.1 ETHANOL

For a person who is not alcohol dependent, Table 2 provides an estimate of the lower limit of the single dose of ingested ethanol that would result in the defined peak blood alcohol levels and associated symptoms/risks. Calculations for Table 2 estimate the oral dose of ethanol assuming that all the ethanol was absorbed by the body and no metabolism or elimination took place before the peak blood alcohol level was reached. The calculations are based on the rapid distribution of ethanol in the body's water and are corrected for the difference in density between ethanol (0.789 g/mL) and water (approximately 1 g/mL) and the proportion of water in blood (0.8065).

The formulae for the conversion between the peak blood alcohol concentration and the amount of ethanol ingested are given by Donovan (2009) while information on the water content of humans of various ages are derived from Wells et al (2005) and Donovan (2009).

Table 2. Blood alcohol concentrations and associated effects from oral consumption of ethanol by different population groups

BAC[a] mg/dL	Ingested ethanol (mL)[b]					Symptoms and risks
	3 year old	14 year old girl	14 year old boy	Adult female	Adult male	
50–150	7-21	23-69	29-86	26-79	36-109	Impairment in concentration, judgement and motor coordination leading an increased risk of injury
150–250	21-35	69-115	86-143	79-132	109-181	Slurred speech Unsteady walking Nausea Double vision Increased heart rate Drowsiness Mood, personality and behaviour changes
300	42	138	172	158	218	Speech incoherent/confused Memory Loss Vomiting (risk of aspiration) Heavy breathing Unresponsive/extremely drowsy
>400	>56	>184	>229	>211	>290	Breathing slowed and shallow Coma Death

a: BAC – blood alcohol concentration
b: Mean total body water, 3 year old – 9 L (Wells et al 2005), 14 year old girl – 29.3 L, 14 year old boy – 36.5 L, female adult – 33.5 L and male adult – 46.2 L (Donovan 2009)

3.2 ISOPROPANOL

It should be noted that the calculations included in Table 2 are applicable to isopropanol and methanol in terms of estimating blood alcohol concentrations, with minor corrections for the density of these alcohols relative to ethanol. Isopropanol has a density 0.786 g/mL and methanol has a density of 0.792 g/mL, so any adjustments are very minor.

It has been reported that ingestion of as little as 0.5 mL/kg bw of a 70% solution of isopropanol can cause symptoms (IPCS 1990). This equates to 24.5 mL of isopropanol for a 70 kg adult or 5.25 mL for a 15 kg child. However, the symptoms expected at this dose were not reported.

A lethal dose has been reported to be as low as 240 mL and death has been reported at a blood isopropanol concentration of 150 mg/dL (IPCS 1990). However, blood alcohol concentrations as high as 560 mg/dL have been survived following dialysis. In contrast, a more recent publication noted that serum isopropanol concentrations above 500 mg/dL are 'clinically significant', while concentrations greater than 1500 mg/dL produce deep coma (Kraut and Mullins 2018).

A lethal oral dose in children of 100 mL has been reported, while ingestion of 6 mL/kg bw induced coma at a blood level of 380 mg/dL (IPCS 1990). Paediatric patients have survived serum levels from 128 to 520 mg/dL with supportive care (IPCS 1990).

An interspecies physiologically-based pharmacokinetic model was used to derive a chronic reference dose (RfD) for isopropanol of 10 mg/kg bw per day for decreases in foetal weight in rats (Gentry et al 2002). However, this chronic no effect level of exposure is higher than the acute dose reported to result in coma in children (IPCS 1990).

3.3 METHANOL

Blood methanol concentrations greater than 50 mg/dL are associated with severe toxicity, while concentrations above 150-200 mg/dL will be fatal in untreated patients (Pressman et al 2020).

Moon (2017) Carried out a detailed review of dose-response information for methanol, noting the wide range of doses associated with particular effects. Table 3 summarises the information from this study.

Table 3. Dose response information for methanol

Adverse health effect	Exposure dose (oral)	
	mg/kg bw	g/person[a]
Headache and respiratory changes	429	27.8
Vision affected	3429	222.9
Breathing difficulty, nausea, vomiting, circulatory system change	6422	417
Blindness	-	3.2-11.9
Death	-	15.8-474

Source: (Moon 2017) [a] Calculated using a body weight of 65 kg

It is clear that different sources of information do not provide a cohesive picture of the dose-response relationship for methanol. This inconsistency is likely to be related to individual's biochemistry (activity of alcohol metabolising enzymes) and the provision of treatment in cases of intoxication.

4 EXPOSURE ASSESSMENT

Unintentional ingestion of hand sanitiser is likely to be due to 'one-off' events or, at worst, infrequent events. As indicated by the available surveillance information, events are most likely to involve very young children engaged in exploratory behaviours. Exposure to components of hand sanitisers may potentially occur through ingestion, inhalation or dermal exposure. Considering the containerised nature of hand sanitisers, inhalation exposure is likely to be negligible. Evidence for dermal absorption of alcohols from hand sanitisers is discussed below. Ingestion is the most likely route of exposure to substantial amounts of hand sanitiser, and child unintentional exposure the most likely scenario.

For hand sanitiser, exposure through ingestion can be defined as:

$$E_{ing} = \frac{C \times V}{BW}$$

Where E_{ing} is the exposure through ingestion (mg/kg body weight (bw) or mL/kg bw), C in the concentration of the component of interest in the ingested fluid (mg/L or mL/L), V is the volume of fluid ingested (L) and BW is the body weight of the exposed individual or the mean body weight of an age group (kg).

For human case reports, effect levels of exposure are often reported as the amount of the substance of interest ingested, without regard to the case's body weight. For comparison to such studies, the exposure expression simplifies to C x V.

4.1 EXPOSURE PARAMETERS

4.1.1 Dermal absorption of alcohol from hand sanitisers

Dermal absorption of ethanol from hand sanitisers was assessed in a cohort of health care workers (*n* = 86) (Ahmed-Lecheheb et al 2012). Ethanol, acetaldehyde and acetate were determined in blood and urine of workers before and after a 4-hour shift. The mean usage of hand sanitizer was 27.5 g per 4-hour shift (range 1.2-59.8 g). Ethanol was detected in blood from one worker before exposure (0.39 mg/L) and in the blood of a different worker after exposure (0.22 mg/L). The worker with a positive ethanol test post-exposure had only used 7.9 g of hand sanitizer during the 4-hour shift. Acetaldehyde was detected in the blood of a second worker, but they were found to have a history of liver disease and were subsequently excluded from the study. All urinary alcohol tests were negative. The limits of detection for the analyses were not reported.

Five workers in a health care facility volunteered to take part in a study of the potential impact of use of ethanol-based hand sanitisers on blood ethanol levels (Miller et al 2006). Volunteers applied 5 mL of hand sanitiser (62% ethanol) to both hands and rubbed until dry. The process was repeated 50 times over a 4-hour period. All blood ethanol levels were below the limit of detection (5 mg/L) before commencement of the study and remained below 5 mg/L at the end of the study. No adverse reactions were noted during the study. Eleven volunteers used hand sanitiser (62% ethanol) every 5 minutes for a 10-hour period on each of three consecutive days (Reisfield et al 2011). At each application approximately 1 mL of hand sanitiser was applied, hands were rubbed for 30 seconds, then residual sanitiser was allowed to evaporate. Subjects provided a urine sample at the beginning and end of each day and on the morning following the last application day. Urine samples were analysed for ethanol and the ethanol metabolites ethyl glucuronide (EtG) and ethyl sulphate (EtS). Ethanol was not detected in any of the urine samples. EtG was mainly detected in end-of-day urine samples, with concentrations in the range 74-2001 µg/L. EtS was detected

in fewer samples, but in most cases was also only detected in end-of-day samples. While the authors of this study believe that these results were due to dermal absorption, contributions from inhalation absorption cannot be excluded.

In a 4-week study, a 25-year-old teetotal male (80 kg body weight) applied 5 mL of hand sanitiser (62% ethanol), followed by rubbing for 30 seconds to spread the sanitiser over the complete hand surfaces and then allowed residues to evaporate (~1.5 minutes) (Salomone et al 2018). This process was carried out four times on the hour for five hours to give a total of 20 applications each day. Urine samples were collected before and after the 20 applications. Hair samples (beard, chest, head) were collected periodically through the course of the study. Samples were analysed for EtG. All pre-application samples (morning) did not contain detectable concentrations of EtG, while post application samples all contained detectable EtG concentrations (mean = 156 µg/L, range 19-1150 µg/L). Urinary EtG concentrations of 100 and 500 µg/L have been used in clinical and forensic contexts, respectively, as indications of alcohol consumption. EtG was consistently not detected in hair samples. The authors of this study reported these results as indicative of dermal absorption and/or inhalation.

The studies above provide equivocal evidence regarding dermal absorption of ethanol from hand sanitisers and none of the studies provide sufficient evidence to determine a rate of dermal absorption.

4.1.2 Composition of hand sanitiser

Table 1 gives the stated ingredients for a range of hand sanitisers available in New Zealand. Some of these ingredients are permitted food additives in New Zealand (e.g. butyl hydroxytoluene, tocopherol, glycerol, propylene glycol, cellulose, hydroxypropyl methyl cellulose).[2] Given that it is unknown what the content of the remaining minor components is in the hand sanitiser products, these components have not been further considered in this assessment. However, they are likely to be of negligible toxicological concern.

For case reports of adverse effects from hand sanitiser ingestion all adverse effects reported have been ascribed to the alcoholic component of the products (see section 2.2.1). For the current exposure assessment, it has been assumed that alcohols will be present at the concentrations recommended by WHO (2010): 80% ethanol or 75% isopropanol. The information in Table 1 suggests that the alcohol content of products available in New Zealand may be lower than this.

4.1.3 Exposure cohort

As outlined in section 2.2.1.2, cases of unintentional ingestion of hand sanitiser are almost universally in the age range up to 5 years. In particular, the age group 1-2 years is usually the highest risk group for exposures of this type. This is due to their independent mobility and high level of exploratory behaviour. This age group was used as the basis for the current exposure assessment.

A New Zealand handbook of exposure factors recommended the use of a mean body weight of 11 kg for children in this age group (Cressey and Horn 2016).

4.1.4 Amount of hand sanitiser ingested

McCulley et al (2021) reported on 315 incidents of child exposure to hand sanitiser for which an estimate of the amount ingested was available. Unfortunately, the majority of estimates

[2] https://www.legislation.gov.au/Details/F2021C00324 Accessed 23 September 2021

were qualitative, with the largest group (*n* = 183) having ingested amounts described in terms of 'taste/lick/drop' (median = 1 taste, lick or drop). The next largest sub-group (*n* = 53) had ingested amounts reported in millilitres, with a median of 15.4 mL and a range from 1 to 60 mL. Other descriptors of ingested dose included mouthful, sip, bite, solid and gram.

While quantitative data were not provided, Miller et al (2008) noted that the exposures in children under 6 almost invariably occurred as a brief taste or accidental ocular or dermal exposure.

For the current assessment, the data from McCulley et al (2021) were used, with exposure calculated for a median ingestion of 15.4 mL and a maximum of 60 mL. It has been assumed that these values relate to products containing 80% ethanol or 75% isopropanol.

4.1.5 Conversion of ingested alcohol volumes to blood alcohol concentrations

Alcohols distribute rapidly in the body's water and the peak blood alcohol concentration (BAC) can be estimated from the equation:

$$BAC\ (mg/dL) = (A/TBW) \times 80.65$$

Where A is the weight of alcohol ingested (mg), TBW is the total body water (L) and 80.65 is the percentage of water in blood (Donovan 2009).

Equations have been derived to calculate TBW for children from body weight (bw), height (h), age (a) and gender (0 for males, 1 for females) (Wells et al 2005):

$$Ln(TBW) = -2.952 + (0.551 \times Ln(bw)) + (0.796 \times Ln(h)) - (0.047 \times gender) + (0.008 \times a)$$

Where Ln is the natural logarithm, bw is expressed in kilograms, h is expressed in centimetres and a is expressed in years.

Using the mean age for the selected exposure cohort (1.5 years) and median weights (11.0 kg for males and 10.3 kg for females) and heights (82 cm for both genders) from New Zealand growth charts (Ministry of Health 2015) estimates of TBW of 6.1 and 6.6 L for females and males, respectively. The average of these two estimates (6.4 L, rounded) was used in the current exercise.

The weight of alcohol ingested is derived from the volume multiplied by the density (0.789 g/mL for ethanol and 0.786 g/mL for isopropanol).

4.2 EXPOSURE ESTIMATES

Table 4 summarises estimates of exposure to alcohol (ethanol or isopropanol) from ingestion of hand sanitiser, based on the parameters outlined above.

Table 4. Estimates (median and maximum) of potential exposure to ethanol or isopropanol from ingestion of hand sanitiser for a child, 1-2 years

	Estimated exposure to alcohol			
	Ethanol		Isopropanol	
	Median	Maximum	Median	Maximum
Volume of hand sanitiser ingestion (mL)	15.4	60	15.4	60
Volume of alcohol ingested (mL)	12.3	48	11.6	45
Weight of alcohol ingested (g)	9.7	37.9	9.1	35.4
Exposure (mg/kg bw/event)	0.88	3.4	0.83	3.2
BAC (mg/dL)	122	480	115	450

5 RISK CHARACTERISATION

The inconsistent and sometimes conflicting nature of dose-response information for alcohols makes definitive characterisation of risks problematic and the following sections provide largely qualitative assessments of the likely risks from ingestion of hand sanitiser by young children.

5.1 ETHANOL

The available studies provide equivocal evidence regarding dermal absorption of ethanol from hand sanitisers and none of the studies provide sufficient evidence to determine a rate of dermal absorption. Consequently, only risks due to oral ingestion have been considered.

At a median level of ingestion of ethanol-based hand sanitiser by a young child (1-2 years), resulting in a BAC of approximately 120 mg/dL, the child could exhibit mild signs of intoxication, including impaired concentration and motor co-ordination (Table 2). The child would be expected to recover fully.

At the maximum reported level of ingestion (60 mL) of ethanol-based hand sanitiser by a young child (1-2 years) the peak BAC may approach 500 mg/dL and severe depression of the central nervous system is possible.

5.2 ISOPROPANOL

While paediatric patients have been reported to have survived isopropanol BACs as high as 520 mg/dL with supportive care (IPCS 1990), fatalities have been reported at lower BACs. Due to the uncertainty around the dose-response relationship, ingestion of isopropanol at the median reported ingestion rate for hand sanitiser (approximately 15 mL equivalent to a BAC of 115 mg/dL) or above should be viewed as cause for concern.

6 CONCLUSIONS

Hand sanitisers are used for hand hygiene, particularly in locations where access to water for handwashing may be limited. Hand sanitisers are predominantly composed of alcohol, either ethanol or isopropanol. Although instances of methanol-based products have been reported this is likely to be due to ignorance or malicious activity on the part of the manufacturer. The alcohol content of hand sanitisers is typically about 60%, although WHO suggest higher concentrations; 80% for ethanol and 75% for isopropanol.

For ethanol and isopropanol, toxicity is associated with the parent compound, while for methanol toxicity is primarily due to the major metabolite, formic acid. The severe effects of ethanol and isopropanol are due to depression of the central nervous system. The severity of effects due to ethanol and isopropanol are associated with the blood alcohol concentration (BAC). For ethanol, BAC in the range 50-150 mg/dL are associated with mild intoxication, characterised by impaired concentration and motor coordination. BAC greater than 400 mg/dL are potentially life-threatening in the absence of supportive treatment. Less information is available on the dose-response relationship for isopropanol, however, it appears likely that BAC greater than 300 mg/dL may be associated with severe effects.

Unintentional exposure to alcohols in hand sanitisers is most likely to be due to exploratory behaviour by young children. This is consistent with available surveillance data. Information from a US study suggests that incidents will typically involve ingestion of volumes up to 60 mL of hand sanitiser (median 15.4 mL).

There is insufficient information to determine the extent of dermal absorption of alcohols from use of hand sanitisers.

Surveillance suggests that serious health effects from ingestion of alcohol-based hand sanitisers are rare, but not unknown. This supports the assertion that most exposure events do not progress past a taste. However, exposure estimates for plausible exposure scenarios (up to 60 mL of products containing 80% ethanol or 75% isopropanol) for young children (1-2 years) indicate that BACs associated with severe central nervous system depression could occur through exploratory ingestion of alcohol-based hand sanitisers.

While exposure estimates were not derived for methanol in hand sanitisers, surveillance data suggests that methanol is an inappropriate ingredient for hand sanitisers.

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