HEALTH RISK ASSESSMENT: METHYLATED SPIRITS

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HEALTH RISK ASSESSMENT: METHYLATED SPIRITS

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CONTENTS

LIST OF TABLES

LIST OF TABLES

GLOSSARY

Acute toxicity	1. *Adverse effects* of finite duration occurring within a short time (up to 14 d) after administration of a single *dose* (or *exposure* to a given *concentration*) of a test substance or after multiple doses (exposures), usually within 24 h of a starting point (which may be exposure to the *toxicant*, or loss of reserve capacity, or developmental change, etc.) 2. Ability of a substance to cause *adverse effects* within a short time of dosing or *exposure*
Adverse effect	A change in biochemistry, physiology, growth, development morphology, behaviour, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to other environmental influences
Central nervous system (CNS)	The processing centre for the nervous system comprising the brain and the spinal cord.
Chronic toxicity	Adverse effects due to exposure to a substance continuously or repeatedly over a period of time. Chronic toxicity can be due to repeated exposure of substance which is easily removed from the body or can be due to prolonged internal exposure because a substance remains in the body for a long time.
Denatured alcohol	Ethanol which has additives designed to discourage recreational or incidental consumption
Dermal	Cutaneous, pertaining to the skin
Dose	Total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue
Dose response	Association between dose and the incidence of a defined biological effect in an exposed population
Dose response assessment	Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose–response assessment is the second of four steps in risk assessment
Epithelium	Sheet of one or more layers of cells covering the internal and external surfaces of the body and hollow organs

Erythema	Redness of the skin due to congestion of the capillaries
Exposure assessment	Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.
Hazard identification	The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment.
Incidence	Number of occurrences of illness commencing, injury, or of persons falling ill, during a given period in a specific population usually expressed as a rate
Injury	Any physical harm or damage serious enough to warrant medical treatment by a health professional either at the scene or in a hospital or primary care practice.
Irritant	Producing inflammation or irritation
Necrosis	Morphological changes indicative of cell death
No observed adverse effects level (NOAEL)	Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure
Ocular	Pertaining to the eye
Oral	Pertaining to or via the mouth
Rhinitis	Inflammation of the mucous lining of the nose
Risk characterisation	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.
Sensitisation	Process in which repeated administrations of a stimulus results in the progressive amplification of a response

EXECUTIVE SUMMARY

The purpose of this report is to develop a generic health risk assessment for methylated spirits intended for sale to the general public. This report will only consider domestic, non-occupational, exposure to methylated spirits.

Methylated spirits is a common household product which is readily available at a range of retail outlets. Methylated spirits is composed of 70–99% ethanol, water and denatonium benzoate. Other ingredients (concentration ≤0.25%) can include methyl isobutyl ketone, methyl violet and fluorescein. Denatonium benzoate is added to methylated spirits to make the product have an intensely bitter taste to reduce the amount of liquid likely to be consumed.

Data from the New Zealand Poisons Call Centre lists 60–80 calls a year relating to methylated spirits, ranking it between 6th and 12th annual most common cause of calls over the period 2008–2012. The majority of calls across all age groups relate to ingestion of methylated spirits. Smaller numbers of calls relate to eye, skin and inhalation exposures. Approximately 40% of calls relate to 0–3 year olds being exposed to methylated spirits during exploratory play.

Methylated spirits is not classified as acutely toxic, but ingestion of small quantities can cause serious health effects due to the high ethanol concentration.

Risk assessment of 2–3 year olds drinking and spilling methylated spirits during exploratory play suggests the scenario is unlikely to result in systemic toxicological risk if the denatonium benzoate acts as a deterrent to ingestion. There is no evidence supporting a toxicological risk from dermal or inhalation exposures for this scenario.

In the worst case scenario of a 2-3 year old child being undeterred by the bitterant and drinking 20–30 ml of methylated spirits, there are likely to be transient health effects relating to the central nervous system. Coma and death could result from a 2–3 year old drinking 50 ml of methylated spirits.

The use of methylated spirits for household cleaning by adults and children, resulting in dermal or inhalation exposure, is unlikely to represent a health risk.

Methylated spirits contacting with the eye will cause immediate discomfort and may damage the eye lasting over a week. Symptoms are likely to resolve within two weeks.

Risk assessment of chronic dermal exposure to methylated spirits during household cleaning by adults, results in a margin of exposure of between 22 and 89 using rat NOAELs as the benchmark dose. Safety factors of 100-1000 are typically applied to derive health-based exposure limits from toxicological NOAELS. On this basis, MoEs less than 100 may indicate a need for a more detailed risk assessment. Further data on the NOAEL of methylated spirit ingredients and the dermal and inhalation transfer rates at low concentrations would assist in reducing the uncertainty of this assessment.

Cancer is not expected to be an endpoint of concern for incidental exposure to this product. However data are limited on: the genotoxicity and carcinogenicity of methyl violet.

1. INTRODUCTION

1.1 Purpose

The purpose of this report is to develop a generic health risk assessment for methylated spirits intended for sale to the general public. This report will only consider domestic, non-occupational, routine and incidental exposure to methylated spirits. In some instances, occupational exposure information will be used to contextualise non-occupational exposures, specifically in terms of adverse health outcomes and critical exposure levels.

Exposure scenarios were developed for the most common or likely exposure events to assess the health risk to exposed groups. Detailed scenarios resulting in injury due to the flammable nature of methylated spirits will not be considered in this risk assessment.

Methanol used to be a common denaturing ingredient in methylated spirits. Methanol is hazardous to human health and was banned in New Zealand as an ingredient in methylated spirits intended for public use in 2006[1]. This risk assessment will not consider formulations including methanol.

1.2 Consumer Products Description – Methylated Spirits

Methylated spirits is a common household substance in New Zealand, which is used as a household cleaner and fuel for camping stoves or as a BBQ starter fuel. It is available through a wide range of retail shops including supermarkets, hardware, decorating, department, camping and automotive parts stores. In 2014 the cost ranged from $4 to $12 a litre.

Methylated spirits is a liquid product containing a high concentration of ethanol plus some form of denaturant to discourage it's consumption by people. Ethanol is also referred to as ethyl alcohol in some of the report references. For consistency in the rest of this report, only the term ethanol will be used.

Methylated spirits is regulated in New Zealand by the Environmental Protection Agency Denatured Ethanol Group Standard 2006[1]. There are three possible formulations for denaturing ethanol intended for sale to the general public:

- 15.6 g denatonium benzoate per 1000 litres ethyl alcohol to be denatured (15.6 ppm)
- 0.25% by volume methyl isobutyl ketone (MIBK) together with 5-10 g denatonium benzoate per 1000 litres of ethyl alcohol to be denatured (5-10 ppm)
- 0.25% by volume tertiary butyl alcohol together with 10 g denatonium benzoate per 1000 litres of ethyl alcohol to be denatured (10 ppm).

[1] http://www.epa.govt.nz/Publications/gs-denatured-ethanol.pdf Accessed 31 July 2014

The group standard also states that “when a substance is packaged in quantities less than 5 L, that package must be child resistant unless being sold or supplied to a place of work where children do not have access and the substance is for use in that place of work.”

A review of methylated spirits products available to the public from national retailers, internet retail sites and shops in Christchurch and Hamilton is summarised in Table 1.

Ingredient information was sourced from product material safety data sheets, product labels or correspondence with the producers. No formulations using tertiary butyl alcohol were found in domestic retail products and this formulation is not considered further in this assessment.

Table 1: Description of methylated spirits formulations commonly available to New Zealand public

	Ingredients	**Concentration**	**Packaging/Presentation**
A	Ethanol Water Denatonium benzoate Methyl violet	> 95-99 %v/v < 5 %v/v 15.6 g in 1000L ~1.0 g in 1000L	I L – child safety cap 4 L – child safety cap or no child safety cap 5 L – no child safety cap 20 L
B	Ethanol Water Methyl isobutyl ketone Denatonium benzoate Fluorescein Methyl violet 10B	> 95 %v/v < 5 %v/v 0.25 %v/v 6.6 ppm 1 ppm 1.0 g in 1000L	I L – child safety cap 4 L – child safety cap or no child safety cap
C	Ethanol Water Methyl isobutyl ketone Denatonium benzoate Fluorescein Fragrance	70 %v/v < 30 %v/v 0.25 %v/v 6.6 ppm 1.0 ppm unknown	500 ml pump spray bottle No child safety cap Clear liquid with lemon, vanilla or lavender fragrance added. Lemon type has pictures of lemons on the front.

2 HAZARD IDENTIFICATION

The hazard identification considers the toxicological hazards associated with the product methylated spirits. Here, the product and each of its ingredients are reviewed for data relevant to evaluation of toxicity by all routes. Where key data are not available on the product or its ingredients, data gaps are identified.

2.1 Absorption and metabolism

2.1.1 Oral

Ethanol is rapidly absorbed from the gastrointestinal tract into the blood stream providing systemic exposure to the chemical. Approximately 20% of consumed alcohol is absorbed into the blood stream via the stomach. The small intestine more efficiently absorbs alcohol and can absorb most of the alcohol left after the stomach (Health Protection Agency 2014).

Ethanol is metabolised in the body by enzymes, the primary ones are alcohol dehydrogenase, aldehyde dehydrogenase, specific forms of cytochrome P450 and catalase (Zakhari 2006). Most (90%) of the ethanol is metabolised by the liver with smaller amounts metabolised in the stomach. Some ethanol is excreted from the body via the lungs, via the kidneys into urine or in sweat.

MIBK is rapidly metabolised in the body to the major metabolite 4-hydroxy-4-methyl-2-pentanone (HMP; CAS No 123-42-2) which is also readily metabolised in the body.

Fluorescein and its metabolites are mainly eliminated via renal extraction, systemic clearance of 500 mg can occur in 72 hours.

2.1.2 Inhalation

Ethanol vapour can be absorbed into the blood stream via inhalation. However it has not been shown in human studies to result in high enough blood alcohol concentrations to lead to adverse effects. Prolonged periods of inspiration of air containing alcohol at 2–12 mg/L result in absorption of 55%–60% of the inspired ethanol. However, some of the ethanol is thought to stay in the respiratory system and not enter the blood stream. (Campbell and Wilson 1986; Kruhoffer 1983).

2.1.3 Dermal

Ethanol is not readily transferred to the blood stream through the skin. This is partially due to rapid evaporation of ethanol from the skin's surface (Pendlington et al 2001).

High concentrations of ethanol are a common ingredient in hand disinfectant rubs. Repeated application of a 95% ethanol hand rub over a short period of time (Table 2) showed that ethanol could be transferred to the blood stream, but at low levels which would be easily metabolised by the body in a short time (Kramer et al 2007; Wigmore 2009).

Table 2: Maximum blood alcohol concentration achieved after repeated use of ethanol based rub (Kramer et al 2007).

Experiment	Application of 95% ethanol rub	Maximum blood alcohol concentration: Median (95% CI)
Hygienic	20 x (4 ml of rub applied to hands for 30 s, 1 min wait)	2.1 (2.0–2.1) mg/dL
Surgical	10 x (4 ml of rub applied to hands and forearms for 3 min, 5 min wait)	1.8 (1.6–1.9) mg/dL

Animal experiments with guinea pigs showed that the methylated spirits component, MIBK, can be absorbed orally, by inhalation or through the skin and transferred to the arterial blood. In the guinea pigs a maximum percutaneous uptake of 1.1 µmol/min/cm^2 was observed 10–45 minutes after the start of a dermal exposure.

Denatonium benzoate exposure to the skin is unlikely to result in systemic exposure to the substance (Cosmetic Ingredient Review Expert 2008).

2.2 Acute Toxicity of Similar Products and Associated Ingredients

There are no data available on the acute toxicity of the product sold as methylated spirits.

Ethanol can enter the blood stream through ingestion, the lungs or skin, resulting in exposure of organs of the body and the central nervous system.

Acute systemic exposure to ethanol and its metabolites can result in behavioural and motor coordination changes at low level blood alcohol concentrations. Higher levels of blood alcohol lead to depression of the respiratory system, with the possibility of coma and death. Other symptoms of acute alcohol intake include memory loss, nausea and vomiting (Health Protection Agency 2014). Aspiration of vomit by drowsy or unconscious people who have consumed ethanol can also lead to death.

Consumption of ethanol is associated with an increased risk of injury, domestic violence, intentionally inflicted harm (Borges et al 2006; Taylor et al 2010) and can affect the development of the unborn baby during pregnancy.

The minor ingredient, denatonium benzoate, has been described as having moderate acute oral toxicity, with high doses causing congestion and haemorrhage of the respiratory system (CPSC 1992). Denatonium benzoate was toxic after

inhalation with effects on the lungs, liver and spleen (European Food Safety Authority 2008; 2012).

The methylated spirits ingredient MIBK caused low acute and chronic oral toxicity in rats. The major effects noted due to repeated high concentrations were to the liver and kidneys (NICNAS 2013).

Human exposure studies have shown that high concentrations of MIBK can cause irritation of the nose and throat and a transient anaesthetic effect. Neurological symptoms (headache, nausea and vertigo) generally increased with exposure level and decreased rapidly following the end of the exposure to MBIK (US EPA 2013).

A cosmetic ingredient review reported that ingestion of methyl violet at therapeutic doses can cause nausea, vomiting, diarrhea and abdominal pain (Diamante et al 2009).

2.3 Irritation

No toxicology studies were found describing the dermal or eye irritancy of methylated spirits formulations. However, studies using a related denatured alcohol product, SD Alcohol 40-B, containing similar ingredients are summarised below. SD Alcohol 40-B is ethanol with the added ingredients 6ppm denatonium benzoate and 1200 ppm t-butyl alcohol, but does not contain MIBK or methyl violet. SD Alcohol 40-B is an ingredient in cosmetics sold in New Zealand.

Multiple dermal irritation studies using human subjects have been conducted for concentrations of SD Alcohol 40-B ranging from 12% to 98.2%. No evidence was given that SD Alcohol 40-B is a skin irritant. At the highest concentration, 91 individuals used a deodorant body spray containing 98.2% SD Alcohol 40-B. A volume of 0.1 ml of the solution was applied to 10 patches on the back three times a week for three weeks. Only four minimal reversible reactions were observed, suggesting the 98.2% Alcohol 40-B was not a skin irritant at this dose (Cosmetic Ingredient Review Expert 2008).

Ethanol is not considered to be a skin irritant (Cosmetic Ingredient Review Expert 2008). The other ingredients have been shown to be minor irritants at concentrations higher than those found in methylated spirits (Table 4). Information was not found at lower concentrations.

Inhaling high concentrations of ethanol can cause irritation to the throat and nasal passages (NICNAS 2013a).

Eye contact with small amounts of 50–100% ethanol liquids has been observed to cause necrosis of the surface of the cornea and eye irritation in rabbits (Carpenter and Smyth 1946; Guillot et al 1982). Iris lesions were observed to be fully reversible eight days following the contact, however, cornea opacity and swelling of the eye was still observable at eight days. All symptoms subsided after two weeks (NICNAS 2013a).

Table 3: Dermal irritation information for methylated spirits ingredients.

Ingredient	Dose or concentration effects	Study type	Concentration in methylated spirits	Reference
Ethanol	80% Skin irritation unlikely, if occurs will be minor irritation.	Human	70–99 (%v/v)	(Loffler and Kampf 2008; NICNAS 2013a)
MIBK	5-10 ml for 24 hours. Slight temporary skin irritation. No clinical evidence of absorption. 10 ml/day for a week. Drying and flaking of skin surface.	Rabbit / Guinea Pig Rabbit	2.5 ml/L	(Johnson 2004)
Denatonium benzoate	0.05% solution. Irritation unlikely. 2 g/kg bw on a patch for 24 hours. Moderate temporary erythema, no oedema.	Human Rabbit	0.002 (%w/w) 0.016 g/L	(CPSC 1992)
Methyl violet	0.25% solution. Dermatitis observed.	Human (case study)	0.0001 (%w/w)	(Diamante et al 2009)
Fluorescein	Unknown			

An unpublished Japanese study applied solutions of 0.05% and 0.005% denatonium benzoate to the forearm of 30 subjects. The authors stated that irritation is unlikely to occur (CPSC 1992). A cosmetics ingredient review similarly concluded that denatonium benzoate was not a skin irritant or skin sensitiser and is unlikely to be absorbed through the skin (Cosmetic Ingredient Review Expert 2008).

Denatonium benzoate was not an eye irritant when tested in a 0.05% solution, but an EFSA review classifies denatonium benzoate as severely irritant to the eyes (European Food Safety Authority 2012).

Exposure to MIBK on shaved rabbit skin caused erythema which persisted for 24 hours following a 10 hour application. Repeated exposures over a week caused drying and flaking of the skin surface (NICNAS 2013).

Undiluted MIBK caused irritation when applied to rabbit eyes, reversible after 60 hours (NICNAS).

Application of 1–2% methyl violet to infant's mouths may cause blistering, ulceration and lesions. Contact of methyl violet with the eye can cause severe pain, removal or damage of corneal epithelium cells, congested and swollen conjunctivae and reduction in visual acuity (Diamante et al 2009).

Topical administration of fluorescein to the eye of patients can result in temporary irritation, rash, discolouring of the skin and urine (Alford et al 2009). Ocular exposure to fluorescein was not found to be damaging in rabbits[1].

2.4 Sensitisation

Toxicological data were not available describing sensitisation potential of methylated spirits as a product.

Ethanol is not known to carry sensitisation potential.

Björkner (1980) lists a case study of a 30 year old male. Contact with products containing ethanol and denatonium benzoate resulted in pruritus on the hands, arms and hands along with asthma-like symptoms. Concentrations of denatonium benzoate as low as $2x10^{-6}$ mg/L produced an erythema reaction.

Contact of 0.25–1% methyl violet with the skin can cause allergic contact dermatitis and 2% methyl violet has caused necrosis on skin surfaces in a 2 year old (Diamante et al 2009).

Possible sensitisation reactions from acute exposure can occur if fluorescein is inhaled, ingested or comes into contact with the skin (0.5–1% of patients), but documented cases during medical procedures involve higher concentrations (7–30 mg/kg bw) than are present in methylated spirits (Alford et al 2009).

2.5 Genotoxicity

A chromosome aberration assay using hamster ovary cells, with a highest concentration of 0.225% of the similar product, SD Alcohol 40-B, showed no increase of cells with chromosome aberrations, polyploidy or endoreduplication compared to historical controls (Cosmetic Ingredient Review Expert 2008).

The IMAP human health tier II assessment for ethanol states that “overall, the data indicate ethanol has no mutagenic or genotoxic potential” (NICNAS 2013a).

The limited available study data does not indicate that denatonium benzoate damages genetic material and does not represent a carcinogenetic concern (Cosmetic Ingredient Review Expert 2008).

MIBK and its metabolite HMP are not considered to have mutagenic or genotoxic potential. Following a chronic two year inhalation study with rats and mice the chemical has been classed as possibly carcinogenic to humans. There are no human data suggesting a carcinogenic risk of MIBK (NICNAS 2013b).

Methyl violet was found to be positive in an Ames genotoxicity study in Salmonella strain TA100 (Yamaguchi et al 1988). On the other hand, Chung et al (1981) found methyl violet to not be mutagenic in the Salmonella assay.

[1] Toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+2128 (Accessed 12 September 2014)

2.6 Chronic toxicity and carcinogenicity

No chronic toxicity data on methylated spirits were available for review. Data exist on several key components of methylated spirits and these results are reviewed below.

Chronic exposure to ethanol can result in disease of the liver, pancreatitis, heart conditions, pneumonia, damage to the brain and nervous system and suppression of the immune system (Ben-Eliyahu et al 1996). Chronic exposure to ethanol in the context of alcoholic beverages has also been associated with a higher risk of some cancers which is discussed further below.

Ethanol and its metabolite acetaldehyde are considered to be carcinogenic (Baan et al 2007). Oral ethanol exposure increases the risk of developing cancers of the mouth, throat, oesophagus, large bowel and rectum, breast and liver. The risk of cancer increases with the frequency and amount of exposure. Ethanol intoxication suppresses the natural killer cell activity, which may underlie the association between alcohol intake and cancer (Ben-Eliyahu et al 1996).

Repeated dose inhalation studies of MIBK in rats and mice showed no effects at lower concentrations (≤1000 mg/m^3), but decreased activity levels and increased liver and kidney weights were observed when the animals were repeatedly exposed to higher concentrations of MBIK (US EPA 2003).

Animal chronic dietary feeding studies have shown that methyl violet has carcinogenic potential with effects in the liver, lymphoid tissues, thyroid and causing mononuclear cell leukaemia (Littlefield NA et al 1985).

2.7 Risk Assessments

The French Agency for Food, Environmental and Occupational Health published an assessment of the risks of ethanol exposure through inhalation and or skin contact by the general population[1]. This included looking at exposure to ethanol containing cleaning products. They concluded that short or long term use of ethanol containing household products did not pose a health risk to the general population during acute or chronic exposures.

[1] https://www.anses.fr/en/content/assessing-risks-ethanol accessed 31 July 2014

2.8 At Risk and Vulnerable Groups

No evidence was found regarding at risk groups from the minor ingredients in methylated spirits. Therefore, only ethanol will be considered in this section.

There are a number of at risk groups from methylated spirits due to the effects of exposure to ethanol:

- young children
- the developing foetus
- elderly
- women
- people who have had gastric surgery
- Asian populations
- alcohol-dependent people.

Young children are at higher risk from the ethanol in methylated spirits due to their small body size compared to the amount of product they may consume, their exploratory nature and their lack of understanding of the risk. Children under five may also have a limited ability to metabolise the ethanol in methylated spirits due to their immature hepatic ethanol dehydrogenase activity (Hussain et al 1998). Their developing nervous system also renders them more susceptible to chemicals that cause central nervous system toxicity such as ethanol and MIBK.

Infants may also be at greater risk of dermal absorption of ethanol due to the immature skin structure. Children up to the age of three have been admitted to hospital for ethanol intoxication after being wrapped in alcohol soaked cloths to relieve abdominal pain (Lachenmeier 2008).

Ethanol in the blood stream of a pregnant woman passes directly to the developing foetus through the placenta. This can cause a number of effects on the foetus including death. In other cases the effects can be premature birth, birth defects, restricted growth, permanent damage to the brain and developmental delay. Such effects are called foetal alcohol spectrum disorder (Health Protection Agency 2014)

Older people do not metabolise ethanol in the body as efficiently as younger people. The ratio of body water to fat tends to fall and alcohol can have a faster effect on the brain (Health Protection Agency 2014). Therefore a smaller dose of methylated spirits would be needed in older people to cause a health risk.

Women are likely to have higher blood alcohol concentrations than men drinking the same amount. This is due to women generally being smaller and having a higher fat to water ratio than men, resulting in less fluid in their bodies than men. They may also have less of the enzymes needed to metabolise the ethanol (Health Protection Agency 2014).

Higher blood alcohol levels for 30 minutes post consumption and shorter times to reach peak blood alcohol levels were also observed in a study of women who had had gastric bypass surgery (Klockhoff et al 2002) compared to women with similar age and body mass index but who had not had gastric surgery. Therefore, less

methylated spirits in a single dose may produce adverse health effects in people with reduced stomach size due to gastric surgery than the general public.

People from different ethnic groups have been shown to have genetic differences in the alcohol and acetaldehyde dehydrogenase enzymes, which results in different rates of ethanol metabolism and consequent tissue damage. A half of Taiwanese, Han Chinese and Japanese populations have reduced activity acetaldehyde dehydrogenase enzymes, resulting in increased levels of acetaldehyde after ethanol consumption and negative physiological responses (Zakhari 2006).

Alcohol-dependent people who have built up a tolerance to alcohol may use methylated spirits as their drink of choice due to the high alcohol content irrespective of cost or presence of bittering agents. A 2010 newspaper report from Christchurch includes comment by a person working with methylated spirits consumers that addiction occurs after three months[1].

2.9 Methylated Spirits Injuries and Use Patterns

Multiple case studies of people presenting to health care establishments relating to methylated spirits formulations which exclude methanol were not located in the published literature or internet.

The sections below present surveillance data related to methylated spirits – excluding types containing methanol. It is possible that poison and health care records would record the diagnosis after drinking methylated spirits as acute alcohol intoxication without recording the source of the alcohol. This may explain the lack of international data relating to methylated spirits.

2.9.1 New Zealand

In New Zealand, data on hazardous substance exposure incidents is collated in the Hazardous Substances Surveillance System (HSSS) by the Massey University Centre for Public Health Research (CPHR).

Information provided by the New Zealand National Poisons Centre[2] on the 20 substances accounting for most calls to the centre for each year during the period from mid-2008 to end of 2012 was reviewed. Methylated spirits was in this 'top 20' list every year with between 61 and 81 calls a year. There were 305 incidents recorded from July 2008 to December 2012, with 11 incidents resulting in more than one call. Of the 305 incidents, 17 related to the workplace and are not considered further in this report.

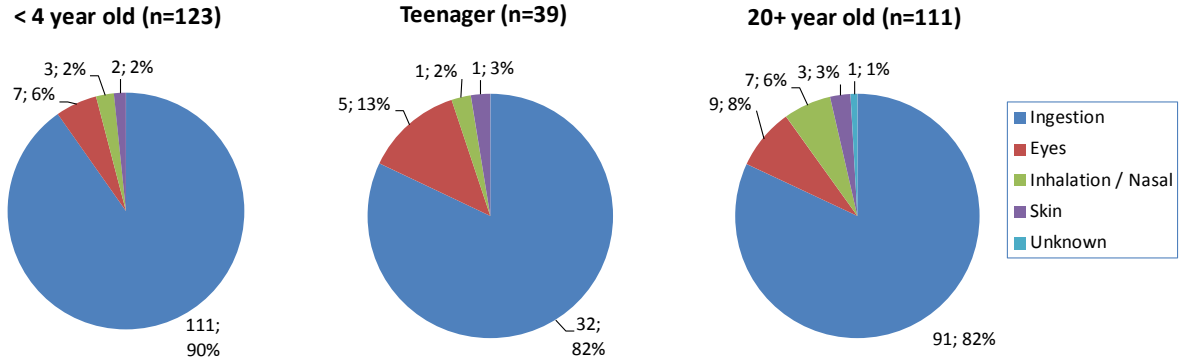
Figure 1 summarises the number of methylated spirits related calls for different exposure routes reported by the Poisons Centre. The greatest proportion of calls (244/288) related to the ingestion of methylated spirits. Calls relating to methylated

[1] http://www.stuff.co.nz/national/3578972/Meths-drinking-on-the-increase
[2] http://www.poisons.co.nz/index.php Accessed 23 January 2014

spirits contact with the eyes and skin as well as inhalation were received for people in all age groups.

Of the 123 incidents involving children under four years of age, 119 were due to exploratory play and 4 due to unintentional exposures. Of the 39 incidents involving teenagers, the reason for exposure was abuse for 13 incidents, intentional harm for 5 incidents and unknown or unintentional for the remainder. A similar pattern was observed in the 91 adult ingestion related calls, with the reason for ingestion as abuse for 32 calls and intentional harm for 13 calls.

Figure 1: Methylated spirits incidents causing Poison Centre calls for different non-workplace exposure routes mid-2008 to end of 2012.



The use of methylated spirits for intentional self-harm has also been noted overseas (Hieda et al 2005; Jones 2011; Sanap and Chapman 2003), but this manner of injury is outside the scope of the current assessment.

The calls to the Poisons Centre provide evidence that different exposure pathways are occurring in the domestic setting. However, the number of calls due to different exposure pathways is likely to be biased by the perception of risk posed by the pathway and the age groups involved.

Hospital admissions data indicates for the period 2006 to 2012 there have been 73 inpatient and day patient hospital events associated with methylated spirits. The number of recorded events per year ranged from 6 to 18.

A closer examination of the 2012 data showed the 9 hospital event cases were all in the 15–54 age range and 7 of the cases were associated with burns.

No fatalities with methylated spirits recorded as the underlying cause of death were reported in New Zealand in the period 2006 to 2010.

The hospital data described above do not capture treatment at Hospital Emergency Departments unless the patient is admitted to the hospital. It is also likely that intoxication from methylated spirits is recorded more generically as intoxication or

alcohol intoxication (M Ardagh Professor of Emergency Medicine, University of Otago, Christchurch, personal communication, 29 August 2014).

From the experiences of Christchurch Emergency Department, methylated spirits consumption is still a reason for presentation to the department. Unpublished data, collected during a recent study of the effects of alcohol in the emergency department during the equivalent of 14 days (Stewart et al 2014), included two individuals who were admitted on multiple occasions due to intentional methylated spirits consumption.

The 2007/08 New Zealand Alcohol and Drug Use Survey (Ministry of Health 2010) asked participants if they had ever tried solvents (e.g. aerosols, glue, petrol, butane, paint thinners, paint, methylated spirits) for recreational purposes. Overall, 1% (0.7–1.3) of adults 16–64 years had used solvents at some point in their life. The age of first use of solvents was 14 years or younger for 41.8% (95%CI: 27.2–56.4) and 15–17 years old for 51.8% (95%CI: 35.7–67.6) of those who had ever used solvents.

The prevalence of solvent recreational consumption was 0.1% (0.0–0.2), equating to about 2800 people in New Zealand. However this survey does not isolate methylated spirit consumers, the questions group all solvents together. Due to the survey protocol it is unlikely to have included people from one of the groups likely to be at higher risk for methylated spirits consumption; people with no fixed address.

The Christchurch City Mission Alcohol and Other Drug Service (J Spence, personal communication, 25 August 2014) reported their clients who use methylated spirits are generally chronic alcoholic dependent people. Some people use methylated spirits because it is cheap, although for a few it is the substance of choice regardless of cost. They have no records of young people regularly using methylated spirits, their youngest client using methylated spirits being 30 years old. This pattern was confirmed by the Auckland City Mission.

2.9.2 Pacific Islands

The Healthy Behaviour and Lifestyle of Pacific Youth Study surveyed random samples of school students aged 11–17 years, from Pohnpei State in Federated States of Micronesia, Tonga and Vanuatu (Smith et al 2007). The number of 15 year old boys and girls who had tried methylated spirits at least once is given in Table 4.

Table 4: Estimated prevalence (%) of 15 year old students from three Pacific Islands who had ever used methylated spirits.

	Tonga		Vanuatu		Pohnpei	
	Total	Yes (%) (95% CI)	Total	Yes (%) (95% CI)	Total	Yes (%) (95% CI)
Boys	292	20 (16–24)	455	5 (4–7)	136	5 (2–8)
Girls	342	2 (<1–3)	428	4 (2–5)	174	9 (6–12)

2.9.3 Other countries

In a study during 1986 of blood samples taken from drunk drivers, 77 samples out of 21,153, were found to contain unexpected volatile agents as well as ethanol. These volatile agents matched ingredients found in methylated spirits on sale in Sweden (Jones et al 1989).

2.10 Summary

Methylated spirits is mainly ethanol diluted with water plus denaturing ingredients at very low concentrations. Limited information was found on the health effects of the commercially available products or mixtures of these ingredients.

The body may be systemically exposed to the ingredients of methylated spirits, due to absorption into the blood stream, either through the gastro-intestinal tract, skin or lungs.

The main ingredient, ethanol, has the ability to cause dose-dependent, short and long-term systemic health effects, including central nervous system symptoms, damage to organs and cancer. At high acute doses, death can result from repression of the respiratory system.

Ethanol and MIBK have been shown to cause central nervous system symptoms or irritation of the respiratory system when inhaled at higher concentrations than would be expected from domestic use of methylated spirits.

Dermal exposure to methylated spirits is unlikely to cause skin irritation or sensitisation. However, methyl violet, fluorescein and MIBK have been observed to cause adverse dermal effects at much higher concentrations than used in methylated spirits formulations, and some limited data indicate a potential mutagenicity concern about methyl violet.

Methylated spirits is a severe irritant to the eye and may cause necrosis of the surface of the cornea due to the high ethanol concentration.

The population groups most at risk from methylated spirits exposure are those who are most susceptible to ethanol exposure or those who are alcohol dependent. Susceptibility to ethanol is via reduced ability to metabolise ethanol and its metabolites (young, elderly, Asian ethnic groups) or groups with less body fluids (young, elderly and women). The young are also an at risk group as they are unaware of the dangers of the liquid.

At risk groups for the ingredients other than ethanol have not been identified from the literature.

Poisons Centre information suggests incidental exposures to methylated spirits of concern to the public are happening on a regular basis in the country, with 61–81 enquiries a year. Approximately a quarter of calls are for under-four year olds

resulting from exploratory activities. For all age groups, most of the calls relate to ingestion of methylated spirits, with a small proportion regarding eye, skin and inhalation exposures.

Hospital admittance records are unlikely to identify the alcohol type causing the intoxication of patients and cannot be used to establish the rate of hospitalisation due to methylated spirits from non-burn injuries.

3 DOSE-RESPONSE

3.1 Introduction

This section provides dose-related information for methylated spirits for the formulations given in Table 1 and summarised in Table 5 below and for the individual ingredients in methylated spirits when available.

Table 5: Concentration (%w/w) of ingredients found in methylated spirit products in New Zealand

Ingredient	Formulation A	Formulation B	Formulation C
Ethanol	94-99 (95-99 %v/v)	94 (> 95 %v/v)	65 (70 %v/v)
Water	< 5	< 6	< 35
MIBK		0.25	0.25
Denatonium benzoate	0.002	0.001	0.001
Methyl Violet	0.0001	0.0001	
Fluorescein		0.0001	0.0001

When available, human and case study data will be provided in this section. When this is unavailable, information from animal studies is given.

3.2 Methylated Spirits Components

3.2.1 Ethanol

For a person who is not alcohol dependent, Table 6 provides an estimate of the lower limit of the single dose of ingested methylated spirits that would result in the defined peak blood alcohol levels and associated symptoms/risks. Calculations for Table 6 estimated the dose of methylated spirits assuming that all the ethanol from the methylated spirits was absorbed by the body and no metabolism or elimination took place before the peak blood alcohol level was reached.

The formulas for the conversion between the peak blood alcohol concentration, the amount of ethanol ingested and the corresponding dose of methylated spirits are given by Wells et al (2005) and Donovan (2009). The methylated spirits dose response depends on total body water of the person which depends on age and sex.

Table 6: Blood alcohol concentrations and associated effects from oral consumption of methylated spirits at 99% and 70% ethanol levels for different population groups

BAC[a] mg/dL	Methylated Spirits Dose (ml)[b] : 99% ethanol (70% ethanol)					Symptoms and risks
	3 year old	14 year old girl	14 year old boy	Adult female	Adult male	
<50–150	7–21 (10–29)	23–69 (32–97)	29–86 (29–121)	26–79 (37–111)	39–109 (51–154)	Impairment in concentration, judgement and motor coordination leading an increased risk of injury
150–250	21–35 (29–49)	69–115 (97–162)	86–143 (121–202)	79–131 (111–186)	109–181 (154–256)	Slurred speech Unsteady walking Nausea Double vision Increased heart rate Drowsiness Mood, personality and behaviour changes
300	42 (53)	138 (175)	172 (218)	158 (200)	217 (275)	Speech incoherent/confused Memory Loss Vomiting (risk of aspiration) Heavy breathing Unresponsive/extremely drowsy
>400	> 55 (> 78)	> 184 (> 260)	> 229 (> 324)	> 210 (> 297)	> 290 (> 410)	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)

Those people who regularly drink alcohol or ethanol containing substances can develop a central nervous system tolerance which means they may only be slightly impaired at blood alcohol levels of 200–300 mg/dL (Jones and Holmgren 2003).

Rosewarne (1986) provides a description of a 38 year old male with a past history of multiple admissions to hospital for alcohol abuse who was unconscious at admittance at hospital after drinking 750 ml of methylated spirits containing 95% ethanol. The blood ethanol level was 107 mmol/L (493 mg/dL), above the level

known to have caused death. The patient was placed in the intensive care unit overnight and was well enough to be sent to the wards the following day.

A meta-analysis of alcohol consumption (Corrao et al 2004) has shown the risk of oral cavity-pharynx, oesophageal, laryngeal, colon, rectal, liver and breast cancer as well as stroke, essential hypertension and liver cirrhosis increases with regular consumption of alcohol. Increasing dose of alcohol consumption was associated with increasing risk of these conditions (Table 7). Therefore chronic consumption of methylated spirits would be associated with a high risk of these conditions.

Table 7: Relative risk of cancer and non-cancer conditions at different chronic intakes of alcohol and the equivalent dose of methylated spirits (Corrao et al 2004).

Condition	No. of cases	Relative risk (95% CI) for selected alcohol intake [equivalent ml of 99% ethanol methylated spirits]		
		25 g/day [31 ml/day]	50 g/day [63 ml/day]	100 g/day [125 ml/day]
Cancer (cancer site)				
Oral cavity and pharynx	4507	1.86 (1.76–1.96)	3.11 (2.85–3.39)	6.45 (5.76–7.24)
Larynx	3789	1.43 (1.38–1.48)	2.02 (1.89–2.16)	3.86 (3.42–4.35)
Esophagus	3233	1.39 (1.36–1.42)	1.93 (1.85–2.00)	3.59 (3.34–3.87)
Breast	32,175	1.25 (1.20–1.29)	1.55 (1.44–1.67)	2.41 (2.07–2.80)
Liver	1321	1.19 (1.12–1.27)	1.40 (1.25–1.56)	1.81 (1.50–2.19)
Rectum	1420	1.09 (1.08–1.12)	1.19 (1.14–1.24)	1.42 (1.30–1.55)
Colon	5360	1.05 (1.01–1.09)	1.10 (1.03–1.18)	1.21 (1.05–1.39)
Non-cancer conditions				
Liver cirrhosis	2202	2.90 (2.71–3.09)	7.13 (6.35–8.00)	26.5 (22.3–31.6)
Hemorrhagic stroke	1192	1.19 (0.97–1.49)	1.82 (1.46–2.28)	4.70 (3.35–6.59)
Ischemic stroke	893	0.90 (0.75–1.07)	1.17 (0.97–1.44)	4.37 (2.28–8.37)
Essential hypertension	5801	1.43 (1.33–1.53)	2.04 (1.77–2.35)	4.15 (3.13–5.52)
Chronic pancreatitis	247	1.34 (1.16–1.54)	1.78 (1.34–2.36)	3.19 (1.82–5.59)

3.2.2 Non-ethanol ingredients

Table 8 provides a list of the lowest observable effect or no effect doses for the ingredients in methylated spirits other than ethanol. Insufficient data were available to create a human dose response profile for these ingredients.

Column 4 provides the equivalent dose of methylated spirits that would need to be ingested to result in adverse effects from the individual ingredients. The MIBK, denatonium benzoate and methyl violet doses listed as causing an effect, would require large volumes of methylated spirits to be ingested to reach the same dose. The disproportionally lower concentrations of the non-ethanol ingredients mean that the estimated consumption volumes of methylated spirits are much larger than could be consumed before the ethanol dose would result in significant toxicity.

No dose-response data could be located for fluorescein at low concentrations, but adverse reactions have been noted for medical diagnostic doses at concentrations equivalent to drinking 70+ litres of methylated spirits.

Table 8: Lowest recorded oral doses associated with toxicological effects for individual non-ethanol ingredients in methylated spirits.

Ingredient	Dose and effects	Study type	Equivalent dose of methylated spirits	Reference
MIBK	50 mg/kg bw/day (13 weeks) No observed effects 1040 mg/kg bw/day (17 weeks) Increased kidney weights.	Rat (oral)	0.025 L/kg bw/day 0.52 L/kg bw/day	(US EPA 2003)
Denatonium benzoate	16 mg/kg bw/day (2 years) No observed effects	Rat (oral)	1 L/kg bw/day	(Cosmetic Ingredient Review Expert 2008)
Methyl violet	2.5 mg/kg bw/day (20 days) Changes to maternal weight gain. Clinical signs of toxicity increasing with increasing dose.	Rat (oral)	2.5 L/kg bw/day	(Diamante et al 2009)
Fluorescein	No data on dose-response or long-term effects			

Table 9 provides a list of the lowest located concentration for inhalation responses for all ingredients in methylated spirits. Insufficient data were available to create a human dose-response profile for methylated spirits or its ingredients.

Table 9: Inhalation concentration response information for methylated spirits ingredients.

Ingredient	Concentration and effects	Study type	Reference
Ethanol	12 mg/L (6 hours/day, 5 day/week, 4 weeks) No clinical signs of toxicity or gross pathological or tissue related changes of the major organs were observed. 6 mg/L is reported as irritating in humans 17 mg/L at 30°C with no acclimatisation was intolerable.	Rat Human Human	(NICNAS 2013a) (Mason and Blackmore 1972)
MIBK	$NOAEL_{HEC}$[a] : 0.073–0.409 mg/L 6 hours/day, 5 day/week, 2–4 weeks 0.01 mg/L for two hours with light physical exercise 3 out of 8 men reported nose and throat irritation. 0.03–0.1 mg/L for 1 minute Threshold for irritation of lungs 2 mg/L for 30 minutes daily Workers experienced weakness, headache, nausea and sore throats. Enlarged liver and colitis in some workers.	Rat Human Human Human	(US EPA 2003) (Johnson 2004)
Denatonium benzoate	0.06 mg/L for 4 hours (water solution aerosol) No observed effects 0.13 mg/L for 4 hours (dust) Respiratory and circulatory changes, changes to fur and posture.	Rat	(European Food Safety Authority 2008)
Methyl violet	Unknown		
Fluorescein	Unknown		

a: $NOAEL_{HEC}$ is NOAEL dosimetrically adjusted for difference between humans and animals in absorptivity of MIBK in blood.

3.3 Estimated Toxicity of Methylated Spirits

3.3.1 Acute

There are minimal data for acute exposure from methylated spirits. An acute toxicity estimate (ATE) can be constructed from the acute toxicity data available for the ingredients. The methodology given in the United Nations guidelines for classifying health hazards of mixtures (United Nations 2009) will be followed for the ingredients in methylated spirits.

The composition of the methylated spirit formulations given as concentrations (% w/w) in Table 5 show that only ethanol and water have concentrations above 1%. Water is not considered to be acutely toxic and will not be considered further in this section. The other ingredients do not have to be considered in the calculation of an acute toxicity estimate unless they are shown to be toxic at very low concentrations.

Table 10 provides animal study acute toxicity data for different transfer mechanisms for methylated spirits ingredients. The table reports the lowest estimates of LD_{50} or LC_{50}[1] for the studies relating to rats and rabbits, the preferred test species for evaluation of acute toxicity.

Mixture acute toxicity is calculated according to formula (1) and the results are given in Table 11.

$$\frac{100}{ATE_{mix}} = \sum_{i=1}^{n} \frac{C_i}{ATE_i} \quad (1)$$

The mixture is made up of *n* components with concentrations (expressed as percentages) equal to C_i and acute toxicity estimates ATE_i. ATE_{mix} is the acute toxicity estimate for the mixture. The approach uses dose additivity without consideration of organ systems affected or the mechanism of toxicity.

[1] LD_{50} / LC_{50} are doses or concentrations that are lethal to 50% of test animals.

Table 10: Lowest median animal lethal acute doses for oral, dermal and inhalation exposures to ingredients of methylated spirits found in the literature.

Ingredient	Oral LD_{50} (g/kg bw)	Dermal LD_{50} (g/kg bw)	Vapour LC_{50} (mg/L)
Ethanol	7 [Rat][a]	> 2.0 [Rabbit][aa]	124.7 for 4 hours [Rat][aa]
MIBK	> 1.9 [Rat][b]	> 16 [Rabbit][b]	3.7 for 4 hours [Animal][b]
Denatonium benzoate	0.29 [Rat][c]	> 2.0 [Rat][c]	0.14 for 4 hours [Rat][c]
Methyl Violet	0.42 [Adult Rat][d] 0.09 [Young Rat][e]	unknown	unknown
Fluorescein	6.7 [Rat][f]	unknown	unknown

a: Canadian Centre for Occupational Health and Safety, Registry of toxic effects of chemical substances[1]
aa: (NICNAS 2013a), b: OECD SIDS initial assessment report, 2009[2],
c: EU Draft Assessment Report for Denatonium Benzoate, 2008[3],
d: (Lewis 2004) , e: (Diamante et al 2009), f: (Alford et al 2009)

Table 11: Estimated human acute toxicity LD/C_{50} estimates for methylated spirits based on animal studies.

Formulation	Oral LD_{50} (g/kg bw)	Dermal LD_{50} (g/kg bw)	Vapour LC_{50} (mg/L)
A	> 7.0–7.4	> 2.0–2.1	124–131
B	> 7.4	> 2.1	121
C	> 10.6	> 3	168

Death in non-alcohol dependent humans has been noted in children at acute alcohol doses of 3 g/kg bw[4] and 5–8 g/kg bw[5] in adults (Lohr 2005).

The probable oral lethal dose for humans ingesting methyl violet has been estimated at 50–500 mg/kg bw[6].

[1] http://www.ccohs.ca/products/databases/samples/rtecs.html accessed 26th August 2014
[2] http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=42e15215-0b5d-4123-94c4-bae1556212f4. Accessed 14 August 2014.
[3] http://dar.efsa.europa.eu/dar-web/provision - Requested 14 August 2014
[4] 3 g alcohol is 4 ml of 99% ethanol methylated spirits or 5ml of 70% ethanol methylated spirits.
[5] 5–8g alcohol is 6–10 ml 99% ethanol methylated spirits or 9–14 ml of 70% ethanol methylated spirits.
[6] http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+4366 accessed 8th September 2014.

3.3.2 Chronic

For non-cancer endpoints, the individual components of methylated spirits that share common toxicological effects are ethanol and MIBK. However, due to the very low concentration of MIBK, the CNS effects of methylated spirits are dominated by the systemic doses of ethanol achieved. The remaining components are below 1% and, as assessed under the UN GHS system, contribute negligibly to overall non-cancer toxicity of the mixture.

For cancer risk assessment considerations, ethanol is considered a carcinogen in the context of chronic ingestion of alcoholic beverages (IARC 2012). However, as this is not a relevant exposure scenario for this risk assessment, episodic exposures to methylated spirits by any route would not be expected to contribute meaningfully to cancer risk.

The trace amount of methyl violet, which has been reported to result in some positive carcinogenicity findings, is at a concentration below UN GHS cut off levels for carcinogenicity classifications of mixtures. Therefore, methylated spirits, under expected use patterns (excluding solvent abuse), is not considered to present a carcinogenicity risk.

4 EXPOSURE ASSESSMENT

4.1 Exposure scenarios for methylated spirits in New Zealand

This section will consider specific exposure scenarios that could realistically occur in New Zealand and provide estimates of the range of doses for each scenario:

- incidental exposure to 2–3 year olds
- incidental exposure due to household cleaning.

4.2 Incidental exposure by young children

Infants and young children (0–3 year olds) account for 40% of calls to the New Zealand Poisons Centre relating to methylated spirits. Data from the American Association of Poison Control Centres indicated that 75–80% of single substance exposure cases due to ethanol-based household cleaners was associated with the 5 years and under age group (Bronstein et al 2011; Bronstein et al 2012). A recent review of the literature relating to ingestion of ethanol via household products in the US shows the under five year olds remain at the highest risk for exposures (Rayar and Ratnapalan 2013).

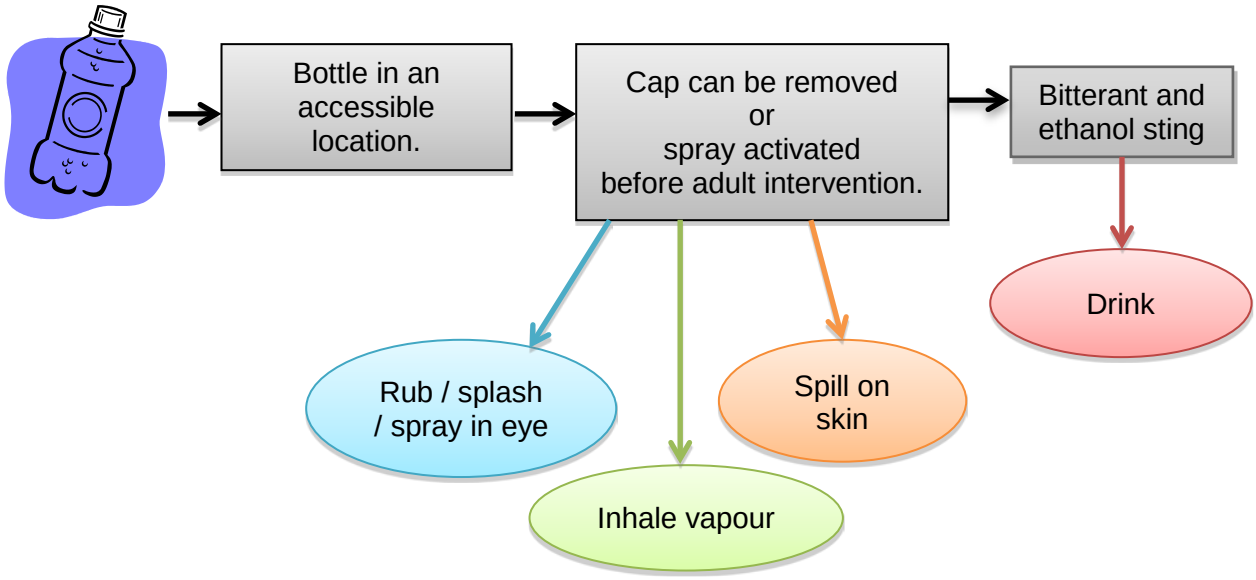
Given that methylated spirits is a common household product in New Zealand, it is a realistic scenario that children aged 2–3 years may have occasional access to methylated spirits. In the following scenarios the age group 2–<3 years will be considered. The 5th and 50th percentile body weights for this age group are 10.9 kg and 13.6 kg (US EPA 2011).

This scenario will consider a child having access to a bottle of methylated spirits and being able to access the liquid inside. Figure 2 illustrates the components of the exposure including the current hurdles to being exposed to the liquid.

A number of hurdles must be overcome before a child can access the liquid; the location of bottle and the ability to undo a child safety cap (if present) before being observed by someone who will intervene.

Removal of the cap could result in four types of exposure; oral ingestion, inhalation, and contact with the skin or possibly eyes given the motor coordination of the age group. A spray bottle would increase the risk of contact with the eye or inhalation, if the spray mechanism was operated.

Figure 2: Child exposure pathways from incidental exposure



4.2.1 Child - Ocular exposure

This section will consider the contact of methylated spirits with the eye either through accidental splashing of the eye (99 %v/v ethanol) or through spraying the face using the pump spray bottle (70 %v/v ethanol). If the spray bottle was sprayed directly into the face, a proportion of the spray could be expected to enter the eyes. Due to the high ethanol concentration, contact with the eye will cause immediate discomfort (NICNAS 2013a), reducing the possibility of a second or subsequent spray.

Accidental splashing of the eyes during attempting to drink the liquid could range anything from a single drop (~0.1 ml) to much larger quantities. Experiments conducted for this report using the spray bottle used for Formulation C of methylated spirits, found a single pump of the bottle resulted in 0.5–0.6 gm (0.6–0.7 ml) of liquid being expelled.

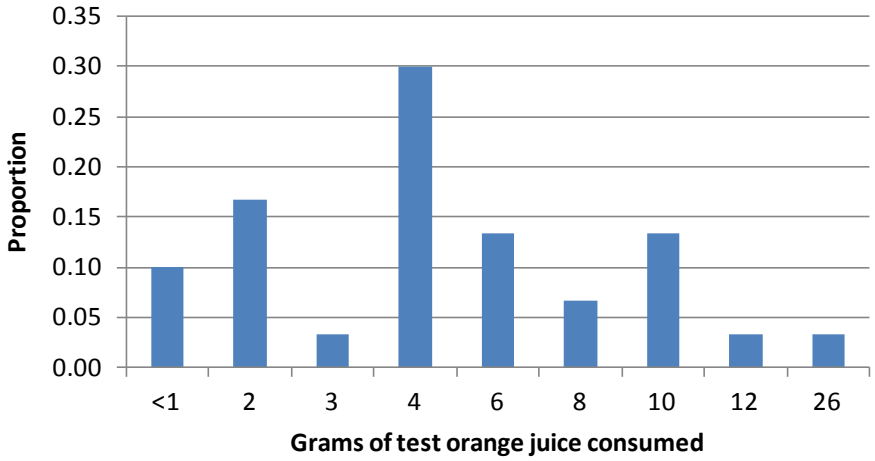
Therefore, the amount of methylated spirits expected to contact the eye would be in the range <0.1 to 0.7 ml.

4.2.2 Child - Oral exposure

Methylated spirits contains a high concentration of ethanol and a bitterant denatonium benzoate, both of which are likely to reduce the amount of liquid consumed by a child. In an experiment using denatonium benzoate (10 ppm) in orange juice, 30 children aged 17–36 months were observed while drinking the juice (Sibert and Frude 1991). The weight of orange juice consumed by the children is given in Figure 3. Most children, 80%, had 8 or less grams of orange juice. One child had 26 grams of juice and showed no response to the bitterant being present, suggesting at 10 ppm, denatonium may not deter all young children.

In another study using 11.4 ppm of denatonium benzoate in a soapy solution, children aged 18–47 months reduced the amount of liquid they consumed (Berning et al 1982). Only 2–3 grams of liquid was consumed compared to 7–12 grams of the control soapy liquid. No children took more than two sips of the liquid and all those that reacted, reacted within 5 seconds. This supports the contention that the presence of denatonium benzoate deters consumption to below the dose required to elicit acute toxicity.

Figure 3: Proportion of children drinking different amounts of orange juice with denatonium benzoate additive (Sibert and Frude 1991).



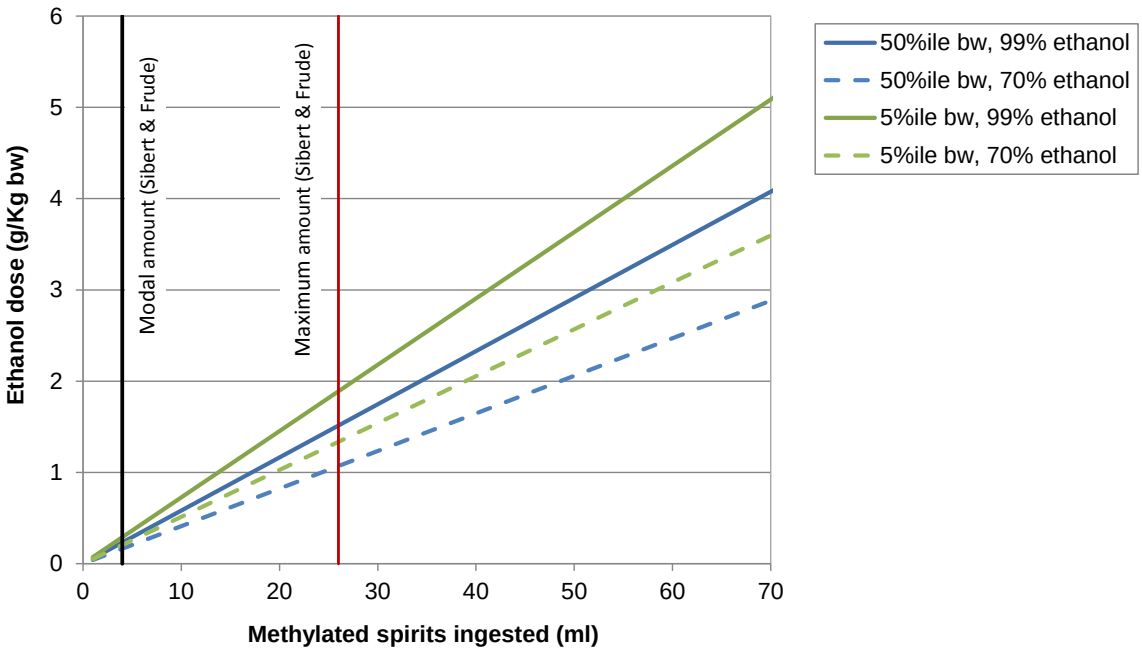
Using the range of consumption amounts of a solution of 10 ppm denatonium benzoate in orange juice, the methylated spirits dose and associated ethanol and MIBK doses are given in Table 12.

Table 12: Child (2 - <3 year old) estimated exposures from ingested methylated spirits.

		Most likely dose: 4ml (mg/kg bw)		**Maximum dose: 26ml** (mg/kg bw)	
Body weight		5th percentile [10.9 kg]	50th percentile [13.6 kg]	5th percentile [10.9 kg]	50th percentile [13.6 kg]
Methylated spirits	70% v/v	320	260	2100	1700
	99% v/v	290	240	1900	1500
Ethanol	70% v/v	210	160	1300	1100
	99% v/v	290	230	1900	1500
MIBK		0.73	0.59	4.8	3.8

Figure 4 shows the body weight averaged dose of ethanol that would result from a child ingesting methylated spirits of different amounts.

Figure 4: Ethanol dose for different child weights and methylated spirits formulations



4.2.3 Child - Dermal exposure

This section considers the scenario of the child spilling the bottle of methylated spirits over themselves, from either knocking over the bottle or spilling the liquid while attempting to drink from a bottle.

Table 13 summarises the parameters and exposure estimates for the child spilling methylated spirits on themselves. Ethanol and MIBK will be considered in this exposure scenario. Denatonium benzoate is not considered a systemic exposure risk from dermal transfer (Cosmetic Ingredient Review Expert 2008) and data could not be located on dermal transmission of methyl violet or fluorescein. As dermal transfer is proportional to concentration, neither of these ingredients is expected to contribute to an adverse health outcome for this acute exposure scenario.

The dermal contact time has been set to 15 minutes, to reflect an unsupervised child. Methylated spirits will rapidly evaporate from the skin and other surfaces but this factor has not been included in calculations.

Table 13: Dermal absorption exposure estimate for an child (2 to <3 year old) spilling methylated spirits

Parameters:				
Absorption Flux for undiluted liquids; ethanol[a] MIBK[b]	F_{absorp}	 0.25 mg/cm^2/hour 6.6 mg/cm^2/hour		
Time available for absorption	T_{max}	15 minutes		
Concentration in methylated spirits; ethanol MIBK	C	 560–800 mg/cm^3 2 mg/cm^3		
Proportion of child's surface area exposed	P_{BS}	Half		
Thickness of film layer on skin	L_{film}	0.1 cm (simulating soaked clothing)		
		5th percentile	**50th percentile**	**95th percentile**
Total body surface area[c]	$AREA_{BS}$	5200 cm^2	6100 cm^2	7000 cm^2
Body weight[c]	BW	10.9 kg	13.6 kg	17.1 kg
Surface area of skin exposed $AREA_{derm} = AREA_{BS} \times P_{BS}$	$AREA_{derm}$	2600 cm^2	3050 cm^2	3500 cm^2
Estimated Dermal Uptake based on flux rates: $U_{flux} = F_{absorp} \times T_{max} \times AREA_{derm}$				
Ethanol		160 mg	190 mg	220 mg
MIBK		4340 mg	5090 mg	5850 mg
External exposure to the skin: $U_{ext} = AREA_{derm} \times L_{film} \times C$				
Ethanol (70–99% v/v)		145–208 g	171–244 g	196–280 g
MIBK		520 mg	610 mg	700 mg
Estimated maximum systemic exposure due to dermal uptake: (Lower value of U_{flux} and U_{ext}) / BW				
Ethanol		15 mg/kg bw	14 mg/kg bw	13 mg/kg bw
MIBK		48 mg/kg bw	45 mg/kg bw	41 mg/kg bw

a: (Pendlington et al 2001), b: (Johnson 2004), c: (US EPA 2011)

MIBK and ethanol may be absorbed through the skin and into the blood stream. The systemic exposure values calculated in Table 12 will be maximum estimates for the following reasons:

- flux rates are from studies using undiluted liquids, and the flux is proportional to the concentration of the ingredient
- not all the MIBK will be absorbed into the skin
- the calculations do not include metabolism of ethanol and MIBK, both of which are readily metabolised in the body.

However, due to the immature skin structure, dermal transfer could be greater in infants and young children than adults. This will also be the case if the skin is damaged (Lachenmeier 2008).

4.2.4 Child – Inhalation exposure

If a child spills methylated spirits from the bottle, the liquid would evaporate from warm surfaces and vapours could be inhaled by the child. Inhalation studies in adults have failed to show transfer of ethanol to the blood stream (Campbell and Wilson 1986; Mason and Blackmore 1972) and there are no child case studies to suggest the child would transfer ethanol to the blood stream after breathing for a short time (15 minutes) the vapours from the spilled methylated spirits.

The other ingredients of methylated spirits which are already in small concentrations would be further diluted in an inhaled vapour. Therefore it is assumed inhalation of vapours does not provide an exposure route for methylated spirits to enter the blood stream.

4.3 Exposure during household cleaning.

Methylated spirits is a common household cleaning product. For this scenario there are three possible exposure pathways:

- splash in the eye
- dermal absorption through the hands from methylated spirits soaked cloths
- inhalation of vapour in an enclosed room.

Two age groups will be considered, adults and a child who may be assisting the adult. A 3–5 year old child (50 percentile bw: 17.8 kg) will be chosen to provide a worse-case scenario in terms of exposure per kg body weight.

For cleaning, the pump bottle with 70% v/v ethanol methylated spirits may be used to disinfect surfaces. A manufacturer recommends a solution of 1 part methylated spirits to 5 parts water for cleaning glass and 1 part methylated spirits to 64 parts water for cleaning floors.

4.3.1 Ocular

The amount of methylated spirits expected to contact the eye would be <0.1 to 0.7 ml, which reflects the range of a single drop in the eye to accidentally spraying directly into the eye.

4.3.2 Dermal

There is insufficient data to estimate a dermal exposure to methylated spirits, so the exposure assessment for household cleaning will consider the exposure to the ingredients of methylated spirits.

For systemic exposure from dermal absorption, two cleaning scenarios will be considered:

1. shorter duration exposure to a product with a higher ethanol concentration (70% v/v) mimicking cleaning and disinfecting surfaces and sinks
2. longer duration cleaning of windows with diluted methylated spirits (16.6% solution).

Table 15 summarises the model parameters and exposure estimates for the two cleaning scenarios. The most likely estimate is given by an adult with 50th percentile weight and the worse-case estimate is for a 3–5 year old, assisting the adult.

The dermal transfer of ethanol is limited by the absorption rate across the skin barrier, while the MIBK transfer is potentially limited by the concentration of MIBK in methylated spirits. No data were found on transfer rates for methyl violet or fluorescein, so for the non-ethanol ingredients, the exposure was calculated assuming 100% absorption, with new methylated spirit liquid reapplied to the hands every two minutes.

This approach will provide an upper bound of the maximum blood concentration of the methylated spirits ingredients, as products will be metabolised over the duration of cleaning and 100% of the ingredients will not be absorbed by the skin.

According to the US Exposure Factors Handbook (US EPA 2011) the 50th to 95th percentile of frequency of cleaning the inside of windows is 4–52 times a year, and 2–12 times a year for cleaning the outside of windows. The 50th to 95th percentile frequency of wiping off kitchen counters is 1–6 times a day, and thoroughly cleaning counters is 4–30 times a month.

Table 14: Exposure model for methylated spirits used for household cleaning

Parameters:			
Absorption Flux for undiluted liquids; ethanol[a] MIBK[b]	F_{absorp}	 0.25 mg/cm^2/hour 6.6 mg/cm^2/hour	
Time available for absorption[c]; surface cleaning window cleaning	T_{max}	 0.5–2 hours 3.5–7 hours	
Concentration in methylated spirits; ethanol MIBK methyl violet fluorescein Dilution of 95% v/v methylated spirits for window cleaning	C	 560 mg/cm^3 2 mg/cm^3 0.001 mg/cm^3 0.001 mg/cm^3 1:5	
Thickness of film layer on skin	L_{film}	0.1 cm (simulating holding a soaked cloth)	
		Adult 50thpercentile	**Child (3-5) 50th percentile**
Half surface area of hand[c]	$AREA_{derm}$	250 cm^2	93 cm^2
Body weight[c]	BW	80 kg	17.8 kg
Estimated Dermal Ethanol Dose based on flux rates: $D_{flux} = \frac{F_{absorp} \times T_{max} \times AREA_{derm}}{BW}$ **External exposure to the skin – refreshed every 2 minutes (Non-ethanol):** $D_{ext} = \frac{AREA_{derm} \times L_{film} \times C \times T_{max} \times 60/2}{BW}$			
Estimated maximum systemic exposure due to dermal uptake from surface cleaning:[d]			
Ethanol	mg/kg bw	0.4–1.6	0.7–2.6
MIBK	mg/kg bw	10–37	17–63
Fluorescein	mg/kg bw	0.005–0.02	0.008–0.03
Estimated maximum systemic exposure due to dermal uptake from window cleaning:[d]			
Ethanol	mg/kg bw	2.7–5.5	4.6–9.1
MIBK	mg/kg bw	10.9–22	18–37
Fluorescein	mg/kg bw	0.005–0.011	0.009–0.018
Methyl Violet	mg/kg bw	0.005–0.011	0.009–0.018

a: (Pendlington et al 2001), b: (Johnson 2004), c: (US EPA 2011),
d: Minimum of D_{flux} and $_{Dext}$

4.3.3 Inhalation

An experiment in a 27 m^3 enclosed room at 30°C, where ethanol was allowed to evaporate from a 2322 cm^2 tray resulted in an estimated end concentration of ethanol in the air of 17 mg/L (~14,000 ppm) after 2½ hours. None of the test subjects in the room experienced any symptoms of intoxication, nor was ethanol found in the blood or urine (limit of detection 5 mg ethanol in 100 ml). However, the conditions in the room were intolerable to anyone entering the room who were not acclimatised to the vapour (Mason and Blackmore 1972).

The vapour from domestic cleaning or maintenance is unlikely to exceed the concentration achieved in this study, given the room temperature, size and minimal ventilation. Therefore the exposure estimate for blood alcohol after an exposure would be expected to be below 5 mg/dL.

4.4 Other exposure pathways

4.4.1 Camp stove fuel

One of the domestic uses of methylated spirits is to fuel camp stoves. This poses two exposure routes not assessed in this report; the risk from combustion of the fuel resulting in toxic fumes (Guillaume et al 2013) and the risk of burns from refuelling, loose clothing, hair or knocking over the stove. If the stoves are used as recommended by the manufacturer, in well ventilated places and the equipment is allowed to cool before refilling these risks can be minimised.

4.4.2 Habitual drinkers

Some alcohol dependant people may drink methylated spirits by choice, due to its high ethanol content. Damage to the heart, liver, pancreas, brain and risk of cancer, increases with increasing chronic dose of ethanol (Corrao et al 2004). This, combined with a reduced immune system, will result in a high risk of health effects for this group. For example a person drinking 100 g ethanol (125 ml of methylated spirits) a day is 27 times more likely to develop liver cirrhosis than non-alcohol drinkers and 9 times more likely than someone drinking 25 g ethanol (2½ standard drinks) a day.

5 RISK CHARACTERISATION

5.1 Acute systemic exposure

Risk associated with acute exposure scenarios to methylated spirits are assessed based on ethanol. The concentration of the other ingredients are below the 1% threshold suggested by the United Nations Guidelines for classifying health hazards (United Nations 2009) and information given in the dose response section does not support including them in the acute systemic exposure characterisation.

The acute single-exposure scenarios given in Table 16 explore two different scenarios, exploratory play by children (2 to <3 year old) and household cleaning by adults and young children assisting them.

Health risk has been assessed by comparison of the estimated systemic exposure to ethanol converted to blood alcohol concentration and compared to information provided by New Zealand Health Protection Agency (2014 : Table 1).

Table 15: Summary of acute systemic exposure scenarios for methylated spirits (99% ethanol) and the associated health effects from the ethanol component

Exposure scenario	Estimated exposure to methylated spirits	Estimated systemic exposure to ethanol[a]	Estimated health effects from ethanol component[b]
Child (2-<3 year old) – Exploratory play			
Oral	4 ml (Bitterant restricts drinking) 26 ml (99% v/v ethanol)	0.23 – 0.29 g/kg bw 1.5 – 1.9 g/kg bw	Unlikely to cause toxicity Changes to vision, mobility, speech and mood. Drowsiness.
Dermal	260–350 ml on skin	0.014 – 0.015 g/kg bw	Unlikely to cause toxicity
Inhalation	No evidence that inhalation will contribute to systemic exposure		
Adults – Household cleaning / maintenance			
Dermal	25 ml on hands at any given time	0.0004 – 0.006 g/kg bw	Unlikely to cause toxicity
Inhalation	No evidence that inhalation will contribute to systemic exposure		
Child (3 – 5 year old) assisting with household cleaning			
Dermal	9 ml on hands at any given time	0.0007 – 0.009 g/kg bw	Unlikely to cause toxicity
Inhalation	No evidence that inhalation will contribute to systemic exposure		

a: Range: 50th percentile body weight – 5th percentile body weight
b: (Health Protection Agency 2014, Table 1)

The combined effect of an infant playing with an open methylated spirits bottle, resulting in drinking and spilling the liquid is unlikely to result in systemic toxicological risk if the denatonium benzoate acts as a deterrent to ingestion. Dermal uptake of ethanol is at a level unlikely to be a toxicological concern, although the dermal transfer rate of babies and children may be higher than exhibited in adults (Lachenmeier 2008).

If the bitterant does not restrict drinking volume, as has been shown in the literature, then methylated spirits can be lethally toxic at small quantities (55 ml for a three year old) due to the ethanol component.

Dermal and inhalation single exposures to methylated spirits through household cleaning and maintenance are unlikely to produce systemic toxic effects.

5.2 Chronic dermal exposures

The ingredients of methylated spirits are readily metabolised and so they are not expected to accumulate in the body.

No chronic health based exposure limits for methylated spirits have been established. Hence, the risks associated with chronic dermal exposure from household cleaning were assessed using a margin of exposure (MoE) approach. The margin of exposure for substance i is calculated from the reference dose or in this case the animal benchmark dose (BMD_i) derived from chronic studies, divided by the estimated human exposure (H_i) (European Food Safety Authority 2005) or for a mixture of substances

$$MoE_{mixture} = \frac{1}{\frac{H_1}{BMD_1} + \frac{H_2}{BMD_2} + \frac{H_3}{BMD_3} + \cdots}$$

The no observable adverse effect level (NOAEL) from daily dose multi-week rat studies has been used as the benchmark dose. Oral dose NOAEL data was available for ethanol, MIBK and methyl violet and these ingredients were used to calculate the margin of exposure for methylated spirits. In order to convert these oral doses to internal doses, oral absorption rates are assumed to be 100% in the absence of established values.

The margin of exposure for the two cleaning scenarios for the mixture of chemicals in methylated spirits is dominated by the possible dermal absorption of MIBK through the skin. The only data on dermal absorption is for an undiluted solution of MIBK, compared to the 0.25–0.04% solutions considered in the cleaning scenarios. The approach used to estimate the absorption of MIBK effectively assumes the entire dermal dose will be absorbed. Given the volatility of MIBK this is highly unlikely and is likely to overestimate the absorption of MIBK into the blood stream and therefore underestimate the margin of exposure for the mixture.

Table 16: Margin of exposure estimates for methylated spirit solutions used during household cleaning scenarios. Interval reflects the expected time range the activity is likely to be undertaken.

	MoE methylated spirits	**MoE ethanol** $NOAEL_{ethanol}$ = 1.28 g/kg bw/day[a]
Surface and sink cleaning using undiluted methylated spirits (C: 70% ethanol)	22-89	819 - 3277
Window cleaning with 16.5% solution of methylated spirits (B: 95 % ethanol) in water.	33-59	234 - 468

a: http://apps.echa.europa.eu

Safety factors of 100-1000 are typically applied to derive health-based exposure limits from toxicological NOAELS. On this basis, MoEs less than 100 may indicate a need for a more detailed risk assessment. Further data on the NOAEL and dermal absorption of the ingredients in methylated spirits would assist in reducing the uncertainty of this assessment.

The margin of exposure for ethanol suggests that household cleaning by adults is unlikely to be associated with chronic dermal toxicological risk from exposure to ethanol.

5.3 Local (concentration-based) effects

5.3.1 Skin effects

Methylated spirits is not expected to be a skin irritant for most people. Human studies have shown any mild irritation is likely to be short term.

5.3.2 Eye effects

Methylated spirits will cause irritation if it comes in contact with the eyes due to the high ethanol content. While there is no cited evidence of long term damage to the human eye, it has been shown to cause lesions lasting over a week in rabbit studies.

6 CONCLUSIONS

Methylated spirits is a common household product, which is composed of 70–99% ethanol and low concentrations of other ingredients which can include water, MIBK, methyl violet and fluorescein. Denatonium benzoate is also added to methylated spirits as a bitterant, which is likely to minimise the risk of consuming volumes of methylated spirits that will cause adverse systemic health effects. The concentration of denatonium benzoate is sufficiently low as to not contribute meaningfully to the overall toxicological hazards of the mixture.

Data from the New Zealand Poisons Call Centre lists 61–81 calls a year relating to methylated spirits, ranking it between the 6th and 12th most common cause of calls a year over the period 2008–2012. The majority of calls, across all age groups, relate to ingestion of methylated spirits. Smaller numbers of calls relate to eye, skin and inhalation exposures. Approximately 40% of calls relate to 0–3 year olds' exploratory playing.

Methylated spirits is not classified as acutely toxic, but ingestion of small quantities can cause serious health effects due to the high ethanol concentration.

Risk assessment of 2–3 year olds drinking and spilling methylated spirits during exploratory play suggests the scenario is unlikely to result in systemic toxicological risk if the denatonium benzoate acts as an effective deterrent to ingestion. There is no evidence supporting a toxicological risk from dermal or inhalation exposures for this scenario.

In the worst case scenario of a 2-3 year old child being undeterred by the bitterant and drinking 20–30 ml of methylated spirits, there are likely to be transient health effects relating to effects on the central nervous system. Coma and death could result from a 2–3 year old drinking 50 ml of methylated spirits.

The use of methylated spirits for household cleaning by adults and children resulting in dermal or inhalation exposure is unlikely to cause a health risk.

Methylated spirits contacting with the eye will cause immediate discomfort and may damage the eye lasting over a week. Symptoms are likely to resolve within two weeks.

Risk assessment of the chronic dermal exposure to methylated spirits during household cleaning by adults, results in a margin of exposure of between 22 and 89 using rat NOAELs as the benchmark dose. Safety factors of 100-1000 are typically applied to derive health-based exposure limits from toxicological NOAELS. On this basis, MoEs less than 100 may indicate a need for a more detailed risk assessment. Further data on the NOAEL of methylated spirit ingredients and the dermal and inhalation transfer rates at low concentrations would assist in reducing the uncertainty of this assessment.

Cancer is not expected to be an endpoint of concern for incidental exposure to this product. However data are limited on: the genotoxicity and carcinogenicity of methyl violet.

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