Science for Communities

HEALTH RISK ASSESSMENT: REED DIFFUSER FLUID

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ACRONYMS AND ABBREVIATIONS

ADI	Acceptable daily intake
ATSDR	Agency for Toxic Substances and Disease Registry
bw	Body weight
CNS	Central nervous system
DEGEE	Diethylene glycol monoethyl ether
DIC	Disseminated intravascular coagulation
DPGBE	Dipropylene glycol *n*-butyl ether
DPGME	Dipropylene glycol monomethyl ether
DPGMEA	Dipropylene glycol methyl ether acetate
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
ED	Emergency department
ESR	Institute of Environmental Science and Research Limited
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GP	General practitioner
HBGV	Health-based guidance value
HERA	Human and Environmental Risk Assessment on ingredients of household cleaning products
HSDIRT	Hazardous Substances Disease and Injury Reporting Tool
ICU	Intensive care unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	Dose of a substance that is acutely lethal to 50% of a group of test animals
LOAEL	lowest observed adverse effect level

MMB	3-methoxy-3-methyl-1-butanol
NOAEL	no observed adverse effect level
NPIS	National Poisons Information Service (UK)
OECD	Organisation for Economic Co-operation and Development
PGBE	Propylene glycol monobutyl ether
p-RfD	Provisional reference dose
PSS	Poisoning severity score
RfD	Reference dose
SCCP	(European) Scientific Committee on Consumer Products
STEL	Short-term exposure limit
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

EXECUTIVE SUMMARY

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

Reed diffusers are a variety of air freshener, used to broadcast fragrance into a living or working space. The diffusers include a reservoir containing a fragrant solution and a series of 'wicks', made of rattan, bamboo or similar, to draw up the fragrant solution and release it into the air. The fragrant solutions have been reported to be composed of a solvent (70-90%), essential oils (10-30%) and small quantities of fragrances and other proprietary additives. However, reed diffusers may be refilled by the owner and this indicative composition cannot be assumed.

The most common solvents appear to be glycol ethers. While toxicology will differ between the various glycol ethers, effects on the kidneys and liver and depression of the CNS appear to be common toxicological features.

A very wide range of essential oils are likely to be used in reed diffuser fluids, with human toxicological information available for a relatively narrow range of these oils. While it is difficult to make any general statements about the toxicity of these materials, CNS depression, seizures and liver effects have been reported.

Exposure to reed diffuser fluids is most likely to be due to exploratory behaviour by young children. This is consistent with available surveillance data. Information from a British study suggests that incidents will typically involve ingestion of 10-40 mL of fluid.

While no appropriate acute toxicological studies were identified to provide suitable exposure reference points, case reports of ingestion of glycol ethers or essential oils suggest that exposure to these substances during ingestion of reed diffuser fluid would be likely to be at levels where adverse effects would be expected. This is consistent with finding from the New Zealand NPC, with 21% of cases exposed to reed diffuser fluid recommended to be medically examination. While most cases reported suggest that adverse health effects will resolve, a study on acute exposure to DEGEE reported chronic kidney failure and a death following eucalyptus oil intoxication has been reported.

Controlling risks associated with ingestion of reed diffuser fluid is complicated by the fact than many of the products are used as an open container and often sit within easy reach of young children. The fluids are sold with relatively little information on the composition of the fluid or information on any associated risks.

1 INTRODUCTION

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

1.1 CONSUMER PRODUCTS DESCRIPTION – REED DIFFUSERS

Reed diffusers are a variety of air freshener, used to broadcast fragrance into a living or working space. The diffusers include a reservoir containing a fragrant solution and a series of 'wicks', made of rattan, bamboo or similar, to draw up the fragrant solution and release it into the air. The fragrant solutions are mainly composed of a solvent (70-90%), essential oils (10-30%) and small quantities of fragrances and other proprietary additives (Panchal et al 2016). However, other sources have reported that reed diffuser fluid may contain up to 90% essential oil (Crandon et al 2010). Solvents used include dipropylene glycol monomethyl ether (DPGME), propylene glycol monobutyl ether (PGBE), diethylene glycol monoethyl ether (DEGEE), 3-methoxy-3-methyl-1-butanol, petroleum distillates and alcohols (Panchal et al 2016; Staton-Growcock and Sztajnkrycer 2007).

2 HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health impact assessments for reed diffuser fluids were found for New Zealand or elsewhere.

2.2 HEALTH EFFECTS – REED DIFFUSER FLUID

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 substances injuries and diseases.[1] During the 2019 year, of 29 notifications for people 19 years or younger, 4 (14%) related to ingestion of liquid from reed diffusers or essential/fragrance oils from another source (Shunnie Xie, Environmental Health Indicators Programme, Massey University, personal communication). All four notifications were for children aged 0-4 years.

During 2019, the New Zealand National Poisons Centre (NPC) advised on the management of 94 patients exposed to the contents of a reed diffuser (Dr Adam Pomerlau, Director, National Poisons Centre, personal communication). Additionally, advice was provided to 13 patients who were exposed to a diffuser oil in an unspecified container, and 173 patients with exposures to essential oils. Of the 94 known reed diffuser exposures, 77 (82%) involved children aged 0-2, 90% were due to age-appropriate child exploratory behaviour, and 20 (21%) were advised to be medically assessed.

2.2.1.2 Incident surveillance - International

During the period January to November 2009, the National Poisons Information Service (NPIS) in Cardiff, Wales received 27 calls related to reed diffusers (Crandon et al 2010). All incidents involved young children (8 months to 4 years), with a mean age of 21 months. One incident involved eye contact, while four involved ingestion of beads or pearls included in the diffuser container. The remaining 22 cases involved ingestion of the diffuser liquid.

A similar analysis was carried out by NPIS for the period 1 January 2010 to 31 December 2012 (Panchal et al 2014). A total of 324 individuals reported exposure to reed diffuser material, with 305 (94%) exposures by children less than five years. Ingestion was the most common route of exposure (305/324; 94%). Of cases who ingested reed diffuser material, the majority (*n* = 247) were exposed to the liquid only, followed by exposure to water beads only (*n* = 36), liquid and beads (*n* = 11) and sucking on the reeds (*n* = 11). Poisoning severity scores (PSS) were available for 304 ingestion cases, including 246 (81%) at PSS 0 (asymptomatic), 52 (17%) at PSS 1 (minor toxicity) and 6 (2%) at PSS 2 (moderate toxicity). No cases were assessed at PSS 3 (severe toxicity). While these data suggest that serious harm from reed diffuser liquid ingestion is likely to be rare, the modest number of cases summarised means that the possibility of serious harm cannot be excluded. Symptoms included nausea and vomiting (*n* = 32), coughing (*n* = 7), central nervous system (CNS) depression/drowsiness (*n* = 4), gagging (*n* = 3), and lip swelling, redness or irritation (*n* = 3). Sore mouth, dysphonia, bronchospasm, hypoxia, sinus tachycardia and pallor were reported in two cases each, while abdominal pain, diarrhoea, appetite suppression, facial oedema, bad taste, tongue blistering, epiglotic swelling, stridor, ectopic beats, tremor, tonic-clonic

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

convulsions and fever were each reported for single cases. Dermal exposure was reported for four cases, with only one case symptomatic with skin irritation. Three cases suffered eye exposure, with eye pain reported in two cases and conjunctivitis with irritation reported in one case.

Reports of reed diffuser exposure were further updated in 2016, with review of 754 cases reported over the period 1 January 2010 to 31 December 2014 (Panchal et al 2016). This includes the period covered by the study summarised above (Panchal et al 2014). The majority of cases (*n* = 712; 94%) were children less than five years. Ingestion continued to be the most common route of exposure (*n* = 706; 94%), with the distribution of materials ingestion being similar to the earlier study. The amount of liquid ingested was known for 76 cases, with a median of 20 mL and an interquartile range of 10-40 mL. The distribution of cases across PSS scores was virtually identical to the earlier study, with no cases at PSS 3. Nausea and vomiting, coughing and CNS depression continued to be the most commonly observed symptoms. The reed diffusers involved were classified on the basis of the primary solvent. The three most common solvents were propylene glycol monobutyl ether (PGBE, *n* = 228), dipropylene glycol monomethyl ether (DPGME, *n* = 87) and 3-methoxy-3-methyl-1-butanol (MMB; *n* = 17). Liquids based on MMB were more likely to result in adverse symptoms (PSS 1 or 2), than liquids based on PGBE, but the prevalence of adverse symptoms was not significantly different between liquids based on MMB and those based on DPGME.

2.2.1.3 Case reports

An otherwise healthy 19-month-old male presented to an emergency department after ingesting an unknown amount of reed diffuser liquid, based on MMB (Staton-Growcock and Sztajnkrycer 2007). The child exhibited symptoms of emesis (vomiting), excessive salivation, dysphonia, erythema of the face and chest and a mildly ataxic gait. All symptoms resolved within 12 hours and no oral or oesophogeal tissue damage was reported.

2.3 HEALTH EFFECTS - REED DIFFUSER COMPONENTS

The liquid contents of reed diffusers are composed of two primary ingredients; a solvent with suitable evaporative properties, usually a glycol ether, and an essential oil. While systematic toxicological information on either of these components is largely lacking, some information is available.

2.3.1 Reed diffuser base

The liquid contained in a reed diffuser is predominantly a neutral base, with appropriate diffusion and vapourisation characteristics. A sample of products available in the UK indicated that the major component of the liquid could be essential oil (up to 90%), glycol ethers (up to 85%), ethanol (up to 80%) or hydrocarbons (up to 78%) (Crandon et al 2010). The substituted alcohol, MMB, has been reported as a base in some diffuser solutions, making up 40-90% of the solution (Staton-Growcock and Sztajnkrycer 2007). A more recent publication reported isopropanol and petroleum distillates as other potential bases (Panchal et al 2014). Specific bases mentioned in the literature include propylene PGBE, DPGME, dipropylene glycol *n*-butyl ether (DPGBE) and dipropylene glycol methyl ether acetate (DPGMEA) (Panchal et al 2016). Panchal et al. (2016) reported that the majority of reed diffusers contain glycol ethers.

While New Zealand-specific information is not easy to obtain, diethylene glycol monoethyl ether (DEGEE) appears to be commonly used as a reed diffuser base.[2]

[2] https://www.purenature.co.nz/products/reed-diffuser-base Accessed 25 November 2020

The toxicological information on glycol ethers mainly relates to inhalation or dermal exposure, with little information available on oral exposure. Additionally, most epidemiological information relates to occupational exposure and to chronic exposure. The concerns behind the current risk assessment will relate to acute (single event) exposure.

DEGEE

DEGEE is of very low acute toxicity following oral administration in experimental animal species, with LD_{50} values in the range 3,600 – 8,690 mg/kg bw in mice, rats, Guinea pigs and rabbits (SCCP 2006). Non-fatal clinical signs included CNS depression, ataxia and coma (ECETOC 2005a). Repeated oral dose studies identified effects on the kidneys, liver and testes (ECETOC 2005a).

In an isolated case report, an alcoholic male (aged 44) drank approximately 300 ml of a liquid containing 47% DEGEE (about 2000 mg/kg bw, assuming a body weight of 70 kg) (Brennaas 1960). Severe symptoms of CNS and respiratory injury (dyspnoea), thirst and acidosis occurred. The urine contained albumin. The subject recovered following treatment for symptoms.

Six cases (four women and two men, aged 35-89 years) of toxicity were assessed, associated with a medication containing DEGEE as an excipient (Vial et al 2004). All cases were admitted for acute renal failure and five had severe metabolic acidosis. Despite prompt renal dialysis, five cases developed neurological complications. Kidney biopsy in five cases showed acute proximal tubular necrosis. All cases had consumed an oral herbal medication containing 6% DEGEE. There was evidence to suggest that cases had recently received doses of DEGEE ranging from 7.5 g/day to 38 g/day over 3 days. One case died from infectious complications, four developed chronic renal failure, while one had abnormal serum creatinine values.

The potential for renal toxicity has also been demonstrated in *in vitro* studies in human kidney cell lines (Srivastava et al 2019) and *in vivo* animal studies (ECETOC 2005a).

PGBE

The few acute toxicity studies available suggest a low level of acute oral toxicity, with LD_{50} of 1900 and 3300 mg/kg bw determined in rats (ECETOC 2005a; OECD 2003). Signs of toxicity (rodent) included lethargy, CNS depression, coma, hypopnoea (slow or shallow breathing) and dacryorrhea (excessive lacrimation).

Sub-chronic oral toxicity studies (F344 rat, 13 weeks) elicited no adverse effects at any of the doses administered. The maximum dose was 1000 mg/kg bw/day (ECETOC 2005a).

No human epidemiological studies or case reports were found for oral exposure to PGBE.

DPGME

Acute oral toxicity studies in rats and dogs suggest very low acute toxicity, with LD_{50} >5000 mg/kg bw (ECETOC 2005a). Clinical signs noted included CNS depression in rats and respiratory paralysis in dogs.

Sub-chronic (rats, 4 weeks) toxicity studies resulted in increased liver weight, accompanied by centrilobular hypertrophy at the highest dose level (1000 mg/kg bw per day) (ECETOC 2005a).

No human epidemiological studies or case reports were found for oral exposure to DPGME.

DPGBE

Acute oral toxicity studies in rats and mice suggest very low acute toxicity, with LD_{50} >1400 mg/kg bw (ECETOC 2005a; OECD 2003). Adverse clinical signs included CNS and respiratory depression, weight loss, lethargy, coma, hypopnea, hyperpnea, dacryorrhea, blood around the eyes, rough coat, and ataxia (OECD 2003).

No adverse effects were seen in sub-acute (SD rats, 14 days) oral toxicity studies at the highest dose administered (400 mg/kg bw per day by gavage or 750 mg/kg bw per day in the diet) (ECETOC 2005a). A sub-chronic oral toxicity study (SD rats, 13 weeks) revealed increases in liver weight in the highest dose group (1000 mg/kg bw per day), but without histopathology. Clinical chemistry in the high dose group was consistent with liver injury.

No human epidemiological studies or case reports were found for oral exposure to DPGBE.

DPGMEA

Acute oral toxicity studies in rats suggest very low acute toxicity, with LD_{50} >5000 mg/kg bw (OECD 2003). Adverse clinical signs included laboured respiration, lethargy, watery eyes, and unconsciousness (OECD 2003).

No repeated dose studies were reported (OECD 2003).

No human epidemiological studies or case reports were found for oral exposure to DPGMEA.

2.3.2 Essential oils

Any of a wide range of essential oils could potentially be used in reed diffusers. The information summarised in the following sections is dictated as much by the available literature, as by the essential oils potentially used. The information is mainly available in the form of case reports.

A retrospective study of essential oil exposure calls to the New South Wales' Poisons Information Centre during 2014-2018 identified 4412 essential oil exposures (Lee et al 2020). Most of the exposures (63%) were related to persons under 15 years. The oil types most frequently involved were eucalyptus (46.4%), tea tree (17.0%), lavender (6.1%), clove (4.1%) and peppermint (3.5%).

An analysis of childhood (0-14 years) poisonings at four locations in Queensland during 1998-1999 identified 1516 incidents (Reith et al 2001). In terms of essential oils, presentations were reported for eucalyptus oil (*n* = 39), other essential oils (*n* = 29) and melaleuca (tea tree) oil (*n* = 13). Admissions were reported for eucalyptus oil (*n* = 20), other essential oils (*n* = 14) and melaleuca oil (*n* = 8).

In the case reports summarised in the following sections the material ingested is described as the essential oil. Where a dilution or inclusion in a formulated product was reported, this information has been provided.

Clove oil

Clove oil is an essential oil extracted from the clove plant (*Syzygium aromaticum*). The oil can be derived from flower buds, leaves or the stem of the plant. The essential oil is largely made up of eugenol (60-95%).[3]

A 2-year-old boy was examined one hour after accidental ingestion of approximately 10 mL of clove oil (Brown et al 1992). Seizures began an hour later and recurred over the following 8 hours. The following morning a diagnosis of disseminated intravascular coagulation (DIC; widespread formation of blood clots resulting in blockage of small blood vessels) was made, and consequent depression of platelet counts was observed. Symptomatic treatment with heparin was initiated. On the fourth day the patient's condition deteriorated with hepatocellular necrosis leading to development of hepatic encephalopathy and renal impairment. Hepatic damage was subsequently considered to be the root cause of the DIC. By 18 days post-ingestion the child was discharged, with his condition considered to be normal.

A 2-year-old boy presented at an emergency department one hour after ingesting 5-10 mL of clove oil (Hartnoll et al 1993). Within three hours he had deteriorated into a deep coma, with marked acidosis. At 24-hours after ingestion, the patient was still unconscious and there was laboratory evidence of deteriorating liver function. A diagnosis of DIC was subsequently made. The patient was treated for the clotting abnormalities, although his consciousness level deteriorated with further worsening of liver function test results. The patient's neurological state started to improve after five days and he eventually made a full recovery.

A 3-month-old female developed fulminant hepatic failure after ingesting less than 8 mL of clove oil (Eisen et al 2004). Blood analysis at 26 hours post-ingestion showed acute hepatic injury and an evolving coagulopathy. Treatment by intravenous *N*-acetylcysteine was initiated at 32.5 hours post-ingestion and the patient was discharged at five days post-ingestion.

While liver toxicity is a common feature of case reports of clove oil poisoning, coagulopathy is not always reported. A 15-month-old boy developed fulminant liver failure after ingesting 10-20 mL of clove oil (Janes et al 2005). *N*-acetylcysteine treatment at 24-hours post-ingestion improved indicators of hepatic impairment. Slow improvement was seen over the following 7 days.

A 3-year-old boy ingested an unknown amount of clove oil, which was being used as a dental analgesic (Kim et al 2018). The patient was lethargic with occasional bouts of emesis when presenting to an emergency department. Liver enzyme levels were elevated. *N*-acetylcysteine treatment was initiated 7 hours after ingestion. On hospital day 3, the patient's neurological status improved and liver enzyme concentrations began to normalise. He was discharged on day 4.

In a further case report, a 7-month-old infant was unintentionally administered a teaspoon (5 mL) of clove oil (Lane et al 1991). The patient was treated by gastric lavage and charcoal administration. The reported adverse effects included acidosis, urinary abnormalities and CNS depression. All symptoms resolved within 48 hours. The case report did not include results of tests of liver function.

The findings of these case reports are consistent with observations that the main ingredient of clove oil (eugenol) is hepatotoxic in rats and dogs following high acute doses (JECFA

[3] https://en.wikipedia.org/wiki/Oil_of_clove Accessed 2 October 2020

1982). However, the acute toxicity of eugenol is generally quite low, with LD_{50} of 1200 mg/kg bw or greater in rodent species. It has been suggested that the hepatic toxicity of eugenol is mediated through a quinone intermediate, resulting from cytochrome P-450 metabolism of eugenol (Eisen et al 2004).

Eucalyptus oil

Eucalyptus oil is a generic term for oils distilled from the leaves of any *Eucalyptus* species. The main components are eucalyptol (1,8-cineole) and alpha-terpineol.[4]

A review of 109 cases of eucalyptus oil poisoning in Victoria, Australia found that in 81 of the cases access to the oil was from a 'vaporiser' (Day et al 1997). However, it is uncertain what proportion of these vaporisers may have been reed diffusers. The formula for most of the vaporiser solutions included eucalyptus oil (usually as the main ingredient), camphor, menthol and methyl salicylate in varying concentrations in a propylene glycol base. In 13 of the cases ingestion was definitively confirmed, with nine of these cases involving ingestion of less than 5 mL. Ingestion from storage bottles included some instances of ingestion of quite large volumes (>100 mL). The majority of cases were in the age range 1-3 years.

A review of what appears to be the same 109 cases focused on clinical effects and dose-response relationship (Tibballs 1995). Clinical effects were observed in 59% of cases, with 31 cases (28%) experiencing depression of consciousness. This was reported as drowsiness in most cases (*n* = 28), but three cases, who were reported to have ingested 5, 10, and 7.5 mL, were unconscious when presenting to ED. Vomiting (37%), ataxia (15%) and pulmonary disease (11%) were other commonly reported effects. The study author classified cases in terms of the severity of poisoning (nil, minor, moderate or major), with associated mean (range) doses of eucalyptus oil of 1.7 mL (0.2-5.0), 2.0 mL (0.2-7.0), 2.5 mL (0.6-5.0) and 7.5 mL, respectively. It was concluded that significant depression of consciousness should be anticipated after ingestion of 5 mL or more of eucalyptus oil.

In contrast, a review of eucalyptus oil poisoning cases (*n* = 41) amongst children <14 years in southeast Queensland during 1984-1991 reported that most of the children (*n* = 33, 80%) were asymptomatic, despite some ingesting more than 30 mL of eucalyptus oil (Webb and Pitt 1993). Only two children had symptoms or clinical signs on presentation to hospital. The estimated ingested doses were high in this review, with one case ingesting 45 mL and four ingesting more than 30 mL. The high proportion of asymptomatic cases is unexpected, given the outcomes in other case studies available. However, it should be noted that reported ingestion doses are often inferred and may not be accurate.

A 53-year-old male was brought to hospital in an unconscious state following intentional ingestion of approximately 500 mL of eucalyptus oil (Hume et al 2019). The patient was placed on mechanical ventilation. No spontaneous breathing was observed and he was unresponsive to painful stimuli. His state of consciousness started to improve at 7 days and he was removed from mechanical ventilation on day 15. The patient made a complete neurological recovery. It was noted that the mechanism of CNS depression in eucalyptus oil poisoning is currently unknown.

Two adult males (22 and 26-years-old) who had unintentionally ingested eucalyptus oil presented at an emergency department with seizures and severe metabolic acidosis (Ittyachen et al 2019). One patient reported ingesting about 15 mL of eucalyptus oil. Both patients were intubated due to low Glasgow Coma Scale scores. Acidosis was corrected

[4] https://en.wikipedia.org/wiki/Eucalyptus_oil Accessed 5 October 2020

within 24-36 hours by bicarbonate infusion. Mechanical ventilation was able to be discontinued on the second day of admission and the patients were discharged two days later.

A 3-year-old boy was seen by a medical expert within 30 minutes of ingesting about 10 mL of eucalyptus oil (Patel and Wiggins 1980). The patient was deeply comatose. The pupils were constricted, muscle tone was markedly reduced and no tendon reflexes could be elicited. Blood pressure was depressed (75/40 mmHg). The patient was intubated and gastric lavage with sodium bicarbonate was carried out. By 2 hours after admission, pulse, blood pressure and respiration rates were normal. The patient returned to consciousness after 5 hours and was discharged after 48 hours.

A 17-month-old female was admitted after unintentionally ingesting a small amount (0.5 mL) of eucalyptus oil (Sitaraman and Rao 2019). The patient was reported to be drowsy, but no seizures occurred. The patient was treated by gastric lavage with saline. The next day, the patient was alert and active and was discharged. No recurrence of adverse effects was reported.

The proconvulsive potential of eucalyptus oil was highlighted in a small case series report (Mathew et al 2020). A 24-year-old male unintentionally ingested approximately 5 mL of eucalyptus oil. He experienced multiple episodes of tonic-clonic seizure. He was brought to an ED within 30 minutes in an unconscious condition. Despite treatment (lorazepam, phenytoin, midazolam, lacosamide, levetiracetam), the seizures continued and he developed multiorgan failure and died on day 5. He had no history of prior seizures, stroke, febrile seizures, head trauma, or family history of seizures. A 31-year-old male presented with generalised tonic-clonic seizures after ingesting 10-15 mL of eucalyptus oil, taken for abdominal pain. Following treatment with lorazepam and levetiracetam, his condition improved over 6 hours and he was discharged after 5 days. At one month follow-up, there was no recurrence of the seizures.

Lavender oil

Lavender essential oil may be prepared from English lavender (*Lavandula augustifolia*) or lavandin (*Lavandula x intermedia*), also known as Dutch lavender. The lavandin product contains higher levels of terpenes than the English lavender product, including camphor.[5]

An 18-month-old boy was admitted to a paediatric ICU 4 hours after unintentional ingestion of a small amount of a homemade lavandin extract (Landelle et al 2008). Depression of the CNS was observed, including deep drowsiness and limited response to pain stimuli. The neurological state normalised spontaneously within 6 hours. Although acetone, presumably from the lavandin extraction process, was detected in the lavandin extract and in patient clinical samples, the observed CNS depression was considered to be due to components from the plant material.

Tea tree oil

Tea tree oil is an essential oil with a fresh camphoraceous odour, derived from the leaves of the tea tree (*Melaleuca alternifolia*); a tree native to Queensland and New South Wales.[6]

A 4-year-old boy was brought to ED approximately 2 hours after his mother had unintentionally administered approximately 2 teaspoons (10 mL) of tea tree oil (Morris et al

[5] https://en.wikipedia.org/wiki/Lavandula#Lavender_oil Accessed 5 October 2020
[6] https://en.wikipedia.org/wiki/Tea_tree_oil Accessed 5 October 2020

2003). On arrival, the patient was unresponsive and was intubated. The patient regained consciousness 15 minutes later, but remained intermittently somnolent and combative. The patient was extubated 6 hours after presentation and his level of alertness slowly improved. He was discharged 24 hours after admission.

Further case reports were summarised in a European data package for tea tree oil (EFSA 2011). Doses ingested ranged from half a teaspoon (about 2.5 mL) to half a cup (100-125 mL). Symptoms included CNS, gastrointestinal and dermal (rash) effects. In all cases, the subjects recovered after periods of 5 hours to 6 weeks.

Other essential oils

A 38-year-old woman, known to be epileptic but with the epilepsy well medically controlled, consumed five or six cakes containing an unknown amount of fennel oil (Skalli and Bencheikh 2011). Two hours after consuming the cakes, the woman suddenly developed a typical generalised tonic-clonic seizure and remained unconscious for 45 minutes. Involuntary diarrhoea accompanied her epileptic seizure. The patient's last previous seizure had been three years before. The authors of the report suggested that the seizures may have been induced by fenchone, a major component of fennel oil, while the diarrhoea may have been caused by another component, limonene.

3 DOSE-RESPONSE INFORMATION

In the current context, concerns associated with oral exposure to reed diffuser fluid will be related to single exposure (acute) events. For the chemicals that make up reed diffuser fluid, single exposure events are usually only considered in the determination of the LD_{50}; the dose that is lethal to half the exposed animals. This is not a suitable exposure reference dose for human exposures. In the absence of relevant acute animal studies, the findings of studies up to subchronic in duration are summarised in the following sections.

3.1 REED DIFFUSER BASE

3.1.1 DEGEE

DEGEE has twice been assessed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) due to its use as a carrier solvent for flavours and its potential carryover into food (JECFA 1976; 1993). On both occasions JECFA concluded that there was insufficient information to allocate an acceptable daily intake (ADI).

Short-term exposure limits (STELs) have been derived for several countries, however, these relate to inhalation exposure, not oral exposure (ECETOC 2005b).

US Environmental Protection Agency (USEPA) derived provisional sub-chronic and chronic reference doses (p-RfD) for DEGEE (USEPA 2009). The sub-chronic p-RfD was derived from the no observed adverse effect level (NOAEL) (167 mg/kg bw/day) from a 90-day pig study (Gaunt et al 1968). Effects seen above the NOAEL included effects on the liver (degeneration of hepatocytes) and the kidneys (renal tubular degeneration). An uncertainty factor of 300 (10 x interspecies, 10 x intraspecies, 3 x database inadequacies) was applied to give a p-RfD of 0.6 mg/kg bw/day. The chronic p-RfD was based on the same toxicological endpoint, but included an extra 10-fold uncertainty factor for extrapolation from a sub-chronic to a chronic timeframe, giving a chronic p-RfD of 0.06 mg/kg bw/day. No acute reference dose was derived.

3.1.2 PGBE

The toxicity of PGBE has been assessed under the Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA) project (HERA 2005). While no HBGV was derived, an oral NOAEL of 350 mg/kg bw/day was identified from a 13-week drinking-water study in rats. Effects above the NOAEL included increases in liver weight in males and increases in kidney weight in females, but without associated histopathological changes. Haemolysis has been associated with lower molecular weight ethylene glycol ethers, but was not observed with PGBE.

The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) reviewed the same study and concluded that the changes in organ weight were not adverse effects and concluded that the NOAEL was the highest dose administered (1000 mg/kg bw/day) (ECETOC 2005a).

In a 14-day oral rat study, no haematological or other adverse effects were observed at any dose (ECETOC 2005a). The maximum dose was 400 mg/kg bw/day.

3.1.3 DPGME

In rats exposed to DPGME by gavage for four weeks, tentative salivation and liver effects (increased relative weight and centrilobular hypertrophy) were observed only in the highest dose group (1000 mg/kg bw/day) (ECETOC 2005a). The NOAEL was 200 mg/kg bw/day.

No other toxicological studies involving oral administration have been reported.

3.1.4 DPGBE

Rats were administered doses of DPGBE of up to 400 mg/kg bw/day by gavage for 14 days (ECETOC 2005a). No haemolytic or other adverse treatment-related effects were observed at any dose. This suggests a NOAEL of at least 400 mg/kg bw/day.

Doses up to 750 mg/kg bw/day were administered to rats in the diet for 14 days (ECETOC 2005a). No haemolytic or other adverse treatment-related effects were observed at any dose. This suggests a NOAEL of at least 750 mg/kg bw/day.

In a 13-week oral rat study, slight decreased body weights, minor changes in clinical chemistry and slightly increased body weights were observed in the highest dose group (1000 mg/kg bw/day) (ECETOC 2005a). The NOAEL was concluded to be the next highest dose (450 mg/kg bw/day).

3.1.5 DPGMEA

While little toxicological information is available on DPGMEA, it has been examined in detail as a case study for 'read across' of toxicological characteristics from structural similar compounds (dipropylene glycol methyl ether, propylene glycol methyl ether and propylene glycol methyl ether acetate) (Ball et al 2014). It was concluded that the toxicology of these compounds is very similar and general conclusions can be drawn including:

- The NOAEL for short-term toxicity studies (up to 28 days) will be >900 mg/kg bw/day based on increases in liver and kidney weight, without evidence of cytotoxicity.
- For longer term studies (90 days and longer) the NOAEL is not substantially different and no new toxicological endpoints are apparent.
- None of the compounds are expected to be developmentally toxic.

3.2 ESSENTIAL OILS

Little toxicological information is available on essential oils, but in some instances information is available on the major components of the oils.

3.2.1 Clove oil

Clove oil is predominantly eugenol (60-95%). Eugenol and related hydroxyallylbenzene flavouring agents were most recent assessed by JECFA at the Committee's 65th meeting (JECFA 2006). JECFA confirmed a previously established acceptable daily intake (ADI) for eugenol of 0-2.5 mg/kg bw/day, based on a 19-week rat study. No acute reference dose was established for eugenol.

EFSA established a lower ADI of 1.0 mg/kg bw/day, based on maternal toxicity in reproductive and developmental toxicity studies in rats and rabbits (EFSA 2012b). An acute reference dose was not considered to be necessary, although it was noted that eugenol is harmful if swallowed. The EFSA assessment was for clove oil and it was noted that "the material tested in the toxicological studies is not considered to cover the technical specification for clove oil (including up to 20 % of other components) and it cannot be concluded whether the reference values derived for eugenol will also apply to clove oil" (EFSA 2012b).

3.2.2 Eucalyptus oil

No assessments were found for eucalyptus oil, but assessments were found for eucalyptol (1,8-cineole), the major component of eucalyptus oil.

JECFA considered eucalyptol as a flavouring agent at the 61st meeting (JECFA 2004). HBGV are not usually assigned for flavouring agents, but short-term studies (28 days) oral (gavage or diet) in rats and mice gave NOAELs in the range 300-1500 mg/kg bw. Histopathological changes in the liver were seen in male rats at high doses, but not in female rats or mice of either gender. The changes seen were reported to be typical of metabolic adaptation.

3.2.3 Lavender oil

The composition of lavender varies across different *Lavandula* species and growing locations, but linalool, linalyl acetate, eucalyptol and camphor have been reported to be major components (>10%) of lavender oil (Bialon et al 2019; Chen et al 2020; Dong et al 2020; Sayout et al 2020).

JECFA have established a group ADI for linalool and linalyl acetate of 0-0.5 mg/kg bw per day, based on a NOAEL of 50 mg/kg bw per day for linalool in a 90-day rat study (JECFA 1999). The NOAEL was the limit dose (the highest dose administered) for the study and 50 mg/kg bw per day is probably a conservative estimate of the NOAEL.

EFSA have assessed linalool and linalyl acetate as flavourings (EFSA 2012a). Linalool was reported to have a NOAEL of 117 mg/kg bw per day in a 28-day rat study, based on effects on the liver and kidneys. This NOAEL was considered to be applicable to linalyl acetate, as it is metabolized to linalool *in vivo*.

Camphor is somewhat unusual, in that a reasonable body of human toxicological data is available (EFSA 2008). Based on a case series of 81 individuals who had ingested camphor, it was determined that cases ingesting an acute dose less than 2 mg/kg bw remained asymptomatic. A second case series of 64 cases concluded that clinically significant camphor toxicity was not seen at doses below 30 mg/kg bw and were rarely seen at doses below 50 mg/kg bw.

Eucalyptol was discussed in the previous section.

3.2.4 Tea tree oil

The main components of tea tree oil are terpinen-4-ol, γ-terpinene and α-terpinene (EFSA 2011).

Tea tree oil has been assessed in the European Union as an active ingredient in pesticide formulations (EFSA 2011). While human case reports were summarised, no human dose-response information was presented. No short-term (or long-term) animal toxicity studies were available for tea tree oil, other than for LD_{50} determination. Toxicity studies of the major components of tea tree oil (1 week – 24 months, rats and mice) were summarised. Lowest NOAELs for α-pinene, α-terpinene and 1,8-cineole were all approximately 30 mg/kg bw/day. Based on the NOAEL for α-terpinene and an uncertainty factor of 100, an ADI of 0.3 mg/kg bw/day was derived for tea tree oil.

3.3 CONCLUSIONS

Little toxicological information is available to allow assessment of potential risks from acute exposure to components of reed diffuser fluid. Animal studies are either acute, with lethality as the endpoint of interest, or sub-chronic (repeated dose). Lethality studies are inappropriate for the assessment of adverse effects in humans, while sub-chronic studies will likely identify no effect levels that are overly conservative for assessment of single exposure events in humans.

4 EXPOSURE ASSESSMENT

Unintentional ingestion of reed diffuser fluid 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.

For reed diffuser fluid, 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).

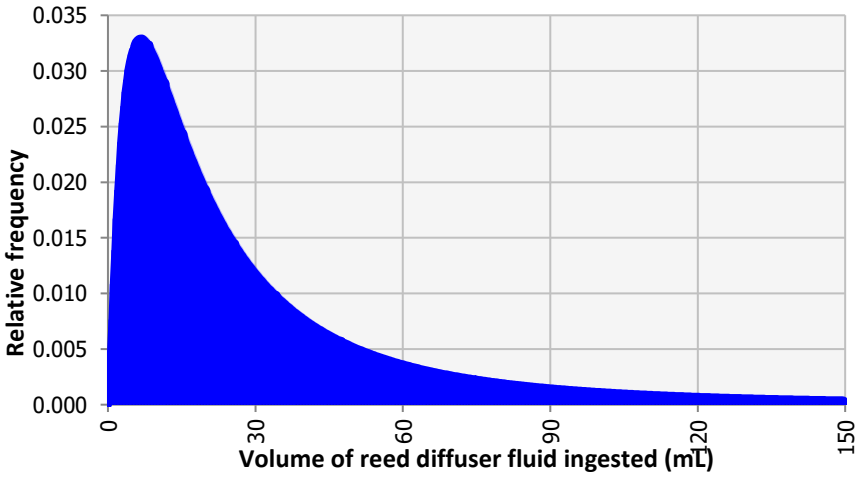
For human case reports, effect levels of exposure are often reported as the amount of the substance of interest ingested, without regard to the case's body weight. For comparison to such studies, the exposure expression simplifies to C x V.

4.1 EXPOSURE PARAMETERS

4.1.1 Amount of reed diffuser fluid ingested (V)

From a review of 754 cases of reed diffuser ingestion, the amount of liquid ingested was known for 76 cases, with a median of 20 mL and an interquartile range of 10-40 mL (Panchal et al 2016). It should be noted that the dose will be those reported by the case or the cases caregiver and may not necessarily be accurate. The distribution of ingested volumes is obviously right-skewed (i.e. the interquartile range is not symmetrical around the median). The three available summary statistics (the 25th, 50th and 75th percentiles) were used to define a lognormal distribution (Figure 1). The resulting distribution has a mean of 34 mL and a 95th percentile of 110 mL.

Figure 1. Distribution (lognormal) fitted to the reported summary statistics for volume of reed diffuser fluid ingestion (Panchal et al 2016)



4.1.2 Composition of reed diffuser fluid

As discussed in section 1.1, little definitive information is available on the composition of reed diffuser fluid. It should also be noted that users are able to 'reload' the diffusers themselves and the final composition of the fluid may differ from that sold. Crandon reported that essential oils may make up 90% of reed diffuser fluid (Crandon et al 2010). Two scenarios were considered:

- The fluid is largely (90%) composed of carrier solvent
- The fluid is completely (100%) composed of essential oils.

4.1.3 Exposure cohort

As outlined in section 2.3, cases of unintentional ingestion of reed diffuser fluid are almost universally in the age range up to 4 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).

4.2 EXPOSURE ESTIMATES

Table 1 summarises estimates of exposure to reed diffuser solvent and essential oil, based on the parameters outlined above.

Table 1. Estimates (mean and 95th percentile) of potential exposure to reed diffuser fluid component for a child, 1-2 years

	Estimated exposure to reed diffuser fluid components			
	Reed diffuser fluid base		Essential oils	
	Mean	P95	Mean	P95
Exposure (mL/event)	31	99	34	110
Exposure (mL/kg bw/event)	2.8	9.0	3.1	10

P95: 95th percentile

5 RISK CHARACTERISATION

Risk characterisation for exposure to components of reed diffuser fluids is hampered by the lack of acute health-based guidance values for the substances likely to be included.

The information reported by Panchal et al. (2016) suggests that young children may ingest volumes of reed diffuser fluid up to or exceeding 100 mL. Case reports indicate that ingestion of quantities of the component ingredients considerably less than 100 mL can result in adverse health outcomes. In most cases the adverse effects have been reported to be transitory and reversible, although this finding was not universal. Ingestion of 7.5 to 38 g/day of DEGEE has been reported to result in chronic kidney failure (Vial et al 2004).

A study in which a dose-response relationship for ingestion of eucalyptus oil was presented indicated that ingestion of 7.5 mL or more could be associated with severe poisoning symptoms (Tibballs 1995). Ingestion of such quantities appears highly likely from reed diffuser fluid ingestion events.

6 CONCLUSIONS

Reed diffusers are a variety of air freshener, used to broadcast fragrance into a living or working space. The diffusers include a reservoir containing a fragrant solution and a series of 'wicks', made of rattan, bamboo or similar, to draw up the fragrant solution and release it into the air. The fragrant solutions have been reported to be composed of a solvent (70-90%), essential oils (10-30%) and small quantities of fragrances and other proprietary additives. However, reed diffusers may be refilled by the owner and this indicative composition cannot be assumed.

The most common solvents appear to be glycol ethers. While toxicology will differ between the various glycol ethers, effects on the kidneys and liver and depression of the CNS appear to be common toxicological features.

A very wide range of essential oils are likely to be used in reed diffuser fluids, with human toxicological information available for a relatively narrow range of these oils. While it is difficult to make any general statements about the toxicity of these materials, CNS depression, seizures and liver effects have been reported.

Exposure to reed diffuser fluids is most likely to be due to exploratory behaviour by young children. This is consistent with available surveillance data. Information from a British study suggests that incidents will typically involve ingestion of 10-40 mL of fluid.

While no appropriate acute toxicological studies were identified to provide suitable exposure reference points, case reports of ingestion of glycol ethers or essential oils suggest that exposure to these substances during ingestion of reed diffuser fluid would be likely to be at levels where adverse effects would be expected. This is consistent with finding from the New Zealand NPC, with 21% of cases exposed to reed diffuser fluid recommended to be medically examination. While most cases reported suggest that adverse health effects will resolve, a study on acute exposure to DEGEE reported chronic kidney failure (Vial et al 2004) and a death following eucalyptus oil intoxication has been reported (Mathew et al 2020).

Controlling risks associated with ingestion of reed diffuser fluid is complicated by the fact than many of the products are used as an open container and often sit within easy reach of young children. The fluids are sold with relatively little information on the composition of the fluid or information on any associated risks (Adam Pomerlau, Director, National Poisons Centre).

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