Science for Communities

HEALTH RISK ASSESSMENT:

E-CIGARETTE LIQUIDS: ACUTE TOXICITY HAZARDS AND HEALTH RISKS

December 2021

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PREPARED FOR: Ministry of Health

CLIENT REPORT No: FW21041

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ACRONYMS AND ABBREVIATIONS

bw	Body weight
CDC	US Centers for Disease Control and Prevention
EP	European Pharmacopoeia
ESR	Institute of Environmental Science and Research Limited
GRAS	Generally Recognised as Safe
NAS	US National Academy of Sciences
NPC	New Zealand National Poisons Centre
NPDS	National Poison Data System (USA)
PG	Propylene glycol
SCHEER	EU Scientific Committee on Health, Environmental, and Emerging Risks
SERPA	Smokefree Environments and Regulated Products Act 1990
SERPR	Smokefree Environments and Regulated Products Regulations 2021
USFDA	US Food and Drug Administration
USP	United States Pharmacopoeia
VG	Vegetable Glycerine
WHO	World Health Organization

EXECUTIVE SUMMARY

The health effects considered in this report include poisonings from e-liquids, intrinsic toxicological properties of e-liquid components, and injuries from explosions or burns and not health effects from vaping itself in the course of the intended use of e-cigarettes. This report does not consider the chronic long term health risks from vaping and therefore does not discuss the overall health considerations of e-cigarettes as alternatives to tobacco smoking or as smoking cessation aids. The purpose of this report is to summarise the literature on e-cigarette liquid acute toxicity hazards and risks.

Acute illnesses and injuries have occurred in New Zealand and internationally from oral and dermal contact with nicotine-containing e-liquids, through unintentional ingestion, exploration behaviour from children, and intentional harm. Nicotine is a potent acute neurotoxicant and drives the acute toxicity consideration for e-liquids. There has been a trending increase in calls to the New Zealand National Poisons Centre (NPC) since 2016. Child exploration accounts for over half of the NPC calls, and the potential for child exposures resulting in nicotine poisoning is widely recognised internationally as a main concern over the health risks of e-liquid exposures outside their intended use. Exposure scenarios developed in this report indicate that a toddler swallowing small volumes (only a fraction of a mL) of e-liquid with allowed nicotine salt concentrations of up to 50 mg/mL under the Smokefree Environments and Regulated Products Regulations (2021) (SERPR), would quickly exceed the European Food Safety Authority's Acute Reference Dose for nicotine of 0.008 mg/kg, and be at increasing risk for acute intoxication or potentially death. Spilling a small volume of e-liquids on skin can also produce acute toxicity. The presence of flavourings enhance the attractiveness to these liquids to children and could amplify the likelihood of acute poisoning.

The SERPR includes specifications for ingredients and contaminants in e-cigarette products. Propylene glycol and vegetable glycerin are glycol carriers, allowed under SERPR, that are of low toxicity and have not been documented internationally to result in acute illnesses through their presence in e-liquids. Flavouring chemicals are regulated under SERPR, and although many are "Generally Recognised As Safe" by the U.S. Food and Drug Administration, some flavouring chemicals have been found to be cytotoxic to pulmonary and immune cells *in vitro*, and to induce pro-inflammatory responses. Explosions and burn injuries from e-cigarette devices have also been reported internationally, although no specific data on such injuries could be found for New Zealand, and only a single case of an exploding device was found which did not result in injury. Fewer of these cases appear in the scientific or clinical literature in recent years, indicating that product safety quality assurance measures may have reduced the likelihood for these events.

1 INTRODUCTION

Electronic cigarettes pose complex public health questions regarding health risk that include considerations of addiction, harm reduction, and product safety.

The purpose of this report is to summarise the literature on e-cigarette liquid (e-liquid) injuries and toxicity hazards that relate to product safety. This report does not explore the overall health risk/benefit considerations of e-cigarettes when used by consumers as alternatives to tobacco smoking or as smoking cessation products. This report will only consider domestic, non-occupational, incidental exposure to e-liquids. The solid state components of e-cigarettes themselves and the complex consideration of generated aerosol exposures to heated e-liquids in normal vaping use, with their highly varying ingredients and contaminants, are beyond the scope of this report. The report focuses on the intrinsic toxicological hazards of e-liquids in liquid form only.

In New Zealand, the sale of e-cigarettes and other vaping devices is allowed but with a number of limitations and restrictions specified in recent legislation (New Zealand Government 2021a; 2021b). By contrast, in Australia, e-cigarettes can be sold only if consumers have a prescription (TGA 2021). The difference in the approach is an illustration of the ongoing public health debate about potential smoking cessation and harm reduction benefits vs product safety risks and marketing to youth, considering the addictive nature of nicotine as a consumer product.

1.1 E-LIQUID COMPOSITION AND REGULATIONS

Risk assessment of e-liquids considers three basic components: Nicotine, glycol carrier solvents, and flavourings. Each of these components has potential health significance from a product safety perspective, and each has recent regulatory status in New Zealand. New Zealand has a recently amended the legal regulatory framework that encompasses e-cigarettes and e-liquids through the Smokefree Environments and Regulated Products Act (1990) (SERPA). The amendments to SERPA came into force 11 November 2020 and is still in process of implementation. The related Smokefree Environments and Regulated Products Regulations (2021) (SERPR) has relevant sections that govern the composition and product safety of vaping products.

The SERPR specifies what ingredients of e-liquids are permitted, and also provides for restrictions on specific constituents in vaping products, including maximum limits for major ingredients and prohibitions on other ingredients and contaminants. The relevant provisions of SERPR will be discussed below in terms of the individual components of e-liquids. This report will not review all of the various provisions of the SERPR, such as advertising and point of sale restrictions, that are not directly related to chemical hazards and exposures or product safety assessments.

1.1.1 Glycol Carriers

The glycol carriers can be either propylene glycol (PG) and/or vegetable glycerin (VG) or glycerol in varying ratios depending on the product. These glycols are considered to be essentially non-toxic, although low level mucous membrane irritation can result from PG inhalation exposure. PG is also considered to cause rare, low severity allergic reactions in cosmetics uses (LaKind et al 1999). Low grade/low purity PG may contain trace levels of ethylene glycol and other contaminants. However, in SERPR, the quality of PG and VG,

must comply with the United States Pharmacopeia (USP) or the European Pharmacopoeia (EP).

1.1.2 Nicotine

Nicotine is the principal drug in most e-liquid formulations. The nicotine concentration range in e-liquid products allowed for sale in New Zealand is described in SERPR (New Zealand Government 2021b):

* The strength of free-base nicotine in a vaping substance must not exceed 20 mg/mL.
* The strength of nicotine salt in a vaping substance must not exceed 50 mg/mL.
* The total nicotine content in a container of vaping substance sold at retail must not exceed 1,800 mg, whether it is present as free-base nicotine or nicotine salts.
* Nicotine quality must comply with the USP or EP monograph purity standards.

A recent independent analysis of nicotine contents of e-liquids in New Zealand by ESR (J. Doncliff and R. Somerfield, personal communication, 2021) found significant discrepancies between labels and actual contents. Reported discrepancies included the finding of nicotine in one-third of products tested that claimed to be zero nicotine, including 1 with nicotine at 0.46 mg/mL. Ethanol was also found in 95% of the products, some in excess of 3% ethanol by weight. Discrepancies in nicotine concentration were commonly in excess of 10% higher or lower than the stated concentration on labels. These discrepancies place an additional layer of variability in any risk assessment involving nicotine dose estimates that presume accuracy in labels. For example, it has been noted that nicotine dose and concentration information might not be accurate in some case reports since nicotine concentration can be either lower or higher than what is stated on the label (Gupta et al 2014).

1.1.3 Flavouring Chemicals

In New Zealand, under the SERPA, flavours of e-liquids that are allowed for sale through retail shops are restricted to **tobacco flavour**, **mint** or **menthol** (New Zealand Government 2021a). The SERPA also dictates that other flavourings beyond these three may be sold by a Specialist Vape Retailer (SVR). However, the SVR: *"must sell the product only from the retailer's approved vaping premises or the retailer's approved Internet site".* Additionally, the following restrictions and qualifications apply:

* Tobacco extracts used for flavourings in vaping substances must not contain tobacco specific nitrosamines in excess of the applicable limits in clause 13 (Table 1).

* Flavours must be water-soluble, and flavours other than tobacco extracts must meet food standards in the Australia New Zealand Food Standards Code 2002.

Table 1. Substances that, under the SERPR, are permitted in vaping devices or e-liquids if their presence is technically unavoidable, and if they do not exceed the maximum limits

Compounds	Limit value (no more than)
Diacetyl (or 2,3-butanedione)	22 mg/L
Pentane 2,3-dione (or acetylpropionyl)	22 mg/L
Formaldehyde	22 mg/L
Acrolein	22 mg/L
Acetaldehyde	200 mg/L
Ethylene glycol	1,000 mg/L
Diethylene glycol	1,000 mg/L
Metals	
Aluminium	12 mg/L
Antimony	4 mg/L
Arsenic	0.4 mg/L
Cadmium	0.6 mg/L
Chromium	0.6 mg/L
Iron	12 mg/L
Lead	1 mg/L
Mercury	0.2 mg/L
Nickel	1 mg/L
Tin	12 mg/L
Tobacco-specific nitrosamines (TSNAs)	
Total TSNAs, including—	50 µg/L
• N-nitrosonornicotine	
• N-nitrosoanatabine	
• N-nitrosoanabasine	
• 4-methyl-N-nitrosamino-1-(3- pyridyl)-1-butanone	

Internationally, the flavouring chemicals found commercially are wide ranging, and account for the largest chemical variation across e-liquid products. Most of the flavouring chemicals have been approved for food use and are considered Generally Recognised As Safe (GRAS) by the U.S. Food and Drug Administration (USFDA). GRAS status reflects the USFDA conclusion that acute and chronic oral toxicity and allergenicity risks are low, but does not specifically consider any possible effects on lung tissue from inhalation. GRAS is therefore a food-additive use-specific conclusion.

In a survey of available e-liquid flavourings in Europe, a Dutch research group found that, of the 219 unique ingredients present in more than 100 e-liquids, 213 were flavourings (Krusemann et al 2020). The mean number of flavourings per e-liquid was found to be 10. The most frequently used flavourings were vanillin (present in 35% of all liquids), ethyl maltol (32%) and ethyl butyrate (28%) (Table 2).

Table 2. The top 18 most frequently identified flavourings in a sample of 320 e-liquids in Europe

Rank	Flavour Chemical	% of total e-liquids studied	Flavour Description	Prevalence across EU[a]
1	Vanillin	42 %	Sweet, powerful, creamy, vanilla-like	35 %
2	Ethyl butyrate	41 %	Ethereal, fruity with buttery-pineapple-banana, ripe fruit and juicy notes	28 %
3	Cis-3-hexenol	35 %	Strong, fresh, green, grassy	18 %
4	Benzyl alcohol	32 %	Faint, sweet, almond fruity, somewhat chemical	14 %
5	Ethyl maltol	31 %	Sweet, fruity-caramellic, cotton candy	32 %
6	Ethyl vanillin	25 %	Intense, sweet, creamy, vanilla-like	19 %
7	γ-Decalactone	23 %	Coconut-peach	18 %
8	Methyl cyclopentenolone	23 %	Very strong, caramellic-maple, lovage	18 %
9	Ethyl methyl butyrate	22 %	Strong, green, fruity, apple with strawberry notes	16 %
10	Isoamyl alcohol	20 %	Breathtaking, alcoholic odour; in dilution a winey-brandy taste	4 %
11	γ-Nonalactone	19 %	Strong, fatty, coconut odour and taste	10 %
12	Menthol	18 %	Strong trigeminal cooling sensation with a slight mint note	12 %
13	Isoamyl isovalerate	16 %	Fruity, green-apple, pineapple, tropical, mango, apricot, cognac	11 %
14	Ethyl propionate	15 %	Strong, ethereal, fruity, rum-like	11 %
15	Linalool	15 %	Sweet floral-woody with slight citrus notes	15 %
16	γ-Octalactone	13 %	Sweet-coumarinic, coconut-like odour and taste	7 %
17	Cis-3-hexenyl acetate	12 %	Strong, fruity-grassy-green odour with banana notes	9 %
18	Maltol	11 %	Sweet, fruity, berry, strawberry, caramellic	23 %

EU: European Union

Adopted from Krusemann et al (2020), analyses were by gas chromatography-mass spectrometry

[a] Prevalence is reported as the number of e-liquids containing the respective flavouring as percentage of the total number of e-liquids

1.1.4 Other Chemical Constituents or Contaminants

The SERPR restrictions on specific constituents in vaping products, include maximum limits for diacetyl and 2,3-pentanedione, two of the so-called “diketone” or ‘buttery’ flavouring class of chemicals, both of which are known to have respiratory toxicity associated with their

production in industrial settings. In other cases, blanket prohibitions on substances based on function, such as colourings, are provided by the SERPR.

Under the SERPR, as shown in Table 3, there is a list of substances that vaping products must not contain above specified limits and only if unavoidable. Most of these are prohibited based on their intrinsic toxicological hazards, or their potential to facilitate the formation of toxic by-products when heated in presence of other substances.

Table 3. Chemicals or chemical properties prohibited in e-liquids under the SERPR

Section	
(a)	Carcinogenic, mutagenic, reprotoxic substances (CMRs), including- (I) additives that have CMR properties in unburnt form; (II) additives in quantities that increase, to a significant or measurable degree, the toxic or addictive effect or CMR properties of the product when it is consumed:
(b)	Specific target organ toxicity (STOT-RE) Category I substances other than benzoic acid-nicotine salts:
(c)	Respiratory sensitisers:
(d)	Radioactive substances:
(e)	Colouring substances:
(f)	Any pharmacologically active substance (medical, psychoactive, narcotic, anabolic, or herbal) other than nicotine:
(g)	Vegetable oils
(h)	Mineral oils
(i)	Additives and stimulant compounds that are associated with energy and vitality, including caffeine and taurine:
(j)	Glucuronolactone:
(k)	Ethylene glycol
(l)	Diethylene glycol:
(m)	Polyethylene glycol:
(n)	Food or dietary supplements:
(o)	Vitamins or other additives that create the impression there are health benefits or reduced health risks:
(p)	Probiotics:
(r)	Formaldehyde releasers: (I) quaternium (II) imidazolidinyl urea (III) diazolidinyl urea (IV) 2-bromo-2-nitropropane-1,3-diol (or 2-bromo-2-nitro-1,3-propanediol) (V) dimethyl-dimethyl hydantoin (DMDM hydantoin): (VI) (benzyloxy)methanol (or phenylmethoxymethanol): (VII) 2-chloro-N-(hydroxymethyl)acetamide; (VIII) hexahydro-1,3,5-tris(hydroxyethyl)-s-triazine: (IX) sodium hydroxymethylglycinate
(s)	The following sugars and sweeteners: (I) glucose (II) sucrose (III) fructose (IV) lactose (V) maltose (VI) saccharose

Section	
	(VII) acesulfame potassium (VIII) aspartame (IX) sodium saccharinate (X) stevia
(t)	The following preservatives: (I) triclosan (II) phenoxyethanol (III) isothiazolinone (IV) long chain parabens, including isopropyl paraben and its salts isobutylparaben, phenylparaben, benzylparaben, and pentylparaben

2 HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health risk assessments for e-liquids were found for New Zealand.

2.2 ACUTE HEALTH EFFECTS

This report does not address the chronic health impacts of vaping products when used (inhaled) as they are intended. Therefore, only single ingestion or dermal contact exposure and risks scenarios are considered. Toxicological properties of individual components of e-liquids are discussed, but the toxicological properties of heated aerosols generated from these liquids and chronically used are beyond the scope of this report.

2.2.1 Poisonings from e-liquids

New Zealand

There have been no deaths from acute poisonings involving e-liquids reported in New Zealand, although cases have been reported overseas, and the potential for this remains, both from child exploration and intentional suicide attempts.

According to the New Zealand National Poisons Centre (NPC) from August 2016 to 31 October 2021, there have been 433 contacts to the NPC regarding concerns over e-liquid toxicity, 49% of which were referred to a medical practitioner. The trend has been increasing, with 135 calls received in the first 10 months of 2021 (Table 4 and Table 5).

Table 4. Calls to the New Zealand National Poisons Centre for e-liquid exposures and illnesses

E-liquid exposure records/ year of contact	Containing nicotine	Unknown if nicotine	No nicotine	Total e-liquid	All human exposure records***
2016*	9	0	0	9	8,224
2017	34	3	4	41	21,066
2018	48	3	6	57	21,312
2019	67	0	1	68	22,924
2020	120	1	3	123	24,168
2021**	135	0	0	135	19,886
Total records	413	7	13	433	117,580

Source: Ms Lucy Sheffelbien and Dr Eeva-Katri Kumpula, NZ NPC 2021

*From 11 August to 31 December 2016 (3.5 months). **01/01 - 31/10/2021 (10 months). ***For general reference – these record numbers contain all records, whereas e-liquid record counts are “incidence counts”, i.e. multiple records about the same patient and incident (from multiple contacts) have been collapsed into one.

Table 5. Distribution across age groups of calls to the New Zealand National Poisons Centre about e-liquid exposures containing nicotine

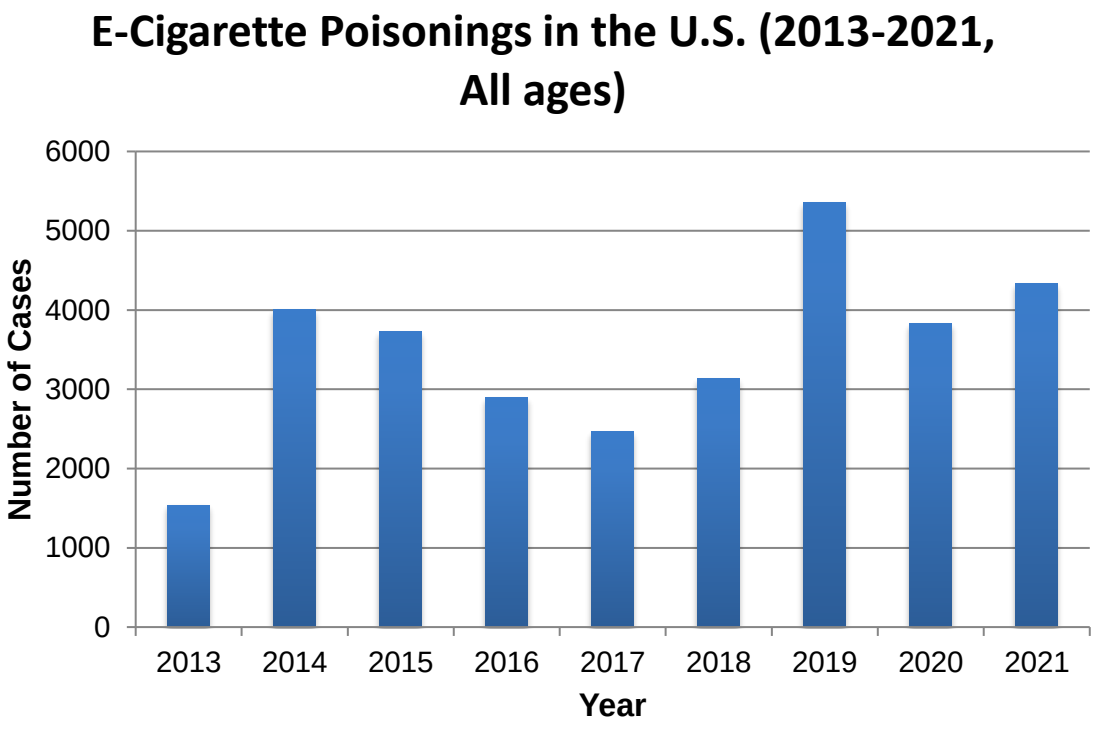
Patient age group	Patients	% of total
Under 1	32	8%
1	124	30%
2	50	12%
3-5	32	8%
6-12	7	2%
13-15	12	3%
16-17	14	3%
18-19	20	5%
20-69	70	17%
Unknown child	15	4%
Unknown adult	30	7%
Unknown age	7	2%
Total	413	100%

(Courtesy NZ NPC, 2021).

International

In the United States, as of 31 October 2021, U.S. national poison control centres have managed 4,335 exposure cases about e-cigarette devices and liquid nicotine for the year 2021 for all ages. This number has remained somewhat consistent since 2014 (Figure 1).

Figure 1. U.S. National Poisoning Statistics for E-Cigarettes and E-Liquids 2013-2021



Source: adapted from AAPCC 2021

In Australia, 70 cases (exposure incidents) were reported to the Poisons Information Centre in 2016 (Wylie et al 2019). The reported median concentration of the 43 commercial nicotine solutions involved in these cases was 20.2 mg/mL, (range, 0.06–200 mg/mL), but confirmatory testing was not performed and actual concentrations may be higher or lower than labelled, as noted earlier. Most exposed individuals had only mild symptoms at the time of the call to the PIC, mainly gastrointestinal disturbances; twelve had moderate symptoms, usually a gastrointestinal disturbance combined with sedation. The potential risks, however, should not be underestimated. Almost all exposures of children to nicotine-containing e-liquid required hospitalisation for monitoring of possible toxic effects. Research from the Queensland Poisons Information Centre, found that, across Australia, 76 of the 202 e-liquid poisoning victims between 2009 and 2016 were children, including 62 toddlers.

The death of an 18-month old infant in Victoria, Australia highlights the severe risk to infants gaining access to highly toxic nicotine e-liquids (Coroners Court of Victoria 2019). The New Zealand NPC data confirm that child exploration is a major factor in e-liquid poisoning concerns, with 58% of calls relating to children under the age of five (Table 5.).

The European Scientific Committee on Health Environmental and Emerging Risks (SCHEER) concluded that, with regard to acute poisonings and explosion risks from e-cigarettes, *"The overall weight of evidence for risk of poisoning and injuries due to burns and explosion, is strong. However the incidence is low."* (SCHEER 2021).

According to the SCHEER (2021) review, the stated nicotine concentrations in poisoning cases varied, ranging from 0 to 20 mg/mL.The percentage of e-liquids with high nicotine concentrations (e.g. 18 mg/mL) was highest within the unflavoured category (40%). The reason for this is hypothetically attributed to the fact that unflavoured e-liquids are often used as a 'nicotine booster' by consumers in order to add nicotine to hand-made e-liquid mixes (Havermans et al 2021). Another recent paper reporting that the top flavour categories in an analysis of 277 refill fluids were "fruity", "minty/mentholic", "floral", "caramellic", and "spicy" (Omaiye et al 2019). Among the analysed e-liquids (of which 170 contained nicotine), 85% had total flavour concentrations >1 mg/ml, and 37% were >10 mg/ml (1% by weight). Of the 170 e-liquids containing nicotine, 56% had a total flavor chemical/nicotine ratio >2.

2.2.2 Case reports

Oral exposure to e-liquids is the most common route of intoxication. Multiple toxicological events can be associated with ingestion of e-liquids but the most serious is neurological cholinergic crisis. Low doses of nicotine frequently also have stimulant effects (e.g., tachycardia). Vomiting is common with enteral exposures. Signs of central nervous system toxicity include ataxia and seizures. As doses increase, loss of nicotinic acetylcholine receptor specificity may occur and result in signs of muscarinic cholinergic toxicity, including extreme secretions and gastrointestinal disturbance. The highest levels of poisoning can result in neuromuscular blockade, respiratory failure, and death. Small ingestions for a child could therefore be deadly. With an estimated median lethal dose between 1 and 13 mg per kilogram of body weight, 1 teaspoon (5 ml) of a 1.8% nicotine solution could be lethal to a 90-kg person.

Oral exposure

Chen and colleagues reported a case of a 24-year-old woman in the U.S. who intentionally ingested up to 3000 mg of liquid nicotine intended for e-cigarette use. She was found without a pulse and despite aggressive supportive care, ultimately died from multiple acute infarcts, consistent with severe anoxic brain injury. The patient's toxicology testing was notable for plasma nicotine and cotinine levels each greater than 1000 ng/mL (Chen et al 2015).

Vomiting, tachycardia, grunting respirations, and truncal ataxia developed in a 10-month-old boy after he ingested a “small” amount of e-liquid nicotine (Bassett et al 2014). The vaping (or “vape”) shop that compounded the product reported that it contained a nicotine concentration of 1.8% (18 mg/mL) and unknown concentrations of oil of wintergreen (methyl salicylate), glycerin, and PG.

Seo and colleagues reported on a case of infant mortality in South Korea in which a 15-month old infant had ingested 5 mL of liquid nicotine (concentration: 10 mg/mL) used to refill an e-cigarette, her parents apparently mistaking it for cold medicine (Seo et al 2016). She involuntarily vomited immediately after ingestion but lost consciousness and was unresponsive. The infant was treated in hospital for 12 hours after which she was declared brain dead.

Dermal exposure

Dermal exposures to e-liquids have also been documented to result in acute toxicity. Specifically, although no deaths have been documented, dermal exposure to liquid nicotine products may produce significant systemic toxicity with delayed onset (Moore 2017). A study of 4745 poisoning cases in the under 5 year-old range in the U.S. found that 2.6% of the e-liquid poisoning cases from 2013 to 2017 involved dermal exposure (Chang et al 2019). The New Zealand NPC data include 6% of cases involving dermal exposure.

In one case report, a 15-month old girl developed delayed symptoms of nicotine toxicity after dermal exposure to a 3% (30 mg/mL) nicotine liquid solution. The patient was found playing with several bottles of “vape juice” and had the liquid on her hands, face and chest. The authors concluded that dermal was the primary route of exposure, although it is unclear how the possibility of oral exposure was excluded. She was initially asymptomatic at home, but presented to an outside emergency department upon recommendation from the poison control center. Three hours after initial exposure, and 2 hours after her arrival to the ED she developed multiple episodes of non-bilious, non-bloody vomiting, followed by excessive salivation, diaphoresis and labile mood. Initial laboratory studies were negative. She was decontaminated with soap and water, and symptoms slowly improved. Upon her arrival to the tertiary care hospital five hours after initial exposure, she was tachycardic (HR 145-186 bpm) and hypertensive (128/75 mm/Hg). Vomiting, diaphoresis and salivation had resolved. She did have a faint erythematous rash over exposed skin and labile mood. Her symptoms continued to improve and she was discharged home the day after initial exposure (Moore 2017).

2.2.3 Explosions and Burns

In addition to chemical toxicity from e-liquids, the liquids in contact with heated metal wires and a battery (often lithium), poses an explosivity risk if the product is not adequately safeguarded from components mixing or contacting the battery. Such incidents appear to be rare occurrences.

An incident involving an exploding e-cigarette device in Canterbury in January 2019 reportedly caused damage to a woman's home, but no reported injury (Redmond and Hayward 2019).

According to the U.S. Consumer Reports organisation, explosion and burn injuries from e-cigarettes increased starting in 2014 and although somewhat rare, were more common than previously thought and were quite serious when they did happen (Cooper 2016):

"The injuries can be serious, including flame burns, chemical burns, and blast injuries, mostly to the face, hands, thighs, and groin. Many require complex care involving emergency medicine personnel, plastic surgeons, burn care providers, and even vocational counselors and psychologists."

In Europe, the SCHEER has noted that the potential exists for injuries due to burns and explosions. However, the EU injury database does not yet include the relatively new product "electronic cigarette" category to allow for collecting information related to cases of injuries due to burns and explosions of the electronic cigarette devices (SCHEER 2021).

Seitz and Kabir (2018) reported on reviews of literature on explosion and burn injuries from e-cigarettes in the U.S. Thirty-one articles were included in the review and described 164 cases. Most patients (90%) were male and between 20 to 29 years old. In the majority of cases (65%), e-cigarettes exploded in pockets, compared to exploding in the face or hand. Common burned areas included the thigh, hand, genitals, and face. Burn severity was typically second-degree burns (35%) or a combination of second-degree and third-degree burns (20%). In all, 48 patients required skin grafting, with 19 reporting a median hospital stay of 5 days. This review has several implications, including the need for regulation of batteries and education of consumers regarding battery safety.

2.3 TOXICITY OF E-LIQUID INGREDIENTS

2.3.1 Nicotine Toxicity and Dose Response

Nicotine is a highly potent neurotoxicant. In acute toxicity cases, initial stimulatory effects occur within minutes and may include agitation, diaphoresis, nausea and vomiting, tachycardia, bronchoconstriction and seizures. At higher doses, a second phase involving bradycardia, hypotension, respiratory failure and coma may occur 1 to 4 hours after exposure (Royal Children's Hospital Melbourne 2019). Virtually any ingestion may cause some form of mild toxicity. The minimum potentially lethal dose varies in the literature as reported above, due to uncertainties around precision of ingested doses, is reported to range from 0.5 mg/kg or higher (Royal Children's Hospital Melbourne 2019), to over 4.4 mg/kg (Maessen et al 2020; Mayer 2014).

Scarpino and colleagues describe a biphasic neurotoxicological syndrome with nicotine intoxication, with one poisoning case exhibiting plasma nicotine and cotinine levels of over 2000 ng/mL two days after ingestion, initial loss of consciousness and cardiac arrest, following days later with brain death and fatal outcomes (Scarpino et al 2020).

Just a few drops of liquid nicotine could result in acute intoxication. The risk of lethality depends on the weight of the child and the concentration of liquid nicotine. According to the Children's Safety Network, ingesting less than a quarter of a teaspoon (approx.1.25 mL) of 1.8% concentrated liquid nicotine (approx. 22.5 mg) can be fatal to a 20 kg child (~1.1 mg/kg bw) (Children's Safety Network 2015). Seo and colleagues similarly considered that a lethal dose of nicotine could be as little as 40 mg in adults and 1 mg/kg in children (Seo et al 2016). However, some have recommended that children who have ingested 0.2 mg/kg or

more of nicotine and who are symptomatic be referred for medical assessment (Seo et al 2016).

Regarding lethality of nicotine from a single dose, it should be noted that there is some disagreement in the literature about the true threshold for acute human lethality. The widely cited value of 60 mg (approximately 1 mg/kg for an adult) as a lethal dose, was critically examined and discussed by SCHEER (Mayer 2014; SCHEER 2021). The 60 mg dose that is widely cited, was apparently taken from a century old report of an expert author's best guess at the time, and not able to meet current day standards of rigor or precision (Mayer 2014). Supporting this conclusion, a systematic review of e-liquid ingestion poisonings internationally found 31 poisoning cases, including 11 fatalities (Maessen et al 2020). In their review, Maessen and colleagues found that the minimum lethal dose, based on plasma nicotine/cotinine levels, was 4.4 to 8.9-fold higher than the 60 mg dose, or approximately 4.4 to 8.9 mg/kg for adults. Although an equivalent estimate was not presented for children, a point of departure could be estimated as 1/10 the adult range (i.e. 10x assessment factor for intraspecies variability), or 0.44 to 0.89 mg/kg in children.

Table 6 places the magnitude of difference in the dose range and potency for acute lethal toxicity between nicotine and the glycol carriers and flavourings into a comparative table. It is clear from this table that nicotine is far more hazardous than the glycol or flavouring components, and the risk assessment will focus therefore on exposure to nicotine.

Table 6. Acute toxicity of common e-liquid components

Component	CAS No.	Endpoint	Oral LD_{50} (mg/kg)
Propylene glycol	57-55-6	LD_{50} (oral) LD_{50} (dermal)	20,000 (rats)* 20,800 (rabbit)*
Vegetable glycerin	56-81-5	LD_{50} (oral) LD_{50} (dermal)	12,600 (rats)* >10,000 (rabbit)*
Menthol (DL)	89-78-1	LD_{50} (oral) LD_{50} (dermal)	2,046 (rats)* 5,000 (rat)*
Tobacco flavour	No data	No data	
Vanillin	121-33-5	LD_{50} (oral) LD_{50} (dermal)	3,978 (rats)** > 5,000 (rabbits)**
Ethyl maltol	4940-11-8	LD_{50} (oral) LD_{50} (dermal)	1221 (rats)** > 2,000 (rabbits)**
Nicotine	54-11-5	LD (human) LD_{50} (oral, rodents) LD_{50} (dermal, rats)	1 – 9 (adults)*** 0.5 – 2.5 (infants)*** 50 (rats) 3 (mice) 285 (rat)

* Pubchem 2021. https://pubchem.ncbi.nlm.nih.gov/compound/Propylene-glycol#section=Acute-Effects; ** ECHA (2010b); *** Maessen et al (2020)

Table 7 shows the acute and chronic reference doses used in risk assessments internationally for nicotine.

Table 7. Summary of acute and chronic reference dose values for nicotine.

Organisation	Key study	Route	Endpoint	NOAEL (mg/kg bw)	UF	ARfD (mg/kg b.w.)	ADI (mg/kg bw per day)
UK PSD, 2007 **AFFSA, 2009**	Woolf *et al*. 1997 (human study)	Dermal, acute	Clinical symptoms	0.01 (LOAEL)	100	0.0001	0.0001
US EPA, 2008	Yuen *et al*. 1995 (rat study)	Oral, 10 days	Hepatotoxicity	1.25	1000	Only AOEL derived (0.00125 mg/kg bw per day). No consumer exposure expected	
BfR, 2009; EFSA 2009	Lindgren *et al*. 1999 (human study)	iv, acute	EEG and heart rate frequency changes	0.0035 (LOAEL)	10; 44% oral bioavail ability	0.0008	0.0008

NOAEL: no observed adverse effect level, LOAEL: Lowest observed adverse effect level, UF: uncertainty factor, ARfD: acute reference dose, ADI: acceptable daily intake, UK PSD: United Kingdom Pesticide Safety Directorate, AFFSA: Agence Française de Sécurité Sanitaire des Aliments, US EPA: United States Environmental Protection Agency, BfR: German Federal Institute for Risk Assessment, EFSA: European Food Safety Authority, AOEL: Acceptable Occupational Exposure Level, iv: intravenous

When considering a point of departure for toxicological risk assessment, the European Food Safety Authority (EFSA) developed an acute reference dose (ARfD) for nicotine, in order to set residue limits for nicotine that is found in wild culinary mushrooms (EFSA 2009). In their risk assessment, EFSA derived an ARfD of 0.0008 mg/kg bw using a LOAEL of 0.0035 mg/kg nicotine by intravenous administration, and an uncertainty factor of 10x and an oral bioavailability factor of 0.44 to account for differences in oral vs i.v. exposures (Table 7, 8).

Lethal dose thresholds as presented in Table 6, are not used as the basis for the risk assessment in this report, although it is noted that the difference between the EFSA ARfD for heart rate increase is only slightly more than 20-fold lower than the reported lethal dose in humans.

According to a review by England and colleagues, the current research database supports that repeated exposures to nicotine contribute critically to the known adverse effects of tobacco exposure, including reduced pulmonary function, auditory processing defects, impaired infant cardiorespiratory function, and may contribute to cognitive and behavioral deficits in later life. Nicotine exposure during adolescence is associated with deficits in working memory, attention, and auditory processing, as well as increased impulsivity and anxiety (England et al 2017). Recent animal studies suggest that nicotine has a priming effect that increases addiction liability for other drugs.

Nicotine is not believed, based on current data, to be a direct or complete carcinogen (Price and Martinez 2019), and cancer risk is not further considered in this report.

Nicotine is also a concern for acute toxicity from dermal contact. Liquid nicotine can be harmful when swallowed or absorbed through the skin (Children's Safety Network 2015). Maina and colleagues measured nicotine trans-dermal migration using e-liquid with 0.8 mg/mL nicotine and found significant dermal absorption after 2 hours and progressing

through 24 hours (Maina et al 2016). There are no reports of fatalities in the international literature from nicotine exposures dermally, and poison centre call surveillance reports only 2.6% of cases (Maessen et al 2020). One study found that the presence of some flavouring chemicals significantly enhances the dermal absorption rate of nicotine when compared with nicotine in PG alone (Frasch and Barbero 2017).

The EFSA ARfD value for nicotine of 0.0008 mg/kg in Table 7 is used as the toxicological point of comparison in this risk assessment.

2.3.2 Propylene Glycol and Glycerin Toxicity

Propylene glycol (PG; 1,2-dihydroxypropane; 1,2-propanediol; methyl glycol; and trimethyl glycol) is a clear, colourless, slightly viscous liquid at room temperature. It is practically odourless and tasteless. PG is used by the chemical, food, and pharmaceutical industries as a humectant to absorb extra water and maintain moisture in certain medicines, cosmetics, or food products (Fowles et al 2013; LaKind et al 1999). It is also used as a solvent for food colours and flavours, and also in the paint and plastics industries. PG has been widely used for decades as a solvent for many intravenous drugs, and in some oral preparations such as cough syrups. PG is listed as GRAS by the USFDA. Substances listed as GRAS are deemed as generally safe under conditions of intended use as a food additive. Thus, GRAS substances are safe for ingestion, but not necessarily for other routes of administration like inhalation.

PG is well absorbed orally and can also be absorbed through skin or mucous membranes from topical preparations (NASEM 2018). Following absorption, the kidneys eliminate 45% of the PG, and the liver metabolises the remainder to lactic acid, pyruvic acid, or acetone. Thus, patients with impaired liver and/or kidney function are generally thought to be at increased risk for developing PG toxicity following high-dose oral or intravenous administration.

No human fatalities are known to have occurred in relation to consumer product use, or from acute accidental or occupational exposures to PG (Fowles et al 2013; LaKind et al 1999; NASEM 2018).

In clinical toxicology case reports, PG exposure occurs from its use as a carrier molecule for intravenous pharmaceuticals that, under scenarios of continuous infusion or with multiple medications, can result in a total dose that saturates metabolising enzymes (Hayman et al 2003). One case involving an iatrogenic exposure to Lorazepam reported severe metabolic acidosis from PG metabolism (Zosel et al 2010); the peak blood concentration of PG administered intravenously was 659 mg/dL. Another example, described by Zar et al (2007), reported infusion of 1699 g PG over 7 days or up to 213 g PG/day, as a continuous infusion of i.v. Lorzepam, resulting in confusion, hyperosmolality, lactic acidosis, and acute kidney injury. In these cases, a clinically measured anion gap metabolic acidosis, with concomitant osmolar gap, is typically reported, and a full recovery occurred following supportive treatment (Doty and Sahn 2003).

Although the clinical case reports of PG exposures demonstrate that high-dose oral and intravenous exposure to PG can induce toxicity (Belkoniene et al 2019), the relevance of those studies to potential health effects of PG from ingestion or dermal contact with e-liquids depends on the dose and pharmacokinetics of PG following ingestion. There are no studies of clinical measures of potential acute PG toxicity (e.g., anion gap, lactic acidosis) among heavy users of e-cigarettes, or which have measured blood/serum levels of PG following use of vaping devices containing PG-based liquids.

The acute lethal dose values for PG in rodents are summarised by the Agency for Toxic Substances and Disease Registry (ATSDR 1997). One study in rabbits found the minimal dose causing lethality by the oral route was 18.9 g/kg (Fowles et al 2013). ATSDR reports NOAELs of 10,000 mg/kg for reproductive effects in mice.

Based on analyses of case reports, Lim and colleagues attempted to arrive at a "safe" dose of PG for repeated administration of antiseizure drugs that are routinely compounded in 40 percent PG (Lim et al 2014). They suggested a maximum cumulative dose of 69 g/day in a paediatric population. It is unclear from their analysis what a maximum safe oral dose of PG would be in a single event setting. If one conservatively assumes that the entire 69 g daily dose occurs in one sitting, with 100% absorption, this would amount to a dose of approximately 1 g/kg for an adult, or 6.3 g/kg for an 11 kg child.

The daily inhaled dose of PG from vaping is considerable. Burstyn estimated the potential levels of exposure to PG from e-cigarettes, "assuming extreme consumption of the liquid per day via vaping (5 to 25 ml/day and 50–95 percent propylene glycol in the liquid)" and concluded that: "levels of propylene glycol in inhaled air can reach 1–6 mg/m^3." (Burstyn 2014). With an assumption of complete absorption via inhalation, Burstyn concluded that "estimated levels of exposure to PG and glycerin are close enough to TLV to warrant concern." However, putting these values in perspective with the clinical data from intravenous administration of PG in adults, Speth and colleagues (1987) reported that doses from 5 to 21 g/day, which are comparable to the 5 to 25 ml/day calculated by Burstyn, were not associated with any evidence of adverse effects. In the study by Speth and colleagues, peak plasma concentrations of PG from i.v. drug delivery ranged from 48 µg/ml (5.1 g/day; ~88 mg/kg/day) to 425 µg/ml (21 g/day; ~488 mg/kg/day). Investigators have found clinical evidence of toxicity at serum PG concentrations that exceeded 250 µg/ml (Hansen et al 2015), although it is important to note that these are following intravenous administration.

In 1974, the World Health Organization (WHO) recommended a maximum dose of 25 mg/kg bw/day of PG when ingested chronically as a food additive (JECFA 1974). Thus, for a typical young adult with a body weight of 60 kg, this would be equivalent to 1.5 g/day, which is considerably less than the 5–25 ml/day "worst case" exposure to PG from vaping estimated by Burstyn (2014). The WHO estimate contains a conservative margin of safety from the toxicological endpoints used in the assessment.

Glycerin (glycerol), is GRAS for use as a food additive by the USFDA and is widely used in cosmetics and over the counter medications that include analgesics, dermal protectants, and ophthalmic drugs. It is used as a laxative and can be administered clinically orally or intravenously for some procedures (Cosmetic Ingredient Review 2014).

There are no reliable estimates for human lethal doses of glycerin, although an oral LD value of 1428 mg/kg in rodents is reported from a secondary source (Cosmetic Ingredient Review 2014). The same source states that there were no signs of toxicity when human subjects were orally administered 30 mL glycerin. Adverse effects in human subjects following the oral administration of glycerin reportedly include: mild headache, dizziness, nausea, vomiting, thirst, and diarrhea (Cosmetic Ingredient Review 2014).

Propylene glycol sensitisation

It has well known that some individuals can develop allergic reactions to PG following repeated dermal applications (Al Jasser et al 2011; Fowles et al 2013; LaKind et al 1999; Zug et al 2008). Although most dermal reactions to PG are the result of irritation, true immunological reactions have been confirmed through patch testing. In a patch test of 1,226 patients who received an application of 5 percent PG in Vaseline, or 10, 30, or 50 percent in water, 208 (17 percent) of the subjects had evidence of irritation and/or allergic dermatitis

(LaKind et al 1999). Of those showing some dermal reaction, 195 were from irritation, but 13 exhibited an allergic reaction (NASEM 2018). However, a more recent analysis of allergic dermatitis found an incidence of only 2.1 percent in a large sample (5,083 subjects in 2007–2008), and this was significantly decreased from previous years (3.8 percent of 4,095 subjects in 1996–1998) (NASEM 2018).

In contrast, a review of 45,138 skin patch test patients exposed to 20% PG concluded that some or all of the 1044 (2.3%) "positive" reactions were likely to be irritant effects rather than true sensitisation. In this review, 271 (0.6%) patients exhibited clear irritant reactions. PG was concluded to possess a very low sensitising potential (Lessmann et al 2005). This study serves to illustrate that the interpretation of skin patch testing is complicated when the test material is also a slight irritant in some individuals, and this appears to be the case with PG.

2.3.3 Flavourings

The flavouring chemicals used in e-liquids are predominantly approved food additives and many are GRAS according to the USFDA. The acute oral toxicity of these compounds is generally low and the amount ingested in a given formulation will be small in relation to their acute toxicity thresholds.

In the exposure scenarios in this report, two of the most commonly encountered flavourings, vanillin and ethyl maltol are considered to be constituents of the e-liquid. Acceptable Daily Intakes (ADI) for these food additives are The European REACH registration dossiers for vanillin and ethyl maltol, cite oral LD50 values in rats of 3978 mg/kg and 1221 mg/kg, respectively (ECHA 2010a; 2010b). In the REACH dossier for ethyl maltol, no mortality or clinical signs were observed in rats orally exposed to 340 mg/kg ethyl maltol in an Organisation for Economic Co-operation and Development Good Laboratory Practice compliant study. An acute reference dose could be approximated with uncertainty factor of 100 to be 3.4 mg/kg.

Some food flavourings may carry allergenic properties. For example, cinnamaldehyde is widely used as a flavouring agent in foods and confectionary and is known to cause skin sensitisation in some people. However, oral allergy to cinnamon flavouring has only been sporadically reported (Isaac-Renton et al 2015). In these cases, a variety of sources have been implicated, including candy, chewing gum, mouthwash, lip sunscreen, cinnamon toast, volatile oils, and toothpaste. The clinical presentation of intraoral allergic reactions varies greatly, and, as a result, clinicians often do not recognise the diagnosis. Allergic reactions to e-liquids are considered in the SERPA, which prohibits respiratory sensitisers.

A regulatory approach to reducing contact sensitisers in e-liquids has been proposed to restrict such ingredients to a 0.1% maximum threshold concentration (i.e. 1 mg/mL) in the e-liquid (Costigan and Belmonte, 2017).

An increasing number of scientific studies *in vitro* have reported pro- or anti-inflammatory properties and induction of oxidative stress in human cells with some flavouring chemicals (Table 8). These observations have not formed a basis for statements on risks of acute systemic effects of oral exposures, and most of the studies focus on pulmonary cell types and inhalation exposures. It is presently unknown whether some of these properties may influence inflammatory processes in the gastrointestinal tract or systemically.

Table 8. In-vitro Toxicological Effects of E-Liquid Flavourings

Toxicological Effect	Flavouring	Cell type(s)	
Cytotoxicity	Alpha pinene; decanal, eugenol; hexanal, nonanal; trans-2-hexen-1-al; cinnamaldehyde, ethyl maltol; limonene	Pulmonary epithelial Macrophage	(Morris et al 2021; Muthumalage et al 2019)
Pro-Inflammatory cytokine release	Ethyl maltol; alpha pinene; hexanal; cinnamaldehyde	Pulmonary epithelial Macrophage	(Bengalli et al 2017; Lerner et al 2016; Morris et al 2021)
Reduced Inflammatory cytokine release	Linalool; L-carvone; diketones	Macrophage	(Morris et al 2021)
Oxidative Stress (ROS)	2,3-Pentanedione 2,3-Hexanedione 2,3-Heptanedione Ethyl maltol Vanillin	Pulmonary epithelial Macrophage	(Morris et al 2021; Muthumalage et al 2019)

3 EXPOSURE ASSESSMENT

For e-liquids, 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 is 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.

3.1 EXPOSURE PARAMETERS

3.1.1 Exposure subject

Cases of unintentional ingestion of e-liquid are predominantly in the age range up to 5 years. The 1-2 year old age group is taken to be the highest risk group for exploratory exposures.

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).

3.1.2 Oral Ingestion Scenarios

Case reports internationally have found that volumes of e-liquid ingested by infants and toddlers range from 1-10 mL (SCHEER 2021). For the purposes of this report, ingested volumes for scenarios are assumed to be 0.5 or 5.0 mL of e-liquid.

The SERPR regulation allows for the existence of e-liquid products of up to 50 mg/mL concentration, as nicotine salt, or 20 mg/mL as the free base. A more typical concentration of nicotine in e-liquid formulations is 1 to 10 mg/mL, with 1.8 mg/mL reported as the most commonly used (NASEM 2018; SCHEER 2021). For the purpose of this report, e-liquid nicotine concentrations of 1.8 or 20 mg/mL are considered.

The acute intoxication case reports that allow the estimation of lethal doses of nicotine, are external doses that do not consider % absorption, and so although the rate of oral absorption through ingestion is likely to be less than 100% (EFSA has used a value of 44% in its risk assessment on nicotine (EFSA 2009)), a conservative approach of 100% absorption is made in the risk assessment.

Scenario 1: Exploratory taste (low volume) by toddler

Body weight = 11 kg
Volume ingested: 0.5 mL
Absorption % = 100% for nicotine, PG and flavours
Nicotine concentration: 1.8 or 20 mg/mL (scenario 1a and 1b)
Carrier: PG
Flavour: Ethyl maltol + Vanillin (6% by weight of each) (Omaiye et al 2019)

*Dose = C * V * F_{abs} / BW*

Typical Nicotine E-Liquid:
[1.8 mg/mL * 0.5 mL * 1.0] / 11 kg = 0.082 mg/kg (nicotine)
[888 mg/mL * 0.5 mL * 1.0] / 11 kg = 40.4 mg/kg (PG)
[60 mg/mL * 0.5 mL * 1.0] / 11 kg = 2.7 mg/kg (ethyl maltol or vanillin)

Highest Allowed Nicotine E-Liquid:
[20 mg/mL * 0.5 mL * 1.0] / 11 kg = 0.91 mg/kg
[830 mg/mL * 0.5 mL * 1.0] / 11 kg = 37.7 mg/kg (PG)
[60 mg/mL * 0.5 mL * 1.0] / 11 kg = 2.7 mg/kg (ethyl maltol or vanillin)

Scenario 2: Larger volume swallowed by toddler

Body weight = 11 kg
Volume ingested: 5 mL
Absorption % = 100%
Nicotine concentration: 1.8 or 20 mg/mL (scenario 2a and 2b)
Carrier: PG
Flavour: Ethyl maltol + Vanillin (6% by weight of each) (Omaiye et al 2019)

*Dose = C * V * F_{abs} / BW*

Typical Nicotine E-Liquid:
Dose (nicotine) = [1.8 mg/mL * 5 mL * 1.0] / 11 kg = 0.82 mg/kg
Dose (PG) = [888 mg/mL * 5 mL * 1.0] / 11 kg = 404 mg/kg (PG)
Dose (flavouring) = [60 mg/mL * 5 mL * 1.0] / 11 kg = 27 mg/kg (ethyl maltol or vanillin)

Highest Allowed Nicotine E-Liquid:
Dose (nicotine) = [20 mg/mL * 5 mL * 1.0] / 11 kg = 9.1 mg/kg
Dose (PG) = [830 mg/mL * 5 mL * 1.0] / 11 kg = 377 mg/kg (PG)
Dose (flavouring) = [60 mg/mL * 5 mL * 1.0] / 11 kg = 27 mg/kg (ethyl maltol or vanillin)

Table 9 summarises the dose estimates from oral exposures in the two scenarios, in comparison with reference doses.

Table 9. Estimates of oral exposure to nicotine and other e-liquid components from ingestion of flavoured e-liquid for a child, 1-2 years (11 kg)

	Exposure Scenarios			
	Typical Nicotine (1.8 mg/mL)		Maximum Allowed Nicotine (20 mg/mL)	
Volume of e-liquid ingested (mL)	**Low (1a) 0.5**	**High (2a) 5.0**	**Low (1b) 0.5**	**High (2b) 5.0**
Weight of nicotine ingested (mg)	0.9	9	25	250
Nicotine Dose (mg/kg bw/event)	0.08*	0.82*	0.91*	9.1*
Weight of PG ingested (mg)	440	4400	415	4150
PG Dose (mg/kg bw/event)	40	400	37.7	377
Weight of Ethyl maltol ingested (mg)	30	300	30	300
Ethyl maltol Dose (mg/kg bw/event)	2.7	27	2.7	27
Weight of Vanillin ingested (mg)	30	300	30	300
Vanillin Dose (mg/kg bw/event)	2.7	27	2.7	27

PG: propylene glycol

* Yellow highlighted values exceed the acute reference dose of 0.008 mg/kg bw (EFSA 2009)

3.1.3 Dermal absorption of nicotine from e-liquids

Nicotine is the only component of e-liquids that has been shown to have any dermal toxicity potential. PG, VG, vanillin, and ethyl maltol have all been found to cause no acute toxicity or clinical signs at limit doses of toxicity testing. The dermal toxicity assessment therefore only considers nicotine absorption. The absorbed dose of nicotine from e-liquid was calculated in a previous publication (Frasch and Barbero 2017). Their calculated maximal absorption used a finite dose with the fraction absorbed empirically determined to be 0.3 (30%). Empirical data show that only about 25-30% of the finite dose is absorbed over 4 hours.

$$mT = 0.3 \times \text{nicotine load} \times A_{exp}$$

Where mT = total mass of nicotine absorbed (at 4 hours, only about 25-30% was observed to be absorbed)

Nicotine load N_L = 1.01 g/mL (density of PG) x 0.0069 mm film x 145 cm^2 = 1.00 mL.

N_L = 6.9 $\mu L/cm^2$ (@ 25 mg/mL) = 172.5 $\mu g/cm^2$

A variation on their dermal absorption is described in scenario 3 below:

Scenario 3: dermal exposure to a toddler, with 1 mL (10 mg/mL nicotine) spilt on the hands and unwashed for 4 hours.

Table 10. Dermal absorption exposure estimates for nicotine to a toddler

Parameters:		
Fraction of nicotine absorbed – finite dose scenario	F_{absorp}	0.3 (Frasch and Barbero 2017)
Time available for absorption	T_{max}	4 hours (Frasch and Barbero, 2017)
Nicotine concentration in e-liquid	*C*	10 mg/mL (Frasch and Barbero, 2017; half maximal allowed under SERPR)
Surface area of skin exposed	$AREA_{derm}$	One hand (145 cm^2) (Cressey and Horn, 2016)
Thickness of glycol based film layer on skin	L_{film}	0.0069 cm (Frasch and Barbero, 2017)
Nicotine load	N_L	6.90 μL/cm^2 (calculated) = 172.5 μg/cm^2 (calculated for 25 mg/mL C)
Body weight[c]	*BW*	11 kg (Cressey and Horn, 2016)
Absorbed nicotine dose through skin: $U_{ext} = AREA_{derm} \times L_{film} \times C$ x F_{abs}		
E-liquid nicotine (10 mg/mL)		3 mg
Estimated systemic dose (mg/kg)		
Nicotine from 1 mL on skin total:		0.27 mg/kg
Nicotine from 1 mL on skin for 4 hours:		0.092 mg/kg (approximately 30% of total)

* Yellow highlighted values exceed the acute reference dose of 0.008 mg/kg bw (EFSA 2009)

4 RISK CHARACTERISATION

Nicotine represents the most significant driving factor in e-liquid toxicity by any exposure route. The exposure assessments in this report suggest that even small ingestions or dermal exposures of typical concentrations of nicotine in e-liquids exceed the EFSA ARfD and thus pose an acute toxicity risk to children (Tables 9 &10). The 20 mg/mL allowed upper limit for nicotine strength in e-liquids poses a particularly potent acute toxicity risk for accidental ingestion, exceeding not only the EFSA ARfD, but also published estimates of doses that can cause human fatality.

This calculated risk is supported by epidemiological data. Acute nicotine toxicity can be fatal, and although no incidents of such fatalities have been reported in New Zealand, there is ample evidence from international experience for this to be a possible risk in New Zealand.

The exposure scenarios suggest that, if a child were to ingest 0.5 mL of e-liquid, most e-liquids would pose an acute toxicity risk, and the nicotine strength would need to be no greater than 0.2 mg/mL to avoid acute toxicity in the form of heart rate increase, which is the basis for the EFSA ARfD. Similarly, spilling 1 mL of a typical e-liquid on the hands without washing hands off for several hours could also result in toxicity.

Child safety caps on e-liquid containers are one way to reduce the likelihood of such exploration exposures occurring. Some products may already employ these safety measures, although this does not appear to be required under SERPR. A public education campaign on this issue may also help prevent inadvertent intoxications.

A less severe and less common property of e-liquids, is sensitisation potential from PG or some individual flavouring chemicals, such as cinnamaldehyde. It is not possible to capture, with the information currently available, dose thresholds for allergenicity of these mixtures, but the SERPR contains provisions that, in theory, prevent introduction of respiratory sensitisers into vaping products.

The toxicology of inhaled flavouring chemicals is under investigation by numerous researchers internationally, and it is anticipated that future *in vitro* and *in vivo* toxicology studies will enable better assessments and regulatory intervention where necessary to protect public health from product safety issues.

5 CONCLUSIONS

- Electronic cigarette liquids containing nicotine are highly toxic by all routes of exposure, and there is clear evidence of acute intoxications, including deaths, overseas.

- No acute fatalities have occurred in New Zealand as a result of e-liquid exposure.

- Child exploration is clearly a major concern for e-liquid exposures and represents the majority of calls (62%) to the New Zealand NPC. One child fatality has occurred in Australia. Child safety caps to reduce likelihood of children becoming exposed to e-liquids are used in some products, but this does not appear to be required currently under SERPA/SERPR.

- The vast majority of reported intoxications and calls to the New Zealand NPC from e-liquids involve oral ingestion.

- An acute oral dose as small as 0.5 mL of a 1.8 mg/mL nicotine e-liquid solution could pose a risk of acute intoxication and possibly death in a toddler, according to historical assumptions about nicotine toxicity. The maximally allowed nicotine content in e-liquids (20 mg/mL as free base under SERPR) poses an even greater serious acute toxicity risk for small children.

- An acute dermal dose to achieve toxicity is less likely, though still achievable.

- There is no authoritatively accepted threshold dose for nicotine acute lethality. For many years, 1 mg/kg has been accepted as an acutely toxic and potentially lethal dose for nicotine. More recently, the EU and others have considered that a fatal dose is more likely to be 4.5 to 8.9-fold higher. In either case, extreme caution and product safety measures should be implemented to safeguard against small children imbibing these liquids.

- The SERPA provides a framework for public health measures to be taken in the face of data gaps on product safety to guide inclusion and exclusion of ingredients and contaminants from vaping devices and to establish maximum limits for each.

- Child exploration oral or dermal exposure to glycols and flavouring chemicals in e-liquids is unlikely to present an acute life-threatening situation, but acutely toxic doses and non-life threatening illness can still be achieved in the oral ingestion scenarios presented in this report.

- Allergic reactions to e-liquids have not been tracked, but some components of e-liquids are known skin sensitising agents. The SERPR provides a mechanism to identify and prohibit respiratory allergens in e-liquids, and as flavouring chemicals are becoming better studied, it is recommended that this area be watched for scientific developments.

- Explosion and burn injuries have been reported internationally, and may be on the rise, but although at least one case of an exploding device was noted, no injuries from e-cigarette explosions in New Zealand have been reported. Product safety QA/QC measures for batteries and device design may help prevent such events,

although exploring precise elements of such measures would require a separate review.

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