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REVIEW ARTICLE

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Solvent-based paint and varnish removers: a focused toxicologic review of existing and alternative constituents

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Abstract

Paint and varnish removers constitute a major potential source of organic solvent exposure to contractors and home improvement enthusiasts. Unfortunately, the leading paint remover formulations have traditionally contained, as major ingredients, chemicals classified as probable human carcinogens (eg, methylene chloride) or reproductive toxicants (eg, *N*-methylpyrrolidone). In addition, because of its unique toxicology (ie, hepatic conversion to carbon monoxide compounding generic solvent narcosis and arrythmogenesis), high volatility, and rigorous requirements for personal protective equipment, methylene chloride exposures from paint removers have been linked to numerous deaths involving both occupational and consumer usage. The aim of this review is to summarize the known toxicology of solvent-based paint remover constituents (including those found in substitute formulations) in order to provide health risk information to regulators, chemical formulators, and end-users of this class of products, and to highlight any data gaps that may exist.

KEYWORDS

carboxyhemoglobin, carcinogen, methylene chloride, narcosis, *N*-methyl pyrrolidone, organic solvents, paint remover, paint stripper, reproductive toxicants, varnish remover

1 | INTRODUCTION

Paint and varnish removers are an important class of products marketed to consumers, contractors, small businesses (eg, furniture and bathtub refinishers), and large operations (eg, aircraft maintenance). In addition, municipal and private entities may use similar formulations for graffiti removal. In light of recent revelations of worker and consumer fatalities utilizing this class of products, considerable attention has focused on chemical safety issues, including potential alternative formulations (CDTSC, 2014; CDTSC, 2016; CDTSC, 2018a; CDTSC, 2018b; Erikson, 2018; Morose, Marshall, & McCarthy, 2020; Morose, Marshall, McCarthy, Harripersaud, & Giarrosso, 2017; Morris & Wolf, 2006). The objective of the present analysis was to briefly review the known toxicology of a variety of solvent-based paint and varnish remover constituents, including both those currently in commerce and those referenced in the literature as being considered for alternative formulations. In doing so, we aimed to: 1) briefly summarize available data; 2) identify toxicologic "data gaps"; and 3) help decision-makers avoid what have been termed "regrettable substitutions" (NAS, 2014).

2 | METHODS

Common constituents of commercially available and prototype solvent-based paint and varnish removers were identified by consulting the Consumer Product Information Database (CPID, 2019) (formerly the Household Product Database [HPD] within TOXNET), the Hazardous Substances Data Bank (HSDB, 2020) of the National Library of Medicine, the California Department of Public Health's resource documents on paint stripper composition and required personal protective equipment (CDPH, 2013, 2014), the Toxic Use

Correction added on 12 May 2020, after first online publication: The article keywords were missing and have been added.

Reduction Institute (TURI) of the University of Massachusetts resource page on paint and coating removal (TURI, 2020), and the open literature on "paint stripper safety".

Potential carcinogenicity and reproductive/developmental toxicity of these constituents were tabulated utilizing authoritative databases, including the USA Environmental Protection Agency's Integrated Risk Information System (IRIS, 2019), Department of Health and Human Services' National Toxicology Program (NTP, 2016), California Environmental Protection Agency's (CalEPA's, 2019) "Proposition 65" (Safe Drinking Water and Toxic Enforcement Act) List, and the International Agency for Research on Cancer's (IARC's) Monographs on the Evaluation of Carcinogenic Risks to Humans. Information on other specific organ system toxicity was extracted from the IRIS, NTP, IARC, and CalEPA documents, from databases maintained by professional organizations (ie, the American Conference of Governmental Industrial Hygienists [ACGIH] and American Industrial Hygiene Association [AIHA]), and selectively from the primary toxicology literature (as accessed through the National Library of Medicine's PubMed system). Excluded categories of chemical paint stripper products included caustics and abrasives, leaving a broad category of "solvent-based" strippers as the subject of the present review. Minor constituents (such as surfactants) have also been omitted from consideration.

Also beyond the scope of the present review were safety issues (eg, flammability), product effectiveness/ease of use, and environmental issues (volatile organic compound [VOC] reactivity status; ecotoxicology), all of which may influence the choice of alternative paint stripper formulations (Morose et al., 2020).

3 | RESULTS

Based upon literature review, most commercially available solvent-based paint strippers clustered in a relatively small number of formulation categories:

1 Methylene chloride (dichloromethane)-based strippers (most including methanol, toluene, or acetone as minor constituents).
2 *N*-methylpyrrolidone (NMP)-based strippers, with or without formic acid or benzyl alcohol as minor constituents.
3 Strippers utilizing dibasic esters (DBEs; eg, dimethyl, -adipate, -glutarate, and -succinate), with or without triethyl phosphate.
4 Benzyl alcohol-based strippers.
5 A newly introduced stripper utilizing methyl acetate and 1,3-dioxolane (Erikson, 2018).

The constituents enumerated above are tabulated in Table 1, which includes Chemical Abstracts Service (CAS) Registry Number, carcinogen or reproductive toxicant classification by authoritative bodies (when available), and selected general toxicology information. Chemical constituents of particular interest are discussed in the paragraphs that follow:

Methylene chloride (CAS # 75–09-2; CH_2Cl_2), also referred to as dichloromethane (DCM), is a clear, sweet-smelling, volatile liquid that is non-flammable under most conditions. With a molecular weight of 84.9 g/mol, DCM has a vapor density relative to air of 2.93, resulting without adequate air circulation in its relative accumulation near floor level and in sumps (eg, tanks, mixing vessels, and bathtubs) (ACGIH, 2001; NTP, 2016). DCM's boiling point is remarkably low (~40 °C). With absent air exchange, DCM's saturation vapor pressure of 349–440 Torr at 20–25 °C would translate to concentrations of 460 000–580 000 parts per million (ppm) at room temperature, indicating that evaporation of an unrestricted volume of DCM within a confined space could actually generate an oxygen-deficient atmosphere (ACGIH, 2001; NTP, 2016). Given DCM's remarkable volatility, its current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for an 8-h time-weighted average (PEL-TWA: 25 ppm) and 15-min short-term exposure (PEL-STEL: 125 ppm), as well as the National Institute for Occupational Safety and Health's (NIOSH's) immediately dangerous to life or health level (IDLH: 2300 ppm) are of considerable practical importance (NIOSH, 1994; OSHA, 1998).

DCM is a major constituent in many paint and varnish removers ("paint strippers"), as well as being used as a constituent in adhesives, as a blowing agent in polyurethane foams, a metal degreaser, and historically in the decaffeination of coffee and in the production of cellulose acetate fibers and films (ACGIH, 2001; NTP, 2016). Under the Federal OSHA standard, only full-face, pressure demand, supplied-air respirators are approved for use with DCM above its PEL because of the compound's high toxicity and ability to quickly saturate vapor cartridges (OSHA, 1998). To underscore the relevance of this requirement, for two paint stripper-related fatalities investigated by the California Department of Public Health, DCM exposure levels were estimated to range between 3700 and 30 000 ppm (Jennifer McNary, MPH, CIH, personal communication, 6/4/2012). In the former case, the decedent had been wearing a half-face vapor-cartridge respirator prior to being overcome by DCM vapor (Macisaac et al., 2013).

In terms of toxicokinetics, DCM is readily absorbed by ingestion, inhalation and skin contact, the latter two routes being significant in occupational and avocational settings (Stewart & Dodd, 1964) (ACGIH, 2005; Divincenzo, Yanno, & Astill, 1971; USEPA, 2011). DCM is distributed throughout the body, with evidence of sequestration in adipose tissue in at least one human volunteer study (Engstrom & Bjurstrom, 1977). Metabolism of DCM involves two main hepatic pathways, one utilizing cytochrome P450 2E1 (CYP2E1) metabolism (the end products being, carbon monoxide [CO] > > CO_2), and the other glutathione *S*-transferase theta-1 (GSTT1) (producing formaldehyde, a known carcinogen, as an intermediate). The CYP/CO-generating pathway results in increases in carboxyhemoglobin (COHb) and exhaled breath CO, and is believed to be saturable (USEPA, 2011). As with all hepatic mechanisms, the actual balance of metabolic products can be affected by co-exposures, prior enzyme induction, individual genetics, and nutritional status. Extensive human volunteer studies dating from the early 1970s document a dose–

TABLE 1 Toxicology of paint remover constituents

Constituent	CAS #	Acute/subacute toxicologic concerns	Metabolism/toxic mechanism (s)	Carcinogenicity*	Reproductive (R) or developmental (D) toxicity	Year listed
Methylene chloride	75–09-2	Respiratory irritation, narcosis, cardiac dysrhythmias, death	Metabolism to COHb	EPA – B2		1985
			Metabolism to CH_2O	Prop. 65		1988
				NTP – Reasonably		1989
				IARC – 2A		2017
N-Methylpyrrolidone (NMP)	872–50-4	Skin irritation			EPCRA/TRI – R + D	1994
					Prop. 65 – D	2001
Toluene	108–88-3	Narcosis			Prop. 65 – D**	1991
				IARC – 3		1999
Acetone	67–64-1	Respiratory irritation				
Methyl acetate	79–20-9	Respiratory irritation	Metabolism to methanol			
		Ocular toxicity				
Methanol	67–56-1	Narcosis	Metabolism to formic acid		NTP/CERHR – *Possible* D	2003
		Ocular toxicity			Prop. 65 –D	2012
Formic acid	64–18-6	Ocular toxicity				
Benzyl alcohol	100–51–6	Contact allergy		NTP – *No evidence*		1989
Dibasic esters (DBEs)		Olfactory toxicity (rodent finding only)	Metabolism to corresponding dicarboxylic acids			
Dimethyl adipate	627–93-0					
Dimethyl glutarate	1119-40-0					
Dimethyl succinate	106–65-0					
1,3-Dioxolane	646–06-0					
Triethyl phosphate (TEP)	78–40-0					

*See Appendix 0 for official carcinogen classification categories.

**Toluene was initially listed under the California Environmental Protection Agency's (CalEPA's) Proposition 65 (Prop. 65) as a developmental toxicant (D). In 2009, female reproductive toxicity (R) was added as an endpoint, based upon a publication by the American Conference of Governmental Industrial Hygienists (ACGIH). Upon internal review, Office of Environmental Health Hazard Assessment (OEHHA) elected to drop the R designation in 2014 based on inadequate supporting data. (https://oehha.ca.gov/proposition-65/crnr/change-identification-reproductive-toxicity-endpoints-listing-toluene-known).

[a]Abbreviations: CERHR, Center for the Evaluation of Risks to Human Reproduction; COHb, carboxyhemoglobin; EPCRA, Emergency Planning and Community Right-to-Know Act; IARC, International Agency for Research on Cancer; NTP, National Toxicology Program; TRI, Toxic Chemical Release Inventory

response relationship for COHb formation as a function of both DCM concentration and duration of exposure (DiVincenzo & Kaplan, 1981; Stewart et al., 1972). Occupational intoxications in which serial COHb levels were measured have documented both permeation of DCM through inadequate personal protective equipment (Shusterman, Quinlan, Lowengart, & Cone, 1990) and the potential for a delayed peak of COHb levels to occur after removal from exposure (Macisaac et al., 2013). The latter phenomenon likely reflects post-exposure hepatic CO formation as DCM is released from fat stores.

Exhaled breath figures prominently in the elimination of DCM and, in particular, its metabolite, CO. Elimination of native (unmetabolized) DCM also occurs in urine (ACGIH, 2005; Stewart, Hake, & Wu, 1976). Enhanced elimination of CO_2 also occurs (CO_2 being generated not only as a direct metabolic product of DCM, but also via the buffering of metabolically released hydrochloric and formic acids). Biological monitoring for DCM exposure can be carried out directly (analyzing for DCM in whole blood, exhaled breath, or urine) or indirectly (analyzing for whole blood COHb) (DiVincenzo & Kaplan, 1981). The ACGIH recommends biological monitoring utilizing native DCM in urine samples taken at the end of a work shift (ACGIH, 2005).

The acute toxicity of DCM vapor exposures includes a spectrum of severity, from eye, nose and throat irritation, to mild narcosis (lightheadedness, nausea, headache, and psychomotor retardation), to frank narcosis, respiratory depression, and death. Deficits in auditory vigilance and hand–eye coordination, as well as alterations in visual evoked response have been documented in human volunteers exposed to DCM at 200 ppm for 4–8 h (USEPA, 2011). Of note, the Federal OSHA 8-h PEL-TWA for DCM was 500 ppm from the Agency's inception in 1971 until 1997. Additive central nervous system (CNS) effects of solvent narcosis and impaired O_2 delivery due to elevated COHb are likely. Interestingly, in some fatalities COHb levels have been found to be normal (or only marginally elevated), suggesting that rapid respiratory depression may occur before significant in vivo conversion of DCM to CO can occur. Also of relevance in interpreting post-mortem COHb levels, DCM, like other halogenated solvents, can sensitize the myocardium to arrhythmogenesis, potentially leading to the rapid demise of some exposed individuals (Himmel, 2008; Zhou et al., 2011). Finally, the ischemic and arrhythmogenic cardiac effects of CO itself are well-documented (Allred et al., 1989; Sheps et al., 1990). Thus, at least two organ systems may manifest acute life-threatening impairment due to DCM's combined intrinsic and metabolite-based toxicity. Other acute toxic effects can include chemical skin burns from direct contact (Wells & Waldron, 1984), corneal damage due to ocular splashes, and indirect consequences of narcosis (eg, falls or other trauma).

The subacute and chronic toxicity of DCM has been extensively studied, particularly in experimental animals. Given DCM's extensive hepatic metabolism, considerable attention has focused on this organ. In animal bioassays, elevations of transaminases, centrilobular vacuolization, disruption of the endoplasmic reticulum, and fatty changes have been observed with subacute inhalation exposures in the range of 500 to 5000 ppm (ACGIH, 2001; USEPA, 2011). In humans, a transient increase in serum alanine aminotransferase was found in one worker who had a brief but intense exposure to DCM liquid and vapor from a ruptured hose (Puurunen & Sotaniemi, 1985). On a cohort basis, in a study of workers chronically exposed to a DCM/methanol mixture (plus acetone) in the production of cellulose triacetate fibers (DCM levels ranging from 60 to 475 ppm), a dose-related increase in mean serum bilirubin was observed, although none of the hepatic enzymes assayed appeared to be affected when the group was compared with workers whose solvent exposure was to acetone alone (Ott, Skory, Holder, Bronson, & Williams, 1983). Other endpoints documented in experimental animals have included changes in brain histology and neurotransmitters in gerbils exposed to DCM at levels as low as 210 ppm (Briving et al., 1986).

Based on the finding of site-specific tumors in 2-year rodent bioassays in both mice (liver and lung malignancies) and rats (benign mammary tumors), the NTP of the National Institute for Environmental Health Sciences (NIEHS) concluded that DCM is *reasonably anticipated to be a human carcinogen*, and the USA Environmental Protection Agency (EPA) concluded that DCM *is likely to be carcinogenic in humans*. Both agencies, as well as the IARC, while considering DCM a probable human carcinogen by extrapolation from animal studies, consider the human epidemiologic data either *limited* or *inadequate* to address the question directly (NTP, 2016; USEPA, 2011). Findings of an increased incidence of hepatobiliary cancer and astrocytomas (as well as other specific malignancies) in exposed human cohorts have been variable, and continue to be the subject of discussion (ACGIH, 2001; IARC, 2017; USEPA, 2011).

With regard to potential reproductive and developmental effects of DCM, the USA EPA (USEPA, 2011) pointed out numerous methodological limitations in its review of published animal studies, and drew limited conclusions. With rare exception, however, fertility, litter size, and pup survival were not affected, although some minor changes in skeletal ossification were observed. In addition, the authors cautioned that "… there are no studies that have adequately evaluated neurobehavioral and neurochemical changes resulting from gestational dichloromethane exposure". By contrast, the USA EPA unequivocally labeled DCM as a mutagenic agent, attributing its genotoxic effects to two active metabolites, formaldehyde and *S*-(chloromethyl) glutathione.

To summarize, DCM is a highly volatile solvent that requires extraordinary engineering controls and/or personal protective equipment to use safely (OSHA, 1998; Stull, Thomas, & James, 2002). When used indoors in the absence of adequate ventilation/other exposure controls, it has been associated with multiple fatalities due to the combination of solvent narcosis, arrhythmogenesis, and impaired oxygen delivery from its secondary metabolite, CO (Chester, Rosenman, Grimes, Fagan, & Castillo, 2012; Fechner, Ortmann, Du Chesne, & Kohler, 2001; Goulle, Lacroix, Vaz, Rouvier, & Proust, 1999; Hall & Rumack, 1990; Leikin, Kaufman, Lipscomb, Burda, & Hryhorczuk, 1990; Macisaac et al., 2013; Manno, Rugge, & Cocheo, 1992; Takeshita et al., 2000; Winek, Collom, & Esposito, 1981). DCM can produce psychomotor impairment at exposure levels formerly permitted under Federal standards. In addition to

its acute toxicity, it has been labeled a probable human carcinogen by three authoritative agencies. Due to its high hazard index, DCM as a component of commercially available paint strippers has been prioritized by both the USA EPA and CalEPA as a candidate for replacement by alternative (less hazardous) chemicals (USEPA, 2017; CDTSC, 2018a; Morose et al., 2017 & 2020; Morris & Wolf, 2006), and in fact was banned in paint removal products available to the general public in late 2019 (USEPA, 2019).

***N*-Methylpyrrolidone** (NMP; CAS # 872–50-4; C_5H_9NO) is a clear, colorless liquid with a molecular weight of 99.13 g/mol. It reportedly has a fish-like odor, with a boiling point of 202 °C and a low vapor pressure of 0.29 Torr at 20 °C (equivalent to 382 ppm at saturation) (ACGIH, 2007a; OSHA, 2018). No Federal OSHA PEL currently exists for NMP, although CalEPA/OSHA maintains an 8-h PEL-TWA of 4 mg/m^3 (or 1.0 ppm). It is widely used as an industrial solvent, in the petrochemical industry, as a paint stripper constituent, and in vinyl flooring, from which it has been documented to be emitted in vapor form (Bonisch et al., 2012).

Although NMP can be absorbed via inhalation or ingestion, it is rapidly absorbed through intact skin, which in concert with its low volatility suggests that the most important route of exposure for workers and home hobbyists may be dermal (ACGIH, 2007a). In recognition of this fact, the CalEPA/OSHA standard includes a "skin" notation. Human exposure studies via inhalation nevertheless have shown significant uptake, including during simulated work activities with airborne levels ranging between 10 and 160 mg/m^3 (2.5–40 ppm) (Bader, Wrbitzky, Blaszkewicz, Schaper, & van Thriel, 2008; Bader, Wrbitzky, Blaszkewicz, & van Thriel, 2007). NMP metabolites found in the urine consist predominantly of 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) and 2-hydroxy-*N*-methylsuccinimide (2-HMSI), and there is evidence that hepatic CYP2E1 may be involved in NMP's metabolism (DFG, 2006). Although the ACGIH has yet to establish a Threshold Limit Value (TLV®) for NMP, they have established a Biological Exposure Index (BEI®) utilizing end-of-shift urinary 5-HNMP, set to reflect the AIHA's Workplace Environmental Exposure Level (WEEL) of 40 mg/m^3 (10 ppm).

NMP has been found to be a skin irritant in experimental animals (rabbits), and has produced skin irritation among workers repetitively exposed to the solvent (ACGIH, 2007a; DFG, 2006). Acute mucous membrane (eye, nose and throat) irritation, odor/annoyance, and eye blink frequency (a measure of corneal irritation) were studied in human subjects during an 8-h duration controlled exposure study at 2.5–40 ppm exposure. Odor annoyance was evident at >10 ppm, although subjective sensory irritation was reported only at the highest exposure level (40 ppm). However, no objective findings of mucous membrane irritation were found (van Thriel et al., 2007).

NMP has not been classified with respect to its potential carcinogenicity by IARC, NTP, or the USA EPA. In a chronic rodent feeding study (male and female rats exposed for 2 years and, mice of both sexes exposed for 18 months), male rats exposed at the highest dose showed an increased incidence of progressive nephropathy, and both sexes had decreases in body weight. Among mice exposed at the highest dose, there was increased liver weight and increased incidence of hepatic adenomas in both sexes, with a significant increase in hepatocellular carcinomas in male mice only (Malley et al., 2001). NMP has produced negative results for mutagenicity in the majority of assays in which it has been tested (HSDB, 2019a).

Reproductive/developmental studies in rodents have raised the greatest concerns regarding the safety of NMP in the workplace and consumer products. Pregnant rats given NMP by gavage at doses of >250 mg/kg from days 6–20 of gestation experienced decreased weight gain, and those given doses of ≥500 mg/kg gave birth to litters with increased malformation and fetal mortality rates (Saillenfait, Gallissot, Langonne, & Sabate, 2002). Inhalational studies of pregnant rats exposed from gestational days 6–20 also showed decreased maternal weight gain, but only at the highest exposure level (near saturation vapor pressure), and these exposures were not accompanied by fetal malformations or loss (Saillenfait, Gallissot, & Morel, 2003). A single case report links NMP with intrauterine growth retardation and late-term fetal loss in a laboratory worker who had a substantial acute dermal exposure in the early second trimester (Solomon, Morse, Garbo, & Milton, 1996). With regard to potential male reproductive effects, in a 10-week feeding study of rats, the two highest dose groups showed either decreased viability of offspring (300 mg/kg) or depressed spermatogenesis with total infertility (1000 mg/kg) (Sitarek & Stetkiewicz, 2008). NMP was listed as a reproductive/developmental toxicant under the CalEPA's Proposition 65 program list in 2001, and developmental outcomes were subsequently referenced by Cal-OSHA when establishing an NMP PEL in 2013.

To summarize, NMP is a relatively non-volatile solvent with a considerable potential for transcutaneous absorption. It can be irritating to the skin and mucous membranes at sufficient concentrations, but in general is of low acute toxicity. However, it is associated with adverse reproductive/developmental outcomes at high doses. For this latter reason, although NMP was initially promoted as a substitute agent for methylene chloride in paint removers, it has lost favor for this application, and, like methylene chloride, has been identified as a potential target for substitution (CDTSC, 2018b; Morose et al., 2017; Morris & Wolf, 2006; USEPA, 2017).

Toluene (CAS # 108–88-3; C_7H_8), also referred to as methyl-benzene or toluol, is a clear, volatile liquid with an aromatic odor resembling benzene, a molecular weight of 92.14 g/mol, and a boiling point of 110.6 °C. Technical grade toluene may contain significant quantities of benzene, as both are distilled as petroleum byproducts. Its saturation vapor pressure of 21.9 Torr at 20 °C would translate to 29 000 ppm if a sufficient quantity of the compound were allowed to evaporate in a closed space (ACGIH, 2007). The Federal OSHA PEL-TWA is currently 200 ppm with a PEL "ceiling" concentration (PEL-C) of 300 ppm. By contrast, the current Cal-OSHA PEL-TWA is 10 ppm, with a PEL-STEL of 150 ppm and a PEL-C of 500 ppm. Toluene is often included in concentrations ranging from 5% to 20% in paint remover formulations whose primary constituent is methylene chloride. It is also used as a gasoline additive, in inks, paints, and paint

thinners, in rubber cement, fingernail polishes, and in industrial chemical processing. Historically, recreational inhalation of toluene from hobby products ("huffing") led to the reformulation of adhesives used in the assembly of plastic models.

Toluene is readily absorbed by ingestion and inhalation; skin contact is a less important route of exposure. The compound is distributed throughout the body and is reversibly sequestered in adipose tissues; it also readily crosses the placenta. The largest fraction of absorbed toluene is metabolized in the liver (via benzoic acid) to hippuric acid, and subsequently excreted in the urine; a smaller fraction is excreted unchanged in the urine and exhaled breath. Both hippuric acid and the metabolite *o*-cresol are found in urine and have been utilized, along with urinary toluene, as analytes in biological monitoring (ACGIH, 2007b).

The major target organ for toluene toxicity is the CNS, along with the heart. Acutely, toluene produces narcosis, an effect that exploited by recreational users. Fatalities from high-level acute industrial and recreational exposures have been reported, and have generally been attributed to respiratory depression, although cardiac dysrhythmias could be a contributing factor (ACGIH, 2007b; Carreon-Garciduenas et al., 2018; Einav, Amitai, Reichman, & Geber, 1997). Controlled exposure studies with human subjects exposed to 100–150 ppm toluene for ~7 h demonstrated decrements in pattern recognition, pattern memory, and manual dexterity (Baelum et al., 1985; Echeverria, Fine, Langolf, Schork, & Sampaio, 1989). Neurobehavioral assessment of occupational cohorts chronically exposed to toluene have yielded variable results, with the most consistent (and sensitive) endpoint being impaired color vision (ACGIH, 2007b). Chronic recreational toluene users have demonstrated encephalopathic signs, often accompanied by diffuse cortical, subcortical, or cerebellar atrophy (Yucel, Takagi, Walterfang, & Lubman, 2008).

Toluene has not been subject to a standardized 2-year rodent bioassay for carcinogenicity, and is therefore classified by IARC as a Group 3 agent, ie, "Unclassifiable as to carcinogenicity in humans". Toluene is listed under the CalEPA's Proposition 65 list as a developmental toxicant, based upon reports of fetal growth retardation and skeletal abnormalities in rodents.

To summarize, toluene is an acute and chronic neurotoxicant that is not classifiable with respect to its potential for human carcinogenicity. It has been listed by the State of California as an agent capable of producing developmental toxicity in humans.

Acetone (CAS # 67–64-1; CH_3COCH_3), also referred to as dimethyl ketone or 2-propanone, is a sweet-smelling organic solvent with a molecular weight of 58.08 g/mol and a boiling point of ~56 °C. Its vapor pressure of 185 Torr at 25 °C would translate to an equilibrium vapor concentration of 243 000 ppm in a confined space, and its vapor density relative to air (2.0 at 20 °C) gives it the potential to layer out in environments with limited air circulation (ACGIH, 2015). Acetone is commonly used as a solvent in paints and varnishes, as an industrial solvent and degreaser, as a chemical intermediate, and is commonly encountered by consumers in fingernail polish remover. It is found in a concentration of ~10% in at least one commercially available paint stripper. The current Federal OSHA PEL is 1000 ppm (PEL-TWA), with the corresponding Cal-OSHA values being 500 ppm (PEL-TWA), 750 ppm (PEL-STEL), and 3000 ppm (PEL-C).

Acetone is readily absorbed by ingestion, inhalation and skin contact. It is also produced endogenously in diabetic keto-acidosis, or as breakdown product of lipids produced by so-called "ketogenic" diets. It distributes uniformly with body water (USEPA, 2003). As a semi-polar solvent, acetone has a relatively low octanol–water partition coefficient (0.58), and consequently has a limited potential for sequestration in fat (Cumming & Rucker, 2017). The relative role of hepatic metabolism (with shunting into glucose pathways) vs. excretion of the native compound (in exhaled breath > urine) is dependent both on individual physiology and dose rate (USEPA, 2003). In terms of biological monitoring, the ACGIH recommends end-shift urinary acetone concentrations as a BEI (ACGIH, 2014).

With airborne exposures, acetone has been associated with subjective mucous membrane (eye, nose and throat) irritation at levels at >250 ppm, particularly in individuals not habitually exposed (Dalton, Wysocki, Brody, & Lawley, 1997; Matsushita et al., 1969; Wysocki, Dalton, Brody, & Lawley, 1997). With sufficient exposure concentration and duration, narcosis can also occur (ACGIH, 2015; ATSDR, 1994; USEPA, 2003). Acutely, neuropsychological endpoints studied in controlled exposure experiments have yielded conflicting results; some studies show decrements in short-term memory and reaction time, whereas others do not (ACGIH, 2015; USEPA, 2003). Neuropsychological studies of chronically exposed workers have likewise not produced a consistent pattern of results.

Acetone is listed by the USA EPA as "not classifiable as to human carcinogenicity" due to a lack of positive findings in epidemiologic studies and the lack of a structured 2-year animal bioassay (USEPA, 2003). Similarly, the compound has not been found to be genotoxic on in vitro testing (USEPA, 2003). In terms of reproductive and developmental testing, male rats fed extremely high concentrations of acetone in drinking water (ie, 50 000 ppm) showed an increase in abnormal sperm morphology and a decrease in sperm motility, although testicular pathology was apparently not examined after inhalational exposures (USEPA, 2003). In chronic feeding studies, exposure to acetone is accompanied by induction of liver metabolic enzymes (most specifically CYP2E1 and CYP1A), indicating a potential for chronic acetone exposure to affect drug metabolism in exposed workers (USEPA, 2003).

To summarize, acetone is a common solvent that is used in low concentrations in selected paint strippers and is also generated in vivo during lipid metabolism. It is largely devoid of known chronic toxic effects, and its acute sensory (irritant) and narcotic properties appear to be rapidly reversible. Chronic acetone exposure can potentially induce hepatic enzymes and thereby affect drug metabolism.

Methyl acetate (CAS # 79–20-9; $C_3H_6O_2$), is a volatile, colorless liquid with a fragrant, fruity odor. It has a vapor density of 2.8, meaning it is heavier than air and can settle close to the ground. Its boiling point is

56.9 °C and vapor pressure is 173 Torr at 20 °C (ILO, 2014). The Cal-OSHA 8-h PEL for methyl acetate is 200 ppm, with a STEL of 250 ppm.

Methyl acetate can be absorbed by skin contact, inhalation or ingestion, although studies on the quantification of its absorption characteristics are lacking. A study of four healthy males found a mean uptake of 60% of methyl acetate when exposed to 100 ppm for 10 min while resting (Kumagai, Oda, Matsunaga, Kosaka, & Akasaka, 1999). The high vapor pressure of methyl acetate increases the concern for dermal and inhalation absorption, although it is hypothesized that methyl acetate's high vapor pressure may cause it to evaporate from skin rapidly, rather than being absorbed. Once absorbed, methyl acetate is rapidly hydrolyzed to methanol. When rabbits ingested 1000 mg/kg of methyl acetate, methyl acetate could not be detected in blood or urine after 30 min, in contrast to its methanol metabolite (ECHA, 2003). Methanol metabolism and excretion is reviewed separately, below.

Methyl acetate vapors are moderately irritating to the eyes and respiratory tract. It is a CNS depressant at high levels. Few case reports exist of acute toxicity from methyl acetate alone. One case of chronic toxicity involves a 21-year-old who was intentionally inhaling a paint thinner containing methanol and methyl acetate, resulting in optic neuropathy (Ogawa et al., 1988). The authors hypothesized that because the vapor pressure of methyl acetate is twice that of methanol, the relative contribution of methyl acetate to the ultimate methanol dose was greater than would have been anticipated based upon relative concentrations of the two solvents alone.

The USA EPA reviewed methyl acetate and found there is inadequate information to assess carcinogenic potential. It also found there were limited data on reproductive or developmental toxicity (USEPA, 2010). Despite being hydrolyzed to methanol (which is listed as a developmental toxicant under the CalEPA's Proposition 65), methyl acetate is not similarly listed. On the other hand, the compound is listed on the USA Food and Drug Administration's (FDA's) "Generally Regarded as Safe" (GRAS) list as a food additive with a fruit-like fragrance.

Methyl acetate tested as non-mutagenic in *Salmonella* testing (Zeiger, Anderson, Haworth, Lawlor, & Mortelmans, 1992).

In summary, methyl acetate is a volatile, fruity-odored chemical that is absorbed and metabolized to methanol. Acutely, it is moderately irritating to the eyes and respiratory tract. Care should be taken when working with methyl acetate, as it has the same toxic endpoints as methanol.

Methanol (CAS # 67–56-1; CH_4O), also known as wood alcohol, is a clear, highly polar, flammable liquid with a molecular weight of 32.04 g/mol and pungent odor similar to ethanol. It has a boiling point of 64.5 °C and a vapor pressure of 97 Torr at 20 °C, with a relative vapor density of 1.1 compared to air (ILO, 2018). The Cal-OSHA 8-h PEL for methanol is 200 ppm, with a STEL of 250 ppm. Methanol in urine can be used for biologic monitoring, with 15 mg/L at the end of a work shift corresponding to an 8-h exposure at 200 ppm (ACGIH, 2004). The odor threshold is reported to vary from 100 to 1500 ppm.

Methanol is naturally produced by the human body. It is found in food, consumer and industrial products. In 2010, global demand for methanol was 49 million metric tons, and is projected to nearly double by 2021 (Anon., 2017). Most DCM-containing strippers contain between 5% and 40% methanol (CDPH, 2014).

Methanol is absorbed via in inhalation, ingestion and skin contact. In human studies, methanol dermal absorption has been estimated at 0.192 mg/cm^2/min (Dutkiewicz, Konczalik, & Karwacki, 1980). Once methanol is absorbed it is distributed to body water with a volume of distribution of 0.77 L/kg. Methanol is slowly metabolized by alcohol dehydrogenase to formaldehyde. Formaldehyde is then metabolized by aldehyde dehydrogenase to formic acid (see below). At serum methanol levels below 5–10 mg/L, it is believed formic acid is not produced (NTP, 2003). One study exposed 12 male volunteers to 250 mg/m^3 (191 ppm) of methanol for 75 min, which resulted in a mean serum methanol level of 3.8 mg/L, but no change in serum formic acid concentrations (Cook et al., 1991). The time from methanol exposure to generation of toxic metabolic byproducts and resultant injury ranges from 6 to 30 h.

Methanol exhibits dose-dependent kinetics (Jacobsen, Sebastian, Blomstrand, & McMartin, 1988). At serum concentrations of ~10 mg/dL, methanol elimination is first order, with a half-life of about 2.5–3 h (Jones, 1987; Leaf & Zatman, 1952). At concentrations of about 100–200 mg/dL, methanol exhibits zero-order kinetics and is eliminated at about 8.5–9 mg/dL/h (Jacobsen, Webb, Collins, & McMartin, 1988).

The initial symptoms of methanol intoxication are similar to those of ethanol intoxication, with disinhibition and ataxia. Within 6–30 h of exposure, acute toxicity results when formic acid is generated, with resultant metabolic acidosis as well as end-organ toxicity to the eyes, kidney and CNS.

Acute toxic effects due to methanol exposure have been extensively documented. Most case reports focus on methanol absorption via ingestion. Methanol is also absorbed through skin contact and cases of systemic toxicity due dermal exposure to have been reported. Children are at particular risk for methanol dermal absorption because of their greater surface area to volume ratio. Reported cases of infant intoxication by methanol involved skin exposure for up to 24 h over 3 days (Sahbudak Bal et al., 2016). These exposures likely also involved simultaneous inhalation (Darwish et al., 2002).

There are few published cases of dermal intoxication in adults. One set of cases involved frequent massages with methanol-containing cologne over the course of days (Adanir, Ozkalkanli, & Aksun, 2005). One case report described two volunteer firefighters who were exposed to methanol from two overturned rail cars while attempting to access their hazardous materials response station. They were exposed for ~2 min, while wearing short sleeved shirts, short pants, and shoes without socks. They removed these clothes and donned standard firefighting clothing. After 10 min of work both became symptomatic and at 2 h after exposure each had detectable

methanol levels ranging from 130 to 190 mg/L. The first patient had a peak methanol level of 230 mg/L and the second had a peak of 160 mg/L over a period of 48 h (Aufderheide, White, Brady, & Stueven, 1993).

Methanol toxicity due to intentional inhalation of a carburetor cleaner has also been reported (Frenia & Schauben, 1993).

In contrast to acute toxicity, there is limited information on chronic methanol toxicity. Chronic exposure at levels >260 mg/m^3 ranging from 1 to 8 h/day, up to 5 days/week for up to 3 years has been reported to cause symptoms of headache, dizziness, lightheadedness, blurred vision, and nausea and upset stomach (Frederick, Schulte, & Apol, 1984). Chronic exposures may result in irreversible optic damage (Kavet & Nauss, 1990).

As of 2014, methanol had not been evaluated by the IARC, but was given a "medium" priority for future study (IARC, 2014); however, the compound has yet to become the subject of an IARC Monograph.

In 2003, an Expert panel coordinated by the NTP reviewed the developmental toxicity of methanol and found there were insufficient human data to classify the compound as a human developmental toxicant. However, based on animal experimental data they did classify methanol as a "possible" human developmental toxicant (NTP, 2003). Specifically, mouse, rat and primate studies were noted to have demonstrated developmental toxicity, including neural tube defects, in fetuses following maternal inhalation of methanol (Bolon, Welsch, & Morgan, 1994), and testicular degeneration in folate-reduced rats (Lee, Brady, Brabec, & Fabel, 1991). The compound was subsequently added to the CalEPA's Proposition 65 list of "chemicals known to the State of California to cause developmental toxicity in humans" in 2012. It is unclear if methanol, or its metabolic end-product, is the cause of developmental toxicity in animal studies (Rogers, Gift, & Barone, 2013).

Methanol inhalation was shown not to induce chromosome damage in mice; however, rodents appear to be less sensitive to formic acid than primates due to increased clearance (Campbell, Howard, Backer, & Allen, 1991).

To summarize, methanol is a widely available solvent that is a highly toxic when ingested, with potential for toxicity from inhalation after unusually high airborne exposure or after prolonged skin contact. Therapy exists to minimize the injury caused by acute methanol exposure, if it is instituted early (Anderson, 2017). Research is limited on chronic toxicity, carcinogenicity, mutagenicity and developmental toxicity in humans.

Formic acid (CAS # 64–18-6; CH_2O_2), is a colorless combustible liquid with a pungent odor, a molecular weight of 46.02 g/mol, boiling point of 100.5 °C, and a vapor pressure of 34.5 Torr at 20 °C (ILO, 1997). With an OSHA 8-h PEL of 5 ppm, formic acid's highly variable odor threshold (ranging from 1.6 to 360 ppm in the published literature), renders its odor warning properties unpredictable (Amoore & Hautala, 1983).

Formic acid is used as a chemical intermediate, a preservative in livestock feed, in the tanning of leather and in textile dyeing and finishing, and in liquid chromatography. Most recently it has been incorporated into the formulation of some paint removers. Of note, formic acid is produced in vivo from the metabolism of methanol (and its precursor, methyl acetate). Despite a strong suspicion that formic acid is the active metabolite responsible for optic neuritis and retinal toxicity in methanol poisoning, direct evidence of ocular effects from human formic acid intoxications is lacking (Fox & Boyes, 2013).

Formic acid is corrosive; exposure resulting in severe burns may result from contact of the eyes and skin with concentrated acid. If absorbed it can be distributed, resulting in a metabolic acidosis and intravascular hemolysis. Formic acid acts as a mitochondrial toxin causing cellular hypoxia (Liesivuori & Savolainen, 1991). Formic acid is excreted via the kidneys, while simultaneously inducing injury.

Acute toxicity with formic acid is primarily reported in intentional oral ingestion or accidental dermal or inhalation exposure. A 39-year-old chemical delivery driver sustained 3% total body surface area burns to his face and reversible pulmonary injury while transferring 98% formic acid from his truck to a container using a hose that became loose (Yelon, Simpson, & Gudjonsson, 1996). A 3-year-old girl sustained second and third degree burns to 35% of her total body surface area when she was exposed to 90% formic acid (Chan, Williams, & Clark, 1995). After 70 days in the hospital, the first 20 of which required intubation in intensive care and skin debridement and grafting, she was discharged with the need for further wound care and physical therapy.

Formic acid ingestion results in esophageal burns, intravascular hemolysis, metabolic acidosis, pneumonitis with respiratory failure, and kidney injury (Naik, Stephens, Wilson, Walker, & Lee, 1980). Of a case series of 53 cases of formic acid ingestion 15 died and 45 developed inhalation pneumonitis, and 16 developed esophageal stricture (Rajan, Rahim, & Krishna Kumar, 1985).

Subacute exposure to formic acid in humans has been reported on a limited basis. Rats exposed for 2 weeks to formic acid vapor at 118 mg/m^3 developed squamous metaplasia of the respiratory epithelium. The same study found that rats exposed to 15 mg/m^3 for 13 weeks resulted in neutropenia and elevations in serum alkaline phosphatase (NTP, 1992). Formic acid has not been evaluated by the IARC. The USA EPA notes there are inadequate data to assess the carcinogenic potential of formic acid. There are limited data available on reproductive or developmental toxicity of formic acid in animal studies. There are no data for humans. Formic acid was found not to be mutagenic in *Salmonella typhimurium* strains (NTP, 1992).

To summarize, formic acid is a highly irritating, corrosive acid with documented acute dermal, mucosal, respiratory, and systemic toxicity. As a metabolic byproduct of methanol, it is implicated in producing retinal and optic nerve toxicity. There are limited published data on long-term exposures and outcomes to formic acid.

Benzyl alcohol (CAS # 100–51–6; C_7H_8O) is a clear, colorless liquid with a molecular weight of 108.14 g/mol. It has a faint aromatic odor, with a boiling point of 205.3 °C and a vapor pressure of 0.094 Torr at 25 °C (Doubert & Donner, 1989). No Federal OSHA PEL, Cal-OSHA PEL or ACGIH TLV currently exists for benzyl alcohol. AIHA has

recommended an 8-h TWA is 10 ppm (AIHA, 2008). Benzyl alcohol has been used as a solvent in a variety of products (including, most recently, paint removers), a degreasing agent, and as a fragrance component in numerous cosmetics and other topical agents (Lewis, 2004; Mookherjee & Wilson, 2000; Nair, 2001).

Benzyl alcohol can be readily absorbed through the gastrointestinal tract, but absorption is limited with inhalation and dermal exposure in humans. Substantial dermal absorption has been demonstrated in rhesus monkeys when skin was occluded. Dermal exposure is likely to be the greatest exposure route for workers. Once it reaches the liver, the compound is rapidly oxidized by alcohol dehydrogenase to benzoic acid, conjugated with glycine, and subsequently excreted through the urine as hippuric acid (Lington & Bevan, 1994; OECD, 2001; Oelschläger, 1978; Opdyke, 1974). Benzoic acid can be lethal in infants due to the immature liver's inability to conjugate it, as seen in an outbreak of "gasping syndrome" in low birth weight neonates given a saline solution containing benzyl alcohol as a preservative (CDC/MMWR, 1982). Mature hepatocytes can metabolize benzoic acid via conjugation, which may explain the absence of severely toxic inhalation or ingestion exposures in adults. Oxidation of benzyl alcohol to benzoic acid can also occur spontaneously in the air.

Benzyl alcohol has been shown to be a dermal irritant at concentrations of ≥3% in humans. However, patch testing with a concentration of 0.65% had no adverse irritant effects. No toxic effects from direct ocular exposure to 0.07% benzyl alcohol in saline have been reported (Nair, 2001). Guinea pig studies demonstrated dermal sensitization in a Freund's Complete Adjuvant test (FCA test) and an open epicutaneous test. The FCA test involves a solution with an antigen emulsified in mineral oil and applied to the skin along with dried mycobacterium, resulting in potentiation of cell-mediated immune responses to the antigen (Schlede et al., 1989). However, negative results were observed in a Draize test, modified Draize test and maximization test in guinea pigs. The Draize test involves application of a 0.5 mL or 0.5 g of substance to the eye or skin in a restrained, conscious animal and rinsing it off after a set period of time. Effects on the tissue for up to 14 days are recorded (OECD, 2001). Human studies using 5% benzyl alcohol induced positive dermal responses in 0–0.92% of subjects (Chow, Avolio, Lee, & Nixon, 2013; Nair, 2001). Two cases of delayed hypersensitivity contact dermatitis reactions have been reported within 2–3 days of initial exposure (Yip, 2004). Rare cases of non-immunogenic urticaria and angioedema have been reported (Guin & Goodman, 2001; Lahti, 1980).

Benzyl alcohol has not been classified with respect to potential human carcinogenicity by IARC or the USA EPA. The NTP classifies benzyl alcohol as having "no evidence of carcinogenicity", having conducted a 2-year bioassay in rats and mice exposed to 100 and 200 mg/kg/day by gavage (NTP, 1989). A chronic dermal exposure study in mice, using two control groups and a combined 2% benzyl alcohol and 0.016% benzoic acid hair dye demonstrated chronic dermal irritation, including in some controls (whose only dermal intervention was having been shaved). This would imply a high background rate of dermal irritation or irritation secondary to the shaving process. No difference in weights between groups was seen. An increased incidence of malignant lymphomas occurred in treated females, but lymphomas occurred at a lower than expected rate in the two comparison groups: 12% and 22%, compared with rates up to 33% in previous studies (Nair, 2001).

Inhalation of benzyl alcohol 1000 ppm for 8 h and 2000 ppm for 4 h reportedly resulted in 50% mortality in rats within 14 days (Nair, 2001). A guinea pig model showed no skin sensitization to benzyl alcohol (OECD, 2001). Rabbits showed no skin irritation after 4 h of exposure, but developed it after 24 h of continuous exposure. Moderate eye irritation was demonstrated in these groups (EMEA, 1997). Neurotoxic effects were demonstrated with injected benzyl alcohol or with high oral doses in rats (Nordt & Vivero, 2006). Ocular toxicity has been demonstrated, but only through intravitreous injection (Morrison et al., 2006).

Reproductive studies in rats treated with intraperitoneal injections of benzyl alcohol mixed with peanut oil on gestational days 10, 13, 6–10 or 10–14 did not demonstrate teratogenic effects. While, 750 mg/kg benzyl alcohol/corn oil gavage resulted in 38% prenatal maternal mortality of mice dams compared to controls treated with water gavage. However, necropsies were not performed, so documentation of specific organ toxicity is not available. Additionally, the vehicles differed between groups, corn oil in the treated group and water in the control group (Nair, 2001). Developmental concerns have been raised for mildly reduced birth weight and weight gain in pups of mice injected with benzyl alcohol in two studies. However, other studies have shown no difference in weight, mortality or gestation duration (HSDB, 2019b). The reproductive no observed adverse effect level (NOAEL) has been determined to be 550 mg/kg/day in mice. Additionally, it has been classified as non-cytotoxic and non-mutagenic (OECD, 2001). Benzyl alcohol is not listed as a CalEPA's Proposition 65 reproductive hazard.

In summary, benzyl alcohol reportedly has low toxicity with typical dermal and inhalation exposures, as well as a low transcutaneous absorption rate. It showed "no evidence of carcinogenicity" in an NTP bioassay. Historically, the most serious toxicity associated with the compound was lethality in parenterally exposed neonates, who have immature hepatic function. Skin irritation, is the most commonly observed hazard, particularly at exposure concentrations of ≥3%.

Dibasic esters (DBEs; dimethyl adipate CAS # 627–93-0, $C_8H_{14}O_4$; dimethyl glutarate CAS # 1119-40-0, $C_7H_{12}O_4$; dimethyl succinate; CAS # 106–65-0, $C_6H_{10}O_4$). DBEs are generally supplied as a commercial mixture, containing dimethyl-glutarate > succinate > adipate. The generic chemical formula is $C_2H_3O_2$–C_nH_{2n}–$C_2H_3O_2$, with n = 2 for succinate, 3 for glutarate, and 4 for adipate. Collectively, the mixture has a very low vapor pressure (0.2 mmHg at 20 °C) and high water solubility (HSDB, 2019c). The mixture has been promoted as an alternative paint stripper constituent for over three decades.

DBEs have been studied in rodents for both upper respiratory tract and reproductive/developmental toxicity. DBEs have been used as a model for enzymatic activation of water-soluble, non-reactive

gases and vapors (Medinsky & Bond, 2001). In general, water-soluble gases are preferentially deposited in the upper respiratory tract, particularly in rodents. With DBE exposure, carboxylesterase enzyme present in the rat olfactory epithelium is responsible for the release of dicarboxylic acids (succinic-, glutaric-, and adipic-) from DBEs, resulting in olfactory epithelial injury (Keenan, Kelly, & Bogdanffy, 1990; Lee, Valentine, & Bogdanffy, 1992; Trela & Bogdanffy, 1991). This metabolic transformation is more prominent in the olfactory than in the nasal respiratory epithelium, corresponding to the two regions' respective carboxylesterase activities. Interestingly, the severity of nasal histologic changes has been found to be greater in female than in male rats, and carboxylesterase activity is considerably greater in rat than in human nasal tissue (Mattes & Mattes, 1992).

Reproductive and developmental toxicity studies were performed on both male and female rats pre-breeding (and during gestation days 7–16 for the female rats). These inhalation studies achieved maximum exposure levels that exceeded saturation vapor pressure by a factor of 2.5 by using DBE aerosols for the highest-exposure condition. Although some decrease in food intake and weight gain were observed in pregnant rats at the highest dose level, in neither study were reduced fertility, implantation, litter size or viability observed, nor were there increased malformation rates among the offspring (Alvarez et al., 1995; Kelly, Kennedy, & Keenan, 1998).

DBEs have not been subjected to 2-year rodent inhalation (or feeding) studies for carcinogenicity and the compounds are not classified as to potential carcinogenicity by the USA EPA, NTP, or IARC. Similarly, there is a paucity of published information on potential mutagenicity by these compounds.

To summarize, DBEs are normally present as a mixture of three related compounds with low volatility and high water solubility. They preferentially deposit in the upper respiratory tract where, at sufficient concentrations, they can damage the olfactory epithelium in rodents through their conversion to carboxylic acids. Because of inter-species differences in mucosal enzymes, there is less concern regarding potential olfactory toxicity in humans. In fact, the human toxicology literature for DBEs is extremely sparse (HSDB, 2019c). Although they have not undergone carcinogenicity testing, DBEs have been subjected to reproductive/developmental toxicity testing in rodents, with negative results.

1,3-Dioxolane (CAS # 646–06-0; $C_3H_6O_2$) is a clear liquid with an ether-like odor and a molecular weight of 74.08 g/mol. It has a boiling point of 75.6 °C and a vapor pressure of 79 Torr at 20 °C (Riddick, Bunger, & Sakano, 1985), corresponding to an equilibrium concentration of ~96 000 ppm in a confined space. Dioxolane has historically been used as an industrial solvent and chemical intermediate, and more recently as a component in paint strippers (ACGIH, 2002).

The biomedical literature pertaining to 1,3-dioxolane is relatively sparse, with the majority of available materials being unpublished industry-sponsored reports rather than materials appearing in the peer-reviewed/open literature. In terms of toxicokinetics, vapors of the compound were utilized, along with those of 2,4-dimethylpentane, as a model for respiratory tract vapor uptake in dogs (Snipes et al., 1991). Comparing its nasal and lung uptake (66.6% vs. 2.1%), 1,3-dioxolane acts, deposition-wise, like the vapors of many water-soluble compounds that disproportionately impact the upper airway. Unfortunately, inhalation studies conducted with rodents have emphasized internal organ pathology to the exclusion of functional endpoints (eg, respiratory slowing or concentration that elicits a respiratory rate decrease of 50% [RD_{50}]), making it more difficult to compare the compound's airborne irritant potential with that of other agents. Nevertheless, 1,3-dioxolane's high potency as an eye irritant when applied topically (8 on a scale of 0–10) suggests an ability to produce both sensory and pathological irritation.

Absorption, distribution, metabolism, and elimination of 1,3-dioxolane are poorly documented. The USA EPA's Interagency Testing Committee nominated the compound for comprehensive toxicity testing (including "chemical disposition and metabolism") in 1982; however, the following year the agency elected not to act upon that recommendation (USEPA, 1982, 1983). Metabolically, it is known that the compound is a potent inhibitor of ethanol-induced P450 enzyme induction in rodents (Gadeholt, 1984).

In terms of subacute and chronic toxicity in experimental animals, data abstracted from industry studies point to increased liver weights and centrilobular hepatocyte enlargement in male rats exposed to 3000 ppm of 1,3-dioxolane by inhalation over a 13-week period, as well as a reversible decrease in peripheral white blood cell counts in animals exposed to ≥1000 ppm. The only known chronic (2-year) rodent study has been critiqued for its methodology and is considered uninterpretable with respect to the compound's potential for carcinogenicity (ACGIH, 2002).

For potential reproductive/developmental toxicity, female rats were administered varying doses of 1,3-dioxolane (corresponding to a range of 0.025 to 0.2 of the LD_{50} [dose producing lethality in 50% of exposed animals]) during days 8–20 of gestation via gavage. Delayed fetal development was seen at ≥0.1 of the LD_{50}, with increased perinatal death rates at 0.2 of the LD_{50}, and decreased hemoglobin levels in 5-week-old offspring (Sitarek, Baranski, & Berlinska, 1992). Fertility and dominant lethal mutations were studied in male rats exposed both by gavage (0.1–0.2 of LD_{50} for 8 weeks) and by inhalation (2500 ppm for 1 year) prior to mating. In neither study was a decrease in fertility or increase in fetal mortality observed. The authors noted "… in some rats … microscopic examination of testes revealed focal necrosis of seminiferous epithelium and alteration of spermatogenesis". However, no reference was made with a control group (Baranski, Stetkiewicz, Czajkowska, Sitarek, & Szymczak, 1984).

Mutagenesis studies, including point mutations in *Salmonella typhimurium* or *Saccharomyces cerevisiae*, as well as in the mouse lymphoma forward mutation test, were negative. No increase in chromosomal abnormalities was found in Chinese hamster ovary cells exposed in vitro, although a dose-related increase in bone marrow erythrocyte micronuclei was observed in mice given 1,3-dioxolane intraperitoneally (ACGIH, 2002).

To summarize, 1,3 dioxolane is a solvent with modest acute toxicity and low potential for mutagenicity, but some indications of reproductive and developmental toxicity at very high doses. It has not been designated as a carcinogen or reproductive/developmental toxicant by any authoritative body. Significant data gaps for 1,3-dioxolane include a lack of toxicokinetic studies and the absence of a 2-year bioassay for potential carcinogenicity.

Triethyl phosphate (TEP; CAS # 78–40-0, $C_6H_{15}O_4P$) is a clear, colorless liquid with a molecular weight of 182.15 g/mol. It has a mildly pleasant odor, a boiling point of 215 °C and a vapor pressure of 0.39 Torr at 25 °C (Daubert & Danner, 1989). No Federal OSHA PEL, Cal-OSHA PEL or ACGIH TLV currently exists. It has been used as a solvent, plasticizer, flame retardant and an intermediate for pesticides and lacquers (OECD, 2002; Oishi, Oishi, & Hiraga, 1982).

Structurally an organophosphate, TEP is a weak cholinesterase inhibitor. Occupational exposures most commonly involve the skin, although inhalational exposures can occur in workers when transferring the liquid into or from barrels. The potential for consumer exposure is deemed to be low, due to the compound's low vapor pressure, and relatively low dermal penetration. However, it is theoretically possible through inhalation of spontaneously degraded consumer products with TEP-based flame retardants (OECD, 2002). Heavily contaminated water and even some seafood from water sources near chemical factories has been documented in Germany, China and Japan (Lai et al., 2019; OECD, 2002) (Oishi et al., 1982). Therefore, ingestion of contaminated water and seafood is theoretically possible for the surrounding public. Air samples from multiple large USA cities have demonstrated detectable TEP levels (Kim, Wang, Li, & Kannan, 2019).

TEP is metabolized to DEP, which is excreted in the urine (Wang, Li, Martinez-Moral, Sun, & Kannan, 2019). DEP weakly inhibits acetylcholinesterase. Recently, gut microbiome alterations were reported in male rats fed DEP, resulting in a number of hormonal, lipid and cytokine changes (Yang, Li, Pang, Ren, & Fang, 2019). TEP is somewhat structurally similar to tri-*o*-cresyl phosphate (TOCP), whose neurotoxic effects are well-documented (Classen, Gretener, Rauch, Weber, & Krinke, 1996; Morgan & Penovich, 1978; Song et al., 2012; Song, Yan, Zhao, Zhang, & Xie, 2009; Zhao et al., 2004). TEP and TOCP share a similar structural metabolism, with an ethyl chain and an aryl chain being hydrolyzed, respectively (Wang et al., 2019).

Human-specific toxicokinetic studies have not been performed for TEP, nor are there epidemiologic studies of the compound's potential toxicity in humans. Animal toxicity studies demonstrate TEP's behavior as an organophosphate, weakly inhibiting acetylcholinesterase (Gosselin, Smith, & Hodge, 1984). Guinea pigs, mice and rats all have nearly similar LD_{50} for TEP. Such doses result in CNS excitation, followed by inhibition and ultimately death within 24 h due to respiratory failure (Sheftel, 2000). Inhalation of 28 000 ppm for 6 h resulted in 3/3 deaths in rats due to respiratory failure. Responses to lower air concentrations have not been documented. Ingestion by rats of 400 mg/kg TEP for 37 days resulted in peritoneal irritation, ascites and anesthesia without paralysis. TEP was a weak irritant to guinea pig skin (Bisesi, 2001). Rat TEP ingestion models have also shown hepatocellular enlargement without significant serum enzyme fluctuations, adrenal enlargement and CNS cholinesterase depression at 5% of food weight (Gumbmann, Gagne, & Williams, 1968).

Salmonella mutagenicity testing in rats and hamsters was negative (Zeiger et al., 1987). An in vitro cell transformation test was negative (OECD, 2002). Injection of 300 mg/kg TEP in male mice did not evoke chromosomal damage in sperm (Degraeve, Chollet, & Moutschen, 1984).

TEP has not been classified with regard to its potential carcinogenicity by the IARC, NTP or USA EPA. TEP is not currently listed as a CalEPA's Proposition 65 developmental or reproductive hazard. Although high concentrations of TEP have been shown to disrupt embryonic development in invertebrates (sea urchins), we were not able to identify specific mammalian developmental studies (Bottger & McClintock, 2001; HSDB, 2006).

In summary, TEP is a solvent with weak cholinesterase inhibition at high exposures. The potential for dermal and inhalation toxicity is low at expected occupational exposure levels. The compound has not been evaluated for carcinogenicity in a standardized 2-year rodent bioassay, nor has it been subjected to a multigenerational reproductive/developmental bioassay.

4 | CONCLUSIONS

Solvent-based paint removers remain an important class of consumer and industrial products. Numerous commercial formulations exist on the market with two dominant active ingredients, methylene chloride and NMP, having historically dominated the market. Both of these well-studied chemicals have engendered serious toxicologic concerns, with resulting regulatory attention. With the USA EPA's recent regulatory uncoupling of these two agents and separate ban of methylene chloride for consumer (but not commercial) use in paint removal products (USEPA, 2019), one or more alternative chemicals may become prominent replacements. These alternative chemicals are, in general, less well-studied, with significant data gaps existing in the literature. This aim of the present review was to summarize what is currently published about existing and emerging paint remover constituents, and to highlight what information deficiencies exist. Regardless of the chemical(s) used, individuals making decisions regarding substitute chemicals should be afforded enough data to make an informed decision about their potential toxicity. Finally, while human toxicity is the primary focus of the present review, we acknowledge that other considerations, including acute safety issues (eg, flammability), effectiveness/ease of use, and environmental fate, will also ultimately play into these product formulation decisions.

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APPENDIX A CARCINOGEN CLASSIFICATION SCHEME

International Agency for Research on Cancer (IARC)

- Group 1: Carcinogenic to humans
- Group 2A: Probably carcinogenic to humans
- Group 2B: Possibly carcinogenic to humans
- Group 3: Unclassifiable as to carcinogenicity in humans
- Group 4: Probably not carcinogenic to humans

National Toxicology Program (NTP; USA Department of Health and Human Services)

- "Known to be human carcinogens"
- "Reasonably anticipated to be human carcinogens"

USA Environmental Protection Agency's Integrated Risk Information System (IRIS)

- Group A: Carcinogenic to humans
- Group B: Likely to be carcinogenic to humans
- Group C: Suggestive evidence of carcinogenic potential
- Group D: Inadequate information to assess carcinogenic potential
- Group E: Not likely to be carcinogenic to humans

California Environmental Protection Agency's (CalEPA) "Proposition 65" List
(Safe Drinking Water and Toxic Enforcement Act)

- Generic language: "Chemical(s) known to the State of California to cause cancer or reproductive toxicity"
- Chemicals are added based on California labor code (which relies on IARC), the State's qualified experts, other authoritative bodies such as the USA EPA, FDA, NIOSH, NTP or IARC, or if there is a formal labeling requirement by an agency of the State or the Federal Government