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Inhalation of two Prop 65-listed chemicals within vehicles may be associated with increased cancer risk

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ABSTRACT

Chemicals are listed on California's Proposition 65 (Prop 65) for their potential to cause cancer, birth defects or other reproductive harm, and certain chemicals from this list are often detected within interior vehicle dust and air. Therefore, this study examined the potential risk associated with five Prop 65-listed chemicals detected within vehicle interiors: benzene, formaldehyde, di (2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and tris(1,3-dichloro-2-propyl)phosphate (TDCIPP). Exposure estimates based on time spent within a vehicle were derived from a meta-analysis of estimated concentrations from the literature. Regulatory levels established by the California Office of Environmental Health Hazard Assessment (OEHHA) were then used to generate percent reference doses (%RfDs) for chemical-specific daily doses as well as determine the probability of risk (exceedance probability) as a function of %RfD for each chemical-specific daily dose. Based on our meta-analysis, benzene and formaldehyde were detected in vehicle interior air whereas DEHP, DBP and TDCIPP were detected in vehicle interior dust. Benzene and formaldehyde were the only two chemicals with an estimated %RfD > 100 across any of the commute times. For commute times of 20 min or longer, the %RfD was > 100 for maximum exposures based on the "maximum allowable daily level" for benzene, and for 95th-percentile exposures based on the "no significant risk level" for benzene and formaldehyde. Furthermore, the probability of exceeding 100% RfD was highest for cancer risks associated with benzene, followed by cancer risks associated with formaldehyde and the risk of reproductive and developmental toxicity associated with benzene. Lastly, within the entire state of California, the percent of commuters with a 10% probability of exceeding cancer risk associated with benzene or formaldehyde exposure was 78% and 63%, respectively. Overall, our study raises concerns about the potential risk associated with inhalation of benzene and formaldehyde for people who spend a significant amount of time in their vehicles, an issue that is especially pertinent to traffic-congested areas where people have longer commutes.

1. Introduction

California's Proposition 65 (Prop 65), also known as the Safe Drinking Water and Toxic Enforcement Act of 1986, requires businesses to inform Californians about exposure to chemicals known to cause cancer, birth defects or other reproductive harm. Prop 65-listed chemicals represent a wide range of naturally occurring and synthetic chemicals that include additives or ingredients in pesticide formulations, common household products, food, drugs, dyes, or solvents. In some cases, Prop 65-listed chemicals that are used in indoor products have the potential to migrate, abrade, or off-gas from end-use products and accumulate in indoor environments (Mitro et al., 2016). The presence of Prop 65-listed chemicals in indoor air and dust has been well documented (Greco et al., 2020; Hwang et al., 2008; Lucattini et al., 2018; Rudel et al., 2003), suggesting that people may be exposed to these chemicals through inhalation of air and ingestion of dust. While several studies have evaluated the potential risk to Prop 65-listed chemicals detected within indoor environments (Ali, 2019; Ao et al., 2019; Kang et al., 2012; Wang et al., 2013; Zhou et al., 2019), there is minimal information available about the potential risk of Prop 65-listed chemicals due to exposure within personal vehicles.

The interior of a personal vehicle is considered an indoor microenvironment and, due to its small, confined space, chemicals emitted from the interior of the vehicle have the potential to be concentrated (Faber

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and Brodzik, 2017). Chemicals such as phthalates, volatile organic compounds (VOCs), flame retardants and hydrocarbons – some of which are Prop 65-listed – are commonly detected within interior vehicle dust (Müller et al., 2011; Riediker et al., 2003; Zulauf et al., 2019). Furthermore, prior studies have demonstrated that the concentration of certain chemicals within vehicle interiors were 2- to 3-fold higher compared to indoor concentrations within the built environment (Faber and Brodzik, 2017), suggesting that vehicle interiors are an important indoor microenvironment to consider when evaluating exposure to chemicals.

American adults spend an average of 6% of their time within an enclosed vehicle (Klepeis et al., 2001), a large amount of which is spent commuting. In the United Sates, a person spends an average of 52.8 min per day commuting to work (U.S. Census Bureau, 2017). Longer commute times are known to be strongly associated with negative health outcomes such as shorter sleep, obesity, and poor physical/mental health (Ding et al., 2014; Hansson et al., 2011; Oliveira et al., 2015; Sugiyama et al., 2013). Moreover, people who spend a longer amount of time in vehicles are exposed to higher concentrations of particulate matter, carbon monoxide, VOCs, ozone, and flame retardants (Huang et al., 2012; Ramos et al., 2016; Reddam et al., 2020), suggesting that people experiencing long commutes over years and, in some cases, decades likely represent a sub-population vulnerable to excess exposure to vehicle-borne chemicals. Therefore, it is important to evaluate the potential risk associated with exposure to vehicle-specific chemicals as a function of commute time.

The aim of this study was to assess the potential human health risk of Prop 65-listed compounds found in personal vehicles; cumulative risks resulting from other stressors associated with long commutes (e.g., shorter sleep, obesity, etc.) were not considered within this study. We first summarized the estimated concentrations of five Prop 65-listed chemicals in interior vehicle air and dust, and then derived exposure estimates based on time spent within a vehicle. The potential human health risks resulting from exposure to these compounds as a function of commute time were then evaluated using regulatory levels established by the California Office of Environmental Health Hazard Assessment (OEHHA).

2. Methods

Supplementary figure 1 outlines the four phases (chemical identification, exposure assessment, hazard identification, and risk assessment) that were followed to measure the potential risk of Prop 65-listed chemicals to commuters. All four phases are described in detail within Sections 2.1 and 2.2.

2.1. Identification of Prop 65-listed chemicals introduced within vehicles

Based on OEHHA's Prop 65 Fact Sheet (dated June 2019) entitled "Passenger Vehicles and Off-Highway Motor Vehicles", benzene, carbon monoxide, diesel and gasoline engine exhaust, lead, formaldehyde, and phthalates [Dibutyl phthalate (DBP), Di (2-ethylhexyl) phthalate (DEHP), Diisodecyl phthalate (DIDP), and Diisononyl phthalate (DINP)] were identified as Prop 65-listed chemicals either introduced within or generated by vehicles. For the purpose of this study, only chemicals introduced within vehicles during manufacturing (benzene, formaldehyde, and phthalates) were assessed for potential human health risks. In addition, while not currently on OEHHA's fact sheet dated June 2019, tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) was assessed in this study since TDCIPP is a Prop 65-listed chemical that has been detected within indoor vehicle dust (Ali et al., 2013; Brandsma et al., 2014; Brommer and Harrad, 2015; Harrad et al., 2016) and exposure to TDCIPP is significantly associated with longer commute times (Reddam et al., 2020). Therefore, we conducted a meta-analysis of the peer-reviewed literature in order to synthesize measured concentrations of benzene, formaldehyde, phthalates (DBP, DEHP, DIDP and DINP), and TDCIPP that have been detected within dust and air collected within vehicle interiors. Studies selected for review and risk assessment met the following three inclusion criteria: (1) evaluated concentrations of benzene, formaldehyde, phthalates, and TDCIPP in interior car dust or air; (2) published before or during July 2020; and (3) published in English.

2.2. Data collection and analysis

2.2.1. Exposure assessment

Based on dust and air samples collected within vehicle interiors, measured concentrations of benzene, formaldehyde, phthalates and TDCIPP were compiled from the following studies that met all three inclusion criteria listed above: Abdallah and Covaci, 2014; Albar et al., 2017; Ali et al., 2013; Brandsma et al., 2014; Brodzik et al., 2014; Brommer et al., 2012; Brommer and Harrad, 2015; Buters et al., 2007; Carignan et al., 2013; Chan et al., 1991; Chen et al., 2014; Christia et al., 2018; Faber et al., 2014; Fujii et al., 2003; Geiss et al., 2009; GLOBAL 2000., 2005; Harrad et al., 2016; Hoehner et al., 2012; Liang et al., 2019; Lv et al., 2020; Staaf and Östman, 2005; Tokumura et al., 2017, 2016; Wensing, 2009; Xiong et al., 2015; Yoshida et al., 2006; You et al., 2007; Zhou et al., 2017. When compiling concentrations of benzene, formaldehyde, phthalates and TDCIPP, this study did not consider the type and age of vehicles, ventilation conditions, ambient temperatures, sampling methods, and time of sample collection.

For studies where chemical concentrations were reported as a distribution (rather than raw data for individual samples), the minimum, median, and/or maximum (depending on what was reported) were used for estimating the exposure distribution within this study. Using all available data identified from our meta-analysis, the overall minimum, median, and maximum as well as 5th, 25th, 75th, and 95th percentile concentrations were then identified and used to calculate daily doses for benzene, formaldehyde, phthalates, and TDCIPP based on ingestion and inhalation within adults. As DIDP and DINP were not detected within interior vehicle dust nor air, daily doses were not calculated for these chemicals. Daily doses were calculated using adult ingestion and inhalation rates derived from the U.S. Environmental Protection Agency's Exposure Factors Handbook. The dust ingestion rate associated with 12 years through adult was acquired from Table 5-1 (under "Dust: General Population Central Tendency") whereas the inhalation rate was calculated by averaging the "Mean" rate from 16 to < 71 years from Table 6-1. Our risk analysis assumed that the average ingestion and inhalation rate from the EPA Exposure Factors Handbook was applicable to the general population. These rates were multiplied by the overall minimum, median, and maximum as well as 5th, 25th, 75th, and 95th percentile concentrations to produce a distribution of daily doses for each chemical. Time-weighted daily doses were then calculated from 20 to 240 min (using 20-min increments) by first dividing the total daily dose by the number of minutes in one day (1440 min) and then multiplying by the commute time (which ranged from 20 to 240 min). Time-weighted daily doses for oral or inhalation routes of exposure were not calculated for chemicals that did not have corresponding OEHHA-generated safe harbor levels. For example, daily doses based on inhalation of TDCIPP, DBP, and DEHP were not calculated since, as of August

Table 1
OEHHA's safe harbor levels for TDCIPP, DBP, DEHP, benzene, and formaldehyde. N.C. = not calculated by OEHHA as of August 2020.

Endpoint	Cancer (NSRL)		Developmental and Reproductive Toxicity (MADL)	
Route of Exposure	Oral	Inhalation	Oral	Inhalation
TDCIPP	5.4 μg/day	N.C.	N.C.	N.C.
DBP	N.C.	N.C.	8.7 μg/day	N.C.
DEHP	310 μg/day	N.C.	410 μg/day	N.C.
Benzene	6.4 μg/day	13 μg/day	24 μg/day	49 μg/day
Formaldehyde	N.C.	40 μg/day	N.C.	N.C.

2020, inhalation-based safe harbor levels for TDCIPP, DBP, and DEHP were not determined by OEHHA.

2.2.2. Hazard identification

Safe harbor levels were obtained directly from OEHHA (https://oehha.ca.gov/proposition-65/proposition-65-list). If OEHHA concluded that a chemical is a known carcinogen, the "no significant risk level" (NSRL) was used; the NSRL is defined as the daily intake level posing a 10^{-5} lifetime risk of cancer. If OEHHA concluded that a chemical is known to cause birth defects or other reproductive harm, the "maximum allowable daily level" (MADL) was used; the MADL is derived from No Observable Effect Levels (NOELs) or Lowest Observable Effect Levels (LOELs). The NSRL and MADL were reported for chemicals that are known to cause cancer and reproductive/developmental toxicity, respectively, based on OEHHA's conclusions. Values associated with both oral and inhalation routes of exposure were also reported when available.

2.2.3. Risk characterization

Percent reference doses (%RfDs) were calculated by dividing chemical-specific daily doses by chemical-specific safe harbor levels (NSRLs or MADLs) and then multiplying by 100. Chemicals detected within the air of vehicle interiors were divided by safe harbor levels specific to inhalation exposure, whereas chemicals detected within dust of vehicle interiors were divided by safe harbor levels specific to oral exposure. Exceedance probability curves were generated for chemicals with %RfDs that exceeded 100% (the regulatory threshold of concern), where %RfDs calculated for each chemical were assigned exceedance probabilities (i.e., 0.99, 0.95, 0.75, 0.5, 0.25, 0.05 and 0.01). After plotting exceedance probabilities, exponential growth curve equations were then generated for each commute time in order to calculate the probability of exceeding 100% RfD as a function of commute time. In addition, we plotted exceedance probabilities at 100% RfD as a function of commute time to generate third-order polynomial equations and estimate the probability of exceeding 100% RfD at different commute times for each chemical.

Finally, a 10% exceedance probability threshold was selected as a benchmark of concern for estimating the percent of California commuters (by county) that may be at risk from elevated exposure to Prop 65-listed chemicals within vehicles. For each chemical, the commute time associated with a 10% exceedance probability was calculated based on third-order polynomial equations as described above. Commute time for all counties within California were acquired from the U.S. Census Bureau (Table B08534). The percent of the population by county commuting more than the time associated with a 10% exceedance probability was then calculated and plotted on a map using mapchart.net.

3. Results

3.1. Estimated daily doses of benzene and formaldehyde are orders of magnitude higher than TDCIPP, DEHP and DBP

Based on our meta-analysis, concentrations of benzene, formaldehyde, phthalates (DBP, DEHP, DIDP and DINP), and TDCIPP detected within interior vehicle dust and air are reported in Tables S1 and S2, respectively. The overall minimum, median, and maximum as well as 5th, 25th, 75th, and 95th percentile concentrations for each chemical are reported within Table S3. The median concentration of DBP, DEHP, and TDCIPP within interior vehicle dust was 11.8, 488.5, and 3 µg/g, respectively, and the median concentrations of benzene, DBP, DEHP, TDCIPP and formaldehyde within interior car air were 10.35, 198.5, 370, 0.014 and 24.25 µg/m^3, respectively. Concentrations of DIDP and DINP in interior car dust and air were not reported within any studies included within our meta-analysis.

As described in Section 2.2.1, an ingestion and inhalation rate of 0.02 g/day and 15.65 m^3/day, respectively, were used for calculation of daily doses (Table S4). Based on a 24-h exposure scenario, the daily doses for TDCIPP, DBP, DEHP, benzene, and formaldehyde are summarized within Fig. 1; chemicals that did not have corresponding OEHHA-generated safe harbor levels (e.g., inhalation-specific safe harbor levels for TDCIPP, DBP, and DEHP) were not included within Fig. 1. The median daily doses of DEHP, DBP, and TDCIPP based on ingestion of interior vehicle dust was 9.77, 0.236, and 0.06 µg/day, respectively, and the median daily doses of formaldehyde and benzene based on inhalation of interior vehicle air were 379.51 and 161.97 µg/day, respectively.

Time-weighted exposures were calculated for all five chemicals in increments of 20 min (Fig. 2 and Table S5). The estimated median dose of formaldehyde, benzene, DEHP, DBP and TDCIPP for an adult spending 20 min within a car per day was 5.27, 2.25, 0.14, 0.003, and 0.0008 µg/day, respectively – a dose that increases from 20 min to the highest exposure scenario tested (240 min, or 4 h). The estimated median dose of formaldehyde, benzene, DEHP, DBP and TDCIPP for an adult who spent 240 min within a car per day was 63.25, 27, 1.63, 0.04, and 0.01 µg/day, respectively. Similar to the 24-h exposure scenario, chemicals present within interior vehicle air resulted in a higher daily dose – in some cases by five orders of magnitude – relative to chemicals present within interior vehicle dust.

3.2. TDCIPP has the lowest safe harbor level out of all five Prop 65-listed chemicals introduced into vehicles during manufacturing

A summary of OEHHA's safe harbor levels is presented within Table 1. A NSRL was used for chemicals with the potential to cause cancer whereas a MADL was used for chemicals with the potential to cause reproductive and developmental toxicity. For TDCIPP, the NSRL for oral exposure is 5.4 µg/day and was derived based on results from a 2-year chronic toxicity study using rats (Freudenthal and Henrich, 2000). In this study, daily dietary exposure to TDCIPP for 24 months resulted in a dose-dependent increase in the incidence of liver, kidney and testicular tumors, and the tumor incidence data were used to derive a cancer potency estimate of 0.13 (mg/kg-day)$^{-1}$ that served as the basis for the NSRL.

For DBP, the MADL for oral exposure is 8.7 µg/day and was based on a LOEL of 1.5 mg/kg-day (Lee et al., 2004). Dietary maternal exposure of rats to DBP during pregnancy and lactation adversely affected reproductive development of male and female offspring (Lee et al., 2004). OEHHA derived a NSRL and MADL for DEHP, as this chemical has the potential to cause cancer as well as developmental and reproductive toxicity. The NSRL for oral exposures is 310 µg/day and was derived from a cancer potency estimate of 0.0022 (mg/kg-day)$^{-1}$ based on rodent studies conducted by the NTP (1982) and David et al. (1999). In both studies, oral exposure to DEHP resulted in a higher incidence of hepatocellular carcinomas. Additionally, the MADL for oral exposures for DEHP is 410 µg/day for adults and was derived from a NOEL of 5.8 mg/kg-day based on male reproductive effects in the form of testicular damage (David et al., 2000).

OEHHA derived a NSRL and MADL for benzene, as this chemical has the potential to cause cancer as well as developmental and reproductive toxicity. The NSRL for oral and inhalation routes of exposure are 6.4 and 13 µg/day, respectively; these two NRSLs were derived from cancer potency estimates of 0.054 (mg/kg-day)$^{-1}$ and 0.11 (mg/kg-day)$^{-1}$ for oral and inhalation routes of exposure, respectively. These estimates were derived from two different cohorts – the Pliofilm Cohort (Paxton et al., 1994; Rinsky, 1989) and Chinese Worker Cohort (Hayes et al., 1997) – that developed leukemia following occupational exposure to benzene. The MADL for oral and inhalation routes of exposure are 24 and 49 µg/day, respectively, and were derived from a LOEL of 5 ppm based on effects on hematopoiesis within a developmental toxicity study in mice (Keller and Snyder, 1988). For formaldehyde, the NSRL for an inhalation route of exposure is 40 µg/day and was derived from a cancer potency estimate of 0.021 (mg/kg-day)$^{-1}$ based on histopathological

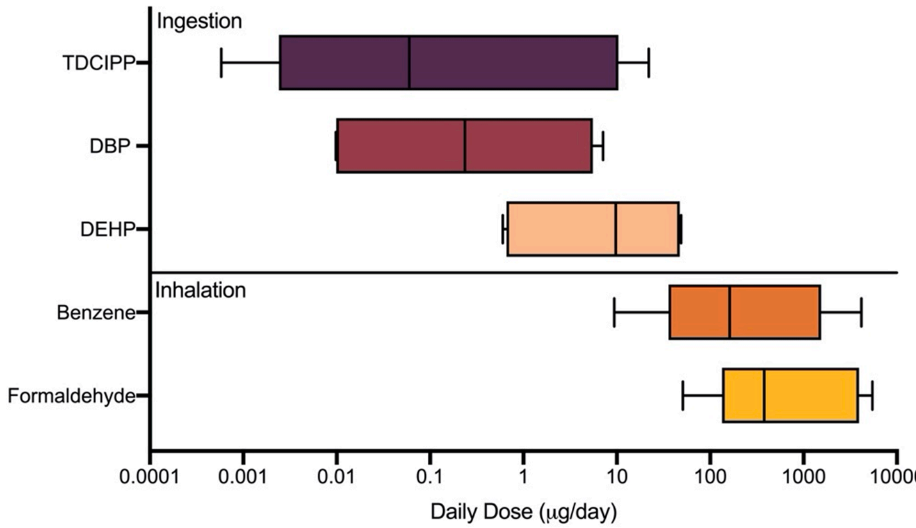

Fig. 1. Estimated daily dose (µg/day) for TDCIPP (N = 117), DBP (N = 10) and DEHP (N = 10) based on ingestion of interior vehicle dust (top), and estimated daily dose (µg/day) for benzene (N = 74) and formaldehyde (N = 52) based on inhalation of interior vehicle air for 24 h (bottom). N = number of data points based on the *meta*-analysis (Tables S1 and S2).

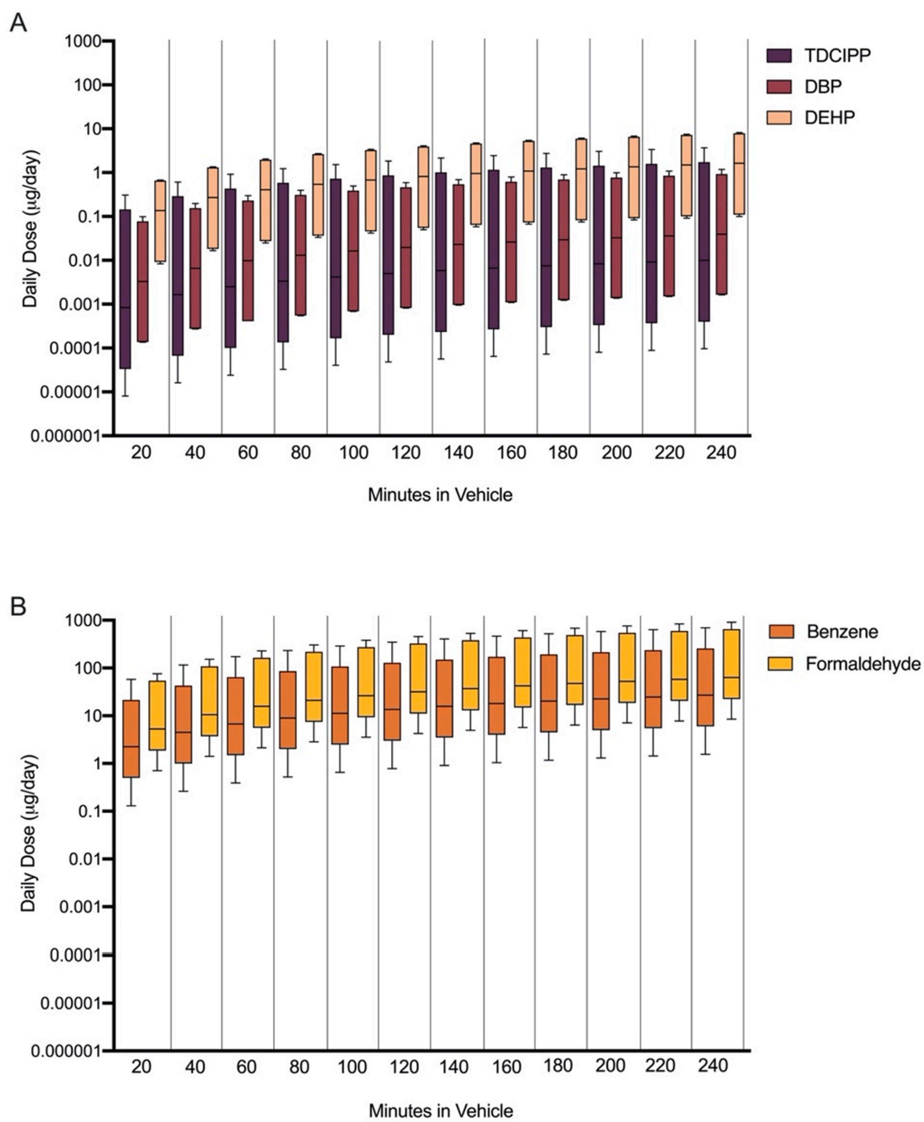

Fig. 2. Distribution of time-weighted daily doses (µg/day) of chemicals found within interior vehicle dust (A) and air (B) as a function of commute time.

changes within the nasal cavity and upper respiratory tract of rats and mice (Kerns et al., 1983).

3.3. Benzene and formaldehyde concentrations are predicted to exceed safe harbor levels following a 20-min commute

Percent RfD (%RfD) was calculated for benzene, formaldehyde, DEHP, DBP, and TDCIPP to evaluate the potential risk associated with exposure to these chemicals from 20 to 240 min (Fig. 3 and Table S6). Each %RfD was calculated by dividing the daily dose by the safe harbor level (NSRL or MADL) and then multiplying by 100; therefore, a %RfD > 100 indicates that the daily dose exceeds levels considered safe by OEHHA.

Benzene and formaldehyde were the only two chemicals with an estimated %RfD > 100 across any of the commute times. Two different %RfDs were calculated for each safe harbor level since a NSRL and MADL were available for benzene. Based on the NSRL for benzene, the %RfD was > 100 resulting from exposures at (1) the 25th percentile or higher combined with commute times of 200 min or longer and (2) the 95th percentile or higher combined with commute times of 20 min or longer (Fig. 3). On the other hand, based on the MADL for benzene, the %RfD was > 100 resulting from exposures at (1) the 75th percentile or higher combined with commute times of 200 min or longer and (2) the maximum combined with commute times of 20 min or longer (Fig. 3). Based on the NSRL for formaldehyde, the %RfD was > 100 resulting from exposures at (1) the 25th percentile or higher combined with commute times of 240 min or longer and (2) the 95th percentile or higher combined with commute times of 20 min or longer (Fig. 3).

3.4. Predicted cancer risks associated with benzene and formaldehyde exposure are higher than the risk of reproductive and developmental toxicity associated with benzene exposure

For benzene and formaldehyde, exceedance probability curves (Fig. 4A-C) were then generated to estimate the probability of risk (exceedance probability) as a function of %RfD (Table S7). The probability of exceeding 100% RfD was dependent on both the chemical and commute time. For cancer risks associated with benzene exposure, the probability of exceeding 100% RfD ranged from 0.024 to 0.775 for commute times of 20–240 min. Similarly, for cancer risks associated with formaldehyde exposure, the probability of exceeding 100% RfD ranged from 0.009 to 0.744 for commute times of 20–240 min. However, the risk of reproductive and developmental toxicity following benzene exposure was substantially lower than cancer risks associated with

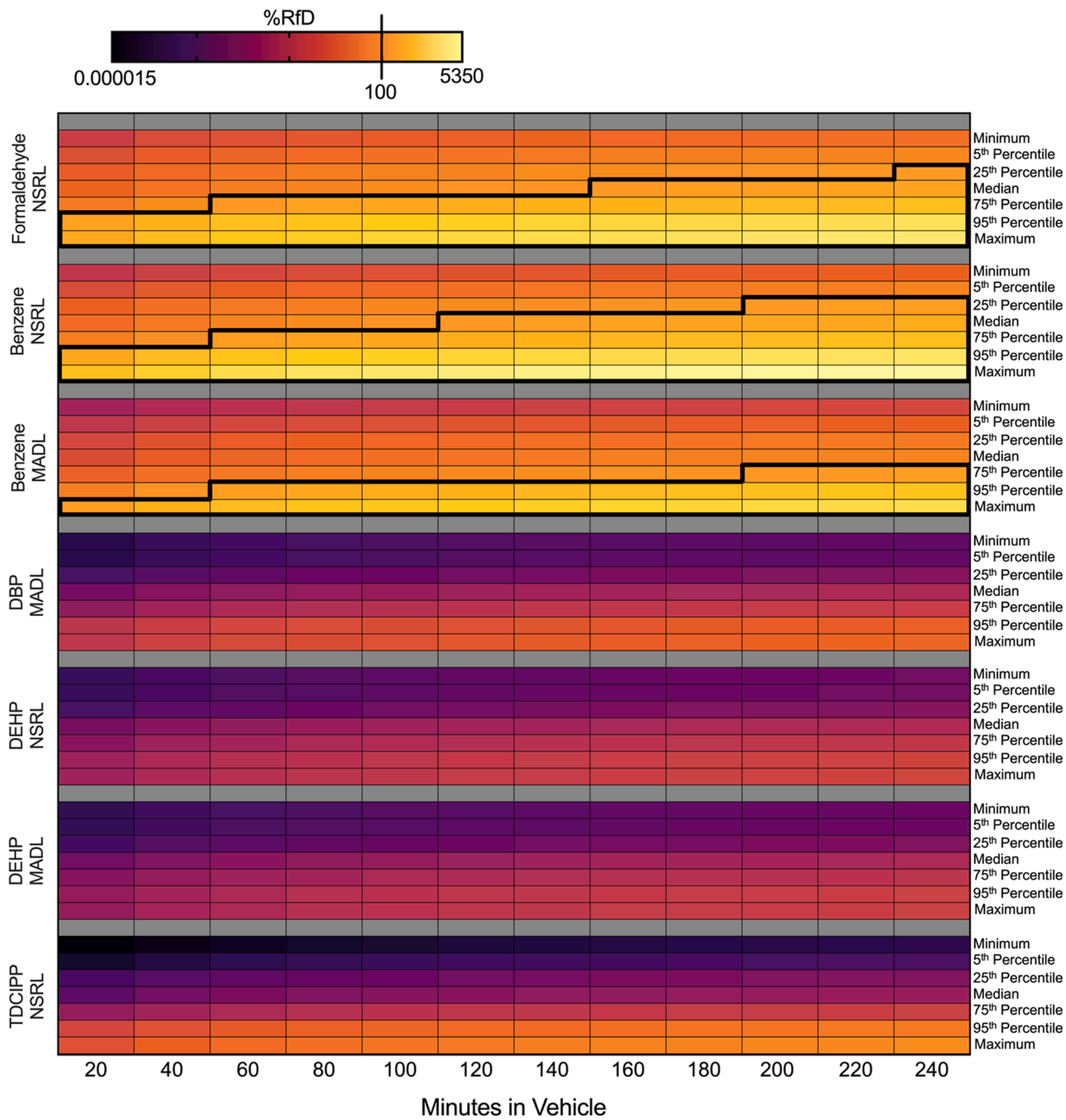

Fig. 3. Heat map showing %RfDs for formaldehyde, benzene (NSRL and MADL), DBP, DEHP (NSRL and MADL) and TDCIPP as a function of exposure distribution and commute time. The %RfD values shown within the heat map were $\log_{10}$-transformed. Cells with %RfD > 100 are outlined with a black solid line.

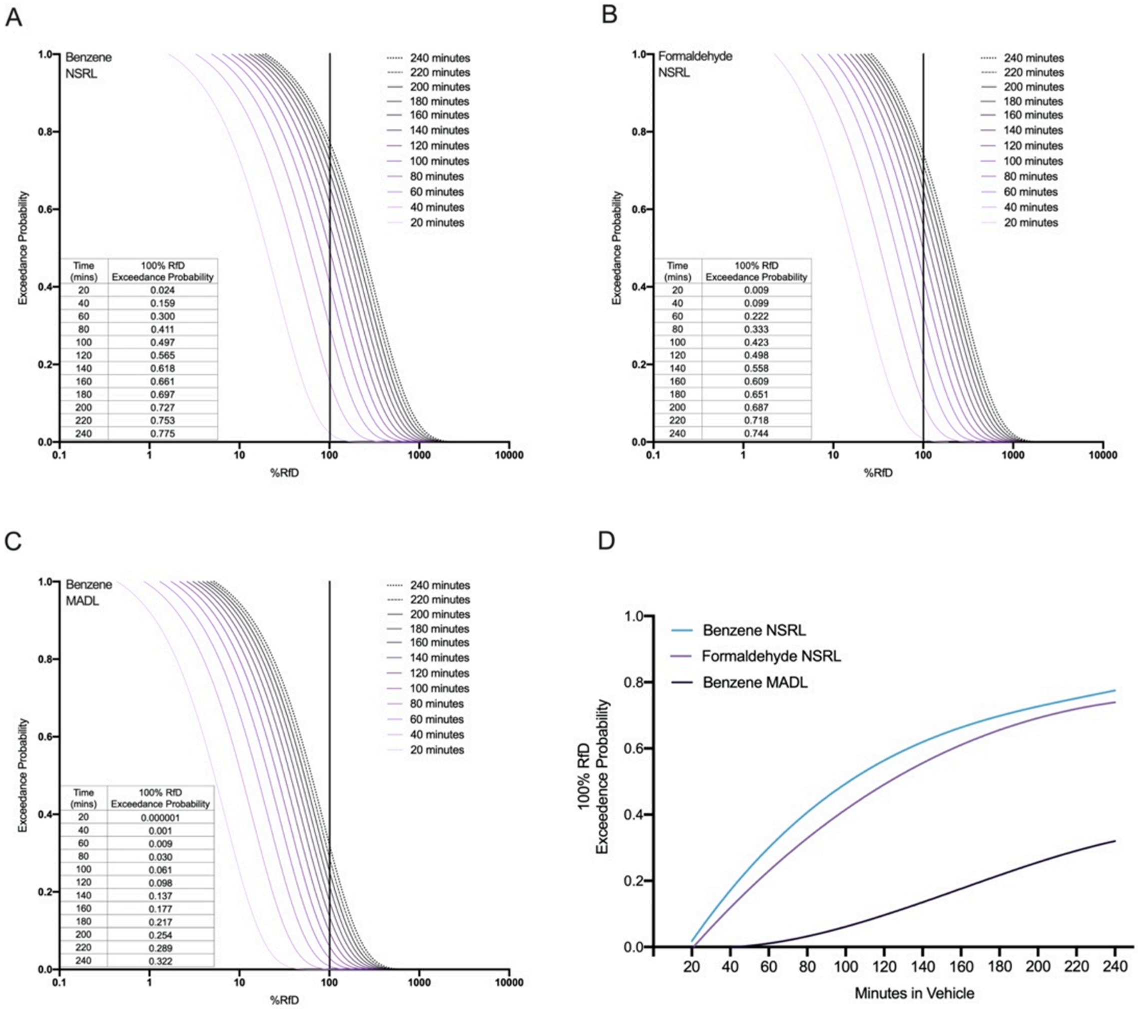

Fig. 4. Exceedance probability curves for cancer risk (NSRL) associated with benzene (A) or formaldehyde (B) exposure as well as risk of reproductive and developmental toxicity (MADL) associated with benzene (C) exposure as a function of %RfD. The inset within panels A, B, and C show the probability of exceeding 100% RfD as a function of commute time. Curves representing the probability of exceeding 100% RfD as a function of commute time for all three different chemical risk scenarios (D).

benzene or formaldehyde exposure (Fig. 4D), as the probability of exceeding 100% RfD ranged from 0.000001 to 0.322 for commute times of 20–240 min.

For all California counties, the percent of commuters with a 10% probability of exceeding 100% RfD (Table S8) is represented in Fig. 5. Within the entire state of California, the percent of commuters with a 10% probability of exceeding cancer risk associated with benzene or formaldehyde exposure was 78% and 63%, respectively, whereas the percent of commuters with a 10% probability of exceeding the risk of reproductive and developmental toxicity associated with benzene exposure was 11%. Across all three risk scenarios and counties, San Francisco County had the highest percentage of commuters with a 10% chance of exceeding risk associated with benzene or formaldehyde exposure.

4. Discussion

Although the risk associated with Prop 65-listed chemicals within indoor environments is well characterized (Ali, 2019; Ao et al., 2019; Zhou et al., 2019), there is limited information on the risk that these chemicals within vehicle interiors pose as a function of commute time. Based on our meta-analysis, benzene, formaldehyde, DBP, DEHP and TDCIPP have all been previously detected within the interior of vehicles. While DBP, DEHP and TDCIPP were previously detected within interior car air and dust, benzene and formaldehyde were only found within the air of vehicle interiors – a finding that is linked to the high volatility of both chemicals. As benzene and formaldehyde are both VOCs, these chemicals are readily emitted into air and, as such, exist almost entirely in the gaseous state. While DBP, DEHP and TDCIPP have been detected in the air of vehicle interiors, based on our meta-analysis these chemicals have been primarily found within dust of vehicle interiors. As DBP, DEHP and TDCIPP are semi-volatile organic compounds (SVOCs), these chemicals are more likely to adsorb onto surfaces of dust particles, furnishing materials, plastics, etc. (Harrad and Abdallah, 2011).

The presence of these compounds within vehicles can be attributed to extensive use in different vehicle parts. Formaldehyde is used in carpets, leather and paints within vehicles, resulting in off-gassing and high concentrations within indoor air (Pang and Mu, 2007). Furthermore, formaldehyde is also used as an adhesive and binder in the production of synthetic fibers, fiberboards, plastics, and textile finishing treatments, products that are commonly present in vehicles (Public Health England, 2017). The high concentration of benzene in vehicles has been attributed to fuel- and exhaust-related emissions that accumulate in the cabin of operating vehicles (Fedoruk and Kerger, 2003). However, several studies have also detected benzene within brand new cars under static conditions, suggesting that interior components are also off-gassing benzene into the air of vehicle interiors (Brodzik et al., 2014; Faber et al., 2013; Yoshida et al., 2006; Zhang et al., 2008).

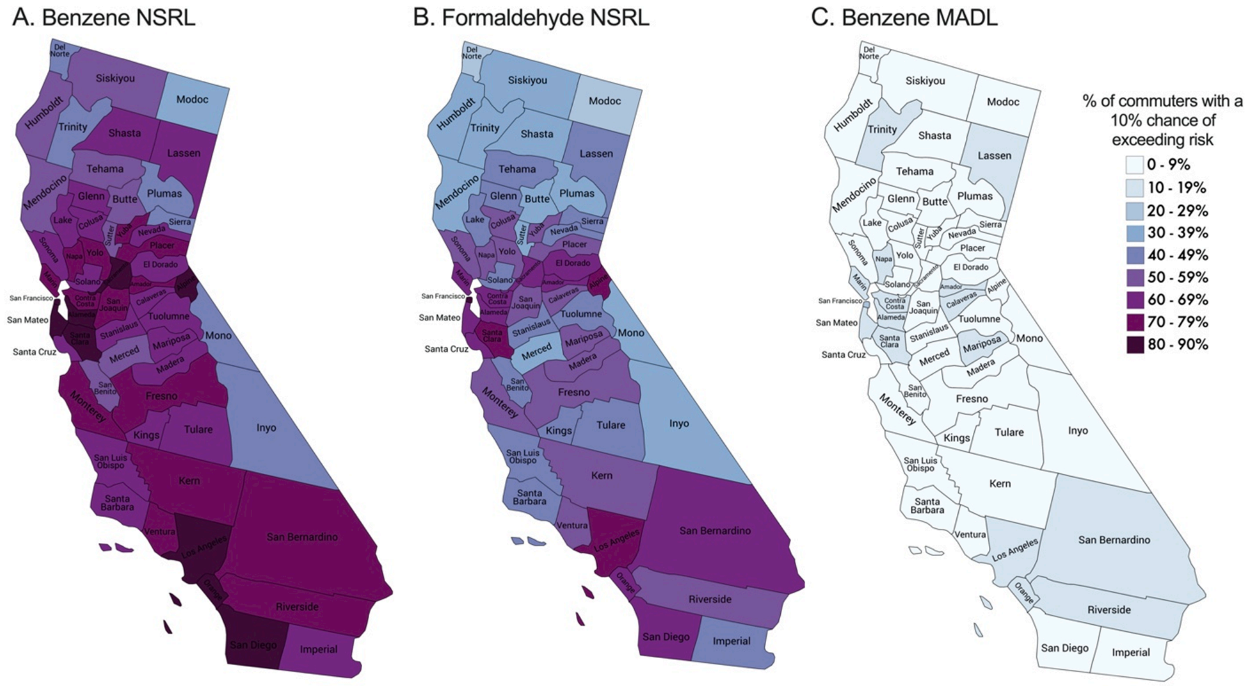

Fig. 5. Maps of California counties showing the percent of commuters with a 10% probability of exceeding cancer risk (NSRL) and/or the risk of reproductive and developmental toxicity (MADL) for benzene or formaldehyde.

Benzene is used to produce styrene, nylon, and phenol which are, in turn, used to produce plastics, resins, and synthetic fibers (Hahladakis et al., 2018; CDC, 2018). Benzene is also used extensively in rubber, dyes, and lubricants and, from these products, benzene residue can off-gas and accumulate within indoor air. Phthalates such as DEHP and DBP are predominantly used as plasticizers in soft plastics, such as in a large variety of polyvinyl chloride (PVC) products including car seat fabric, cable insulation and interior and exterior trim in vehicles (Heudorf et al., 2007; Patil et al., 2017). TDCIPP is a commonly used flame retardant that is used within polyurethane foam of permanently installed seats as well as plastics and electronics present in the vehicle's dashboard and console (Brandsma et al., 2014; Harrad et al., 2016).

Out of the five different Prop 65-listed chemicals assessed in this study, benzene and formaldehyde were the only two chemicals with estimated %RfDs exceeding 100. While this may be partially a result of lower safe harbor levels for benzene and formaldehyde relative to chemicals such as DEHP, the primary drivers are higher airborne concentrations relative to dust combined with higher inhalation rates relative to ingestion. Therefore, our study suggests that the presence of benzene and formaldehyde within air of vehicle interiors pose a higher risk to commuters relative to chemicals detected within dust of vehicle interiors. For benzene and formaldehyde, none of the commute times associated with the minimum or 5th percentile of the exposure distribution resulted in a %RfD that exceeded 100, suggesting that, if a commuter is on the lower end of the exposure spectrum, the daily dose will not exceed safe harbor levels associated with benzene and formaldehyde despite spending up to 4 h in a vehicle. On the other hand, all of the commute times associated with the maximum daily dose exceeded a 100% RfD, underscoring the importance of estimating where a commuter lies within the exposure distribution.

Prior studies have shown that different factors such as interior temperature, ventilation rate and mode, humidity, solar radiation, vehicle age and grade, cabin value, car upholstery material, and travel distance influence the concentrations of benzene and formaldehyde detected within a vehicle (Chen et al., 2014; Xiong et al., 2015; Xu et al., 2016). Lower concentrations of aromatic hydrocarbons, such as benzene, are associated with fabric seats compared to leather seats and vehicles with larger volume cabins (Xu et al., 2016). Furthermore, off-gassing of VOCs may decrease with car age, total car travel mileage, increased ventilation rate, and lower in-car temperature or relative humidity (Chen et al., 2014; Xiong et al., 2015; Xu et al., 2016). These different factors suggest that measures can be taken to reduce a commuter's daily dose and, as a result, decrease the probability of exceeding 100% RfD irrespective of time spent in the vehicle.

Based on our exceedance probability curves, cancer risks associated with exposure to benzene and formaldehyde are substantially higher than the risk associated with reproductive and developmental effects due to benzene exposure. Previous epidemiology studies in professional drivers (i.e., taxi drivers) have found significant associations between their profession and different forms of cancer, including lung, bladder, esophageal, stomach, and rectal cancer (Gubéran et al., 1992; Hansen et al., 1998; Ole Jensen et al., 1987; Tsoi and Tse, 2012). Moreover, additional studies have demonstrated that taxi drivers have a higher risk of cancer resulting from exposure to formaldehyde (Hadei et al., 2019; Pang and Mu, 2007) and benzene (Chen et al., 2016). While studies have previously examined associations between taxi drivers and cancer risks, there are virtually no studies that have investigated the potential association between cancer risk and commute time within the general population. A recent study by Patterson et al. (2020) found that commuting by personal vehicles has been associated with an increased rate of incident cancer compared to commuting by bicycle, rail or walking. Therefore, more research is needed to study the potential role of benzene and formaldehyde exposure in higher cancer incidence associated with longer commutes.

In California, >1.5 million people commute for>2 h a day, with 3% of the population commuting for>3 h a day (U.S. Census Bureau, 2017). Therefore, based on our study, it is possible that a substantial proportion of the population within California may exceed 100% RfD for benzene and formaldehyde on a daily basis. Interestingly, a study by Mapou et al. (2013) found that concentrations of in-vehicle formaldehyde in California communities were about twice as high as New Jersey and Texas communities. This suggests that exposure to benzene and formaldehyde through interior car air is a pertinent issue, especially in California where a large percentage of the population is commuting by personal vehicles.

5. Conclusion

While this study was able to evaluate the potential risks associated with benzene and formaldehyde, risks for other chemicals detected within the air of vehicle interiors were not assessed due to the lack of inhalation-specific safe harbor levels established by OEHAA (TDCIPP, DBP and, DEHP). Moreover, while daily doses were calculated using intake rates, our risk assessment is based on the assumption that chemicals being inhaled and ingested are 100% bioavailable. Despite these limitations, this study highlights the potential risk associated with inhalation of benzene and formaldehyde for people who spend a significant amount of time in their vehicles. Furthermore, while the variability in chemical concentrations from countries with diverse climates may not be directly applicable to the state of California, this study provides a starting point for additional risk analyses. As benzene and formaldehyde are on the Prop 65 list due to cancer and reproductive/developmental toxicity concerns, there is a need for more information on the potential association between commute time within vehicles and exposure to both of these chemicals. As people with long commutes are an already vulnerable sub-population, additional measures may need to be implemented in order to mitigate potential cancer risks associated with benzene and formaldehyde exposure.

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CRediT authorship contribution statement

Aalekhya Reddam: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization. **David C. Volz:** Conceptualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106402.

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