SUPPLEMENTAL FILE B: HUFFING EXPOSURE SCENARIOS

Per- and Polyfluoroalkyl Substances (PFAS): Next Steps for Hazard, Exposure, and Risk Analyses
(CPSC Contract Number 61320622A0005, CPSC Order Number 61320623F2025)
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1. Introduction

The focus of the main report is on the hazards and risks associated with chronic exposure to a subset of targeted PFAS chemicals. However, acute exposures and risks should also be considered for 1,1-difluoroethane (DFE) and 1,1,1,2-tetrafluoroethane (TFE). Specifically, huffing exposure scenarios were considered alongside other identified uses of DFE and TFE. This document summarizes the hazards, exposures, and risks of this activity for aerosolized applications which are huffed.

1.1. DFE

1,1-Difluoroethane (DFE), also known as hydrofluorocarbon 152a (HFC-152a), is a colorless, highly flammable gas that is commonly used as a refrigerant and propellant in aerosolized products, such as air dusters and personal care products. Toxicokinetic data from studies in rats (Avella et al., 2010) and humans (Ernstgård et al., 2012) demonstrate that DFE is rapidly absorbed via inhalation, transported to organs including the brain, heart, kidneys, and liver, and rapidly eliminated from the body when exposure ends.

Inhalant abuse of fluorinated hydrocarbons from misuse of household products such as air dusters is common in the United States, increasingly among adolescents, because these chemicals rapidly cause central nervous system (CNS) depression and euphoria and are easily accessible (Katz and Dorey, 2024). DFE is one such commonly abused substance (Calhoun et al., 2018; Fogelson et al., 2022). "Huffing" is the term typically used to describe the practice of inhaling chemical fumes from common household products to achieve a brief euphoric high. Because of the concern for exposure to very high concentrations of DFE during abuse, this assessment evaluates acute exposure from "huffing" separate from chronic exposure to DFE from typical use of products containing this gas.

1.2. TFE

1,1,1,2-Tetrafluoroethane (TFE), also known as hydrofluorocarbon 134a (HFC-134a) and norflurane, is a colorless, non-flammable gas that is commonly used as a refrigerant and a propellant in aerosolized products, such as air dusters, personal care products, and pharmaceuticals including

pressurized metered dose inhalers for asthmatics. Toxicokinetic data from studies in laboratory animals and humans demonstrate that TFE is rapidly absorbed after inhalation, but pulmonary uptake is low (Gunnare et al., 2006; National Research Council, 2002; European Centre for Ecotoxicology and Toxicology of Chemicals, 2006). Blood concentrations increase rapidly in humans, reaching a steady state within 30–55 minutes (Emmen et al., 2000; Gunnare et al., 2006). Metabolism is negligible, and blood and tissue concentrations decline rapidly after exposure ends (Emmen et al., 2000; Gunnare et al., 2006; NRC, 2002).

TFE has become a substance of inhalant abuse, like DFE, owing to its ease of accessibility and euphoric effects (Katz and Dorey, 2024). Because of the concern for very high exposure to TFE during inhalant abuse, this assessment evaluates acute exposure from "huffing" separate from chronic exposure to TFE from typical use of products containing this gas.

2. Methods

2.1. Literature Search

As described in the main report, a literature search was conducted for the targeted PFAS, including DFE and TFE. Gray literature and peer-reviewed literature were reviewed for acute exposures and corresponding hazards and risks associated with huffing. Studies were identified using methods described in Section 3.1 of the main report.

2.2. Hazard

Acute toxicity values for DFE and TFE were identified by searching the following sources:

- U.S. EPA Acute Exposure Guideline Levels
- U.S. National Oceanic and Atmospheric Administration (NOAA) CAMEO Chemicals database
- U.S. Occupational Safety and Health Administration (OSHA)
- U.S. National Institute for Occupational Safety and Health (NIOSH)
- American Conference of Governmental Industrial Hygienists (ACGIH)
- Occupational Alliance for Risk Science (OARS) Workplace Environmental Exposure Levels (WEELs) table

2.3. Exposure

To determine time-weighted average (TWA) air concentrations during and after huffing sessions, we used EPA's Consumer Exposure Model (CEM) version 3.2 to first obtain the near field (i.e., next to the user), far field (i.e., in the rest of the room), and Zone 2 (i.e., in the rest of the house) air phase concentrations for one spray and then used these results to calculate TWAs for a huffing

session in a postprocessing step. CEM is an exposure modelling tool used to estimate exposure from specific consumer products and is capable of modeling multiple mediated and contact exposure pathways. For the huffing scenario, we selected the 'Spray fixative and finishing spray coatings' product, which includes only the inhalation pathway, for a stay-at-home adult inhaling dust cleaner products in their bedroom. For our baseline scenario, we set (i) the mass of product used to 25 g/use based on Huet et al. (2021) for a 6-hour session where eight 10 oz canisters were used with one inhalation every 3–5 minutes and (ii) the weight fraction to 1. The duration of use was set to 0.5 minutes, which was the lowest duration possible in CEM. Additional variations included varying the mass of product used (i.e., 12.5 and 37.5 g/use) and weight fraction (i.e., 0.001 and 0.000075). All other input parameters were estimated using the CEM Estimator feature or were default inputs.

The resulting time-weighted air concentration(s) includes (i) the concentration of DFE or TFE inhaled while the receptor is huffing in the near-field zone, (ii) the concentration of DFE or TFE inhaled while the receptor is not huffing in the far-field zone (the other side of their bedroom), and (iii) the concentration of DFE or TFE inhaled while the receptor is not huffing in the rest of the home after huffing ends. During postprocessing, we updated the first time step to 1,000,000 ppm to adjust for a high concentration due to spraying towards the face and we accounted for the frequency of use (e.g., duration of the huffing session and frequency of sprays). We modeled two huffing session durations (2 and 6 hours) and set the frequency of sprays to once every four minutes based on Huet et al. (2021). The activity pattern was set to the following: (i) during huffing, the user is in the near field zone for 2 minutes and then in the far field zone for 2 minutes and this is repeated until huffing steps; (ii) after huffing, and until Hour 12, the user is in Zone 2; (iii) between Hours 12 and 24, the user returns to the far field zone. Using the air phase concentrations in each zone and the activity pattern described above, we then calculated the 'personal exposure concentration' and the resulting 1, 2, 4, 8, and 24-hour TWAs.

2.4. Risk

For risk characterization, while a probabilistic approach was used for chronic exposures (see main report), a deterministic approach was used for acute exposures as less uncertainty exists. Information derived from hazard and exposure assessments were used to characterize risk. For DFE and TFE, the time-weighted averages developed in the exposure section were compared to hazard-based TRVs.

3. Results

3.1. Hazard

3.1.1. DFE

The lethal concentration (LC) of DFE in air generally increases with shorter exposures (30 minutes to 1 hour) and decreases with longer exposures up to 4 hours. In a study where rats were exposed for 30 minutes at concentrations ranging from 100,000 ppm to 550,000 ppm, lethality was observed at concentrations ~500,000 ppm after 10–25 minutes (OECD SIDS, 2006). PubChem reports an LC_{50} (concentration in air that killed 50% of the test animals) in mice after 2 hours of 977 g/m^3 or 361,654 ppm. PubChem also reports an LC_{Lo} (lowest lethal concentration) in rats after 4 hours of 64,000 ppm. Another 4-hour approximate lethal concentration of DFE in rats was reported as 383,000 ppm (OECD SIDS, 2006).

Acute and subacute exposure to DFE in laboratory animals produced reversible CNS depression at concentrations of 100,000 ppm or higher (EPA IRIS, 1994). Acute irritation of the lungs was observed in rats exposed to concentrations of 400,000 ppm and above (OECD SIDS, 2006).

Like many halogenated hydrocarbons, DFE causes cardiac sensitization in dogs. Cardiac sensitization refers to increased sensitivity of the heart to epinephrine (i.e., adrenaline), which has the potential to lead to life-threatening arrythmia. Dogs are a commonly used animal model to test this endpoint (Brock et al., 2003). The potential for DFE to sensitize the heart was evaluated in male beagle dogs that were injected with epinephrine while being exposed to 0, 50,000, or 150,000 ppm DFE for 5 minutes. Cardiac arrhythmias were observed in 3 out of 12 dogs exposed to 150,000 ppm (405,000 mg/m^3) and none of the dogs exposed to 50,000 ppm (135,000 mg/m^3) (Reinhardt et al., 1971 as reported in OECD SIDS, 2006). In a recent study designed to mimic exposure that might occur during abuse, Joshi et al. (2017) observed various arrhythmias, such as premature ventricular contractions (PVCs), ventricular tachycardia, and ventricular fibrillation, in male rats exposed to a DFE dose of 20 L/min for 30 seconds that was repeated 4 to 5 times until death occurred. Endogenous plasma epinephrine and cardiac injury biomarker levels were higher in the DFE-treated rats compared to the control rats. Histopathological analysis showed increased hyperemia/congestion in cardiac tissue of DFE-and DFE plus epinephrine-treated rats compared to control rats (Joshi et al., 2017).

Numerous case reports of adverse events involving abuse of products containing DFE have been reported in the human health literature (Burnett et al., 2022). Adverse effects include cardiomyopathy, cardiac arrhythmia, and sudden cardiac death in some cases (Brown et al., 2023). Cardiac arrythmia from abuse of DFE is thought to involve increased sensitivity of the myocardium to endogenous epinephrine (Tormoehlen et al., 2014; Tiscione and Rohrig, 2021; Brown et al., 2023). The mechanisms involved are not fully understood, but altered function of cardiac

channels may contribute. DFE has the potential to slow the repolarization of cardiomyocytes by saturating several cardiac channels (Tormoehlen et al., 2014; Brown et al., 2023). Besides cardiac effects, other symptoms of acute exposure to DFE include coughing, wheezing, nausea, lethargy, confusion, loss of coordination, psychosis, tremors, loss of consciousness, severe frostbite, flame burns, angioedema, rhabdomyolysis, kidney failure, and liver failure (Huet and Johanson, 2020; Fogelson et al., 2022; Vance et al., 2012).

Fatal cardiac arrhythmias are a leading cause of death secondary to DFE huffing along with accidents resulting from being heavily intoxicated (Tiscione and Rohrig, 2021; Huet and Johanson, 2020). Death has also been associated with anoxia due to airway occlusion from the use of a bag to inhale the volatile and/or decreased oxygen in the inspired air, respiratory depression, frostbite compromising the airway, and vagal inhibition of the heart resulting in bradycardia and/or cardiac arrest (Sakai et al., 2011; Huet and Johanson, 2020; Tiscione and Rohrig, 2021; Fogelson et al., 2022). Concentrations of DFE in the blood reported in postmortem cases have ranged from 0.14 to 460 µg/mL and in impaired driving cases from 0.16 to 140 µg/mL (Tiscione and Rohrig, 2021). Long-term abuse of DFE has led to structural damage in the heart (e.g., interstitial edema, intramyocardial hemorrhage, and myocardial necrosis), chronic kidney disease, liver injury, skeletal fluorosis, and multi-organ system failure (Brown et al., 2023; Fogelson et al., 2022; Romero et al., 2022).

DFE is being developed as a propellant for pressurized metered dose inhalers for pharmaceutical use. A Phase 1 preclinical trial observed no adverse effects in eight healthy male volunteers administered four consecutive doses of 50 µL per actuation from a metered dose inhaler within a six-minute timespan (Kuehl et al., 2022). The peak DFE blood concentrations ranged from 0.319 to 1.863 mg/L. Another controlled experiment observed no exposure-related effects when 10 healthy male and female volunteers were exposed for 2 hours on 3 separate occasions to 0, 200, or 1,000 ppm DFE during light exercise (Ernstgård et al., 2012). Average DFE blood concentrations during exposure were 7.4 and 34.3 µM following a few minutes of exposure to 200 and 1,000 ppm, respectively.

Based on the information available, cardiac sensitization appears is the most sensitive effect of acute exposure to DFE in laboratory animals as it has been observed at lower concentrations than death and other serious effects. Fatal cardiac arrhythmia has been reported in human cases involving abuse of DFE, which is thought to involve cardiac sensitization among other possible mechanisms. The American Industrial Hygiene Association (American Industrial Hygiene Association, 2018) developed Emergency Response Planning Guidelines (ERPGs) for acute exposure to DFE. The two higher levels (i.e., ERPG-3 and ERPG-2) are based on the critical effect of cardiac sensitization in dogs and other serious concerns. AIHA recommended the following exposure limits for acute exposure to DFE for up to 1 hour:

- The ERPG-3 for DFE is 25,000 ppm, which is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects. The quantitative basis for this concentration is not entirely clear from the guide, but AIHA concluded this exposure level was sufficiently below than the 4-hour approximate lethal concentration in rats (383,000 ppm), the lowest-observed-adverse-effect concentration (LOAEC) for cardiac sensitization in dogs (150,000 ppm), and the no-observed-adverse-effect concentration (NOAEC) for fetal death and toxicity from a developmental study in rats (50,000 ppm) (unpublished DuPont data as reported in OECD SIDS, 2006).
- The ERPG-2 for DFE is 15,000 ppm, which is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms. For DFE this concentration was based on the no-observed-effect concentration (NOEC) for cardiac sensitization in dogs (50,000 ppm) (Reinhardt et al., 1971). The ERPG-2 is about 1/3 of that level.
- The ERPG-1 for DFE is 10,000 ppm, which is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing more than mild, transient adverse health effects. For DFE this concentration was based on results from the 2-week inhalation study in rats that showed only slight, reversible anesthetic effects during exposure to 100,000 ppm DFE (unpublished DuPont data as reported in OECD SIDS, 2006).

The ERPGs developed by AIHA are listed as Protective Action Criteria (PAC) values for DFE by the U.S. Department of Energy for use in emergency response scenarios (U.S. Department of Energy, 2025). The AIHA recommended a workplace environmental exposure level (WEEL) of 1,000 ppm for DFE as an 8-hour time-weighted average concentration (American Industrial Hygiene Association, 2005). The Occupational Safety and Health Administration (OSHA) has not published a Permissible Exposure Limit (PEL) for DFE.

Table 1 summarizes the acute toxicity reference values for DFE or HFC-152a.

Table 1. Summary of Acute TRVs for DFE.

Value	Units	Effect | Timeframe
~500,000	ppm	LC_{Lo} after 30 minutes in rats
361,654	ppm	LC_{50} after 2 hours in mice
383,000	ppm	$LC_{Approximate}$ after 4 hours in rats
64,000	ppm	LC_{Lo} after 4 hours in rats
150,000	ppm	Cardiac arrythmia after 5 minutes in dogs

Value	Units	Effect | Timeframe
100,000	ppm	CNS depression after acute exposure in rats (unspecified duration)
25,000	ppm	ERPG-3 for life-threatening health effects after 1 hour
15,000	ppm	ERPG-2 for irreversible or other serious health effects or symptoms after 1 hour
10,000	ppm	ERPG-1 for mild transient adverse health effects after 1 hour
1,000	ppm	AIHA Workplace Environmental Exposure Level | 8-hour Time-Weighted Average
15[a]	ppm	IRIS Reference Concentration for chronic inhalation exposure (RfC) - daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime
4 (0.3 to 54)	ppm	Central tendency and probabilistic range for Reference Concentration (chronic), converted from predicted oral POD and 90% confidence interval obtained using the Two Stage Machine Learning Point of Departure Browser[b], available at https://wchiu.shinyapps.io/Two-Stage-ML-Results-Browser/
5	ppm	Conditional Toxicity Value predicted Reference Concentration (chronic), available at https://toxvalue.org/6-CTV/Cover.php

TRV = toxicity reference value; LC_{Lo} = lowest lethal concentration in air; LC_{50} = concentration in air that killed 50% of the test animals (i.e., median lethal concentration); $LC_{Approximate}$ = approximate lethal concentration in air; CNS = central nervous system; ERPG = Emergency Response Planning Guideline; AIHA = American Industrial Hygiene Association; IRIS = Integrated Risk Information System of the U.S. EPA.
[a]The IRIS RfC for DFE was converted from 40 mg/m^3 to 15 ppm for comparison with the other values in this table.
[b]The Two Stage Machine Learning Point of Departure Browser is a web application that allows users to browse surrogate and predicted oral dose points of departure (PODs) for thousands of organic chemicals in terms of mg/kg/day human equivalent doses. Predicted PODs are based on Kvasnicka et al. (2024). The oral POD and 90% confidence interval predicted for DFE were converted from mg/kg/day to mg/m^3 in air by multiplying by 70 kg (adult body weight) and dividing by 20 mg/m^3 (adult breathing rate), and then converted to ppm using a molecular weight of 66.051 g/mol.

3.1.2. TFE

TFE has low acute inhalation toxicity, and clinical trials have demonstrated its safety for use as a propellant in metered dose inhalers (NRC, 2002; ECETOC, 2006).

The lethal concentration (LC) of TFE generally increases with shorter exposures (15 minutes to 1 hour) and decreases with longer exposures up to 4 hours. An LC_{50} value of >800,000 ppm after 15 minutes for rats and a similar LC_{50} value of 750,000 ppm after 30 minutes for rats were reported (NRC, 2002). PubChem reports an LC_{50} value after 2 hours of 1,700 g/m^3 or 408,000 ppm for mice and another LC_{50} value of 1,500 g/m^3 or 360,000 ppm after 4 hours for rats. An LC_{Lo} of 566,700 ppm was reported for rats after 4 hours and another LC_{50} of >500,000 ppm was reported for rats after 4 hours (NRC, 2002).

TFE has reversible anesthetic and narcotic effects in several species at very high concentrations (~500,000 ppm) (NRC, 2002; ECETOC, 2006). A study in rhesus monkeys observed narcosis

within 1 minute of exposure to 500,000 ppm and respiratory depression accompanied by premature ventricular contractions following exposure to 600,000 ppm and above (NRC, 2002).

Like many halogenated hydrocarbons, TFE causes cardiac sensitization in dogs. Two studies tested the potential for TFE to produce cardiac sensitization in male beagle dogs (Mullin and Hartgrove, 1979 and Hardy et al., 1991 [unpublished data reported in NRC, 2002]). In both studies, the exposed dogs were injected with epinephrine 5 minutes into the 10-minute exposure periods. The lowest concentration that resulted in cardiac arrhythmia was 75,000 ppm in one study (Mullin and Hartgrove, 1979) and 80,000 ppm in the other study (Hardy et al., 1991). No signs of a cardiac response were observed at 40,000 or 50,000 ppm (NRC, 2002).

In a study conducted to gather pharmacokinetic data, Vinegar et al. (1997) exposed two healthy adult male volunteers to 4,000 ppm TFE via a mouthpiece. Blood samples were collected prior to exposure and every 30 seconds during exposure using an indwelling cannula. The subjects were also monitored for changes in electrocardiogram, blood pressure, and pulse. The exposures were scheduled to last 30 minutes but were stopped early due to unexpected adverse effects. One subject lost consciousness and their blood pressure and pulse dropped to zero after 4.5 minutes of exposure, which the investigators interpreted as a vasovagal reflex response to blood collection. The subject's pulse and blood pressure were quickly restored by medical personnel. The peak blood concentration of TFE measured for that subject was 1.29 mg/L (1.29 µg/mL) after 2.5 minutes of exposure. The other subject that was exposed to 4,000 ppm TFE experienced a rapid rise in blood pressure and pulse after approximately 10.5 minutes of exposure at which time the exposure was aborted. The subject's blood pressure and pulse returned to normal after 30 seconds. The peak blood concentration of TFE was 0.70 mg/L (0.7 µg/mL) at the point when exposure ended. That subject reported chest tightness that lasted for 3 days after exposure and "flutters" in the chest that were noticed for 2 weeks after exposure (Vinegar et al., 1997).

Emmen et al. (2000) exposed eight healthy volunteers (4 male, 4 female) to increasing concentrations of TFE (1,000 to 8,000 ppm) for one hour in a whole-body exposure chamber once a week for eight weeks. Maximum blood concentrations of TFE were concentration-dependent and averaged 6.0 µg/mL (in females) and 7.2 µg/mL (in males) during exposure to 8,000 ppm. The investigators found no adverse effects on respiratory tract irritation, pulse, blood pressure, electrocardiogram, or lung function (Emmen et al., 2000).

Gunnare et al. (2006) exposed ten male volunteers to 500 ppm TFE for 2 hours during light exercise in a whole-body exposure chamber and observed no remarkable findings in electrocardiogram recordings. The maximum concentrations of TFE in blood were about 10 µM measured during exposure. Markers of inflammation were measured in plasma prior to exposure and 21 hours post-exposure. The authors found plasma fibrinogen was slightly increased in subjects post-exposure, but no changes were seen for the other parameters (i.e., c-reactive protein, serum amyloid A protein, D-dimer, and uric acid) (Gunnare et al., 2006).

There are limited reports in the human health literature about the adverse events associated with inhalant abuse of products containing TFE. Like DFE, abuse has been associated with severe frostbite (Koehler and Henninger, 2014) and fatal arrhythmia (Burke et al., 2021).

Based on the information available, cardiac sensitization appears to be the most sensitive acute adverse effect of TFE observed in laboratory animals, which was observed in dogs at concentrations of 75,000 ppm and higher. Human volunteer studies with lower exposure levels have generally observed no adverse cardiovascular effects. The unexpected adverse effects observed by Vinegar et al. (1997) in humans exposed to 4,000 ppm TFE by mouthpiece have not been replicated in other human studies with similar exposure concentrations, so the effects may have been the result of the exposure methods or other experimental conditions in that study.

The National Research Council Subcommittee on Acute Exposure Guideline Levels (AEGLs) derived acute exposure limits for TFE and based the higher exposure limits (i.e., AEGL-3 and AEGL-2) on the critical effect of cardiac sensitization in dogs (National Research Council, 2002). Because cardiac sensitization is concentration-dependent and peak blood concentrations of TFE are rapidly reached during exposure, the Subcommittee determined that exposure duration is of lesser importance than exposure concentration and recommended the following exposure limits for acute exposures lasting 10 minutes up to 8 hours:

- The AEGL-3 for TFE is 27,000 ppm, which is the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death. For TFE this concentration was based on a concentration of 80,000 ppm which cause marked cardiac toxicity in dogs, but not deaths (unpublished data from Hardy et al., 1991 as reported in NRC, 2002). An intraspecies uncertainty factor of 3 was applied.
- The AEGL-2 for TFE is 13,000 ppm, which is the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. For TFE, this concentration was based on the NOEC of 40,000 ppm for cardiac sensitization in dogs (unpublished data from Hardy et al., 1991). An intraspecies uncertainty factor of 3 was applied.
- The AEGL-1 for TFE is 8,000 ppm, which is the airborne concentration above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. For TFE, this concentration was based on a 1-hour NOEC of 8,000 ppm in healthy human subjects (Emmen et al., 2000) that is supported by a study in rats that showed no adverse effects when rats inhaled air containing 81,000 ppm for 4 hours (unpublished DuPont data as reported in NRC, 2002). No uncertainty factors were applied to the human NOEC.

The AEGLs developed by NRC are listed as Protective Action Criteria (PAC) values for TFE by the U.S. Department of Energy for use in emergency response scenarios (DOE, 2025). The AIHA recommended a workplace environmental exposure level (WEEL) of 1,000 ppm for TFE as an 8-hour time-weighted average concentration (American Industrial Hygiene Association, 2003). The Occupational Safety and Health Administration (OSHA) has not published a Permissible Exposure Limit (PEL) for TFE.

Table 2 summarizes the acute toxicity reference values for TFE or HFC-134a.

Table 2. Summary of Acute TRVs for TFE.

Value	Units	Effect | Timeframe
>800,000	ppm	LC_{50} after 15 minutes in rats
750,000	ppm	LC_{50} after 30 minutes in rats
408,000	ppm	LC_{50} after 2 hours in mice
566,700	ppm	LC_{Lo} after 4 hours in rats
360,000	ppm	LC_{50} after 4 hours in rats
75,000	ppm	Cardiac arrythmia after 5 minutes in dogs
27,000	ppm	AEGL-3 | general population, including susceptible individuals, could experience life-threatening health effects or death after 10 minutes of exposure to airborne concentrations above this
13,000	ppm	AEGL-2 | general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects after 10 minutes of exposure to airborne concentrations above this
8,000	ppm	AEGL-1 | general population, including susceptible individuals, could experience notable discomfort, irritation, or non-sensory effects after 10 minutes of exposure to airborne concentrations above this
1,000	ppm	AIHA Workplace Environmental Exposure Level | 8-hour Time-Weighted Average
19[a]	ppm	IRIS Reference Concentration for chronic inhalation exposure (RfC) - daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime
2 (0.1 to 23)	ppm	Central tendency and probabilistic range for Reference Concentration (chronic), converted from predicted oral POD and 90% confidence interval obtained using the Two Stage Machine Learning Point of Departure Browser[b], available at https://wchiu.shinyapps.io/Two-Stage-ML-Results-Browser/

TRV = toxicity reference value; LC_{50} = concentration in air that killed 50% of the test animals (i.e., median lethal concentration); LC_{Lo} = lowest lethal concentration in air; AEGL = Acute Exposure Guideline Level; AIHA = American Industrial Hygiene Association; IRIS = Integrated Risk Information System of the U.S. EPA.
[a]The IRIS RfC for TFE was converted from 80 mg/m^3 to 19 ppm for comparison with the other values in this table.
[b]PODs predicted by the application are based on Kvasnicka et al. (2024). The oral POD and 90% confidence interval predicted for TFE were converted from mg/kg/day to mg/m^3 in air by multiplying by 70 kg (adult body weight) and dividing by 20 mg/m^3 (adult breathing rate), and then converted to ppm using a molecular weight of 102.032 g/mol.

3.2. Exposure

The 1, 8, and 24-hour TWA air concentrations for each of the four main exposure scenarios (i.e., DFE and TFE, each with huffing session durations of 2 and 6 hours) are shown in Table 3 for all three weight fractions when the mass of product used was set to 25 g/use. Additional results when the mass of product used was varied, as well as results for 2 and 4-hour TWAs are shown in Attachments B-01 to B-04. Changes in TWAs were primarily due to changes in weight fraction, with TWAs decreasing with decreasing weight fractions.

Table 3. Summary of 1, 8, and 24-hour Time-Weighted Average (TWA) Air Concentrations for Various Huffing Scenarios.

Scenario	Chemical	Weight Fraction	1-hour TWA (ppm)	8-hour TWA (ppm)	24-hour TWA (ppm)
6 hours of huffing	DFE	1	126,203	95,109	31,725
6 hours of huffing	DFE	0.001	126.2	95.1	31.7
6 hours of huffing	DFE	0.000075	9.47	7.13	2.38
2 hours of huffing	DFE	1	126,203	126.2	9.47
2 hours of huffing	DFE	0.001	31,696	31.7	2.38
2 hours of huffing	DFE	0.000075	10,568	10.6	0.79
6 hours of huffing	TFE	1	125,778	125.8	9.43
6 hours of huffing	TFE	0.001	94,629	94.6	7.10
6 hours of huffing	TFE	0.000075	31,557	31.6	2.37
2 hours of huffing	TFE	1	125,778	125.8	9.43
2 hours of huffing	TFE	0.001	31,538	31.5	2.37
2 hours of huffing	TFE	0.000075	10,514	10.5	0.79

TWA = time-weighted average; ppm = parts per million.

3.3. Risk

To compare the time-weighted averages developed in the exposure section to hazard based TRVs, we converted mg/m^3 concentration to ppm. Because this is an acute exposure scenario, we plotted TWA from each weight fraction against ERPGs for DFE, AEGLs for TFE, and the AIHA WEEL for both substances described in Section 3.1 (Figure 1, Figure 2). As a final point of reference, we also compared the 24-hour value to the EPA IRIS Reference Concentration (RfC) (Figure 1, Figure 2). These data demonstrate that generally, all exposure estimates that relied on a weight fraction of 1 were higher than the highest ERPG-3 or AEGL-3 levels, with the exception of the 2-hour exposure scenarios under the 24-hour TWA. Generally, this suggests that huffing exposures of the chemical at the highest weight fraction are likely to result in irreversible damage or death. Looking at lower weight fraction estimates, specifically 0.001 and 0.000075, no exposure estimate was higher than any of the acute TRV levels. This suggests that lowering the weight fraction of such compounds in consumer products could prevent inhalant induced deaths.

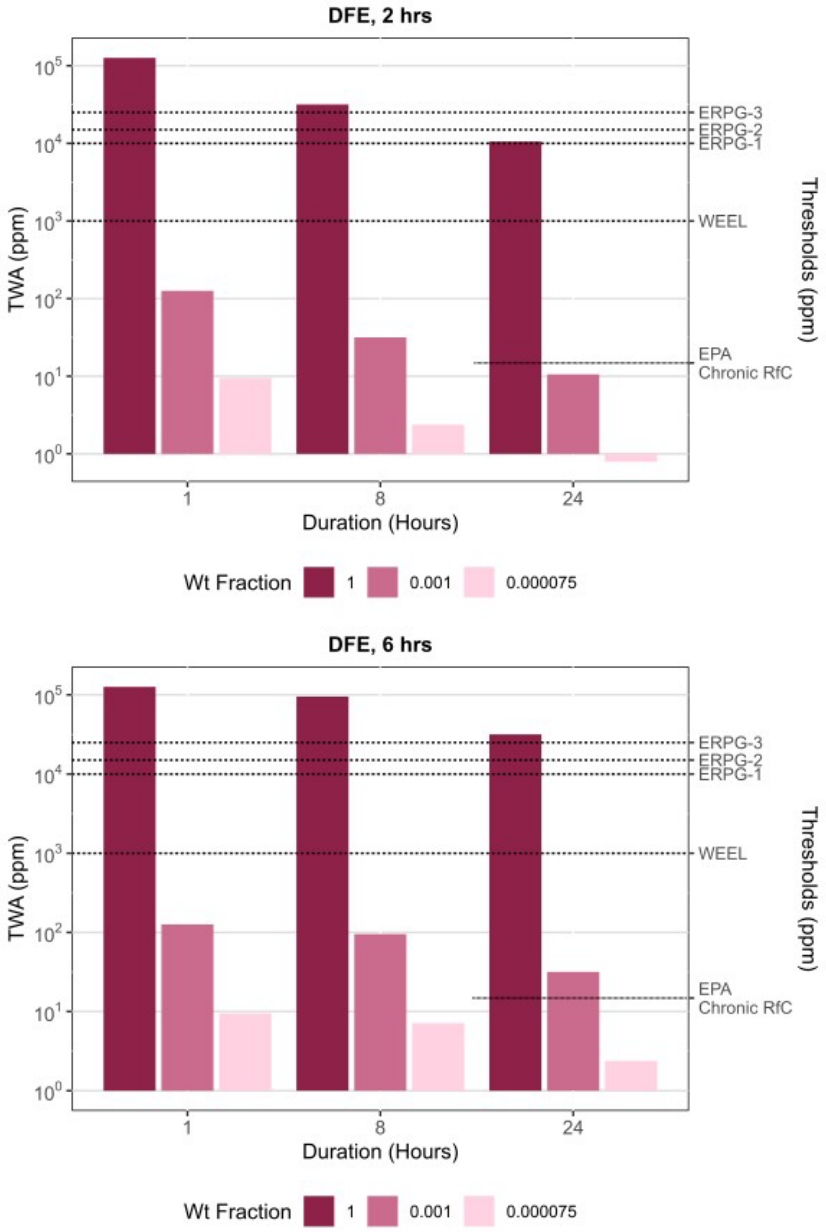

Figure 1. Estimated Exposure for 2 and 6-Hour Huffing Sessions for DFE with Levels of Concern Indicated.

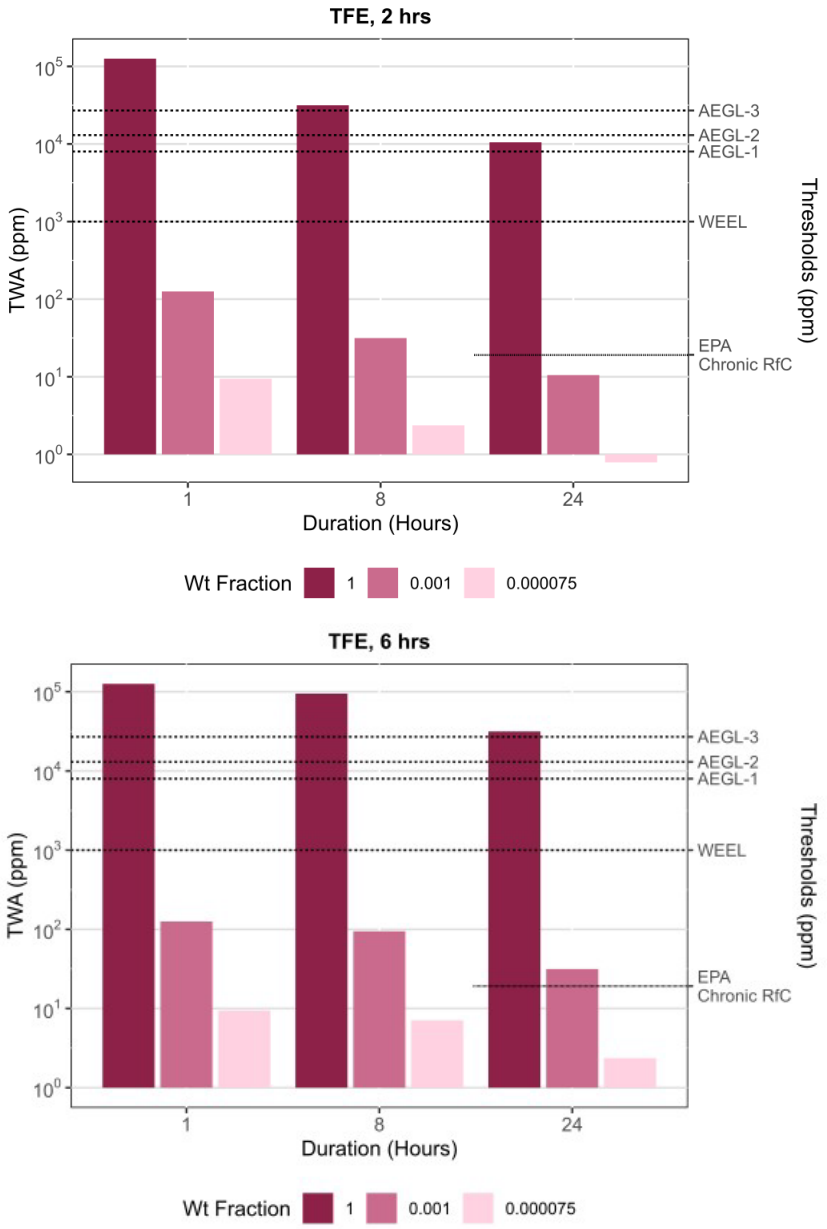

Figure 2. Estimated Exposure for 2 and 6-Hour Huffing Sessions for TFE with Levels of Concern Indicated.

The final point of comparison is the EPA IRIS RfCs (Figure 1, Figure 2), which are developed based upon the assumption of a lifetime chronic exposure. This comparison level was included for the 24-hour exposure value as it is possible that individuals exposed during huffing sessions may be exposed in a repeated and/or intermittent chronic exposure pattern, i.e. an individual huffs daily for many weeks or months. The exact frequency of huffing behavior (e.g., daily, every-other day, weekly, etc.) is not well characterized. Some individuals have died after one huffing event while other individuals have repeatedly huffed. For the 2-hour scenarios, the 24-hour TWA

corresponding to weight fractions of 0.001 and 0.000075 are below the EPA RfC values. For the 6-hour scenarios, the 24-hour TWA for only the lowest weight fraction, 0.000075, is lower than the EPA RfC values.

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