Interim: Sep-2010

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

PERFLUOROISOBUTYLENE (PFIB)

(CAS Reg. No. 382-21-8)

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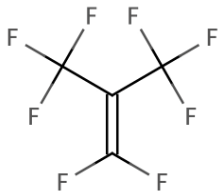

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PROPOSED

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels – AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance 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.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance 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.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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SUMMARY

Perfluoroisobutylene (PFIB) is a colorless gas that is formed during the production of tetrafluoroethylene. It is also produced in relatively small amounts during the heated decomposition of polytetrafluoroethylene (PTFE or Teflon®) and some closely related plastics. It is also produced by the thermal decomposition of the fluorinated primary fluid in the condensation reflow soldering process. PFIB may be synthesized by atmospheric-pressure pyrolysis of tetrafluoroethylene dimer (i.e., octafluorocyclobutane), which gives a 50% yield of PFIB.

Data were insufficient for derivation of AEGL-1 values; therefore, AEGL-1 values are not recommended for PFIB.

In the absence of appropriate chemical-specific data, the AEGL-3 values were divided by 3 to derive AEGL-2 values for PFIB (NRC, 2001). This approach is justified by the steep concentration-response curve observed in several animal studies. No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65 ppm (Bide et al., 2000). Finally, no mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968).

The highest concentration causing no mortality in rats exposed to PFIB for 4-hours (0.25 ppm) was used as the point-of-departure for AEGL-3 values (DuPont, 1966). Clinical signs noted at this concentration included face washing, hyperemia, sneezing, hypernea, dyspnea, and decreased responsiveness. There was 100% mortality (6/6) at the next highest concentration tested (0.5 ppm). An interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3 were applied. The interspecies UF of 1 is considered sufficient because lethality data available for several animal species suggest little interspecies variability; LC_{50} values for given exposure durations are essentially equivalent (Table 9). Reported 1-min LC_{50} values are 107 ppm for mice (Fusheng et al., 1992) and 122 ppm for rats (Smith et al., 1982); 10-minute values are 11.8 ppm for mice (Bide et al., 2000) and 17 ppm for rats (Smith et al., 1982); 15 minute values are 6.1 ppm for mice and 6.7 ppm for rats (Karpov, 1977); and reported 2-hour values are 0.98 ppm (Paulet and Bernard, 1968) and 1.6 ppm for mice (Karpov, 1977), 1.05 ppm for rats and guinea pigs (Paulet and Bernard, 1968), and 1.20 ppm for rabbits (Karpov, 1977). The intraspecies UF of 3 is supported by the steep concentration-response curve for PFIB (described above for AEGL-2), implying limited intraspecies variability. Values were scaled across time using the $c^n \times t = k$, relationship where the exponent, n, is the chemical-specific value of 1.0, derived from rat LC_{50} data ranging from 0.25 to 120 minutes.

The calculated values are listed in the table below.

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S 1. **Summary of AEGL Values for PFIB**						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL–2 (Disabling)	0.67 ppm (5.5 mg/m^3)	0.22 ppm (1.8 mg/m^3)	0.11 ppm (0.90 mg/m^3)	0.028 ppm (0.23 mg/m^3)	0.014 ppm (0.11 mg/m^3)	1/3 the AEGL-3 values.
AEGL–3 (Lethal)	2.0 ppm (16 mg/m^3)	0.67 ppm (5.5 mg/m^3)	0.33 ppm (2.7 mg/m^3)	0.083 ppm (0.68 mg/m^3)	0.042 ppm (0.34 mg/m^3)	Highest concentration causing no lethality in rats (0.25 ppm; 4-hr). 100% mortality at next concentration (0.5 ppm) tested (DuPont, 1966)

NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

2

1. INTRODUCTION

Perfluoroisobutylene (PFIB) is a colorless gas that is formed during the production of tetrafluoroethylene (Kennedy, 1990; Gangal, 2004). It is also produced in relatively small amounts during the heated decomposition of polytetrafluoroethylene (PTFE or Teflon®) and some closely related plastics. It is also produced by the thermal decomposition of the fluorinated primary fluid in the condensation reflow soldering process (Shih et al., 1990). PFIB may be synthesized by atmospheric-pressure pyrolysis of tetrafluoroethylene dimer (i.e., octafluorocyclobutane), which gives a 50% yield of PFIB. No production information was located. Chemical and physical property data are limited; available information is presented in Table 1.

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	PFIB; Octafluoroisobutylene; Octafluoro-sec-butylene; 1-Propene, 1,1,3,3,3-pentafluoro-2-(tri fluoromethyl)	AIHA, 2000; ACGIH, 1991
Chemical formula	C_4F_8	ACGIH, 1991
Molecular weight	200	AIHA, 2000
CAS Reg. No.	382-21-8	AIHA, 2000
Physical state	Colorless gas	AIHA, 2000
Density	1.5922 g/ml at 0 ºC (liquid)	AIHA, 2000
Boiling point	7ºC at 760 mmHg	AIHA, 2000
Conversion factors	1 ppm = 8.2 mg/m^3 1 mg/m^3 = 0.12 ppm	AIHA, 2000

2. HUMAN TOXICITY DATA

2.1. Acute lethality

Makulova (1965) monitored 5 patients (2 men and 3 women) accidentally exposed to PFIB at work. Two were chemical plant operators and the other three were chemical engineer technologists involved in laboratory work. All but one [female] patient reported that the contact with PFIB lasted less than one minute during which time 2 to 5 breaths were taken. Immediately after exposure, all patients developed cough, difficulty breathing, and deep chest pains. Approximately 6 to 8 hours after exposure, these symptoms increased in severity. No ocular or upper respiratory irritation was noted. All patients ran fevers that lasted between 2 and 25 days, and all developed pulmonary edema. The duration of the in-patient stay of the three patients was 13, 17, and 23 days. They were discharged as healthy, and follow-up checkups over 2 years revealed no complications in these patients. One [male] patient remained hospitalized for over 2 months due to exudative pleuritis. Another [female] patient died two days after exposure; post-mortem examination confirmed toxic fluid pneumonia and lung edema, hemorrhage into the left adrenal and full bloodiness of internal organs.

Five workers were accidentally exposed to a gas that contained 2% PFIB, and they reported irritation of the respiratory tract within 24 hours (DuPont, 1976). A majority developed

a cough and exhibited choking or shortness of breath, and a few experienced wheezing. One of the five workers died 11 days after exposure, and another one died 13 days after exposure. Pathological examination revealed pulmonary congestion.

2.2 Nonlethal acute toxicity

A worker was exposed to PFIB for approximately 3 minutes after a spill of a 2% PFIB mixture (DuPont, 1976). He reported a bad odor, bad taste in the mouth, nausea, and weakness. After returning to fresh air, he recovered and experienced no more symptoms. A PFIB concentration of 0.04 ppm was measured one-half hour post-exposure, and it was estimated that the worker could have been exposed to more than 4 ppm PFIB (assumes 10 to 40 air changes/hour for a factory) (Kennedy and Geisen, 1985).

2.3. Developmental/Reproductive Toxicity

One of the exposed workers in the Makulova (1965) study was 15-16 weeks pregnant at the time of exposure. The pregnancy ended in a normal, term delivery, the child was reportedly healthy.

2.4. Genotoxicity

No data were located.

2.5. Summary

Human data are limited to occupational exposures with no definitive concentration or duration parameters. Clinical signs included cough, difficulty breathing, wheezing, nausea, chest pain, weakness, and bad taste. Pulmonary edema and congestion were noted at autopsy.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Groups of two male albino rats were exposed whole-body for up to six hours to nominal concentrations of 0.3, 0.5, or 1.0 ppm of PFIB from a supply cylinder and diluted with an air stream in a mixing chamber (DuPont, 1956; 1961). Nominal concentrations were calculated from the flow rates of PFIB gas and air. Clinical signs of respiratory impairment were noted at 0.5 and 1.0 ppm. At 0.5 ppm, slight dyspnea was noted at the end of the exposure period, and both of these rats died the following night. At 1.0 ppm clinical signs progressed from labored respiration noted during the first two hours of exposure, to gasping, cyanosis, and terminal convulsions, with both rats being dead by 5 hours and 25 minutes after the start of treatment. Pulmonary edema was noted in rats exposed to 0.5 and 1.0 ppm; rats in the 1.0 ppm group also exhibited congestion of the brain. The rats exposed to 0.3 ppm did not show any signs of toxicity

during the exposure; however, a slight increase in respiration rate was noted on the first day after exposure. No treatment-related effects were noted at terminal sacrifice (10 days post-exposure). Data are summarized in Table 2.

TABLE 2. Summary of mortality data in rats exposed to PFIB for up to 6 hours.

Concentration (ppm)	Duration (hours)	Mortality	Clinical Signs	Necropsy findings
0.3	6	0/2	none	none
0.5	6	2/2	slight dyspnea	Pulmonary edema
1.0	4.25	2/2	dyspnea; cyanosis	Pulmonary edema

DuPont, 1956; 1961

Groups of six male ChR-CD rats were exposed whole body for up to 4 hours to 0.25, 0.50, or 1.00 ppm PFIB (DuPont, 1966). Using a Harvard syringe drive, the gas was metered into a T-tube, and a stream of air carried the gas into the 16-liter exposure chamber for the treatment. Concentrations were measured by gas chromatography. All 6 rats exposed to 1.00 ppm died. Clinical signs noted during exposure at 1.0 ppm included face washing, hyperemia, dyspnea, pale ears, rapid respiration, and convulsions (in one animal). All 6 rats exposed for 4 hours at 0.50 ppm were found dead the following day. Clinical signs were similar to those described for the 1.0 ppm group except that no convulsions occurred. Two groups of 6 rats each were exposed to 0.25 ppm for 4 hours. None died from the exposure. No gross effects attributed to the treatment were seen at necropsy in these 12 rats. Clinical signs during exposure included face washing, hyperemia, sneezing, hyperpnea, dyspnea, and they were “mildly responsive”. Half of the rats experienced dyspnea, which lasted for 3 hours after the end of the exposure. Data are summarized in Table 3.

TABLE 3. Summary of mortality data in rats exposed to PFIB for 4 hours.

Conc. (ppm)	Mortality	Fate	Clinical signs	
			During exposure	**Post-exposure**
0.25	0/6	2/6 sacrificed 1-day post-exposure 2/6 sacrificed 2days post-exposure 2/6 sacrificed 7-days post-exposure	Face washing, hyperemia, sneezing, hypernea, dyspnea, mildly responsive	Dyspnea for 3 hr (3/6)
0.25	0/6	6/6 sacrificed 14-days post-exposure	Same as above	Same as above
0.5	6/6	Found dead 1-day post-exposure	Same as 1.0 ppm except no convulsions; mildly responsive	-
1.0	6/6	Found dead during exposure (1:36-2:19 hrs elapsed)	Face washing, hyperemia, hypernea, dyspnea, pale ears, rapid respiration, convulsions (1/6)	-

DuPont, 1966

Groups of 10 male ChR-CD® albino rats were exposed nose-only to varying concentrations of PFIB for 0.25, 0.50, 1, 2, 5, or 10 minutes, followed by a 14-day observation period (Smith et al., 1982). A metered flow of PFIB (>99% pure) from a compressed gas cylinder was dispersed into the small volume exposure chamber using a high rate of flow to rapidly achieve chamber equilibrium. It was diluted with houseline air at 15.6 liters per minute for dispersal into the exposure chamber. Rats were enclosed individually in sealed Parafilm®-wrapped wire-mesh restraining cages and were positioned in the portals so that only their snouts protruded into the chamber. Gross pathological examinations were given to at least two representative rats that died within 24 hours after each exposure. Two to three gas samples per

exposure were collected from the different sampling ports and were analyzed by gas chromatography. There were no deaths or clinical signs noted during exposure; however, the lack of clinical observations may be due to the fact that animals were exposed in nose-only restraints. Most deaths occurred between eight and 24 hours after the exposure. Clinical signs 24 hours after the exposures were similar for all exposure scenarios. Mild to moderate weight loss was observed, sometimes continuing up to 48 hours. At the higher concentrations there were also signs of respiratory impairment (wheezing and labored breathing), but those disappeared within 48 hours. Deaths were often accompanied by nasal and oral discharge of a clear yellow fluid. Pathological examination revealed heavy lungs that contained a foamy exudate characteristic of acute pulmonary edema. Mortality data are summarized in Table 4.

TABLE 4. Summary of mortality data in rats exposed to PFIB for 0.25 to 10 minutes.

Exposure Duration (min)	Average Concentration (ppm)	Mortality	LC_{50} (ppm) (±95%)
0.25	228	0/10	361 (321-415)
	248	2/10	
	318	5/10	
	334	2/10	
	430	6/10	
	468	10/10	
0.5	144	0/10	214 (179-261)
	159	3/10	
	216	6/10	
	260	8/10	
	442	9/10	
1	100	1/10	122 (113-139)
	102	0/10	
	106	5/10	
	130	6/10	
	158	9/10	
	832	10/10	
2	71	1/10	86 (82-91)
	81	1/10	
	86	6/10	
	92	7/10	
	100	9/10	
5	20	0/10	28 (26-29)
	24	1/10	
	27	7/10	
	28	3/10	
	32	9/10	
10	10	0/10	17 (15-19)
	15	2/10	
	17	5/10	
	20	8/10	

Smith et al., 1982

Danishevskii and Kochanov (1961) reported a 2-hour “maximal tolerance” concentration of 1.5 ppm and “absolute lethal” (assumed to be 100% lethality) concentration of 1.8 ppm for albino rats. Histology showed pulmonary hemorrhages and edema, degenerative changes in the kidney, and fatty changes in the liver. No other details were provided.

Karpov (1977) reported a 15-min LC_{50} of 6.7 ppm for rats. Karpov (1977) reported a 2-hour LC_{50} of 11.6 ppm for white rats, and stated that rats exposed to 61-183 ppm PFIB died within 1 minute. Pulmonary edema was given as the cause of death.

Moore, Jaeger and Jaax (1991) studied the effect of exercise on the pulmonary toxicity of PFIB in male Sprague-Dawley rats. Groups of 12 rats trained to exercise on a treadmill were sham-exposed or exposed to 12.2 ppm of PFIB vapor for 10 minutes. They were then exercised on a treadmill until they were so exhausted that they refused to run when prodded with an electric shock. Following 24 hours of observation, they were sacrificed, weighed, and their livers, hearts and kidneys were examined for pathological changes. There was a significant ($p<0.01$) difference in the endurance times of the two groups, with the PFIB-exposed group having about 10 minutes more of endurance (64.71 vs 53.29 min for the PFIB and sham exposed rats, respectively). The PFIB-exposed group showed significantly decreased activity and piloerection starting 6 hours after exposure. Two of the 12 PFIB-exposed rats had breathing difficulty and died 14 and 17 hours after exposure. The PFIB-exposed rats had increased absolute and relative lung weights regardless of whether they had been exercised; however, the PFIB-induced edema was more severe in the exposed rats that had been exercised. No effects of the treatment were seen on the livers, hearts, or kidneys.

Lehnert et al. (1995) also investigated the effects of exercise on PFIB-treated male Fischer 344 rats exposed to 12 ppm for 10 minutes. This treatment regimen reportedly results in a latency period of approximately 8 hours before the occurrence of overt pulmonary edema. The study examined the effect of exercise on these animals during and after the latency period. Initial results indicated that exercise during the latency period did not potentiate the injurious response, as judged by conventional lung gravimetric and histopathologic criteria. However, when overt pulmonary edema was preexistent, exercise had a potentiating effect.

Brown and Rice (1991) conducted an electron microscopy study on female Porton rat lungs during the first 24 hours after a single 1.5-minute exposure to 78 ppm PFIB (96% purity). Rats were sacrificed within 5 minutes of exposure or at 1, 2, 3, 4, 6, 8, 12, 16, or 24 hours post-exposure. Within five minutes after the head-only exposures, changes in the bronchioles and peribronchial alveoli were observed that took the form of alterations in cilial structure, increased pinocytosis and electron lucency. There was occasional vesicle formation of type I alveolar epithelial cells. Intercellular leakage was also noted with minimal fluid accumulation in the alveolar spaces. Gradually there was development of pulmonary edema, which was visible histologically between two and three hours after treatment. Deaths occurred starting at seven hours post-exposure. Rats that were killed for examination 24 hours after treatment had widespread pulmonary edema and interstitial infiltration by lympho-mononuclear cells and macrophages.

Lehnert et al. (1993) also studied damage to the lungs of PFIB-treated rats. Adult male Wistar rats were exposed for 10 minutes to 6.1, 10, 11, 13, or 24 ppm of PFIB. Groups of rats were killed at various times after the exposures for gravimetric and histopathological examination of the lungs. Gravimetric measurements included lung wet weight (LWW), right cranial lobe dry weight (RCLDW), and wet weight. In a second series that involved exposures to 12 and 24 ppm, lungs were examined by transmission electron microscopy. Body weight losses

of about 3% were seen within the first 8 hours after exposure and continued for 48 to 72 hours. No gravimetric increases or pathological changes were noted after exposures to PFIB at 6.1 and 10 ppm. LWW and RCLDW values revealed the clear development of pulmonary edema. At exposure to 11 ppm, the lung injuries began to show up histologically, within hours after the exposure, and the latency periods were inversely proportional to the PFIB concentrations. Significant accumulations of edema fluid were not apparent until 9 hours following the exposure, in correspondence with the gravimetric data. At 18 to 24 hours after exposure, significant amounts of fibrin were detected in the alveolar spaces, but no fibrin was seen at 48 to 72 hours. At the highest concentration, there was no latency period.

An influx of polymorphonuclear neutrophils was not seen until 12 to 24 hours after exposure to 12 ppm of PFIB (Lehnert et al., 1993). Significant increases in alveolar macrophages were seen 10 hours after exposure, with peak increases between 24 and 48 hours. As revealed by transmission electron microscopy, the alveolar epithelial cells and endothelial cells showed abnormal vacuolization and blebbing already at one hour after exposure. The alveolar surface was progressively denuded, leading to the flooding of the alveolar area with vascular constituents including red blood cells. Alveolar macrophages seemed to be relatively insensitive to the toxic effects of PFIB.

Nold et al. (1991) conducted light and electron microscopy to morphologically characterize the development of lung injury following a 2-minute whole-body exposure of thirty-five Wistar Porton female rats to 64 ppm PFIB vapor. Concentrations in the exposure chamber were monitored by a Miran infrared spectrophotometer. Five rats each were necropsied at post-exposure intervals of 5 minutes, 30 minutes, 90 minutes and 4, 12, 24, and 72 hours. At 5 minutes, there was minimal, multifocal, perivascular edema with minimal to moderate eosinophilic pulmonary perivasculitis. By 90 minutes, all rats had mild multifocal perivascular edema in all lung lobes and mild, pulmonary, eosinophilic perivascular inflammation. By 12 hours, and also at 24 hours, all rats showed diffuse severe alveolar edema with deposition of fibrin. The alveolar septa were thickened, and the alveoli contained increased numbers of macrophages as well as occasional eosinophils and neutrofils. There was significant resolution of the pulmonary edema and fibrin deposition by 72 hours.

Paulet and Bernard (1968) exposed groups of ten rats to “heavy products/high boilers” for 2 hours. The “heavy products/high boilers” are by-products formed at high temperatures (700°C) during the synthesis of tetrafluoroethylene from chlorodifluoromethane. Certain volatile and relatively inert by-products readily dissipate; however, other heavier more unstable by-products with high boiling points (above 40°C) accumulate at the base of the distillation column. The physical properties of these compounds lead to the name “heavy products/high boilers.” Analyses of these “heavy products/high boilers” suggested that PFIB (found in concentrations ranging from 0.1 to 3%) is responsible for the high toxicity of “heavy products/high boilers”. A concentration of 0.15% PFIB was assumed in this study. A 2-hr LC_{50} of 1.05 ppm was calculated for PFIB (the 2-hr LC_{50} was 700 ppm for heavy products/high boilers). Data are summarized in Table 5.

TABLE 5. Summary of mortality data for animals exposed to heavy products/high boilers for 2 hours

"Heavy Product" (HP) Concentration (ppm)	Estimated PFIB Concentration (ppm)	Rat		Mouse		Guinea pig		Rabbit	
		Mortality	Average survival	Mortality	Average survival	Mortality	Average survival	Mortality	Average survival
270	0.49	0/10	-	0/10	-	0/5	-	0/3	-
480	0.70	0/10	-	0/10	-	0/5	-	0/3	-
750	1.10	8/10	24 hr	10/10	-	7/10	-	1/5	-
1000	1.50	10/10	15 hr	10/10	7 hr	4/5	24 hr	3/3	12 hr
1530	2.30	10/10	-	10/10	3 hr 20	5/5	-	3/3	-
2000	3.00	10/10	-	10/10	-	5/5	-	3/3	-
3000	4.50	10/10	2 hr	10/10	2 hr 30	5/5	2 hr	3/3	2 hr
3500	5.20	10/10	2 hr	10/10	3 hr	5/5	2 hr 15	3/3	2 hr
5200	7.90	10/10	1 hr 20	10/10	1 hr 10	5/5	0 hr 50	3/3	1 hr 10
PFIB LC_{50}		1.05 ppm		0.98 ppm		1.05 ppm		1.20 ppm	
HP LC_{50}		700 ppm		650 ppm		700 ppm		800 ppm	

Paulet and Bernard, 1968

3.1.2. Mice

As part of a study to examine inhalation toxicologic procedures in small laboratory animals, Bide et al. (2000) whole body exposed male and female CD-1 mice to PFIB for 10 minutes. Animals were observed for at least 20 days after the exposure. The 6 L exposure chamber was a Plexiglas box with conical ends. Concentrations were determined using a MIRAN Analyzer. The LC_{50} was estimated to be 11.8 ppm, with most deaths occurring between 24 and 48 hours after the treatment. In all cases lung edema was the cause of death. Data are summarized in Table 6.

TABLE 6. Summary of mortality data in mice exposed to PFIB for 10 minutes.

Concentration (ppm)	Mortality	Number of deaths by day			
		1	2	3	4
8.3	0/10	-	-	-	-
9.2	0/10	-	-	-	-
10*	0/10	-	-	-	-
10*	2/10	-	2	-	-
12*	2/5	-	2	-	-
12*	1/5	-	1	-	-
13*	5/5	1	1	2	1
13*	4/5	-	3	1	-
15*	9/9	5	4	-	-
15*	8/8	4	4	-	-
65	10/10	10	-	-	-

Bide et al., 2000

*Although not stated in the study report, it is assumed that the duplicate exposures represent males and females separately.

Fusheng et al. (1992) exposed groups of six Kunming mice whole body to 98, 104, 110, 116, or 123 ppm PFIB (97.5% purity) for 1-minute. PFIB concentrations were determined by gas chromatography. The mice showed no clinical signs during the first 3 hours after exposure. After that they gradually showed a decrease in spontaneous movement, depressed respiration, staggering, inflammation of the eyes, prostration, and finally weakness and convulsions leading to death. Surviving animals appeared to recover fully. An LC_{50} value of 107 ppm (95% CI 104-110 ppm) was reported. Mortality data are summarized in Table 7.

TABLE 7. Summary of mortality data in mice exposed to PFIB for 1 minute.

Concentration (ppm)	Mortality	Death time after exposure (hr)
98	0/6	-
104	2/6	23, 26
110	4/6	14, 16, 20, 26
116	6/6	10, 27, 28, 29, 39, 40
123	6/6	10, 16, 17, 8, 18, 18

Fusheng et al., 1992

Danishevskii and Kochanov (1961) reported a 2-hour "maximal tolerance" concentration of 0.61 ppm, "minimal lethal" concentration of 1.2 ppm and "absolute lethal" (assumed to be 100% lethality) concentration of 1.8 ppm for albino mice. Histology showed pulmonary hemorrhages and edema, degenerative changes in the kidney, and fatty changes in the liver. No other details were provided.

Karpov (1977) reported a 15-min LC_{50} of 6.1 ppm for white mice. Karpov (1977) also reported a 2-hour LC_{50} of 1.6 ppm for white mice, and stated that mice exposed to 61-183 ppm PFIB died within 1 minute. Pulmonary edema was given as the cause of death.

Paulet and Bernard (1968) exposed groups of ten mice to "heavy products/high boilers" for 2 hours as described in section 3.1.1. A 2-hr LC_{50} of 0.98 ppm was calculated for PFIB (the 2-hr LC_{50} was 650 ppm for heavy products/high boilers). Data are summarized in Table 5.

3.1.3. Guinea pigs

Paulet and Bernard (1968) exposed groups of five or ten guinea pigs to "heavy products/high boilers" for 2 hours as described in section 3.1.1. A 2-hr LC_{50} of 1.05 ppm was calculated for PFIB (the 2-hr LC_{50} was 700 ppm for heavy products/high boilers). Data are summarized in Table 5.

3.1.4. Rabbits

Karpov (1977) reported a 15-min LC_{50} of 12.2 ppm for rabbits. Karpov (1977) also reported a 2-hour LC_{50} of 4.3 ppm, and stated that rabbits exposed to 61-183 ppm PFIB died

within 1 minute. Pulmonary edema was given as the cause of death.

Paulet and Bernard (1968) exposed groups of three or five rabbits to "heavy products/high boilers" for 2 hours as described in section 3.1.1. A 2-hr LC_{50} of 1.20 ppm was calculated for PFIB (the 2-hr LC_{50} was 800 ppm for heavy products/high boilers). Data are summarized in Table 5.

3.1.5. Cats

Karpov (1977) reported a 2-hour LC_{50} of 3.1 ppm for cats. Pulmonary edema was given as the cause of death.

3.2. Nonlethal Acute Toxicity

3.2.1. Rats

Groups of white rats were exposed to 0, 0.12, 0.24, or 0.49 ppm PFIB for 4 hours (Karpov, 1977). "Impairment of conditioned reflexive activity" was noted in animals exposed to 0.24 and 0.49 ppm. Liver transaminase activity was also increased in these rats (33% and 55% increases for the 0.24 and 0.49 ppm groups, respectively). Pulmonary edema was reported in the 0.24 and 0.49 ppm groups. No significant treatment-related effects were noted at 0.12 ppm.

3.3. Repeat Dose Studies

Four male albino rats were exposed to 0.1 ppm PFIB 6 hours/day for 10 days (DuPont, 1956; 1961). Rats were sacrificed at the end of the exposure period. The PFIB gas was mixed with air in a carboy and then passed into a bell jar containing the rats. Nominal concentrations were calculated from the flow rates of PFIB gas and air. During the exposures, the rats were occasionally restless and had mild respiratory impairment that sometimes proceeded to cyanosis; two of the rats developed moist rales. Occasional body weight loss was noted in two rats during the first week of exposure only. There were no clinical observations or effects on weight gain. All rats survived the treatment period. There were no gross or histopathological effects or organ weight effects noted at necropsy.

In another study, ten male ChR-CD rats were exposed to 0 or 0.098 ppm of PFIB 6 hours/day, 5 days/week for two weeks (DuPont, 1975). PFIB chamber concentrations were determined by gas chromatography using an electron capture detector. Five rats/concentration were sacrificed at 0 and 14-days post-exposure. No treatment-related gross or microscopic changes were observed at the end of the exposure period or after the14-day follow-up period.

McMaster et al. (1989) exposed ten male Sprague-Dawley rats to PFIB by inhalation. The rats had been trained to press a lever for a food reward under a multiple time-out fixed ratio of reinforcement. At certain times in this activity, 30 lever presses resulted in a reward pellet. Multiple 10-minute head-only exposures to PFIB starting at 1.2 ppm were administered at

unspecified intervals of no less than one week. The exposures were increased in 2.4 ppm increments an unspecified number of times. During the experiment, all rats continued to respond within the range of their baseline levels at exposure concentrations below 180 ppm x minutes (presumably cumulative). As the cumulative exposure concentrations approached what would be the estimated LC_{50}, performance deficits were seen in some animals. The animals with performance deficits showed pulmonary edema and histologically-damaged lungs.

3.4. Developmental/Reproductive Toxicity

No data were located.

3.5. Genotoxicity

No data were located.

3.6. Chronic Toxicity/Carcinogenicity

No data were located.

3.7. Summary

Animal lethality data are available for rats, mice, guinea pigs, rabbits, and cats, with the most robust data sets being for rats and mice. Clinical signs include dyspnea, cyanosis, face washing, hyperemia, sneezing, mild responsiveness, rapid respiration, and convulsions. Death is attributed to pulmonary edema which is a consistent necropsy finding. The concentration-response curve is very steep for many species with regard to lethality. For example, no rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65 ppm (Bide et al., 2000). Finally, no mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968). No developmental/reproductive, genotoxicity, chronic toxicity, or carcinogenicity data were located. Selected animal data are summarized in Table 8.

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TABLE 8. Summary of selected animal inhalation data

Species	Duration	Concentration (ppm)	Endpoint	Reference
Rat	0.25 minutes	228	No mortality. Weight loss (10)[a]	Smith et al., 1982
Rat	0.25 minutes	361	LC_{50} (10)	Smith et al., 1982
Rat	0.5 minutes	144	No mortality. Weight loss (10)	Smith et al., 1982
Rat	0.5 minutes	214	LC_{50} (10)	Smith et al., 1982
Mouse	1 minute	98	No mortality. Decreased movement, decreased respiration, staggering, ocular inflammation, prostration (6)	Fusheng et al., 1992
Rat	1 minute	100	10% mortality (10)	Smith et al., 1982
Mouse	1 minute	107	LC_{50} (6)	Fusheng et al., 1992
Rat	1 minute	122	LC_{50} (10)	Smith et al., 1982
Rat	2 minutes	71	10% mortality (10)	Smith et al., 1982
Rat	2 minutes	86	LC_{50} (10)	Smith et al., 1982
Rat	5 minutes	20	No mortality. Weight loss (10)	Smith et al., 1982
Rat	5 minutes	28	LC_{50} (10)	Smith et al., 1982
Mouse	10 minutes	9.2	No mortality. Clinical signs not reported (10)	Bide et al., 2000
Rat	10 minutes	10	No mortality. Weight loss (10)	Smith et al., 1982
Mouse	10 minutes	11.8	LC_{50} (10)	Bide et al., 2000
Rat	10 minutes	17	LC_{50} (10)	Smith et al., 1982
Mouse	15 minutes	6.1	LC_{50}	Karpov, 1977
Rat	15 minutes	6.7	LC_{50}	Karpov, 1977
Rabbit	15 minutes	12.2	LC_{50}	Karpov, 1977
Rat	2 hours	0.25	No mortality. Face washing, hyperemia, sneezing, hypernea, dyspnea, mildly responsive (6)	DuPont, 1966
Rat, mouse, guinea pig, rabbit	2 hours	0.70[b]	No mortality (3-10)	Paulet and Bernard, 1968
Mouse	2 hours	0.98[b]	LC_{50} (10)	Paulet and Bernard, 1968
Rat	2 hours	1.05[b]	LC_{50} (10)	Paulet and Bernard, 1968
Guinea pig	2 hours	1.05[b]	LC_{50} (5-10)	Paulet and Bernard, 1968

Rabbit	2 hours	1.20[b]	LC_{50} (3-5)	Paulet and Bernard, 1968
Mouse	2 hours	1.2	ALC[a]	Karpov, 1977
Mouse	2 hours	1.6	LC_{50}	Karpov, 1977
Mouse	2 hours	1.8	100% mortality	Danishevskii and Kochanov, 1961
Rat	2 hours	1.8	100% mortality	Danishevskii and Kochanov, 1961
Cat	2 hours	3.1	LC_{50}	Karpov, 1977
Rabbit	2 hours	4.3	LC_{50}	Karpov, 1977
Rat	2 hours	11.6	LC_{50}	Karpov, 1977
Rat	4 hours	0.50	100% mortality (6)	DuPont, 1966
Rat	4 hours	1.0	100% mortality (6)	DuPont, 1966
Rat	4.25 hours	1.0	100% mortality (2)	DuPont, 1956; 1961
Rat	6 hours	0.3	No effects (2)	DuPont, 1956; 1961
Rat	6 hours	0.50	100% mortality (2)	DuPont, 1956; 1961

[a]Number in round brackets is the number of animals exposed/group, when this is known.
[b]PFIB Concentration estimated assuming 0.15% PFIB in Heavy Products/High Boilers
[c]ALC = Approximate Lethal Concentration, a concentration at which at least one animal died after a single inhalation exposure

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Essentially no information was located concerning the metabolism and disposition of PFIB. However, Maidment and Upshall (1992) studied retention of inhaled PFIB using female rats that were restrained by stocks at the neck in a head-out plethysmograph while being exposed for 2.25 minutes to 1.2, 6, or 30 ppm of PFIB in a number of repeated exposures. The total exposures amounted to 0.1, 0.5, and 2.5 times a reported LC_{50}. There was no evidence of changes in minute volume or breathing rate that could be related to the repeated exposures. The uptake of PFIB at the tested concentrations was said to be an apparent first-order process in that the percentage of the inhaled PFIB that was retained remained constant, and the rate of uptake increased proportionately with the inhaled dosage. Early tissue damage, if any, did not influence retention in the respiratory tract.

4.2. Mechanism of Toxicity

Arroyo (1997) studied the chemistry of PFIB by using electron paramagnetic resonance spin-trapping techniques and concluded that this highly electrophilic chemical likely undergoes electron transfer that leads to several highly reactive intermediates. PFIB is reactive towards nucleophilic reagents to yield substitution and addition radical byproducts. PFIB reacts with almost all known nucleophiles.

Lailey et al. (1991) suggested that PFIB may exert its toxic effect by depletion of intracellular nucleophiles, including amines, thiols and alcohols. When a lethal concentration of PFIB (purity >96.1%) was inhaled by Porton strain rats, total non-protein thiol (NPSH) and glutathione (GSH) in the lung were reduced by between 30 and 49%, respectively (Lailey et al., 1991). If rats were pretreated to reduce endogenous thiol levels in the lungs before PFIB treatment, the rats were more susceptible to the lethal effects of the gas. Treatments that raised levels of cysteine (CySH) in the lungs before treatment with PFIB protected rats from the lethal effects of PFIB. In a study of the effects of pretreatment of rats with oral N-acetylcyteine (Lailey, 1997), it was found that plasma levels of cysteine, glutathione, and N-acetylcystein were increased for up to seven hours following oral administration of N-acetylcysteine, and this treatment provided substantial protection for rats against the lethal effects of inhaling PFIB.

The pattern of pulmonary damage induced by PFIB is characteristic of highly hydrophobic gases that penetrate into the deep lung. The first sign of cellular damage is at the pulmonary epithelium. However, there is evidence of interstitial edema and increased lymph flow before there is alveolar filling, which suggests that damage to the endothelial cells is an early event. After exposure to an LC_{50} of PFIB, there is no increase in lung weight for up to six hours, after which there is a progressive filling of the alveoli. That filling may lead to death from pulmonary edema between eight and 12 hours after the exposure. No significant pathology is apparent outside the lung other than the congestion induced by flow resistance that is caused by the severe pulmonary edema (Lailey et al., 1991).

Maidment et al. (1994) also noted that there is little evidence of direct pathological damage to

tissues outside the respiratory tract by PFIB. All PFIB-induced tissue damage appears to result from rapid interaction with cells that are either in, or in close proximity to, the respiratory airways. PFIB is a hydrophobic gas that induces a permeability-type edema. Maidment et al. (1994) stated that extensive unreported studies in rats of the toxicopathology of PFIB in their laboratory had "failed to reveal any significant macroscopic or microscopic pathology outside the respiratory system at a number of time points up to 14 days after exposure, when resolution of the initial pulmonary injury is complete."

Gurley et al. (1991) used high-performance capillary electrophoresis to identify proteins from the fluid lining of the lungs of male rats given whole-body exposures to 12 ppm of PFIB for 10 minutes. Comparisons were made with untreated controls. The PFIB concentration was measured using a dual-column gas chromatograph fitted with an electron-capture detector that was sensitive to 1 ppb of PFIB. The lung fluid was obtained using a bronchoalveolar lavage procedure. The edema that was induced involved the translocation of proteins from the blood compartment into the lung's alveolar compartment. Three of the major proteins that were translocated in this way were albumin, transferrin and IgG.

Pathogen-free male Sprague-Dawley rats and pathogen-free male Kunming mice (5/group/species) were exposed whole-body to sublethal concentrations of PFIB in order to determine how PFIB causes lung injury (Wang et al., 2001). A separate group of rats and mice, made neutropenic by i.p. injection with cyclophosphamide, were exposed to PFIB to determine the effect of depleted polymorphonuclear leukocytes (PMN) on PFIB-induced lung injury. All exposures lasted five minutes, and measurement of lung myeloperoxidase (MPO) activity, and lung wet-to-dry ratio, lung lavage, and histopathological examinations were conducted over time. In the first experiment, rats were exposed to 16.8 ppm and mice were exposed to 15.6 ppm for five minutes. The rats were sacrificed 24 hours post exposure for ultrastructural examination. In rats, the total protein concentration in the bronchoalveolar lavage fluid was increased as early as two hours post exposure and reached a peak at 24 hours. A decrease in protein was found at 48 and 72 hours post exposure, but still remained significantly higher than baseline. In mice, lung MPO activity increased as early as 1-hour post exposure and peaked at 20 hours, but it had returned to normal by 60 hours. The lung wet-to-dry weight increased drastically from 20 to 24 hours and recovered slowly from 24-48 hours. In the PMN depletion study, mice were exposed to 22.8 ppm of PFIB for five minutes and followed for up to seven days post exposure. The rats were exposed to 16.8 ppm and sacrificed 24 hours post exposure. After 5 min of exposure, 10 of 16 mice exposed to PFIB without depleted PMN died by 7 days after treatment compared to only 1 of 16 in the PMN-depleted mice, with this difference being statistically significant. There was a lack of increase in MPO activity, but the lung wet-to-dry ratio was slightly increased in the mice. The total protein concentration in the bronchoalveolar lavage fluid of the PMN-depleted and PFIB-exposed rats was significantly increased compared to that of the controls but to a lesser degree in the rats exposed to PFIB only. Vascular congestion, interstitial and intra-alveolar edema, alveolar hemorrhage, and increased numbers of inflammatory cells were observed in the lungs of the rats exposed only to PFIB. Ultrastructural examination showed severe damage to the alveolar structure, excessive vesiculation, exfoliated epithelial cells, and alveoli with exudated erythrocytes, fibrin, and inflammatory cells. The PMN-depleted and PFIB-exposed rats had moderate septal thickening, intra-alveolar edema, fibrin deposition, and macrophage accumulation in the alveolar spaces. The alveolar structures of the PMN-depleted and PFIB-

exposed rats were intact, but vacuoles and blebs in endothelial and epithelial cells were seen. The authors concluded that neutrophil sequestration and accumulation in the lungs is a key factor in acute PFIB-induced lung injury and mortality. They indicated that polymorphonuclear leukocytes (PMN) are not the only contributor to PFIB inhalation-induced lung damage and edema, and suggested that the roles of other effector cells such as monocytes and macrophages should also be clarified.

4.3. Other Relevant Information

4.3.1. Interspecies Variability

Lethality data, available for several animal species, suggest little interspecies variability (Table 9). LC_{50} values for given exposure durations are essentially equivalent except for one two-hour rat value (Karpov, 1977) which is inconsistent with the overall data set. This value suggests that the rat is much less sensitive than would be expected from the other LC_{50} values.

TABLE 9. Comparison of PFIB LC_{50} values for various animal species

Duration	Species	LC_{50} (ppm)	Ratio of LC_{50} values (maximum)	Reference
1 minute	Mouse	107	1.1	Fusheng et al., 1992
	Rat	122		Smith et al., 1982
10 minutes	Mouse	11.8	1.4	Bide et al., 2000
	Rat	17		Smith et al., 1982
15 minutes	Mouse	6.1	1.1	Karpov, 1977
	Rat	6.7		Karpov, 1977
2 hours	Mouse	0.98	1.6	Paulet and Bernard, 1968
	Rat	1.05		
	Guinea pig	1.05		
	Rabbit	1.20		
	Mouse	1.6		Karpov, 1977
	Rat*	11.6*	11.8*	Karpov, 1977

*LC_{50} value inconsistent with overall data base (Karpov (1977) 15-minute rat value and reports from other authors).

4.3.2. Intraspecies Variability

Specific data concerning susceptible populations are not available; however the concentration-response curve for PFIB is very steep, thus, implying limited intraspecies variability. [Data showing steepness of the concentration response curve are as follows: No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice

died at 65 ppm (Bide et al., 2000). No mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968).]

4.3.3 Structure Activity

Clayton (1977) reported that the susceptibility of fluoroalkenes to nucleophilic attack parallels the inhalation toxicity of these compounds: PFIB > hexafluoropropylene > tetrafluoroethylene. However, experimental data supporting this potential relationship are not available.

Clayton (1977) also compared the acute rat inhalation toxicity of several fluoroalkenes. While toxicity may appear to be inversely related to the number of fluorine atoms, there are no mechanistic data to support this assumption. It is more likely that toxicity is related instead to the double bond.

Jugg et al. (1999) investigated the differences in action between PFIB and phosgene, both of which produce pulmonary permeability-type edema. The study attempted to distinguish between damage to the surfactant system of alveoli and effects on type II pneumocytes in the rat lung. Alterations of the lung surfactant system were demonstrated. The progression of the injury was followed for 48 hours after exposure with one or the other of these gases at a concentration equal to the LC_{30} by analyzing the inflammatory cells and protein in bronchoalveolar lavage fluid. Six lung phospholipids were measured by high-performance liquid chromatography after solid phase extraction from lavage fluid. These two gases differed both with respect to the percentage composition of surfactant and the total amount of phospholipids present. PFIB produced increases in phosphatidylglycerol and phosphatidylcholine within the first hour, followed by a substantial decrease in these phospholipids. In contrast, phosgene caused a late increase in all phospholipids beginning 6 hours after the exposure. These findings show that phosgene and PFIB have different mechanisms of action at the alveolar surface. PFIB also caused a large neutrophilia at 24 hours post-treatment, with large numbers of monocytes being present from then on. Phosgene exposure also led to a large neutrophilia between 24 and 48 hours after treatment. Both gases caused a significant reduction in the number of alveolar macrophages.

4.3.4. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases has been described by the relationship $c^n \times t = k$, where the exponent, n, typically ranges from 0.8 to 3.5 (ten Berge et al., 1986). When the rat 0.25 to 120 minute- LC_{50} values from Table 8 are considered in the derivation of the exponent, a value of 1.0 is obtained. When the mouse 1 to 120 minute- LC_{50} values from Table 8 are considered in the derivation of the exponent, a value of 1.1 is obtained (Appendix B).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human studies were available for development of AEGL-1 values.

5.2. Summary of Animal Data Relevant to AEGL-1

No animal studies were available for development of AEGL-1 values.

5.3. Derivation of AEGL-1

No human or animal data were available for derivation of AEGL-1 values for PFIB. Therefore, AEGL-1 values are not recommended (Table 10).

TABLE 10. AEGL-1 Values for PFIB

10-min	30-min	1-h	4-h	8-hour
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human studies were available for development of AEGL-2 values.

6.2. Summary of Animal Data Relevant to AEGL-2

Animal data showing clinical signs consistent with the definition of AEGL-2 are available; however, mortality was observed at the next highest concentration tested. Therefore, these data are more appropriate for derivation of AEGL-3 values.

6.3. Derivation of AEGL-2

In the absence of appropriate chemical-specific data, the AEGL-3 values will be divided by 3 to derive AEGL-2 values for PFIB (NRC, 2001). This approach is justified by the steep concentration-response curve observed in several animal studies. No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65

ppm (Bide et al., 2000). Finally, no mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968). AEGL-2 values are summarized in Table 11 and calculations are in Appendix A.

TABLE 11. AEGL-2 Values for PFIB

10-min	30-min	1-h	4-h	8-h
0.67 ppm (5.5 mg/m^3)	0.22 ppm (1.8 mg/m^3)	0.11 ppm (0.90 mg/m^3)	0.028 ppm (0.23 mg/m^3)	0.014 ppm (0.11 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human studies were available for development of AEGL-3 values.

7.2. Summary of Animal Data Relevant to AEGL-3

Animal lethality data are available for rats, mice, rabbits, guinea pigs, and cats exposed to varying concentrations of PFIB for durations ranging from 0.25 minutes to 6 hours. Potential AEGL-3 points-of-departure include the following: the highest experimental concentration causing no mortality in rats exposed to PFIB for 4-hours (0.25 ppm analytical concentration); 100% mortality was observed at the next highest concentration tested (0.5 ppm) (DuPont, 1966); or the highest experimental concentration causing no mortality in rats exposed to PFIB for 6-hours (0.3 ppm nominal concentration); 100% mortality (2/2 animals) was observed at the next highest concentration tested (0.5 ppm) (DuPont, 1956; 1961). Calculated thresholds for lethality in rats (data in Tables 2, 3, 4, & 5) or mice (data in Tables 5, 6, & 7) using the probit-analysis dose-response program of ten Berge may also be used for derivation of AEGL-3 values. Use of the ten Berge approach would utilize both nominal and analytical data. The highest experimental concentration causing no mortality in rats, mice, guinea pigs, and rabbits exposed to PFIB for 2-hours (0.70 ppm) (Paulet and Bernard, 1968) is also a potential point-of-departure. Mortality was noted in all species at the next highest concentration tested (1.1 ppm); the PFIB concentrations in this study were estimated assuming 0.15% PFIB in heavy products/high boilers.

7.3. Derivation of AEGL-3

The highest concentration causing no mortality in rats exposed to PFIB for 4-hours (0.25 ppm) will be used as the point-of-departure for AEGL-3 values (DuPont, 1966). This approach is chosen over the other approaches discussed in Section 7.2 because it is the only approach utilizing entirely analytical data. Clinical signs noted at this concentration included face washing, hyperemia, sneezing, hypernea, dyspnea, and decreased responsiveness. There was 100% mortality (6/6) at the next highest concentration tested (0.5 ppm).

An interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3 will be applied. The interspecies UF of 1 is considered sufficient because lethality data available for several animal species suggest little interspecies variability; LC_{50} values for given exposure durations are essentially equivalent (Table 9). Reported 1-min LC_{50} values are 107 ppm for mice (Fusheng et al., 1992) and 122 ppm for rats (Smith et al., 1982); 10-minute values are 11.8 ppm for mice (Bide et al., 2000) and 17 ppm for rats (Smith et al., 1982); 15 minute values are 6.1 ppm for mice and 6.7 ppm for rats (Karpov, 1977); and reported 2-hour values are 0.98 ppm (Paulet and Bernard, 1968) and 1.6 ppm for mice (Karpov, 1977), 1.05 ppm for rats and guinea pigs (Paulet and Bernard, 1968), and 1.20 ppm for rabbits (Karpov, 1977).

The intraspecies UF of 3 is supported by the steep concentration-response curve for PFIB, implying limited intraspecies variability. No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65 ppm (Bide et al., 2000). No mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968).

Values will be scaled across time using the $c^n \times t = k$, relationship where the exponent, n, is the chemical-specific value of 1.0, derived from rat LC_{50} data ranging from 0.25 to 120 minutes.

AEGL-3 values are summarized in Table 12 and calculations are in Appendix A.

TABLE 12. AEGL-3 Values for PFIB

10-min	30-min	1-h	4-h	8-h
2.0 ppm (16 mg/m^3)	0.67 ppm (5.5 mg/m^3)	0.33 ppm (2.7 mg/m^3)	0.083 ppm (0.68 mg/m^3)	0.042 ppm (0.34 mg/m^3)

Time scaling from 4-hours to 10-minutes is justified based on the fact that no mortality was noted in rats exposed to 10 ppm PFIB (Smith et al., 1982) or mice exposed to 9.2 ppm PFIB (Bide et al., 2000) for 10-minutes. Applying a total uncertainty factor of 3 to these concentrations, yields 10-min AEGL-3 values of 3.3 and 3.1 ppm, suggesting that the derived 10-min AEGL-3 value is reasonable.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL-1 values are not recommended due to insufficient data. AEGL-2 values are one-third of the AEGL-3 values, and AEGL-3 values are based on a 4-hour threshold for lethality in rats. AEGL values for PFIB are summarized in Table 13.

TABLE 13. Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.67 ppm (5.5 mg/m^3)	0.22 ppm (1.8 mg/m^3)	0.11 ppm (0.90 mg/m^3)	0.028 ppm (0.23 mg/m^3)	0.014 ppm (0.11 mg/m^3)
AEGL-3 (Lethal)	2.0 ppm (16 mg/m^3)	0.67 ppm (5.5 mg/m^3)	0.33 ppm (2.7 mg/m^3)	0.083 ppm (0.68 mg/m^3)	0.042 ppm (0.34 mg/m^3)

NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

8.2. Comparison with Other Standards and Guidelines

Extant standards and guidelines for PFIB are presented in Table 14.

TABLE 14. Standards and Guidelines for PFIB					
Guideline	**Exposure Duration**				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.67 ppm	0.22 ppm	0.11 ppm	0.028 ppm	0.014 ppm
AEGL-3	2.0 ppm	0.67 ppm	0.33 ppm	0.083 ppm	0.042 ppm
ERPG-1 (AIHA)[a]			NA		
ERPG-2 (AIHA)[a]			0.1 ppm		
ERPG-3 (AIHA)[a]			0.3 ppm		
TLV-STEL (ACGIH)[b]	0.01 ppm (ceiling)				
MAC (The Netherlands)[c]					0.01 ppm

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2008)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for PFIB is not established due to lack of data.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for PFIB is just below the level at which pulmonary edema (0.24 ppm) and clinical signs of respiratory irritation (0.25 ppm) were observed in rats exposed for 4-hours.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for PFIB is based on CT product lethality data for animals.

[b]ACGIH TLV-STEL (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Short Term Exposure Limit) (ACGIH 2008) is for a 15-minute exposure, ceiling. Recommended to minimize the potential for acute pulmonary and adverse systemic effects in other organs.

[c]MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]). SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000, is defined analogous to the ACGIH-TLV-TWA.

9. REFERENCES

ACGIH (American Conference of Government and Industrial Hygienists). 2008. TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices: Perfluoroisobutylene. ACGIH, Cincinnati, OH.

ACGIH (American Conference of Government and Industrial Hygienists). 1991. Perfluoroisobutylene. Documentation of the Threshold Limit Values and Biological Exposure Indicies. Sixth Edition. Cincinnati, OH: ACGIH.

AIHA (American Industrial Hygiene Association). 2008. The AIHA 2008 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Handbook. Fairfax, VA.

AIHA (American Industrial Hygiene Association). 2000. Emergency Response Planning Guidelines for Perfluoroisobutylene. AIHA, Fairfax, VA.

Arroyo, CM. 1997. The chemistry of perfluoroisobutylene (PFIB) with nitrone and nitroso spin traps: an EPRpin trapping study. Chemico-Biological Interactions 105(2): 119-129.

Bide, R., D.J. Risk and D. Beifus. 2000. Inhalation toxicologic procedures for exposure of small laboratory animals to highly toxic materials: Part A: Exposures to gases with notes on the toxicity of PFIB. Technical Report DRES TR 2000-065. Defense Research Establishment Suffield, England.

Brown, R.F.R. and P. Rice. 1991. Electron microscopy of rat lung following a single acute exposure to perfluoroisobutylene (PFIB). A sequential study of the first 24 hours following exposure. Int. J. Exper. Path. 72(4): 437-450.

Clayton, J.W. 1977. Toxicology of the fluoroalkenes: review and research needs. Environ. Health Perspect. 21: 255-267.

Danishevskii, S.L. and M.M. Kochanov. 1961. [On the toxicology of some fluoro-organic compounds.] Gig. Truda Prof: Zabol. 5: 3-8.

DuPont (E.I. duPont de Nemours and Company, Inc.). 1956. Toxicity Studies of Pyrolysis Products of Fluorinated Polymers (Teflon Polytetrafluoroethylene) with Cover Letter Date 101292: Initial Submission. Haskell Laboratory Report No. 18-56. DuPont Co., Haskell Laboratory, Newark. DE.

DuPont (E.I. duPont de Nemours and Company, Inc.). 1961. Initial submission: Inhalation toxicity studies on perfluoroisobutylene with cover letter dated 101592. Haskell Laboratory Report No. 1-61. DuPont Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark. DE.

Du Pont Company: "Acute Inhalation Toxicity (Haskell Laboratory Report Number 34-66)". February 25, 1966. [Unpublished information.] E.I. DuPont de Nemours & Co., Haskell Laboratory, Elkton Rd, P.O Box 50, Newark, DE 19714.

DuPont (E.I. duPont de Nemours and Company, Inc.). 1975. Two week inhalation toxicity study. Haskell Laboratory Report No. 684-75. DuPont Co., Haskell Laboratory, Elkton Rd, P.O Box 50, Newark, DE 19714.

Du Pont Company. 1976. Personal Communication to the ERP Committee. October 14, 1976. E.I. DuPont de Nemours & Co., Haskell Laboratory, Elkton Rd, P.O Box 50, Newark, DE 19714.

Fusheng, L., L. Weigang, Y. Songmin, et al. 1992. Acute inhalation toxicology studies on three perfluoroorganic compounds. The Proceedings of the Fourth International Symposium on Protection Against Chemical Warfare Agents, pp. 183-190.

Gangal, S.V. 2004. Perfluorinated Polymers. Kirk-Othmer Encyclopedia of Chemical Technology, 4th Ed., M. Howe-Grant, ed. [Online] Available. http://www.mrw.interscience.wiley.com/ emrw/ 9780471238966/ kirk/article/ tetrgang.a02/current/html.

Gurley, L.R., Buchanan, J.S., J.E. London, et al. 1991. High-performance capillary electrophoresis of proteins from the fluid lining of the lungs of rats exposed to perfluoroisobutylene. Journal of Chromatography. 559(1-2): 411-429.

Jugg, B., J. Jenner and P. Rice. 1999. The effect of perfluoroisobutene and phosgene on rat lavage fluid surfactant phospholipids. Hum. Exp. Toxicol. 18(11): 659-668.

Karpov, B.D. 1977. Establishment of upper and lower toxicity parameters of perfluroisobutylene toxicity. Tr. Lenig. Sanit-Gig. Med. Inst. 111: 30-33.

Kennedy, G.L. and Geisen, R.J. 1985. Setting occupational exposure limits for Perfluoroisobutylene, a highly toxic chemical following acute exposure. J. Occup. Med. 27:675.

Kennedy, G.L., Jr. 1990. Toxicology of fluorine-containing monomers. Critical Reviews in Toxicology 21:149-170.

Lailey, A.F., L. Hill, I.W. Lawston, et al. 1991. Protection by cysteine esters against chemically induced pulmonary edema. Biochem. Pharmacol. 42: S47-S54.

Lailey, A.F. 1997. Oral N-acetylcysteine protects against perfluoroisobutene toxicity in rats. Human and Experimental Toxicology 16(4): 212-216.

Lehnert, B.E., D. Archuleta, M.J. Behr and D.M. Stavert. 1993. Lung injury after acute inhalation of perfluoroisobutylene: Exposure concentration-response relationships. Inhalation Toxicology 5(1): 1-32.

Lehnert, B.E., D. Archuleta, L. Gurley, et al. 1995. Exercise potentiation of lung injury following inhalation of a pneumoedematogenic gas: perfluoroisobutylene. Exp. Lung Res. 21(2): 331-348.

Maidment, M.P. and D.G. Upshall. 1992. Retention of inhaled perfluoroisobutene in the rat. J. Appl. Toxicol. 12: 393-400.

Maidment, M.P., P. Rice and D.G. Upshall. 1994. Retention of inhaled hexafluorocyclobutene in the rat. J. of Applied Toxicolgy 14(6): 395-400.

Makulova, I.D. 1965. [Clinical picture of acute poisoning with perfluroisobutylene.] Gig. Tr. Prof. Zabol. 9:20-23.

McMaster, S.B., K.G. Phillips, A.V. Finger and F. Feliciano. 1989. An analysis of potential behavioral effects of multiple sub-lethal exposures to perfluoroisobutylene. Proceedings of the 1989 Medical Defense Biosciences Review. pp 175-178.

Moore, D.H., J.J. Jaeger and N.K. Jax. 1991. Effects of exercise following exposure to perfluoroisobutylene. Inhalation Toxicology 3(1): 113-122.

Nold, J.B., J.P. Petrali, H.G. Wall and D.H. Moore. 1991. Progressive pulmonary pathology of two organofluorine compounds in rats. Inhalation Toxicol. 3: 123-137.

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

Paulet, G. and J.P. Bernard. 1968. Heavy products appearing during the fabrication of polytetrafluorethylene: Toxicity-physiopathologic action; therapy. Biol-Med. (Paris) 57: 247-301.

SDU. 2000. MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration]). SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment), The Hague, The Netherlands 2000

Shih, M.L., J.R. Smith and J.D. McMonagle. 1990. Gas chromatographic analysis of toxic edemagenic inhalation compounds. Analytical Letters 23(9): 1711-1727.

Smith,W., R.J. Gardner and G.L. Kennedy. 1982. Short-term inhalation toxicity of perfluoroisobutylene. Drug and Chemical Toxicology 5: 295-303.

ten Berge, W.F., A. Zwart and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. J. Hazard. Mater. 13(3): 301-310.

Wang, H., Ding, R., Ruan, J., Yuan, B. Sun, X., Zhang X., Yu, S., Qu, W. 2001. Perfluoro-isobutylene-induced acute lung injury and mortality are heralded by neutrophil sequestration and accumulation. J. Occup. Health 43: 331-338.

APPENDIX A: Derivation of PFIB AEGLs

Derivation of AEGL-1 Values

AEGL-1 values are not recommended due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

Derivation of AEGL-2 Values

Key Study: None. In the absence of appropriate data, the AEGL-2 values are derived by taking one-third of the respective AEGL-3 values. This approach is justified by a steep concentration-response. [No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65 ppm (Bide et al., 2000). Finally, no mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968).]

10-minute AEGL-2: ⅓ 10-minute AEGL-3 = 2.0 ppm ÷ 3 = 0.67 ppm

30-minute AEGL-2: ⅓ 30-minute AEGL-3 = 0.67 ppm ÷ 3 = 0.22 ppm

1-hour AEGL-2: ⅓ 1-hour AEGL-3 = 0.33 ppm ÷ 3 = 0.11 ppm

4-hour AEGL-2: ⅓ 4-hour AEGL-3 = 0.083 ppm ÷ 3 = 0.028 ppm

8-hour AEGL-2: ⅓ 8-hour AEGL-3 = 0.042 ppm ÷ 3 = 0.014 ppm

Derivation of AEGL-3 Values

Key Study: DuPont, 1966

Toxicity endpoint: 0.25 ppm, 4-hours
Highest concentration causing no mortality in rats; 100% mortality (6/6) at the next highest concentration tested (0.5 ppm)

Time scaling: $c^n \times t = k$, where the exponent, n, is the chemical-specific value of 1.0, derived from rat LC_{50} data ranging from 0.25 to 120 minutes

$C^{1.0} \times t = k$
$(0.25 \text{ ppm})^1 \times 4 \text{ hr} = 1 \text{ ppm·hr}$

Uncertainty factors: 1 for interspecies variability. Considered sufficient because lethality data available for several animal species suggest little interspecies variability; LC_{50} values for given exposure durations are essentially equivalent (Table 9).

3 for intraspecies variability. Supported by the steep concentration-response curve for PFIB, implying limited intraspecies variability.

10-minute AEGL-3: $C^{1.0} \times 0.167 \text{ hr} = 1 \text{ ppm·hr}$
$C^1 = 5.9 \text{ ppm}$
AEGL-3 = 5.9 ppm ÷ 3 = 2.0 ppm

30-minute AEGL-3: $C^{1.0} \times 0.5 \text{ hr} = 1 \text{ ppm·hr}$
$C^1 = 2 \text{ ppm}$
AEGL-3 = 2 ppm ÷ 3 = 0.67 ppm

1-hour AEGL-3: $C^{1.0} \times 1 \text{ hr} = 1 \text{ ppm·hr}$
$C^1 = 1 \text{ ppm}$
AEGL-3 = 1 ppm ÷ 3 = 0.33 ppm

4-hour AEGL-3: C = 0.25 ppm
AEGL-3 = 0.25 ppm ÷ 3 = 0.083 ppm

8-hour AEGL-3: $C^{1.0} \times 8 \text{ hr} = 1 \text{ ppm·hr}$
$C^1 = 0.125 \text{ ppm}$
AEGL-3 = 0.125 ppm ÷ 3 = 0.042 ppm

APPENDIX B: Time Scaling Calculations

RAT DATA

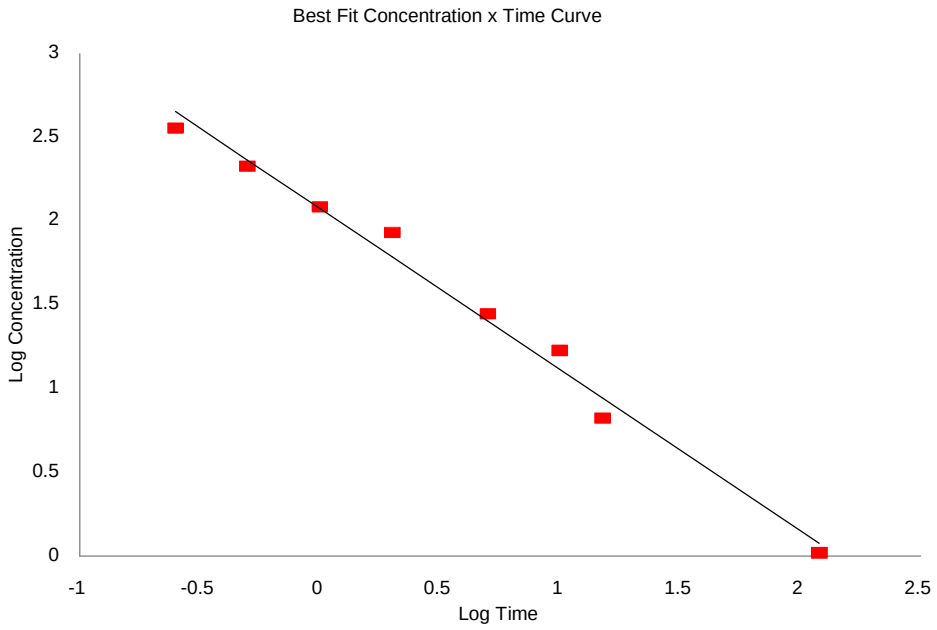
Time	Conc.	Log Time	Log Conc.
0.25	361	-0.6021	2.5575
0.5	214	-0.3010	2.3304
1	122	0.0000	2.0864
2	86	0.3010	1.9345
5	28	0.6990	1.4472
10	17	1.0000	1.2304
15	6.7	1.1761	0.8261
120	1.05	2.0792	0.0212

Regression Output:	
Intercept	2.0774
Slope	-0.9618
R Squared	0.9870
Correlation	-0.9935
Degrees of Freedom	6
Observations	8

n = 1.04
k = 144.53

Minutes	Conc.
30	4.54
60	2.33
240	0.61
480	0.32

Hours	Conc.
0.5	232.79
1.0	119.52
4.0	31.51
8.0	16.18

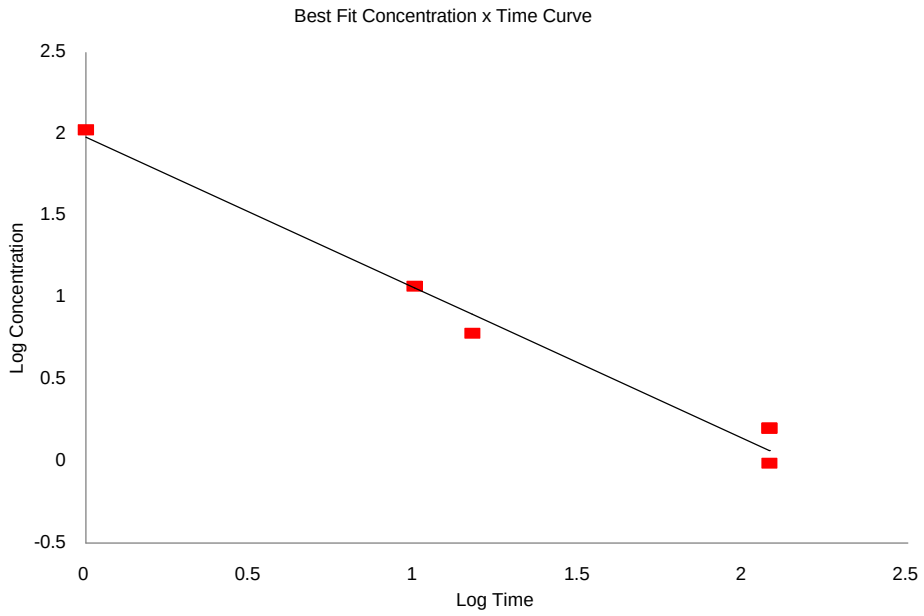


MOUSE DATA

Time	Conc.	Log Time	Log Conc.	Regression Output:	
1	107	0.0000	2.0294	Intercept	1.9844
10	11.8	1.0000	1.0719	Slope	-0.9220
15	6.1	1.1761	0.7853	R Squared	0.9847
120	0.98	2.0792	-0.0088	Correlation	-0.9923
120	1.6	2.0792	0.2041	Degrees of Freedom	3
				Observations	5

n =	1.08
k =	142.03

Minutes	Conc.	Hours	Conc.
30	4.19	0.5	182.80
60	2.21	1.0	96.48
240	0.62	4.0	26.87
480	0.33	8.0	14.18



APPENDIX C: Derivation Summary for PFIB

AEGL-1 VALUES FOR PFIB				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference:				
Test Species/Strain/Number:				
Exposure Route/Concentration/Duration:				
Effects:				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: Total uncertainty factor:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy: Data are insufficient for deriving AEGL-1 values for PFIB; therefore, AEGL-1 values are not recommended. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.				

AEGL-2 VALUES FOR PFIB				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.67 ppm (5.5 mg/m^3)	0.22 ppm (1.8 mg/m^3)	0.11 ppm (0.90 mg/m^3)	0.028 ppm (0.23 mg/m^3)	0.014 ppm (0.11 mg/m^3)
Reference:				
Test Species/Strain/Sex/Number: :				
Exposure Route/Concentrations/Durations:				
Effects:				
Endpoint/Concentration/Rationale : One-third the AEGL-3 values. Justified by a steep concentration-response. [No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65 ppm (Bide et al., 2000). Finally, no mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968).				
Uncertainty Factors/Rationale:				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling: :				
Data Adequacy: Inadequate data set for AEGL-2 effects.				

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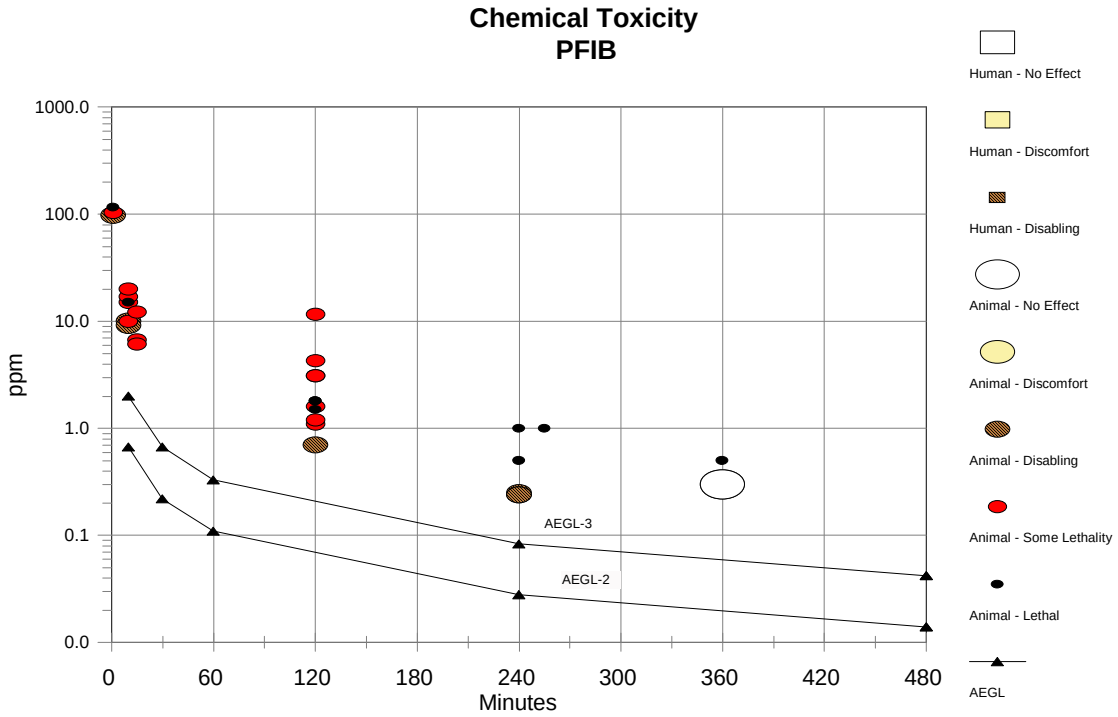
AEGL-3 VALUES FOR PFIB				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
2.0 ppm (16 mg/m^3)	0.67 ppm (5.5 mg/m^3)	0.33 ppm (2.7 mg/m^3)	0.083 ppm (0.68 mg/m^3)	0.042 ppm (0.34 mg/m^3)
Reference: DuPont , 1966. Initial Submission: Acute inhalation toxicity of perfluoroisobutylene in rats with cover letter dated 101592. OTS0571231.				
Test Species/Strain/Sex/Number: rat/ChR-CD /male/6 per group				
Exposure Route/Concentrations/Durations: Rats exposed to 0.25, 0.5, or 1.0 ppm for 4-hours				
Effects: 0.25 ppm: No mortality. Clinical signs included face washing, hyperemia, sneezing, hypernea, dyspnea, mildly responsive 0.5 ppm: 100% Mortality (6/6; found dead 1-day post-exposure). Clinical signs same as 1.0 ppm except no convulsions. Mildly responsive 1.0 ppm: 100% Mortality (6/6; found dead during exposure). Clinical signs included face washing, hyperemia, hypernea, dyspnea, pale ears, rapid respiration, convulsions (1/6)				
Endpoint/Concentration/Rationale: 0.25 ppm for 4-hr/ Highest concentration causing no mortality in rats; 100% mortality (6/6) at the next highest concentration tested				
Uncertainty Factors/Rationale: Total uncertainty factor adjustment was 3. Interspecies: 1 – Considered sufficient because lethality data available for several animal species suggest little interspecies variability; LC_{50} values for given exposure durations are essentially equivalent (Table 9). Reported 1-min LC_{50} values are 107 ppm for mice (Fusheng et al., 1992) and 122 ppm for rats (Smith et al., 1982); 10-minute values are 11.8 ppm for mice (Bide et al., 2000) and 17 ppm for rats (Smith et al., 1982); 15 minute values are 6.1 ppm for mice and 6.7 ppm for rats (Karpov, 1977); and reported 2-hour values are 0.98 ppm (Paulet and Bernard, 1968) and 1.6 ppm for mice (Karpov, 1977), 1.05 ppm for rats and guinea pigs (Paulet and Bernard, 1968), and 1.20 ppm for rabbits (Karpov, 1977). Intraspecies: 3 – Supported by the steep concentration-response curve for PFIB, implying limited intraspecies variability. No rats died when exposed to 0.25 ppm PFIB for 4 hours; whereas 100% lethality (6/6) was noted at 0.5 ppm for 4 hours (DuPont, 1966). No mortality was noted in rats exposed to 228 ppm PFIB for 0.25 min and 100% mortality (10/10) was noted at 468 ppm. No mortality was noted in rats exposed to 20 ppm PFIB for 5 min and 9/10 rats died at 32 ppm. In rats exposed for 10 minutes, no mortality was noted at 10 ppm and 8/10 rats died at 20 ppm (Smith et al., 1982). No mortality was noted in mice exposed to 98 ppm PFIB for 1 minute; whereas, 6/6 mice died at 116 ppm (Fusheng et al., 1992), and no mice died when exposed to 10 ppm for 10 minutes and 10/10 mice died at 65 ppm (Bide et al., 2000). No mortality was noted in rats, mice, guinea pigs, and rabbits exposed to approximately 0.70 ppm PFIB for 2 hours; whereas, 10/10 rats, 10/10 mice, 4/5 guinea pigs, and 3/3 rabbits died when exposed to 1.5 ppm (Paulet and Bernard, 1968).				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n=1.0, derived from rat LC_{50} data ranging from 0.25 to 120 minutes. Time scaling from 4-hours to 10-minutes is justified based on the fact that no mortality was noted in rats exposed to 10 ppm PFIB (Smith et al., 1982) or mice exposed to 9.2 ppm PFIB (Bide et al., 2000) for 10-minutes. Applying an uncertainty factor of 3 to these concentrations, yields 10-min AEGL-3 values of 3.3 and 3.1 ppm, suggesting that the derived 10-min AEGL-3 value is reasonable.				
Data Adequacy: Sufficient for AEGL-3 derivation.				

2

APPENDIX D: CATEGORY PLOT FOR PFIB



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Source	Species	ppm	Minutes	Category	
NAC/AEGL-1		NR	10	AEGL	
NAC/AEGL-1		NR	30	AEGL	
NAC/AEGL-1		NR	60	AEGL	
NAC/AEGL-1		NR	240	AEGL	
NAC/AEGL-1		NR	480	AEGL	
NAC/AEGL-2		0.67	10	AEGL	
NAC/AEGL-2		0.22	30	AEGL	
NAC/AEGL-2		0.11	60	AEGL	
NAC/AEGL-2		0.028	240	AEGL	
NAC/AEGL-2		0.014	480	AEGL	
NAC/AEGL-3		2.0	10	AEGL	
NAC/AEGL-3		0.67	30	AEGL	
NAC/AEGL-3		0.33	60	AEGL	
NAC/AEGL-3		0.083	240	AEGL	
NAC/AEGL-3		0.042	480	AEGL	
	Rat	0.3	360	0	no effects (DuPont, 1956;1961)
	Rat	0.5	360	3	Mortality: 2/2 (DuPont, 1956; 1961)
	Rat	1	255	3	Mortality: 2/2 (DuPont, 1956; 1961)
	Rat	0.25	240	2	Face washing, hyperemia, sneezing, dyspnea, mildly responsive (DuPont, 1966)
	Rat	0.5	240	3	Mortality: 6/6 (DuPont, 1966)
	Rat	1	240	3	Mortality: 6/6 (DuPont, 1966)
	Rat	10	10	2	Wheezing, labored breathing (Smith et al., 1982)
	Rat	15	10	pl	Mortality: 2/10 (Smith et al, 1982)
	Rat	17	10	pl	Mortality: 5/10 (Smith et al, 1982)
	Rat	20	10	pl	Mortality 8/10 (Smith et al., 1982)
	Rat	1.8	120	3	100% mortality (Danishevskii & Kochanov, 1961)
	Rat	6.7	15	pl	LC50 (Karpov, 1977)
	Rat	11.6	120	pl	LC50 (Karpov, 1977)
	rat, mouse, GP, rabbit	0.7	120	2	clinical signs (Paulet & Bernard, 1968)
	rat, mouse, GP, rabbit	1.1	120	pl	Mortality: 8/10 rats, 10/10mice, 7/10 GP, 1/5 rabbit (Paulet & Bernard, 1968)
	rat, mouse, GP, rabbit	1.5	120	3	100% mortality (Paulet & Bernard, 1968)
	mouse	9.2	10	2	“Clinical signs" (Bide et al., 2000)
	mouse	10	10	pl	Mortality: 2/10(Bide et al, 2000)
	mouse	15	10	3	Mortality: 17/17 (Bide et al., 2000)
	mouse	98	1	2	Decreased movement, respiration, staggering, weakness (Fusheng, 1992)
	mouse	104	1	pl	Mortality: 2/6 (Fusheng, 1992)
	mouse	116	1	3	Mortality: 6/6 (Fusheng, 1992)
	mouse	1.8	120	3	100% mortality (Danishevskii & Kochanov, 1961)

mouse	1.2	120	pl	minimal lethality (Danishevskii & Kochanov, 1961)
mouse	6.1	15	pl	LC50 (Karpov, 1977)
mouse	1.6	120	pl	LC50 (Karpov, 1977)
rabbit	12.2	15	pl	LC50 (Karpov, 1977)
rabbit	4.3	120	pl	LC50 (Karpov, 1977)
Cat	3.1	120	pl	LC50 (Karpov, 1977)
Rat	0.24	240	2	Impaired reflexes (Karpov, 1977)

1