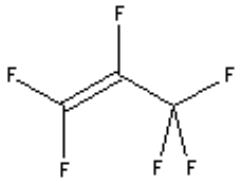
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

HEXAFLUOROPROPYLENE (CAS Reg. No. 116-15-4)



INTERIM

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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

Hexafluoropropylene (HFP, CAS Reg. No. 116-15-4) is a nonflammable and odorless gas. It is used in closed system manufacture of copolymers and hexafluoropropylene oxide. Production has been estimated at greater than 2,270 kg annually. Thermal decomposition of HFP results in the release of hydrogen fluoride.

Information regarding human exposure to HFP is not available. Results of acute inhalation exposure studies in multiple laboratory species indicate that the respiratory tract and the kidneys are the primary targets of toxicity. Clinically, the renal toxicity appears to be more significant and is generally characterized by nephrosis of the proximal tubules. Both the acute single exposure and multiple exposure studies suggest that HFP-induced renal effects that do not result in lethality are reversible upon cessation of exposure and are not cumulative. It is believed that the HFP nephrotoxicity is mediated by the metabolism of HFP to glutathione S-conjugates which are subsequently converted to cysteine S-conjugates. These conjugates, in turn, undergo activation in the kidney to reactive thiols. All of the AEGL values are based upon the continuum of renal toxicity repeatedly demonstrated by animal studies. There were no studies available that examined the carcinogenic potential of HFP and results of genotoxicity studies are equivocal.

Exposure-response data consistent with AEGL-1 severity effects were not available. Adverse signs of labored respiration and unresponsiveness were reported only for lethal or near-lethal exposures. Exposure to 320 ppm for four hours was associated with mild, reversible nephrosis in rats and, therefore, considered inappropriate as a point-of departure (POD) for AEGL-1 development. No effects were reported for a four-hour exposure of rats to 140 ppm (Du Pont & Co., 1960). This no-observed-adverse-effect (NOAEL) was considered an appropriate POD for development of AEGL-1 values. Because similar effects were observed among the species tested and because the exposure concentrations producing these effects did not vary greatly, the interspecies uncertainty factor was reduced to 3. The continuum of HFP toxicity especially regarding very minor effects, is not likely to vary notably among individuals. Therefore, an intraspecies uncertainty factor of 3 was applied. This was also considered appropriate to account for possible metabolism-mediated variability in production of reactive metabolites involved in HFP-mediated nephrosis. AEGL values for all three tiers were developed using the relationship, $C^n \times t = k$, where $n = 1.33$ as empirically determined from rat lethality data (30 to 480-minute durations); the value for the exponent, n, was similar (1.69) for mice. Use of $C^{1.33} \times t = k$ for extrapolating from the four-hour POD to other AEGL-specific exposure durations for all tiers was justified because the critical effect of nephrosis was consistent in the continuum of HFP-induced toxicity.

The most consistent indicators of HFP toxicity in laboratory animals appears to be nephrosis and the consequent renal effects. At higher exposures, behavioral and respiratory effects are also observed. The severity of the renal toxicity generally increased with HFP concentration and was evident in all species (rat, mouse, rabbit, guinea pig) tested. In accordance with the available exposure-response data and the continuum of toxicity involving nephrosis, the AEGL-2 values were based upon an exposure in rats (320 ppm for four hours was considered a no-effect level for impaired ability to escape) that resulted in minor alterations in renal function and reversible nephrosis. Exposure to a slightly higher concentration (690 ppm)

for four hours resulted in impaired motor activity and labored respiration; both being conditions that would impair egress from an exposure and would be inappropriate PODs for AEGL-2 development. Due to the similarities in HFP toxic effects among all animal species tested, the interspecies uncertainty factor was limited to 3. An intraspecies uncertainty factor of 3 was considered sufficient to account for variability in metabolism-mediated differences affecting the response to HFP and for protection of individuals with compromised renal function (approximately 4.5% of the population). Extrapolation from the four-hour POD was performed as described for AEGL-1 using the relationship $C^{1.33} \times t = k$.

Lethality data in four species indicated little species variability in the toxic response to HFP following acute inhalation exposure. Four-hour LC_{50} values among the four species varied approximately four-fold. Estimates of lethality thresholds (e.g., BMC_{01}, BMC_{05}, LC_1) were more variable largely due to the variability in the lethal responses within each species at low exposure levels. Lethality appeared to be associated with renal proximal tubule nephrosis and, in most studies, was assessed up to 28 days following cessation of exposure. The $BMCL_{05}$ (log probit model) estimate of 1677 ppm for rats was selected as the POD for the derivation of AEGL-3 values. A comparison of raw data from several animal studies revealed this to be an exposure associated with reversible renal and pulmonary effects in rats and rabbits. Although the mouse appeared to be a more sensitive species, the experimental data exhibit notable variability in the lethal response (e.g., 0% lethality at 1000 ppm, 40% at 1500 ppm and 10% at 1515 ppm). Data for guinea pigs, also a more sensitive species, are compromised by only four animals per exposure group for the lower exposures. The experiments in rats utilized a wide range of exposure concentrations (140-3440 ppm) and 10 animals per group. Because 4-hour LC_{50} values for four laboratory species varied by no more than 4-fold, an interspecies uncertainty factor of 3 was considered appropriate. An intraspecies uncertainty factor of 3 was applied to account for possible individual variability (e.g., variability in the metabolism of HFP resulting in reactive metabolites) in the toxic effects of HFP. Concentration-time extrapolations were as described for AEGL-1 and AEGL-2 development.

The AEGL values for HFP and their respective critical effects and PODs are summarized in the following table.

Summary of AEGL Values for Hexafluoropropylene (HFP)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	150 ppm 920 mg/m^3	67 ppm 410 mg/m^3	40 ppm 240 mg/m^3	14 ppm 85 mg/m^3	8.3 ppm 51 mg/m^3	Absence of notable toxic effects in rats exposed to 140 ppm HFP for 4 hrs (Du Pont & Co., 1960); UF = 3 x 3
AEGL-2 (Disabling)	350 ppm 2100 mg/m^3	150 ppm 920 mg/m^3	91 ppm 560 mg/m^3	32 ppm 200 mg/m^3	19 ppm 120 mg/m^3	Reversible nephrosis and altered renal function in rats exposed to 320 ppm HFP for 4 hrs. (Du Pont & Co., 1960); UF = 3 x 3
AEGL-3 (Lethality)	1800 ppm 11,000 mg/m^3	800 ppm 4900 mg/m^3	480 ppm 2900 mg/m^3	170 ppm 1000 mg/m^3	100 ppm 600 mg/m^3	Rat $BMCL_{05}$ of 1677 ppm HFP, 4 hr exposure (Du Pont & Co., 1960); UF = 3 x 3.

References

Du Pont & Co. (E. I. du Pont de Nemours & Co.) 1960. The acute inhalation toxicity of hexafluoropropylene. E. I. du Pont de Nemours & Co., Haskell Laboratory.

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.

1. INTRODUCTION

Hexafluoropropylene (HFP) is a nonflammable and odorless gas used in closed system manufacture of copolymers and hexafluoropropylene oxide (HSDB, 2005). Production has been estimated at greater than 2,270 kg annually. Heating HFP to decomposition results in the release of hydrogen fluoride. Chemical and physical properties of HFP are summarized in Table1.

TABLE 1. Chemical and Physical Data for Hexafluoropropylene (HFP)

Parameter	Value	Reference
Synonyms	1,1,2,3,3,3-hexafluoro-1-propene; 1-propene, hexafluoro; HFP	HSDB, 2005
Chemical formula	C_3F_6	
Molecular weight	150.02	Howard and Meylan, 1997
CAS Registry No.	000116-15-4	
Physical state	colorless gas	HSDB, 2005
Solubility in water	insoluble	HSDB, 2005
Vapor pressure	$4.90X10^3$ mm Hg at 25EC	HSDB, 2005
Relative vapor density		
Specific gravity		
Boiling/melting point	-29.6EC/-156.5EC	HSDB, 2005
Conversion factors in air	1 mg/m^3 = 0.163 ppm 1 ppm = 6.1 mg/m^3	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available regarding lethality in humans following inhalation exposure to HFP.

2.2. Nonlethal Toxicity

No data are available regarding nonlethal toxic effects in humans exposed to HFP.

2.3. Developmental/Reproductive Effects

No human developmental/reproductive toxicity data were available regarding HFP.

2.4. Genotoxicity

No human genotoxicity data were available.

2.5. Carcinogenicity

No data were found in the available literature regarding the carcinogenic potential of hexafluoropropylene in humans.

2.6. Summary

There is no information available regarding the effects of inhalation exposure of humans to hexafluoropropylene

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

The results of inhalation toxicity experiments in rats were reported by Haskell Laboratory (Du Pont Co., 1960). Initial experiments revealed that a 6-hour exposure of rats (species/strain/gender not specified) to 880 ppm (nominal) was lethal while exposure to 440 ppm (nominal) for five to six hours was not lethal. Severe respiratory impairment was observed in rats during the 880 ppm-exposure and pulmonary congestion, edema, and kidney injury was noted upon pathological examination. Evidence of pulmonary and renal injury was also observed at 3 to 11 days following the nonlethal (440 ppm) exposure. Later experiments, in which rats were exposed for 6-hours (Table 2), also affirmed the pulmonary and renal toxicity of HFP in rats. Repeated 6-hour exposure of a group of four rats to 220 ppm resulted in the death of two rats after the fifth exposure while the remaining two rats survived 12 exposures. Signs of renal toxicity were observed in both the dead and surviving rats. It must be noted that in these later experiments, a 6-hour exposure to 880 ppm was not lethal.

Table 2. Acute inhalation toxicity of HFP in rats following a single 6-hour exposure

Concentration (ppm)	Mortality (dead/exposed)	Pathology findings
1760	2/2	nephrosis, pulmonary congestion and edema
1250	2/2	nephrosis, pulmonary congestion and edema
880	0/2	nephrosis
735	1/2	nephrosis
600	0/2	nephrosis

Du Pont Co. (1960)

In a more definitive study for determining the LC_{50}, male albino rats (10/exposure group) were exposed for 4 hours to HFP (>99%) at concentrations of 140, 320, 690, 1090, 1520, 1980, 2220, 2520, 2600, 2870, 3020, 3400, or 3440 ppm (Table 3). A continuous flow chamber was used with calibrated flow meters. Nominal and analytical concentrations were in close agreement. Chamber atmosphere was sampled and HFP determined spectrophotometrically. Lethality in rats occurred at exposures at and above 2220 ppm. A 4-hr LC_{50} of 3060 ppm (95% confidence interval: 2780-3370 ppm) was reported in the Du Pont/Haskell Laboratory study. Time of deaths ranged from 2 to 12 days (the observation period was extended an additional 14 days, for a total of 4 weeks, for some rats). Nephrosis of varying severity was associated with a majority of the rats in most exposures. Nonlethal effects of HFP exposure are discussed in Section 3.2.1.

Table 3. Lethality in rats following 4-hour exposure to HFP

Concentration[a] ppm	Mortality ratio	Time of death (days)	Time of sacrifice (Days)	Pathology
3440	6/10	3-9	15	nephrosis (9/10); healing nephrosis (1/10)
3400	4/10	2-5	12	none detected
3020	4/10	7-12	15	nephrosis (6/10); healing nephrosis (4/10)
2870	8/10	4-9	14	nephrosis (10/10)
2600	0/10	-	15	nephrosis (2/10); healing nephrosis (8/10)
2520	2/10	5, 10	17	nephrosis (8/10); acute nephrosis (2/10)
2220	1/10	4	28	nephrosis (9/10); acute nephrosis (1/10); bronchopneumonia (2/10)
1980	0/10	-	14	healing nephrosis (10/10)
1520	0/10	-	28	nephrosis (5/10); healing nephrosis (5/10); pneumonitis (1/10)
1090	0/10	-	28	healing nephrosis (10/10); focal pneumonia (1/10)
690	0/10	-	28	healing nephrosis (7/10)
320	0/10	-	28	healing nephrosis (5/10)
140	0/10	-	5, 7	none detected

[a] Average analytical (based on hourly analysis; 3400 ppm based upon continuous gas thermal conductivity)
Du Pont Co. (1960)

Paulet and Debrousses (1965) provided LC_{50} values for Wistar rats (gender and number not specified) exposed to HFP at various concentrations and durations (Table 4) in a dynamic flow chamber. No further details were available regarding the materials and methods of used in

the inhalation exposure experiments. The minimum lethal concentration for an 8-hour duration was reported to be 2000 ppm.

Table 4. Acute lethality (LC_{50}) of HFP in rats following inhalation exposure.

LC_{50} (ppm)	Exposure Duration (hrs)	Cumulative Exposure Product (ppm·hrs)
15,750	0.5	7875
4000	2	8000
2800	4	11,200
2350	6	13,800
2400	8	19,200

Paulet and Debrousses (1965)

In an effort to establish a non-lethal exposure level of HFP for consecutive 8-hour workshifts, Salvaneschi (1971) conducted inhalation exposure experiments in which groups of Wistar rats (100g; two/gender/group) were exposed to 50, 250, 500, 5000, or 50,000 ppm HFP (98.5%) for periods of two to five hours. The rats were exposed in a "closed circuit" system from which the HFP test atmospheres were sampled at one hour into the exposure and at 30 minutes prior to cessation of exposure. The investigator's conclusions are summarized in the Table 5. Necropsy findings indicated pulmonary edema and hemorrhage the severity of which correlated to time and intensity of exposure.

Table 5. Lethality of HFP in rats exposed by inhalation

Exposure concentration (ppm)	Exposure duration (hrs)	Observations
50,000	<2	100% lethality preceded by torpor, convulsions, loss of equilibrium, respiratory distress
5,000	2	100% mortality at (26 to 46 hrs post exposure); no detectable signs of toxicity during exposure
	5	100% mortality at (7 to 26 hrs post exposure); torpor, respiratory distress during exposure
500	2	1 of 4 died (18 hrs post exposure)
	5	100% mortality; deaths between 19 and 120 hrs post exposure
250	5	no signs of toxicity up to 9 days post exposure
50	5	no signs of toxicity up to 9 days post exposure

Salvaneschi, 1971

One-hour, 2-hour, and 4-hour LC_{50} values of 9226, 4466, and 1826 ppm, respectively, have also been reported for rats (Smirnova, 1971) but details are lacking.

3.1.2. Mice

The Haskell Laboratory study (Du Pont Co., 1960) also assessed lethality in mice (strain and gender not specified) exposed four hours to HFP concentrations of 1000, 1500, 1515, 1990, 2000, 2600, or 3020 ppm (Table 7). Using the data in Table 6, an LC_{50} of 1765.6 ppm (1618.3 - 1926.3; 95% confidence limit) was calculated (Appendix B) by the method of Litchfield and Wilcoxon (1949). The 1000 ppm exposure was not lethal and resulted in no detectable able pathologies.

Table 6. Lethality in mice following 4-hour exposure to HFP

Concentration[a] ppm	Mortality ratio	Time of death	Time of sacrifice (Days)	Pathology
3020	8/10	during exposure to <24 hrs	16	nephrosis (6/10); bronchopneumonia (2/10)
2600	9/10	during exposure to 7 days	17	nephrosis (4/10); albumin in kidney (6/10)
2000	6/10	1-9 days	11	nephrosis (5/10: healing nephrosis (4/10); albumin in kidney (1/10); pulmonary congestion (1/10)
1990	9/10	during exposure to 6 days	14	nephrosis (4/10); albumin in kidney (4/10); pulmonary congestion (4/10)
1515	1/10	4 days	14	nephrosis (9/10); albumin in kidney (1/10)
1500	4/10	1 hr, 23 min. to 5 days	12	nephrosis (1/10); healing nephrosis (6/10); albuminuria (3/10)
1000	0/10	-	10	healing nephrosis (10/10)

[a] Average analytical (hourly analysis)
Du Pont Co. (1960)

Paulet and Debrousses (1965) also provided LC_{50} values for Swiss mice (gender and number not specified) exposed to various HFP at various concentrations and durations (Table 7) in a dynamic flow chamber. No further details were available regarding the materials and methods of the inhalation exposure experiments. The minimum lethal concentration for an 8-hour duration was reported to be 400 ppm.

Table 7. Acute lethality (LC_{50}) of HFP in mice following inhalation exposure.		
LC_{50} (ppm)	**Exposure Duration (hrs)**	**Cumulative Exposure Product (ppm·hrs)**
3000	0.5	1500
1200	2	2400
750	4	3000
680	6	4080
600	8	4800

Paulet and Debrousses (1965)

In a range-finding study for a bone marrow micronucleus assay, groups of four male and four female Crl:CD®-1(ICR)BR mice were exposed for six hours to HFP at concentrations of 750, 1000, 1400, 1900, or 3400 ppm (Du Pont, 1986a). Exposures to 1400 ppm and above resulted in lethality (Table 8). During and after exposure, mice in the 750 and 1000 ppm groups were lethargic and unresponsive. In the higher exposure groups, the mice also exhibited labored or depressed respiration, tremors, and incoordination. Most mice surviving to 11 or 12 days lost body weight.

Table 8. Lethality in mice exposed for 6 hours to HFP			
Exposure concentration (ppm)	**Mortality**		**Time of death**
	Males	**Female**	
750±75	0/4	0/4	
1000±27	0/4	0/4	
1400±57	3/4	1/4	2-3 days post exposure ( ) 3 days post exposure ( )
1900±260	4/4	4/4	1-6 days postexposure ( ) 1-2 days post exposure ( )
3400±130	4/4	4/4	0-1 day postexposure ( ) 0 days post exposure ( )

Du Pont, 1986a

3.1.3. Rabbits

Lethality data for groups of two to six rabbits exposed to HFP (3440, 3020, 2600, 2000, 1500, or 1000 ppm) for four hours are shown in Table 9 (Du Pont & Co., 1960). Strain and gender of the rabbits was not specified. Refer to Section 3.1.1 for study details. Time-to-death was generally greater in rabbits than in mice.

Table 9. Lethality in rabbits following 4-hour exposure to HFP

Concentration[a] ppm	Mortality ratio	Time of death (Days)	Time of sacrifice (Days)	Pathology
3440	5/6	3-19	19	nephrosis (6/6); calcification in myocardium (1/6); brain inflammation (1/6); pulmonary congestion/edema (1/6); pericarditis (1/6)
3020	3/6	4	20	nephrosis (6/6); pulmonary congestion/edema (1/6)
2600	4/6	4-21	22	nephrosis (6/6); pulmonary edema/tracheal congestion (1/6);peritonitis (1/6)
2000	1/2	4	11	nephrosis (1/2); pulmonary congestion/edema (1/2)
1500	0/2	-	12	healing nephrosis (2/2); bronchitis (1/2); tracheal congestion (1/2)
1000	0/2	-	11	residual nephrosis (1/2)

[a] Average analytical (hourly analysis)
Du Pont Co. (1960)

3.1.4. Guinea Pigs

In the Haskell Laboratory study (Du Pont, 1960), groups of four or ten guinea pigs (strain and gender not specified) were exposed to HFP at concentrations of 3440, 3020, 2600, 2000, 1500, or 1000 ppm for four hours. Lethality data are summarized in Table 10. An LC_{50} of 2113.7 (1646.4 - 2713.8; 95% confidence limit) was calculated (Appendix B) by the method of Litchfield and Wilcoxon (1949).

Table 10. Lethality in guinea pigs following 4-hour exposure to HFP

Concentration[a] ppm	Mortality ratio	Time of death (Days)	Time of sacrifice (Days)	Pathology
3440	8/10	2-4	15	nephrosis (10/10); acute pulmonary edema (4/10)
3020	7/10	1-6	16	nephrosis (8/10); pulmonary congestion and/or edema (6/10)
2600	4/10	4-15	17	nephrosis (9/10); healing nephrosis (1/10); myocarditis (1/10); pulmonary edema (2/10)
2000	2/4	1-4	11	nephrosis (4/4); pulmonary congestion/edema (2/4)
1500	2/4	3	12	nephrosis (4/4); pulmonary congestion/edema (2/4)
1000	0/4	-	10	nephrosis (2/4); residual nephrosis (1/4)

[a] Average analytical (hourly analysis)
Du Pont Co. (1960)

3.2. Nonlethal Toxicity

3.2.1. Rats

In addition to assessing lethality in rats exposed to HFP, the Haskell Laboratory acute inhalation toxicity study (Du Pont Co., 1960) also assessed body weight, food and water consumption, clinical toxicity parameters, and pathology evaluations (see Section 3.1.1 for study protocol details). Exposure to 140 ppm was without effect while at 320 ppm there was evidence of effects on renal function (increased urine volume and decreased urine osmolality) and morphology (reversible nephrosis). Rats exposed to 2520 to 3440 ppm were pallid and exhibited signs of discomfort during the exposure period. Renal effects appeared to be most pronounced at about three days postexposure after which recovery was evident. Exposures at or below 1980 ppm were not lethal although reversible nephrosis was a prominent pathology finding.

In the acute exposure study by Salvaneschi (1971), rats exposed to 250 ppm HFP for five hours exhibited no signs of toxicity over a 9-day post exposure observation period but exposure to 500 ppm for 2 hours resulted in death. Exposure to 50 ppm for eight hours or repeated exposures over 32 hours (details were unclear regarding actual exposure durations) to 50 ppm were also without signs of toxicity.

The effects of inhaled HFP on fluoride excretion in rats was reported by Dilley et al., 1974). Fifteen male Sprague-Dawley rats were exposed in three groups of five to 2600 ppm HFP for 30 minutes. The test atmosphere was generated by injecting HFP into the 30-liter test chamber and mixing using an external pump equipped with a flowmeter. The test chamber atmosphere was mixed at the rate of 1 chamber volume/minute for the first 5 minutes

and the rats kept in the chamber for an additional 25 minutes for a total exposure time of 30 minutes. Fluorocarbon atmospheres were sampled and analyzed by gas chromatography at 5, 15, and 30 minutes. Two of the groups were maintained for fluoride excretion tests while rats of the third group were serially sacrificed for pathological examination. The rats exhibited a biphasic urinary excretion of fluoride with two peaks occurring on postexposure Day 1 (3.24 ± 0.18 Fmol) and Day 5 (2.64 ± 0.10 Fmol). There was a significant diuresis over 14 days which was did not correlate to the urinary fluoride ion concentration. Creatinine excretion was unaffected and potassium excretion was significantly elevated relative to controls. There were large quantities (not specified) of glucose and transient occult blood in the urine for three days. Proteinurea was also observed. Gross pathological examination at postexposure Days 3-4 revealed marked hyperemia of the renal medulla, a whitish band in the cortex and small ischemic-appearing areas in the mid-cortical region, all of which were nearly absent at two weeks postexposure. Histopathological findings consisted of marked necrosis and dilation of the proximal tubules with extensive intraluminal sloughing and diffuse eosinophilia. Regeneration was occurring by Day 3 and 4 and was nearly complete at Day 7.

In a 2-week exposure study (Cannon Laboratories, 1976) in which groups of 10 male Sprague-Dawley rats were exposed to HFP at concentrations of 0, 213.5, or 324 ppm, 4 hours/day, 5 days/week for 14 days, there were no signs of HFP-induced toxicity during or after exposure. Concentrations of HFP were monitored by gas chromatography during the exposure period. Half the rats in each group were sacrificed immediately upon cessation of exposure and half were retained for an additional 14 days. Assessments were based upon clinical observations, histopathologic examinations and assessment of urinary fluoride.

A 4-hour inhalation exposure study reported by Potter et al. (1981) examined the renal effects of HFP. In this study, groups of 10 young male Fischer-344 rats were exposed in a dynamic flow system (air flow rate of 15 L/min) for four hours to HFP at concentrations of 380 ppm (380±27), 470 ppm (467±72), 660 ppm (660±191), or 1200 ppm (1188±60). The exposure atmospheres were analyzed by gas chromatography. Controls were exposed to clean air. Rats were killed on days 1 through 5 following the exposure. Exposure to all HFP concentrations resulted in necrosis of the pars recta and pars convoluta of the proximal tubule within 24 hours postexposure. Exposure to HFP resulted in dose-related increases in urinary LDH (which positively correlated with the observed proximal tubule necrosis), increased BUN, increased serum creatinine, and increased diuresis. Regeneration of the epithelial cells in the proximal tubules was observed by postexposure Day 3.

In a multiple exposure study, groups of 10 male Crl:CD®(SD)BR rats were exposed (nose-only) to 0, 10, 50, or 200 ppm HFP (99.9%), 6 hours/day, 5 days/week for two weeks (Du Pont & Co., 1985; Stadler et al., 1990). The test chamber atmospheres were analyzed by gas chromatography at 30-minute intervals. Mean analytical concentrations were 10±0.74, 50±3.6, and 200±12 ppm. Rats in the 200-ppm group exhibited mild diffuse renal tubular degeneration at two weeks of exposure; recovery occurred over a two-week post exposure period. Rats in the 10- and 50-ppm groups showed no signs of toxicity. Based upon results of the 2 -week exposure experiment as well as a subsequent 13-week exposure (0, 10, 50, or 150 ppm), the investigators concluded that HFP-induced kidney damage is not cumulative with repeated exposure and that it is reversible.

3.2.2. Mice

In the Haskell Laboratory acute exposure study (Du Pont & Co., 1960), mice in all HFP exposure groups, including the nonlethal exposure of 1000 ppm for 4 hrs, were pallid and inactive, and exhibited labored respiration during exposure. Following exposure, the mice exposed to 1000 ppm (0/10 mortality) showed initial weight loss. One mouse survived a 4-hour exposure to 1500 ppm convulsed for two days but recovered (4 of 10 died). Pathology examination at scheduled sacrifice (10-17 days post-exposure) revealed signs of nephrosis and pulmonary damage in most of the mice exposed to HFP.

In a later study conducted at Haskell Laboratory (Stadler et al., 1990), mice were exposed to HFP at concentrations of 0, 5, 20, 75, or 200 ppm, 6 hours/day, 5 days/week for two weeks. The two-week exposure to 75 ppm or 200 ppm resulted in lesions of the renal tubules that were of greater severity than those observed in mice following a 13-week exposure to 50 and 150 ppm HFP. Renal tubule damage appeared to be reversible and not cumulative.

In the range-finding experiments for the mouse micronucleus assay (Du Pont & Co., 1986a), there was no lethality in mice following a 6-hour whole body exposure to 750 or 1000 ppm HFP (Table 9). During the exposure, however, these mice were lethargic and unresponsive. During the 11 to 12-day post-exposure observation, one mouse in the 750-ppm group and most mice in the 1000-ppm group were pallid. Two males in the 1000-ppm group had ruffled fur and one had a stained perineum. Males in the 750- and 1000-ppm groups lost 6-33% (average of 21%) of their body weight.

3.2.3. Rabbits

At scheduled sacrifice (10-12 days post exposure), one of two rabbits exposed to 1000 and both rabbits exposed to 1500 ppm HFP for four hours exhibited reversible/residual nephrosis, bronchitis and tracheal congestion (Du Pont & Co., 1964). Renal and pulmonary involvement were also characteristic of exposures to higher concentrations.

3.2.4. Guinea Pigs

Four-hour exposure of a group of four guinea pigs to 1000 ppm HFP was not lethal (Du Pont & Co., 1960). Similar to the other species tested, nephrosis (one incidence characterized as residual nephrosis) was detected in three of the four animals at the scheduled sacrifice 19 days post exposure.

3.3. Developmental/Reproductive Effects

The developmental/reproductive toxicity of HFP has not been evaluated.

3.4. Genotoxicity

In a mouse micronucleus assay (Du Pont & Co., 1986a), mice were exposed for six hours to 0, 100, 310, or 1200 ppm HFP. There were no findings in female mice. In male mice exposed to 1200 ppm, an increase in the frequency of micronucleated polychromatic erythrocytes was

detected but became statistically significant only upon pooling of data across all sample times (24, 48, and 72 hours).

Green and Odum (1985) reported that HFP was not mutagenic in *Salmonella typhimurium* with or without activation. The cysteine conjugate of HFP was also tested with S9 activation and found not to be mutagenic.

Several experiments at Haskell Laboratory (Du Pont & Co., 1986b, c; 1988a, b) evaluated the potential mutagenicity of HFP. Although a positive response was detected in the initial assays using Chinese hamster ovary cells (CHO) with and without activation, subsequent experiments using CHO cells showed no mutagenic activity.

3.5. Carcinogenicity

The carcinogenic potential of HFP has not been evaluated.

3.6. Summary

Lethality data (4-hr LC_{50}) from rats, mice, rabbits, and guinea pigs suggest a two- to four-fold difference in lethal response to inhaled HFP, with mice appearing to be the most sensitive species. The estimated 4-hr LC_{50} for mice, rabbits and guinea pigs in the Du Pont studies was reported as 2000-2600 ppm while for rats the 4-hr LC_{50} was reported as 3060 ppm. In all species, nephrosis was a consistent finding and especially at nonlethal exposures, appeared to be reversible upon cessation of exposure. Pulmonary congestion/edema were more severe with increasing exposure concentration and are consistent findings in animals at lethal concentrations. Based upon the 4-hour exposure studies in multiple species conducted at Haskell Laboratory, exposure concentrations up to 1000 ppm are not lethal and exposures of 1000 to 1500 ppm typically result in renal and pulmonary effects that are reversible upon cessation of exposure.

Acute exposure of rats to HFP at 50-250 ppm (Salvaneschi, 1971) was without significant toxic effect. This is supported by repeated exposure studies (Stadler et al., 1990) showing no lethality in rats exposed to 10 or 50 ppm for 6 hrs/day, 5 days/week for 2 weeks. A similar exposure regimen utilizing 200 ppm resulted in only reversible mild nephrosis. All studies indicate that HFP-induced nephrosis is, to some extent, reversible upon cessation of exposure.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Hexafluoropropylene is readily metabolized. Parent compound was detected only in small amounts in the urine of rabbits exposed by inhalation to 1000 ppm (Ding et al., 1980). The pulmonary absorption of HFP by the rabbits was estimated at 12%. Most of the HFP was detected in the kidneys, lungs, and bones.

The metabolism of HFP appears to be instrumental in its nephrotoxicity. Results of *in vitro* metabolism experiments using rat liver and kidney subcellular fractions revealed two glutathione (GSH) conjugate metabolites (Koob and Dekant, 1990). Incubations with HFP (1 mM) and cytosol or microsomes (with GSH) from liver or kidney resulted in *S*-(1,2,3,3,3-

pentafluoropropenyl)glutathione (PFPG) and *S*-(1,1,2,3,3,3-hexafluoropropyl)glutathione (HFPG). In liver microsomal incubations, PFPG was predominant (240 nmol/min/mg protein) relative to HFPG (36 nmol/min/mg protein) while incubations with liver cytosol produced only HFPG (136 nmol/min/mg protein). HFPG, exclusively, was detected in kidney cytosol incubations (46 nmol/min/mg protein) while no GSH-conjugates were detected in kidney microsomal incubations.

Koob and Dekant (1990) also exposed rats to HFP (800 ppm for one hour) and analyzed the biliary and urinary metabolite profiles. In these rats, bile contained PFPG but no HFPG while the only metabolite in the urine was *N*-acetyl-*S*-(1,1,2,3,3-hexafluoropropyl)-L-cysteine. Because the biliary metabolites were not detected in the urine and because *N*-acetyl-*S*-(1,1,2,3,3-hexafluoropropyl)-L-cysteine was formed exclusively in the kidney, the investigators postulated that HFP-induced nephrotoxicity may be the result of intrarenal bioactivation via GSH-conjugation.

4.2. Mechanism of Toxicity

It is evident from toxicity studies that inhalation of HFP results in pulmonary and renal toxicity. The nephrotoxic mechanism of halogenated alkanes such as HFP has been reviewed by Lock (1988) and appears closely linked with the metabolism of these compounds. Briefly, this nephrotoxicity involves the metabolic formation of glutathione conjugates, their conversion to S-conjugates, and the bioactivation of these S-conjugates. A characteristic of some haloalkane toxicity, including HFP, is that the nephrotoxicity is associated with little or no liver damage, and minimal renal damage following high doses (Kluwe, 1981). As reviewed in Lock (1988), results from *in vitro* studies have shown that cysteine conjugates derived from glutathione conjugates are proximate nephrotoxins. This is consistent with the report by Koob and Dekant (1990) wherein the HFP metabolite, *N*-acetyl-*S*-(1,1,2,3,3-hexafluoropropyl)-L-cysteine, appeared to be instrumental in HFP-induced renal toxicity. It is thought that the cysteine conjugates are further metabolized to a reactive thiol by renal cysteine-conjugate β-lyase. *In vitro* studies with various haloalkane cysteine conjugates (not specifically HFP) and renal cells or isolated renal mitochondria suggest that mitochondria may be a primary target. The mode of action of the appears to be inhibition of mitochondrial respiration.

4.3. Structure-Activity Relationships

As previously noted, glutathione S-conjugates, their subsequent conversion to cysteine S-conjugates, and the activation of these conjugates to reactive thiols may be instrumental in the renal toxicity of haloalkanes in general. The interaction with DNA by reactive thiols has been shown for chlorinated, but not fluorinated, haloalkanes (Lock, 1988). Toxicity data for HFP was considered sufficient for AEGL development and, therefore, no structure-activity relationships were considered in the development of AEGL values for HFP.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human exposure data are available with which to develop AEGL-1 values.

5.2. Animal Data Relevant to AEGL-1

Definitive exposure-response data regarding AEGL-1 type effects were not available. Overt signs (unresponsiveness, labored respiration) observed in laboratory animals exposed to HFP were associated with effects greater than those defined by the AEGL-1 effect tier. Exposure of rats to 140 ppm for four hours was without notable effect (Du Pont & Co., 1960). Salveneschi (1971) reported no signs of toxicity at nine days post-exposure in rats exposed to 250 ppm for five hours. Multiple exposure of rats (6 hrs/day, 5 days/week for two weeks) to 10 or 50 ppm HFP resulted in no signs of toxicity while exposure to 200 ppm produced reversible renal tubular degeneration (Du Pont & Co., 1985; Stadler et al., 1990).

5.3. Derivation of AEGL-1

The 4-hour exposure of rats to 140 ppm HFP (Du Pont & Co., 1960) was selected as the POD for AEGL-1 development. This 4-hour 140-ppm exposure represents a plausible estimate of a threshold for AEGL-1 effects. The next higher exposure (320 ppm) in the Du Pont (1960) study produced mild nephrosis (described as healing nephrosis) in five of 10 rats while a 5-hour exposure of rats to 250 ppm was without effect (Salvenschi, 1971). Single exposure experiments with other species did not utilize exposure concentrations as low as those used in the rat studies. However, because all species tested appeared to exhibited similar effects at similar exposure concnetrations, an interspecies uncertainty factor of 3 was considered appropriate. Although no critical effect has been identified with which to derive the AEGL-1 values, the continuum of HFP toxicity especially regarding very minor effects, is not likely to vary notably among individuals. Therefore, an intraspecies uncertainty factor of 3 to account for possible metabolism-mediated variability in production of reactive species, is considered sufficient. Minor effects of HFP at low concentrations are expected to be consistent with the continuum of effects observed leading to lethality. Therefore, the time scaling exponent of 1.33 calculated form rat lethality data was used for deriving AEGL-1 values. The resulting AEGL-1 values are shown in Table 11 and their derivation is presented in Appendix A. The time scaling exponent of 1.33 was derived from exposure data spanning 30 minutes to 480 minutes and, therefore, considered appropriate for deriving 10-minute exposure values.

TABLE 11. AEGL-1 Values For Hexafluoropropylene

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	150 ppm 920 mg/m^3	67 ppm 410 mg/m^3	40 ppm 240 mg/m^3	14 ppm 85 mg/m^3	8.3 ppm 51 mg/m^3

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human exposure data are available with which to develop AEGL-2 values.

6.2. Animal Data Relevant to AEGL-2

Qualitatively, all test species (rats, mice, rabbits and guinea pigs) exhibited evidence of pulmonary and renal toxicity following exposure to HFP. Most exposures to HFP were accompanied by histopathologic evidence of latent nephrosis which, for nonlethal exposures, appeared to be reversible. Mice were lethargic and unresponsive, and exhibited labored breathing when exposed to 750 ppm for six hours (Du Pont & Co., 1986a). Exposure to 1000 ppm for four hours, although not lethal, resulted in nephrosis, body weight loss, inactivity and pallid appearance of mice (Du Pont & Co., 1960). Studies in rats indicated early signs of renal toxicity (histopathologic evidence of nephrosis) at exposures of 320 ppm for four hours (Du Pont & Co., 1960). Exposure of rats to 620 ppm for 4 hours resulted in altered food and water consumption accompanied by a decrease in urine osmolality. Potter et al. (1981) reported that 4-hour exposure of rats to 380-1200 ppm HFP produced necrosis of the proximal tubule with consequent increases in urinary LDH, blood urea nitrogen, serum creatinine, and diuresis within 24 hours following exposure. However, regeneration of the tubule cells was observed by 3 days post exposure.

6.3. Derivation of AEGL-2

Results of several studies (Du Pont & Co., 1960, 1988a; Stadler et al., 1990) in rodents indicate that HFP-induced histopathologic changes in the kidney are reversible upon cessation of exposure. Animal studies have also shown that acute exposures to approximately 700 ppm HFP and above are associated with labored respiration, and inactivity/unresponsiveness which are consistent with AEGL-2 effects that would compromise escape from an exposure situation. For AEGL-2 development, the 320 ppm exposure of rats for four hours (Du Pont & Co., 1960) was selected as the POD. This exposure was associated with critical effects of reversible nephrosis and minor alteration of renal function but no apparent effects on respiratory function or motor activity. A similar exposure (380 ppm for 4 hours) of rats resulted in reversible clinical chemistry parameters (increased urinary LDH, blood-urea-nitrogen, and serum creatinine) and histopathologic effects (necrosis of the pars recta and pars convoluta of the proximal tubules) that appeared to be reversible upon cessation of exposure (Potter et al., 1981). Salvenschi (1971) reported that a 5-hour exposure of rats to 250 ppm was without effect at nine days post-exposure. Because the critical effects observed at lower exposures are consistent with the continuum of effects observed for lethal exposures, the time scaling exponent of 1.33 calculated from rat lethality data was used for deriving AEGL-2 values. An uncertainty factor of 3 for interspecies variability was considered sufficient to account for extrapolation of animal data to humans due to similarities in HFP toxic effects among all animal species tested and at exposure concentrations that did not vary greatly. An intraspecies uncertainty factor of 3 was considered sufficient to account for variability in metabolism-mediated differences affecting the toxic response to HFP and for protection of individuals with compromised renal function. Based upon 1988 to 1994 estimates, approximately 4.5% of the United States population (20 years of age or older) have physiological evidence of chronic kidney disease (K/DOQI, 2002). Individual variability in glutathione S-transferase activity, and metabolism-mediated effects of HFP are expected to be no

greater than three-fold (Nolan et al. 1985; Mulder et al. 1999). The resulting AEGL-2 values are shown in Table 12 and derivation is presented in Appendix A.

Table 12. AEGL-2 Values For Hexafluoropropylene

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	350 ppm 2100 mg/m^3	150 ppm 920 mg/m^3	91 ppm 560 mg/m^3	32 ppm 200 mg/m^3	19 ppm 120 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human exposure data were available with which to develop AEGL-3 values.

7.2. Animal Data Relevant to AEGL-3

Lethality data for inhalation exposure in several species were available. The 4-hour LC_{50} values for rats, mice, rabbits, and guinea pigs varied up to 4-fold; - 750 ppm to 3060 ppm (Du Pont & Co., 1960; Paulette and Debrousses, 1965) with mice appearing to be a somewhat more sensitive species. Six-hour exposure to 1250 ppm and greater resulted in 75-100% mortality in rats and mice (Du Pont & Co., 1960; 1986a) while 4-hour exposures up to 1000 ppm were not lethal in rats, mice, rabbits, and guinea pigs (Du Pont & Co., 1960). Paulet and Debrousses (1965) reported 6- and 8-hour LC_{50} values of 680 and 600 ppm (mice) and 2350 and 2400 ppm (rats). Data reported by Salveneschi (1971) are inconsistent with other data sets in that lethality occurred in rats exposed to concentrations as low as 500 ppm for two hours; this is notably below the cumulative concentrations associated with lethal responses in other species. In all of the studies reported, time-to-death ranged from 7 hours to 10 days following cessation of exposure and was associated with pathologic findings of nephrosis and pulmonary edema. Although 4-hour LC_{50} values did not vary greatly among species, the estimates of lethality thresholds were more variable among the four species tested. Benchmark dose analyses (EPA, 2005) of 4-hour exposure lethality data reported by Du Pont & Co. (1960) resulted in $BMCL_{05}$ estimates of 1677 ppm for rats (the BMC_{01} for rats was 1737 ppm) . BMCL estimates using the guinea pig and rabbit data from the Du Pont Co., 1960) studies were indeterminable. Results of intermittent, repeated exposure studies indicated that up to 300 ppm HFP is not lethal in rats and that repeated exposure to 75 ppm is not lethal to mice (Du Pont & Co., 1985; Stadler et al., 1990).

7.3. Derivation of AEGL-3

Four-hour LC_{50} values for four species (rats, mice, rabbits, guinea pigs) were similar (Section 7.2) and mortality ratios for mice and rats exposed for six hours exhibited only minor variability. The $BMCL_{05}$ (log probit model) estimate of 1677 ppm for rats was selected as the POD for the derivation of AEGL-3 values (the BMC_{01} was 1737 ppm). A comparison with raw data from several studies in other species indicated this to be a concentration associated with reversible renal and pulmonary effects in rats and rabbits, similar to exposures causing 10% lethality (1515 ppm for 4 hours) and 40% lethality (1500 ppm for 4 hours) in mice and 20% lethality in guinea pigs (1500 ppm for 4 hours). The mouse lethality data were not used for

AEGL-3 development because of notable variability and inconsistencies (e.g., 0% lethality at 1000 ppm, 40% at 1500 ppm and 10% at 1515 ppm) and the guinea pig data are compromised by the use of few animals per exposure group (4) for the lower exposures. The experiments in rats utilized a greater range of exposure concentrations and 10 animals per group. Because 4-hour LC_{50} values for four laboratory species vary by up to 4-fold, an interspecies uncertainty factor of 3 was considered appropriate. An intraspecies uncertainty factor of 3 was applied to account for possible individual variability (e.g., variability in the metabolism of HFP resulting in reactive metabolites) in the toxic response to HFP. Based upon individual variability in glutathione S-transferase activity, metabolism-mediated effects on the toxic response to HFP are expected to vary no more than three-fold (Nolan et al. 1985; Mulder et al. 1999). An analysis of rat LC_{50} values over 30 to 480 minutes (Appendix C) showed that the exposure-time relationship, $C^n \times t = k$, is an exponential function where n is 1.33. The AEGL-3 values are shown in Table 13 and derivations are presented in Appendix A.

Table 13. AEGL-3 Values for Hexafluoropropylene

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	1800 ppm 11,000 mg/m^3	800 ppm 4900 mg/m^3	480 ppm 2900mg/m^3	170 ppm 1000mg/m^3	100 ppm 600 mg/m^3

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values have been developed based primarily upon inhalation exposure studies with rats (Table 14). Data from acute inhalation exposure studies in mice, rabbits, and guinea pigs affirmed that the primary targets of HFP are the respiratory tract (pneumonitis, pneumonia, pulmonary edema) and the kidney (nephrosis). For both targets, effects appeared to increase in severity with increasing exposure concentration and, even for substantial exposures, were reversible upon cessation of exposure. Repeated exposure studies in rats and mice (Du Pont & Co., 1960; Stadler et al., 1990) have shown that the renal effects are not cumulative at exposures up to 200 ppm for two weeks (rats and mice exposed for 6 hrs/day, 5 days/week) or at 150 ppm for 13 weeks (mice exposed for 6 hrs/day, 5 days/week). Due to the reversible nature of HFP-induced effects, definitive point-of-departure thresholds for the AEGL-1 and AEGL-2 severity tiers were difficult to quantify. The AEGL values, however, are based upon critical effects and points-of-departure that result in sufficiently protective values based upon comparison with available animal data. No human exposure data are available.

Table 14. AEGL Values for Hexafluoropropylene					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	150 ppm	67 ppm	40 ppm	14 ppm	8.3 ppm
AEGL-2 (Disabling)	350 ppm	150 ppm	91 ppm	32 ppm	19 ppm
AEGL-3 (Lethality)	1800 ppm	800 ppm	480 ppm	170 ppm	100 ppm

8.2. Comparisons with Other Standards and Guidelines

Very few standards and guidelines are available for HFP (Table 15). The 1-hour AEGL values closely align with the respective ERPG values developed by the AIHA.

Table 15. Extant Standards and Guidelines for Hexafluoropropylene (HFP)					
Guideline	**Exposure Duration**				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	150 ppm	67 ppm	40 ppm	14 ppm	8.3 ppm
AEGL-2	350 ppm	150 ppm	91 ppm	32 ppm	19 ppm
AEGL-3	1800 ppm	800 ppm	480 ppm	170 ppm	100 ppm
ERPG-1 (AIHA)[b]			10 ppm		
ERPG-2 (AIHA)			50 ppm		
ERPG-3 (AIHA)			500 ppm		
PEL-TWA (OSHA)[c]					
IDLH (NIOSH)[d]					
REL-TWA (NIOSH)[e]					
TLV-TWA (ACGIH)[f]					
MAK (Germany)[g]					
MAC[h] (the Netherlands)					

[b]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA, 1996, 2005)**
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-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 protection action.
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.

[c]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1996) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1994; 1999) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[e]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2004) is defined analogous to the ACGIH-TLV-TWA.

[f]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2005) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[g]**MAK (Maximale Argeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 1999) is defined analogous to the ACGIH-TLV-TWA.

[h]**MAC (Maximaal Aanvaaarde 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.

8.3. Data Adequacy and Research Needs

Exposure-response data for effects consistent with AEGL-1 and AEGL-2 tiers would be instrumental in affirming the precision of the AEGL-1 and AEGL-2 values and for more completely describing the toxic response to HFP across the whole continuum of effects. As noted in Sections 5 and 6, currently available data do not allow for an accurate determination of a threshold suitable as a biomarker of exposure and biomarker of effect other than lethality. The available data, however, were considered suitable for development of justifiable AEGL values.

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APPENDIX A
Derivation of AEGL Values

Derivation of AEGL-1 for Hexafluoropropylene (HFP)

Key study: Du Pont & Co. 1960. The acute inhalation toxicity of hexafluoropropylene. E. I. du Pont de Nemours & Co., Haskell Laboratory.

Critical effect: Absence of notable toxicity in rats following a 4-hour exposure to 140 ppm HFP.

Time scaling: $C^n \times t = k$; where $n = 1.33$ calculated from rat lethality (LC_{50}) data (Appendix C).

Uncertainty factors: Total uncertainty factor: 10.
Interspecies: A factor of 3 was applied because effects of HFP exposure were similar among the species tested and likely to be similar in humans.
Intraspecies: Adjustment for uncertainty regarding individual variability was limited to 3. The continuum of HFP toxicity especially regarding very minor effects, is not likely to vary notably among individuals. Therefore an intraspecies uncertainty factor of 3 to account for possible metabolism-mediated variability in production of reactive species among individuals, is considered sufficient. The POD and uncertainty factor selection are considered sufficiently protective for the 4.5% of the population with compromised renal function.

Calculations: $(140 \text{ ppm})^{1.33} \times 4 \text{ hrs} = 2860 \text{ ppm}^{1.33} \cdot \text{hrs}$

10-minute AEGL-1
$C^{1.33} \times 0.167 \text{ hr} = 2860 \text{ ppm}^{1.33} \cdot \text{hrs}$
$C^{1.33} = 17{,}157 \text{ ppm}^{1.33} \cdot \text{hrs}$
$C = 1527 \text{ ppm}$
UF application: 1527 ppm/10 = 153 ppm (rounded to 150 ppm)

30-minute AEGL-1
$C^{1.33} \times 0.5 \text{ hr} = 2860 \text{ ppm}^{1.33} \cdot \text{hrs}$
$C^{1.33} = 5720 \text{ ppm}^{1.33} \cdot \text{hrs}$
$C = 669 \text{ ppm}$
UF application: 669 ppm/10 = 67 ppm

1-hour AEGL-1
$C^{1.33} \times 1 \text{ hr} = 2860 \text{ ppm} \cdot \text{hrs}$
$C^{1.33} = 2860 \text{ ppm}^{1.33} \cdot \text{hrs}$
$C = 397 \text{ ppm}$
UF application: 397 ppm/10 = 40 ppm

4-hour AEGL-1
$C^{1.33} \times 4 \text{ hrs} = 2860 \text{ ppm} \cdot \text{hrs}$
$C^{1.33} = 715 \text{ ppm}^{1.33} \cdot \text{hrs}$
$C = 140 \text{ ppm}$
UF application: 140 ppm/10 = 14 ppm

8-hour AEGL-1
$C^{1.33} \times 8 \text{ hrs} = 2860 \text{ ppm} \cdot \text{hrs}$

$C^{1.33} = 358\ ppm^{1.33} @ hrs$

$C = 83\ ppm$

UF application: 83 ppm/10 = 8.3 ppm

Derivation of AEGL-2 for Hexafluoropropylene (HFP)

Key study:	Du Pont & Co. 1960. The acute inhalation toxicity of hexafluoropropylene. E. I. du Pont de Nemours & Co., Haskell Laboratory.
Critical effect:	Reversible nephrosis and consequent minor alterations of renal function in rats exposed for 4 hours to 320 ppm HFP (1280 ppm @ hrs) was considered an appropriate critical effect and point-of-departure for AEGL-2 derivation. Exposure of rats to 690 ppm for 4 hours (2760 ppm @ hrs) resulted in impaired motor activity and respiratory difficulty during exposure. Exposure of mice to 750 ppm HFP for 6 hours (4500 ppm @ hrs) resulted in similar signs (lethargy, unresponsiveness and labored respiration).
Time scaling:	$C^n \times t = k$; where $n = 1.33$ calculated from rat lethality (LC_{50}) data (Appendix C).
Uncertainty factors:	Total uncertainty factor:10. Interspecies: An uncertainty factor of 3 for interspecies variability was considered sufficient to account for extrapolation of animal data to humans due to similarities in HFP toxic effects among all animal species tested. Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for variability in metabolism-mediated differences affecting the toxic response to HFP and for protection of individuals with compromised renal function (~4.5% of the population).
Calculations:	$(320 \text{ ppm})^{1.33} \times 4 \text{ hrs} = 8588 \text{ ppm}^{1.33} @ \text{ hrs}$
10-minute AEGL-2	$C^{1.33} \times 0.167 \text{ hr} = 8588 \text{ ppm}^{1.33} @ \text{ hrs}$ $C^{1.33} = 51{,}518 \text{ ppm}^{1.33} @ \text{ hrs}$ C = 3490 ppm UF application: 3490 ppm/10 = 349 ppm rounded to 350 ppm
30-minute AEGL-2	$C^{1.33} \times 0.5 \text{ hr} = 8588 \text{ ppm}^{1.33} @ \text{ hrs}$ $C^{1.33} = 17{,}176 \text{ ppm}^{1.33} @ \text{ hrs}$ C = 1528 ppm UF application: 1528 ppm/10 = 153 ppm rounded to 150 ppm
1-hour AEGL-2	$C^{1.33} \times 1 \text{ hr} = 8588 \text{ ppm}^{1.33} @ \text{ hrs}$ $C^{1.33} = 8588 \text{ ppm}^{1.33} @ \text{ hrs}$ C = 907 ppm UF application: 907 ppm/10 = 91 ppm
4-hour AEGL-2	$C^{1.33} \times 4 \text{ hrs} = 8588 \text{ ppm}^{1.33} @ \text{ hrs}$ $C^{1.33} = 2147 \text{ ppm}^{1.33} @ \text{ hrs}$ C = 320 ppm UF application: 320 ppm/10 = 32 ppm

8-hour AEGL-2 $C^{1.33}$ x 8 hrs = 8588 $ppm^{1.33}$ @ hrs
$C^{1.33}$ = 1074 $ppm^{1.33}$ @ hrs
C = 190 ppm
UF application: 190 ppm/10 = 19 ppm

Derivation of AEGL-3 for Hexafluoropropylene (HFP)

Key study: Du Pont & Co. 1960. The acute inhalation toxicity of hexafluoropropylene. E. I. du Pont de Nemours & Co., Haskell Laboratory.

Critical effect: Rat $BMCL_{05}$ (log probit) of 1677 ppm for 4 hours as an estimate of the lethality threshold. Although lethality threshold estimates varied due to variability in lethal response at lower concentrations, the four-hour LC_{50} values for species (rat, mouse, rabbit, guinea pig) varied approximately 4-fold.

Time scaling: $C^n \times t = k$; where $n = 1.33$ calculated from rat lethality (LC_{50}) data (Appendix C).

Uncertainty factors: Total uncertainty factor: 10.
Interspecies: An uncertainty factor of 3 for interspecies variability was considered sufficient to account for extrapolation of animal data to humans due to similarities in HFP toxic effects among all animal species tested.
Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for variability in metabolism-mediated differences affecting the toxic response to HFP and for protection of individuals with compromised renal function.

Calculations: $(1677 \text{ ppm})^{1.33} \times 4 \text{ hrs} = 77{,}748 \text{ ppm}^{1.33} \text{ @ hrs}$

10-minute AEGL-3
$C^{1.33} \times 0.167 \text{ hrs} = 77{,}748 \text{ ppm}^{1.33} \text{ @ hrs}$
$C^{1.33} = 46{,}6395 \text{ ppm}^{1.33} \text{ @ hrs}$
C = 18,290 ppm
UF application: 18,290 ppm/10 = 1829 ppm rounded to 1800 ppm

30-minute AEGL-3
$C^{1.33} \times 0.5 \text{ hrs} = 77{,}748 \text{ ppm}^{1.33} \text{ @ hrs}$
$C^{1.33} = 155{,}496 \text{ ppm}^{1.33} \text{ @ hrs}$
C = 8008 ppm
UF application: 7249 ppm/10 = 801 ppm rounded to 800 ppm

1-hour AEGL-3
$C^{1.33} \times 1 \text{ hrs} = 77{,}748 \text{ ppm}^{1.33} \text{ @ hrs}$
$C^{1.33} = 77{,}748 \text{ ppm}^{1.33} \text{ @ hrs}$
C = 4756 ppm
UF application: 4756 ppm/10 = 476 ppm (rounded to 480 ppm)

4-hour AEGL-3
$C^{1.33} \times 4 \text{ hrs} = 77{,}748 \text{ ppm}^{1.33} \text{ @ hrs}$
$C^{1.33} = 19{,}437 \text{ ppm}^{1.33} \text{ @ hrs}$
C = 1677 ppm
UF application: 1677 ppm/10 = 167 ppm rounded to 170 ppm

8-hour AEGL-3 $C^{1.33}$ x 8 hrs = 77,748 $ppm^{1.33}$ @ hrs
$C^{1.33}$ = 9719 $ppm^{1.33}$ @ hrs
C = 996 ppm
UF application: 996 ppm/10 = 99.6 ppm rounded to 100 ppm

APPENDIX B
LC_{50} and Benchmark Dose Calculations

Du Pont Co. (1960). The acute inhalation toxicity of hexafluoropropylene. Haskell Laboratory.
MICE

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
3020.000	8/ 10	97.40	97.47	-0.07	0.0000
2600.000	9/ 10	90.00	93.30	-3.30	0.0174
2000.000	6/ 10	60.00	70.02	-10.02	0.0478
1990.000	9/ 10	90.00	69.30	20.70	0.2014
1515.000	1/ 10	10.00	26.08	-16.08	0.1341
1500.000	4/ 10	40.00	24.79	15.21	0.1240
1000.000	0/ 10	0(2.00)	2.04	-0.04	0.0000

Values in parentheses are corrected for 0 or 100 percent Total = 0.5248

LC_{50} = 1765.630(1618.340 - 1926.325)*
Slope = 1.28(1.20 - 1.36)*
* These values are 95 percent confidence limits

Total animals = 70 Total doses = 7 Animals/dose = 10.00
Chi-square = total chi-square X animals/dose = 5.2483
Table value for Chi-square with 5 Degrees of Freedom = 11.0700

LC_{84} = 2252.612 LC_{16} = 1383.926 FED = 1.09 FS = 1.07 A = 1.06

Expected Lethal Dose Values

$LC_{0.1}$	640.008
$LC_{1.0}$	898.853
$LC_{5.0}$	1145.559
LC_{10}	1278.487
LC_{25}	1502.443
LC_{50}	1765.630
LC_{75}	2074.919
LC_{90}	2438.388
LC_{99}	3468.251

Du Pont Co. (1960). The acute inhalation toxicity of hexafluoropropylene. Haskell Laboratory.
RATS

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
1090.000	0/ 10	0(0.30)	0.21	0.09	0.0004
1520.000	0/ 10	0(0.70)	1.44	-0.74	0.0039
1980.000	0/ 10	0(2.90)	6.44	-3.54	0.0208
2220.000	1/ 10	10.00	11.85	-1.85	0.0033
2520.000	2/ 10	20.00	22.03	-2.03	0.0024
2600.000	0/ 10	0(7.80)	25.33	-17.53	0.1625
2870.000	8/ 10	80.00	37.70	42.30	0.7618
3020.000	4/ 10	40.00	44.92	-4.92	0.0098
3400.000	4/ 10	40.00	62.02	-22.02	0.2058
3440.000	6/ 10	60.00	63.62	-3.62	0.0057

Values in parentheses are corrected for 0 or 100 percent Total = 1.1763

LC_{50} = 3126.976(2825.977 - 3460.035)*
Slope = 1.33(1.21 - 1.45)*
* These values are 95 percent confidence limits

Total animals = 100 Total doses = 10 Animals/dose = 10.00
Chi-square = total chi-square X animals/dose = 11.7628
Table value for Chi-square with 8 Degrees of Freedom = 15.5100

Expected Lethal Dose Values

$LC_{0.1}$	961.709
$LC_{1.0}$	1427.029
$LC_{5.0}$	1891.550
LC_{10}	2148.908
LC_{25}	2592.216
LC_{50}	3126.976
LC_{75}	3772.054
LC_{90}	4550.209
LC_{99}	6851.983

Du Pont Co. (1960). The acute inhalation toxicity of hexafluoropropylene. Haskell Laboratory.
GUINEA PIGS

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
3440.000	8/ 10	91.90	81.03	10.87	0.0769
3020.000	7/ 10	70.00	74.34	-4.34	0.0099
2600.000	4/ 10	40.00	64.96	-24.96	0.2737
2000.000	2/ 4	50.00	45.89	4.11	0.0068
1500.000	2/ 4	50.00	26.45	23.55	0.2850
1000.000	0/ 4	0(7.80)	9.70	-1.90	0.0041

Values in parentheses are corrected for 0 or 100 percent Total = 0.6564

LC50 = 2113.744(1646.397 - 2713.754)*
Slope = 1.74(1.20 - 2.53)*
* These values are 95 percent confidence limits

Total animals = 42 Total doses = 6 Animals/dose = 7.00
Chi-square = total chi-square X animals/dose = 4.5948
Table value for Chi-square with 4 Degrees of Freedom = 9.4900

LC_{84} = 3685.959 LC_{16} = 1212.144 FED = 1.28 FS = 1.45 A = 1.32

Expected Lethal Dose Values

$LC_{0.1}$	208.428
$LC_{1.0}$	452.573
$LC_{5.0}$	787.301
LC_{10}	1011.547
LC_{25}	1462.242
LC_{50}	2113.744
LC_{75}	3055.523
LC_{90}	4416.912
LC_{99}	9872.257

Du Pont Co. (1960). The acute inhalation toxicity of hexafluoropropylene. Haskell Laboratory.
RABBITS

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
1000.000	0/ 2	0(4.90)	4.15	0.75	0.0014
1500.000	0/ 2	0(8.60)	15.70	-7.10	0.0381
2000.000	1/ 2	50.00	34.39	15.61	0.1080
2600.000	4/ 6	66.67	57.39	9.27	0.0352
3020.000	3/ 6	50.00	69.77	-19.77	0.1854
3440.000	5/ 6	83.33	78.67	4.67	0.0130

Values in parentheses are corrected for 0 or 100 percent Total = 0.3810

LC_{50} = 2393.360(1799.032 - 3184.029)*
Slope = 1.59(1.11 - 2.26)*
* These values are 95 percent confidence limits

Total animals = 24 Total doses = 6 Animals/dose = 4.00
Chi-square = total chi-square X animals/dose = 1.5241
Table value for Chi-square with 4 Degrees of Freedom = 9.4900

LC_{84} = 3794.502 LC_{16} = 1509.598 FED = 1.33 FS = 1.42 A = 1.21

Expected Lethal Dose Values

$LC_{0.1}$	350.900
$LC_{1.0}$	667.203
$LC_{5.0}$	1055.694
LC_{10}	1299.410
LC_{25}	1763.506
LC_{50}	2393.360
LC_{75}	3248.171
LC_{90}	4408.287
LC_{99}	8585.348

Benchmark Dose (log-probit): $BMCL_{05}$ Rat lethality data DuPont & Co. (1960)

==========

Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: C:\BMDS\HFP_BMDDATA.(d)
Gnuplot Plotting File: C:\BMDS\HFP_BMDDATA.plt
Mon Mar 20 10:18:42 2006

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BMDS MODEL RUN

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The form of the probability function is:
P[response] = Background
+ (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Dependent variable = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 14
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model
Default Initial (and Specified) Parameter Values
background = 0
intercept = -4.87452
slope = 0.527375

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-30.8017	7.8602
slope	3.81725	0.987043

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-33.4492			
Fitted model	-41.4795	16.0606	12	0.1885
Reduced model	-65.6908	64.4832	13	<.0001

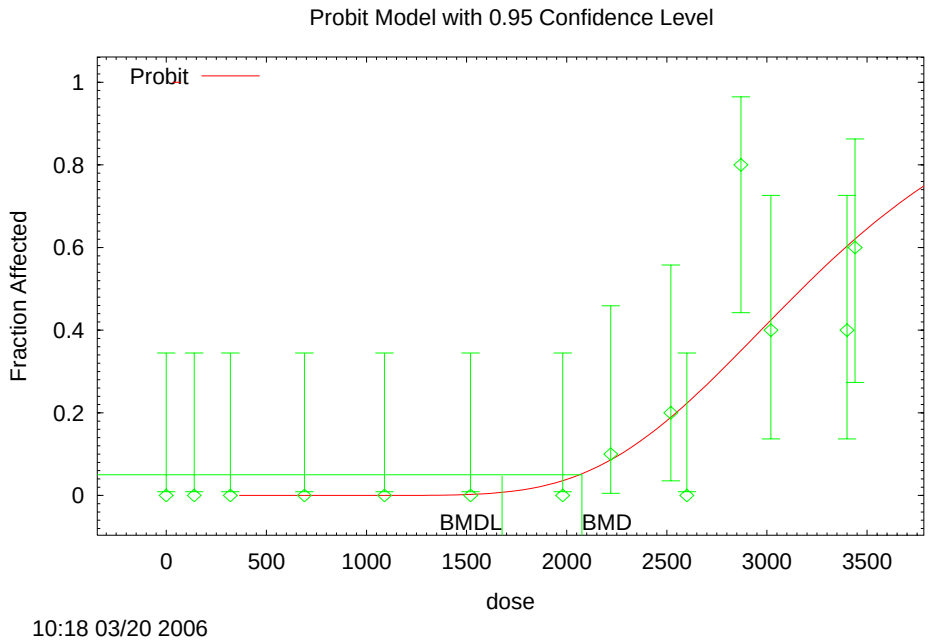
AIC: 86.9591
~~~~~~~~~~

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0
140.0000	0.0000	0.000	0	10	-1.934e-016
320.0000	0.0000	0.000	0	10	-2.827e-009
690.0000	0.0000	0.000	0	10	-0.000157
1090.0000	0.0000	0.000	0	10	-0.01425
1520.0000	0.0023	0.023	0	10	-0.1516
1980.0000	0.0340	0.340	0	10	-0.5929
2220.0000	0.0824	0.824	1	10	0.2018
2520.0000	0.1827	1.827	2	10	0.1412
2600.0000	0.2160	2.160	0	10	-1.66
2870.0000	0.3415	3.415	8	10	3.058
3020.0000	0.4153	4.153	4	10	-0.09795
3400.0000	0.5942	5.942	4	10	-1.251
3440.0000	0.6114	6.114	6	10	-0.07412

Chi-square = 14.12 DF = 12 P-value = 0.2930

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 2075.96
BMDL = 1677.33



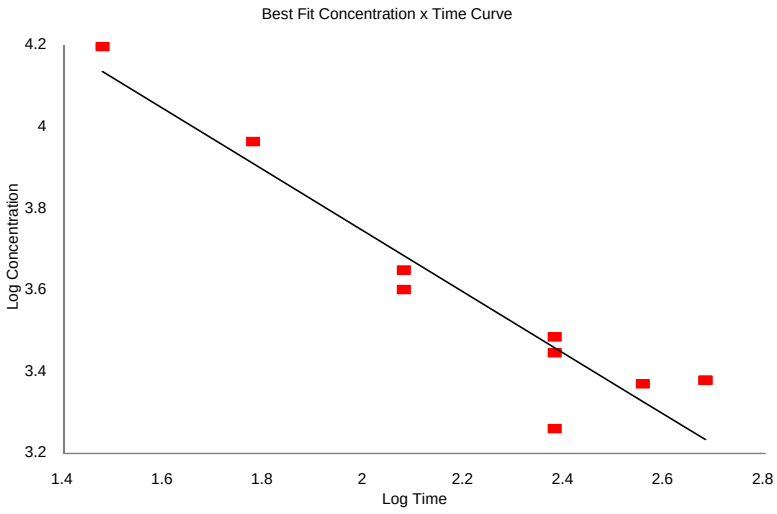
APPENDIX C
Time Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, these workers showed that the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve. The exposure concentration - exposure duration relationship for HFP has been calculated for rats and mice using LC_{50} data for times ranging from 30 to 480 minutes. The values are similar; 1.33 for rats and 1.69 for mice.

1 Rat lethality (Du Pont & Co., 1960; Paulet and Debrousses, 1965)

	Time	Conc.	Log Time	Log Conc.	Regression Output:	
3	30	15750	1.4771	4.1973	Intercept	5.2435
4	60	9226	1.7782	3.9650	Slope	-0.7494
5	120	4000	2.0792	3.6021	R Squared	0.8950
6	120	4466	2.0792	3.6499	Correlation	-0.9460
7	240	2800	2.3802	3.4472	Degrees of Freedom	7
8	240	3060	2.3802	3.4857	Observations	9
9	240	1826	2.3802	3.2615		
10	360	2350	2.5563	3.3711		
11	480	2400	2.6812	3.3802		

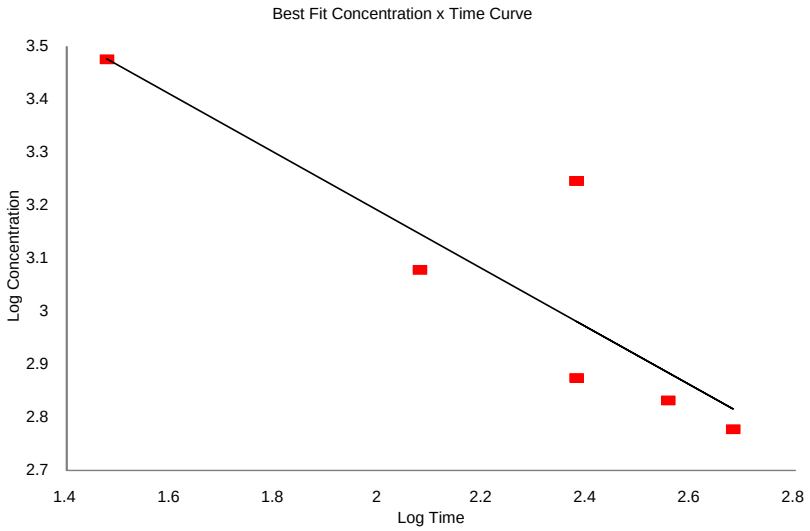
12 n = 1.33
13 k = 9931315



Mouse lethality (Du Pont & Co., 1960; Paulet and Debrousses, 1965)

Time	Conc.	Log Time	Log Conc.	Regression Output:	
30	3000	1.4771	3.4771	Intercept	4.2885
120	1200	2.0792	3.0792	Slope	-0.5491
240	750	2.3802	2.8751	R Squared	0.7578
360	680	2.5563	2.8325	Correlation	-0.8705
480	600	2.6812	2.7782	Degrees of Freedom	4
240	1766	2.3802	3.2470	Observations	6

n = 1.82
k = 64648650



APPENDIX D

DERIVATION SUMMARY TABLES

ACUTE EXPOSURE GUIDELINE LEVELS FOR HEXAFLUOROPROPYLENE (CAS Reg. NO. 000116-15-4)

AEGL-1 VALUES FOR HEXAFLUOROPROPYLENE				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
150 ppm **920 mg/m^3**	**67 ppm** **410 mg/m^3**	**40 ppm** **240 mg/m^3**	**14 ppm** **85 mg/m^3**	**8.3 ppm** **51 mg/m^3**
Reference: Du Pont & Co. 1960. The acute inhalation toxicity of hexafluoropropylene. E. I. du Pont de Nemours & Co., Haskell Laboratory.				
Test Species/Strain/Number: male adult Charles River CD albino rat; 10 per exposure group				
Exposure Route/Concentrations/Durations: whole body inhalation, 140-3440 ppm, 4 hrs; up to 28 days observation; analytically determined concentrations				
Effects: 140 ppm: no effects up to 1980 ppm: reversible nephrosis, pneumonitis at 1090 ppm and above				
Endpoint/Concentration/Rationale: 4-hr exposure to 140 ppm was a no effect level; no evidence of irritation in the rats was observed at this exposure				
Uncertainty Factors/Rationale: total UF of 10 Interspecies: A UF of 3 was applied due to similarity of responses among species. Intraspecies: A UF of was limited to 3 because continuum of toxic effects (nephrosis, pulmonary effects) at higher exposures is the same among four species (rat, mouse, rabbit, guinea pig); UF of 3 considered sufficient to account for metabolism-mediated variability in production of reactive species.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n=1.33 empirically derived from 30 to 480-minute LC_{50} values in rats				
Data Adequacy: The exposure-response relationship for AEGL-1 type effects is not well described by the available data. The AEGL-1 values are derived based upon a no-effect level and are considered sufficiently protective.				

AEGL-2 VALUES FOR HEXAFLUOROPROPYLENE				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
350 ppm **2100 mg/m^3**	**150 ppm** **920 mg/m^3**	**91 ppm** **560 mg/m^3**	**32 ppm** **200 mg/m^3**	**19 ppm** **120 mg/m^3**
Reference: Du Pont & Co. 1960. The acute inhalation toxicity of hexafluoropropylene. E. I. du Pont de Nemours & Co., Haskell Laboratory.				
Test Species/Strain/Sex/Number: male adult Charles River CD albino rat; 10 per exposure group				
Exposure Route/Concentrations/Durations: whole body inhalation, 140-3440 ppm, 4 hrs; up to 28 days observation; analytically determined concentrations				
Effects: 4-hr exposure to 320 or 690 ppm produced reversible nephrosis in 50% and 70% of the rats, respectively. The next higher exposure (1090 ppm) also produced focal pneumonia.				
Endpoint/Concentration/Rationale: The critical effect of reversible nephrosis at 320 ppm was considered an appropriate point-of-departure for AEGL-2 derivation. Use of a higher exposure level resulted in AEGL-2 values too closely approaching the AEGL-3 values.				
Uncertainty Factors/Rationale: Total uncertainty factor: Total uncertainty factor: 10 Interspecies: An uncertainty factor of 3 for interspecies variability was considered sufficient to account for extrapolation of animal data to humans due to similarities in HFP toxic effects among all animal species tested. Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for variability in metabolism-mediated differences affecting the toxic response to HFP and for protection of individuals with compromised renal function.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n=1.33 empirically derived from 30 to 480-minute LC_{50} values in rats				
Data Adequacy: Adequate toxicity data for four species were available that described the continuum of effects following inhalation exposure to HFP. Although a definitive threshold for AEGL-2 effects was not clearly defined, the resulting AEGL-2 values and the uncertainty associated with them are considered acceptable.				

AEGL-3 VALUES FOR HEXAFLUOROPROPYLENE				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1800 ppm **11,000 mg/m^3**	**800 ppm** **4900 mg/m^3**	**480 ppm** **2900 mg/m^3**	**170 ppm** **1000 mg/m^3**	**100 ppm** **600 mg/m^3**

Reference: Du Pont & Co. 1960. The acute inhalation toxicity of hexafluoropropylene. E. I. du Pont de Nemours & Co., Haskell Laboratory.

Test Species/Strain/Sex/Number: male adult Charles River CD albino rat; 10 per exposure group

Exposure Route/Concentrations/Durations: whole-body inhalation exposure for 4 hrs to HFP concentrations of 140-3440 ppm; up to 28-day post exposure observation

Effects: Exposures at or below 1980 ppm were associated with reversible nephrosis and pulmonary effects; at or above 2220 ppm HFP exposures were generally associated with increasing mortality ratios

Endpoint/Concentration/Rationale: The rat $BMCL_{05}$ of 1677 ppm for a 4-hr exposure was used as an estimate of the lethality threshold.

Uncertainty Factors/Rationale:
Total uncertainty factor: Total uncertainty factor: 10

Interspecies: An uncertainty factor of 3 for interspecies variability was considered sufficient to account for extrapolation of animal data to humans due to similarities in HFP toxic effects among all animal species tested. The 4-hour LC_{50} values for rats, mice, rabbits, and guinea pigs varied up to 4-fold; - 750 ppm to 3060 ppm (Du Pont & Co., 1960; Paulette and Debrousses, 1965).

Intraspecies: An intraspecies uncertainty factor of 3 was considered sufficient to account for variability in metabolism-mediated differences affecting the toxic response to HFP and for protection of individuals with compromised renal function.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$, where n=1.33 empirically derived from 30 to 480-minute LC_{50} values in rats

Data Adequacy: Lethality data in four species were sufficient to develop AEGL-3 values.

APPENDIX E
CATEGORY PLOT FOR HEXAFLUOROPROPYLENE

1

2 No human exposure data are available. All plotted data are from animal studies.