ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
OXYGEN DIFLUORIDE
(CAS Reg. No. 7783-41-7)

OF_2

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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 toxicological 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

Oxygen difluoride is an irritating, colorless gas, that has been used as an oxidizing propellant for missiles (Darmer et al., 1972). Due to its powerful oxidizing potential, contact with reducing agents should be avoided. It reacts slowly with water forming hydrofluoric acid and may be explosive when mixed with hydrocarbons. The odor of oxygen difluoride has been reported as being "not displeasing", peculiar, or foul. Odor detection level is reportedly 0.1 ppm with odor being obvious at 0.5 ppm. Rapid accommodation to the odor has been reported. Data were unavailable with which to calculate a Level of Odor Awareness (LOA).

No data were available regarding lethality in humans following inhalation exposure to oxygen difluoride but inhalation reportedly produces effects similar to those produced by ozone (respiratory tract irritation, pulmonary edema and hemorrhage). Intractable headaches were associated with oxygen difluoride vapors at ppb levels. Quantitative exposure-response information for humans is unavailable.

Although acute lethality data are available for monkeys, dogs, rats, and mice, the overall exposure-response relationship for oxygen difluoride is not well defined. Analysis of acute lethality data revealed that 1-hr LC_{50} values varied about 17-fold between the least sensitive (monkey) and most sensitive (mouse) of the four species tested, with larger species appearing to be less sensitive (1-hr LC_{50} values were 1.5, 2.6, 16, and 26.0 ppm, respectively for mice, rats, dogs, and monkeys). Although pulmonary damage was apparent in exposed animals, the chemical does not appear to damage bronchial mucosal surfaces as do other fluorine compounds. For all species tested, delayed death (hours to days) was a typical response pattern.

Using the software of ten Berge, analysis of exposure-response data from Lester and Adams (1965) and Davis (1970) provided an exponent (n) of 1.1 for the equation:

$C^n \times t = k$.

Regression analysis of 5-, 15- and 60-minute LC_{50} values for rats reported by Lester and Adams (1965) and Davis (1970) resulted in a similar value (n = 1.3). Because it was derived from a more comprehensive exposure-response data set, the exponent of 1.1 was used for derivation values for AEGL-specific durations.

Exposure-response data for AEGL-1 severity effects were unavailable. Studies in laboratory species focused on lethality. Where nonlethal responses were reported, the severity of the effects were either not described or likely involved effects (e.g., pulmonary damage) more severe than defined for the AEGL-1 tier. Therefore, AEGL-1 values are not recommended for oxygen difluoride due to insufficient data.

Because the exposure-response relationship for AEGL-2 severity effects is not well described by the available animal data and no human exposure data are available, possible PODs for AEGL-2 development are limited to the nonlethal exposure of animals in the Lester and Adams (1965) and Davis (1970) studies. For the Lester and Adams data, the exposures of rats (10 ppm for 5 minutes and 5 ppm for 15 minutes) were nonlethal, but the presence or extent of pulmonary damage was not assessed in these groups. However, a 5-minute exposure of rats to 20 ppm showed serious pulmonary effects (swelling, acute pneumonia, consolidation of lung lobes; focal atelectasis, polymorphonuclear leukocyte infiltration, pulmonary hemorrhage and

edema). Data from Davis (1970) showed survival of rhesus monkeys exposed to 16 ppm oxygen difluoride for 1 hour and observed for 14 days. Hematology and clinical chemistry findings were negative at 14 days post exposure but gross pathology indicated minor to mild pulmonary congestions and edema in all monkeys exposed to oxygen dilfuoride. Although these findings may support the 1-hour exposure to 16 ppm as a point-of-departure (POD) for AEGL-2 derivation, the resulting AEGL values would exceed the AEGL-3 values developed based upon the 1-hr $BMCL_{05}$ derived from the rhesus monkey lethality data. Although clinical chemistry data for the surviving monkeys was not indicative of progressive pulmonary damage, it is unknown if the pulmonary congestion and edema would have resolved. For these reasons and because of the overall uncertainty in identifying a threshold for AEGL-2 severity effects from the available data, the AEGL-2 values were derived by a three-fold reduction of the AEGL-3 values (NRC, 2001).

For AEGL-3 derivation, a lethality threshold was estimated from the data for rhesus monkeys provided by Davis (1970). Analysis of the 1-hour exposure data for monkeys reported by Davis (1970) resulted in a BMC_{05} of 17.2 ppm, a $BMCL_{05}$ of 7.48 ppm and a BMC_{01} of 14.4. The $BMCL_{05}$ (7.48 ppm) accounts for the variability due to the small number of test animals (4 per group) and is lower than the LC_5 determined by the method of Litchfield and Wilcoxon (1949) but is typically used as the POD for AEGL-3 derivation (NRC, 2001). Extrapolation from the experimental exposure duration to the AEGL-specific exposure durations used an n of 1.1 for the $C^n \times t = k$ relationship (Appendix B) derived using the response data of Lester and Adams (1965) and Davis (1970) and the software package of ten Berge.

Because the available data indicated that larger species (dog and monkey) were less sensitive (a 17-fold difference between the mouse and the rhesus monkey) to the lethal effects of inhaled oxygen difluoride than were smaller species (rats and mice) and because the AEGL-3 derivation is based upon data from a nonhuman primate, the interspecies uncertainty factor was limited to 1. Asthmatics and any individuals with compromised pulmonary function would likely exhibit a more severe response to oxygen difluoride vapor than healthy individuals. Consistent with uncertainty factor application for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride all appear to cause tissue irritation by direct-contact mechanisms) an intraspecies uncertainty factor of 3 was applied to account for greater sensitivity of individuals with compromised respiratory function. Time scaling from the 1-hour experimental duration to other AEGL-specific durations was performed as previously described ($C^n \times t = k$, where $n = 1.1$).

The AEGL values for oxygen difluoride are summarized in the following table.

S 1. Summary of AEGL Values for Oxygen Difluoride

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended; insufficient data
AEGL-2 (Disabling)	4.23 ppm (9.5 mg/m^3)	1.6 ppm (3.5 mg/m^3)	0.83 ppm (1.8 mg/m^3)	0.24 ppm (0.53 mg/m^3)	0.13 ppm (0.29 mg/m^3)	One-third reduction of AEGL-3
AEGL-3 (Lethality)	13 ppm (29 mg/m^3)	4.7 ppm (10 mg/m^3)	2.5 ppm (5.5 mg/m^3)	0.71 ppm (1.6 mg/m^3)	0.38 ppm (0.84 mg/m^3)	1-hr $BMCL_{05}$ of 7.48 ppm for rhesus monkeys (Davis, 1970); total

						UF=3; time scaling n =1.1

NR: Not recommended due to insufficient data; absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

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1. INTRODUCTION

Oxygen difluoride is an irritating, colorless gas, that has been used as an oxidizing propellent for missiles (Darmer et al., 1972). Due to its powerful oxidizing potential, contact with reducing agents should be avoided. It may be explosive when mixed with hydrocarbons (HSDB, 2006).

TABLE 1. Chemical and Physical Data for Oxygen Difluoride

Parameter	Value	Reference
Synonyms	Difluorine monoxide; fluorine monoxide; oxygen fluoride; oxydifluoride	O'Neil et al., 2001
Chemical formula	OF_2	O'Neil et al., 2001
Molecular weight	54.00	O'Neil et al., 2001
CAS Registry No.	7783-41-7	O'Neil et al., 2001
Physical state	Gas	O'Neil et al., 2001
Solubility in water	6.8 ml/100 ml @ 0EC	O'Neil et al., 2001
Vapor pressure	>760 torr	ACGIH, 1991
Relative vapor density	1.86	ACGIH, 1991
Specific gravity	1.9 @ -223.8EC (liquid)	ACGIH, 1991
Melting point/boiling point	-223.8EC/-145.3EC	O'Neil et al., 2001
Conversion factors in air	1 ppm = 2.2 mg/m^3 1 mg/m^3 = 0.45 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

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

2.2. Nonlethal Toxicity

Inhalation of oxygen difluoride reportedly produces effects similar to those produced by ozone; respiratory tract irritation, pulmonary edema and hemorrhage following exposure to 0.5 ppm for several hours (Deichmann and Gerarde, 1969). Exposure to oxygen difluoride at ppb levels reportedly caused intractable headaches in workers conducting animal exposure studies (LaBelle et al., 1945). Sullivan et al. (1995) included oxygen difluoride among the compounds considered by OSHA as potentially causing respiratory effects in construction industry workers, but no exposure-response information was provided. Lester and Adams (1965) reported that oxygen difluoride has a "not displeasing" odor that is detectable at 0.1 ppm and obvious at 0. 5 ppm. However, NIOSH (2005) reported that oxygen difluoride has a peculiar foul odor. Rapid accommodation to the odor has been reported. No additional information was available and, therefore, a Level of Odor Awareness (LOA) could not be calculated.

2.3. Developmental/Reproductive Effects

No human developmental/reproductive toxicity data were available for oxygen difluoride.

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 oxygen difluoride in humans.

2.6. Summary

There are no exposure-response data for inhalation exposure of humans to oxygen difluoride. The chemical reportedly is very irritating and has caused severe headaches at very low (i.e., ppb) levels, and severe irritation, pulmonary edema and hemorrhage following a few hours exposure to 0. 5 ppm.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Monkeys

In a multispecies acute inhalation toxicity study, Davis (1970) exposed rhesus monkeys (two males and two females) to oxygen difluoride (commercial grade, 98% purity) for 15 minutes or one hour. The oxygen dilfuoride was diluted with dry nitrogen prior to entering Longley exposure chambers. An MSA BillionAire was used for concentration monitoring (the

BillionAire analyzer functions by exposing an air-gas sample with a suitable reagent and passing this through a radioactive source within the chamber. The ions that are formed create a current which is a function of the concentration of vapor present and which is measured by an electrometer). The animals were observed during the exposure and for 14 days postexposure. Exposed monkeys exhibited dyspnea (for several days following exposure), gagging, salivation, lacrimation, vomiting, tetany and muscular weakness. Necropsies revealed massive lung edema and hemorrhage and also congestion of the liver, spleen and kidney. No sign of skin irritation was observed even at lethal exposures. The lethality response data for monkeys are shown in Table 2. Time-to-death was not reported. The reported LC_{50} values were 108 ppm and 26.0 ppm, respectively for the 15-minute and 60-minute exposures. Based upon the concentration-time (ct) product, the investigator noted a near linear response for the time range tested (1620 ppmAmin vs 1560 ppmAmin for the 15 minute and 60-minute exposures, respectively).

TABLE 2. Lethal Response of Rhesus Monkeys Exposed To Oxygen Difluoride Vapor

No. exposed	Concentration (ppm)	Mortality ratio
15-minute exposure		
4	60	0/4
4	100	2/4
4	120	2/4
4	140	4/4
60-minute exposure		
4	16.0	0/4
4	21.0	1/4
4	32.0	3/4

Davis, 1970.

A 1-hour LC_{50} of 16 ppm for male and female rhesus monkeys (assumed to be a combined value for two monkeys/gender/group) was reported by Darmer et al. (1972). This value, cited from Davis (1970) is likely a reporting error and should be 26 ppm which is the value reported by Davis.

3.1.2. Dogs

Davis (1970) also reported on the lethality of beagle dogs exposed to oxygen difluoride for 15 minutes or 60 minutes (see Section 3.1.1 for experimental details). Experimental procedures were as described for the experiments with monkeys (Section 3.1.1). The dogs exhibited responses similar to those of the monkeys. Davis reported 15-minute and 60-minute LC_{50} values of 90 ppm and 26.0 ppm, respectively. Similar to the findings in monkeys, the response was near-linear; 1350 ppmAmin and 1560 ppmAmin, respectively, for the 15-minute and 1-hour exposures. Results of this experiment are summarized in Table 3.

TABLE 3. Lethal Response of Beagle Dogs Exposed To Oxygen Difluoride Vapor.		
No. exposed	**Concentration (ppm)**	**Mortality ratio**
15-minute exposure		
4	60	0/4
4	80	1/4
4	100	3/4
60-minute exposure		
4	8.2	0/4
4	16.0	2/4
4	21.0	1/4
4	32.0	4/4

Davis, 1970.

Darmer et al. (1972) reported a 1-hr LC_{50} of 26.0 ppm for groups of 4 male and female beagle dogs (assumed to be a sexes combined value with two dogs/gender/group). Experimental details are described in Section 3.1.1.

3.1.3. Rats

The acute inhalation toxicity of oxygen difluoride in rats was studied by Lester and Adams (1965). In this study, groups of 10 Sprague-Dawley rats (150-175 g; gender distribution in groups not specified but assumed to be 5/gender/group) were exposed to oxygen difluoride (>97% purity) at concentrations of 10, 20, 30, or 40 ppm for five minutes, or 5, 10, or 15 ppm for 15 minutes (Table 2). The oxygen difluoride was injected in a synchronized manner into a dry airstream prior to delivery into a 10-L glass desiccator containing the rats. The rats were observed up to 14 days post exposure. In a separate experiment, a group of 14 rats were exposed for five minutes to 20 ppm oxygen difluoride and terminated (survivors were over anesthetized with diethyl ether) at intervals up to 29 hours. These rats were examined grossly and the lungs examined microscopically. For the 5-minute exposures, the investigators estimated 17 ppm as 50% lethality response. A 5-minute LC_{50} of 17.635 ppm (95% C.I. of 14.351 - 21.669 ppm) was determined by the method of Litchfield and Wilcoxon (Appendix E). Using the U.S. EPA Benchmark Dose (U.S. EPA, 2005) methodology, a $BMCL_{05}$ of 7.4 ppm and a BMC_{01} of 9.2 ppm were calculated for the 5-minute exposure data (Appendix D). For the 15-minute exposure, the investigators estimated 8 ppm as a 50% lethal response (the response data were insufficient for the Litchfield Wilcoxon procedure) and, based upon both the 5-minute and 15-minute data, considered 100 ppm-minutes as an estimate of the CT product associated with a 50% lethal response (only slightly greater than the CT of 85 ppm product for the 5-minute exposure). $BMCL_{05}$ and BMC_{01} values for the 15-minute exposure were 2.3 ppm and 3.6 ppm, respectively) (Appendix D). While the animals exhibited no signs of irritation or distress during the exposures, “widespread pulmonary damage” was considered the cause of death with respiratory difficulties observed only immediately prior to death. The primary target appeared to be at the level of the alveoli as there were no signs of damage to external mucosal surfaces or the bronchial tree. All deaths occurred and also noted that deaths occurred 9 to 66 hours post exposure (Table 4).

TABLE 4. Lethality in Rats Exposed to Oxygen Difluoride.			
Exposure time (min)	**Exposure concentration[a] (ppm)**	**Mortality**	**Time-to-death[b] (hrs)**
5	10 (9.7)	0/10	
5	20 (19.5)	7/10	27, 27, 27, 42, 42, 42, 66
5	30 (29.2)	9/10	10, 10, 17, 17, 17, 27, 29, 31, 39
5	40 (39.0)	10/10	10, 10, 10, 10, 19, 19, 19, 19, 25, 25
15	5 (4.9)	0/10	
15	10 (9.7)	7/10	9, 17, 17, 20, 28, 41, 49
15	15 (14.6)	7/10	15, 24, 30, 30, 30, 41, 55

[a] Values in parehtheses are corrected for the reported 97.4% OF_2 assay efficiency
[b] Times are hours after exposure.
Lester and Adams, 1965

As described for monkeys (Section 3.1.1), Darmer et al, (1972) also reported a 1-hr LC_{50} value of 2.6 ppm for male (N = 10) Sprague-Dawley rats. This is likely the same1-hr LC_{50} value of 2.6 (2.5-2.7) ppm reported by Vernot et al. (1977) for male rats and originally reported by Davis (1970).

Groups of 10-15 male Wistar rats were also exposed for 15 or 60 minutes to oxygen difluoride and observed for 14 days (Davis, 1970) (see Section 3.1.1. for experimental details). The rats exhibited somewhat different signs during exposure than did the monkeys and dogs consisting of tachypnea and muscular weakness only. The response data for rats is summarized in Table 5. Fifteen-minute and 60-minute LC_{50} values of 12.7 ppm and 2.6 ppm, respectively, were reported.

TABLE 5. Lethal Response of Rats Exposed To Oxygen Difluoride Vapor.		
No. exposed	**Concentration (ppm)**	**Mortality ratio**
15-minute exposure		
10	9.5	0/10
10	10.4	1/10
10	11.0	3/10
10	11.9	1/10
10	13.8	9/10
10	15.2	8/10
10	16.5	9/10
60-minute exposure		
10	2.2	0/10
10	2.7	7/10
15	3.0	14/15
10	4.0	10/10

Davis, 1970.

3.1.4. Mice

Both Darmer et al. (1972) and Vernot et .al. (1977) reported a 1-hr LC_{50} of 1.5 ppm for groups of 10 male ICR mice which originates with the work of Davis (1970).

Groups of 15 male ICR mice were also exposed for 15 or 60 minutes to oxygen difluoride and observed for 14 days in the Davis (1970) study (see Section 3.1.1. for experimental details). The rats exhibited somewhat different signs during exposure than did the monkeys and dogs consisting of tachypnea and muscular weakness only. The response data for rats is summarized in Table 6. Fifteen-minute and 60-minute LC_{50} values of 7.5 ppm and 1.5 ppm, respectively, were reported.

.

TABLE 6. Lethal Response of Mice Exposed To Oxygen Difluoride Vapor

No. exposed	Concentration (ppm)	Mortality ratio
15-minute exposure		
15	4.5	8/15
15	5.8	1/15
15	7.5	8/15
15	8.5	4/15
15	9.5	12/15
15	11.0	8/15
15	11.9	15/15
15	15.2	12/15
15	16.5	14/15
60-minute exposure		
15	1.0	5/15
15	2.2	8/15
15	4.2	15/15

Davis, 1970.

3.1.5. Summary of Animal Lethality Data

Lethality data for laboratory species exposed to oxygen difluoride are summarized in Table 7. Comparing 1-hr LC_{50} values reveals about a 17-fold difference between the least sensitive and most sensitive of the four species tested with larger species appearing to be less sensitive. Based upon experimental results from monkeys, dogs, rats, and mice, Davis (1970) summarized that the primary target of oxygen dilfuoride toxicity is the respiratory tract and that there is a considerable difference in susceptibility among the species tested. Specifically, rats and mice were much more susceptible to the effects of oxygen dilfuoride than were monkeys or dogs. For all species tested, delayed death (hours to days) was a typical response pattern.

TABLE 7. Lethality of Inhaled Oxygen Difluoride in Laboratory Species.

Species	Exposure Duration	Response	Reference
Monkey	1 hr	LC_{50} = 26 ppm	Davis, 1970
	15 min	LC_{50} = 108 ppm	Davis, 1970
Dog	1 hr	LC_{50} = 26.0 ppm	Davis, 1970
	15 min	LC_{50} = 90 ppm	Davis, 1970
Rat	5 min	LC_{50} = 17.6 ppm	Lester and Adams, 1965
	15 min	LC_{50} = 8 ppm[b]	Lester and Adams, 1965
	15 min	LC_{50} = 12.7 ppm	Davis, 1970
	1 hr	LC_{50} = 2.6 ppm	Davis, 1970
Mouse	1 hr	LC_{50} = 1.5 ppm	Davis, 1970
	15 min	LC_{50} = 7.5 ppm	Davis, 1970

[a]Estimated

3.2. Nonlethal Toxicity

3.2.1. Monkeys

Exposure of four rhesus monkeys (2 males and 2 females) to 16 ppm oxygen dilfuoride for 1 hour or to 60 ppm for 15 minutes was not lethal (Davis, 1970). The exposure-response data are shown in Table 2. The monkeys exhibited gagging, lacrimation, salivation, muscular weakness, dyspnea, vomiting, and tetany. Neither, the severity of the effects nor the frequency (i.e., occurring in all or just some of the subjects) were specified. Dyspnea reportedly persisted for several days after the exposure. Hematological and clinical chemical evaluations conducted immediately after exposure and at various unspecified times during the 14-day observation period revealed no significant findings in hematologic parameters, uric acid, creatinine, serum alkaline phosphatase, glutamic oxaloacetic transaminase, blood glucose, or extracellular electrolyte composition. Pathological examination showed slight to moderate pulmonary congestion and edema for sublethal exposures.

3.2.2. Dogs

Exposure of male and female beagle dogs (2 per gender) to oxygen dilfuoride concentrations of 60 ppm for 15 minutes or 8.2 ppm for 60 minutes was without lethality over a 14-day observation period (Davis, 1970). Signs of exposure were similar to those described for monkeys with dyspnea reportedly persisting for several days after the exposure. Clinical findings were similar to those reported for monkeys. Exposure response data are shown in Table 3.

3.2.3. Rats

In the lethality study by Lester and Adams (1965), rats exposed to 10 ppm oxygen difluoride for five minutes or to 5 ppm for 15 minutes did not die. The severity of pulmonary damage (if any) for these animals was not specified. The investigators reported that pulmonary damage increased with time and that if damage did not attain sufficient severity to cause death within 9 hours post exposure, then repair of the pulmonary tissue would ensue after 3 days. This contention was based upon the serial sacrificing (0.09, 0.17, 0.58, 0.75, 1, 2, 3.5, 5, 6, 7, 14, 22.5, and 29 hrs after exposure) of rats exposed for five minutes to 20 ppm oxygen difluoride. Microscopic findings in lung tissue were characterized as slight congestion, focal atelectasis, hemorrhage, polymorphonuclear leukocyte infiltration, edema, and acute pneumonia. Gross examination of rats surviving for 14 days following test exposures involving lethality exhibited varying degrees of pulmonary damage (slight to moderate hemorrhage to swelling edema, and consolidation of whole lung lobes), some to the extent of questionable survival.

There was no lethality over a 14-day observation period in groups of 10 male Wistar rats exposed to oxygen dilfuoride at a concentration of 9.5 ppm for 15 minutes or 2.2 ppm for 60 minutes (Davis, 1970). During the exposure, the rats exhibited tachypnea and muscular weakness although the severity and frequency (i.e., occurring in all or just some of the subjects) of the effects were not specified. Dyspnea reportedly persisted for several days after the exposure. No clinical hematological or chemistry data were reported for rats.

3.2.4. Mice

There were no non-lethal exposures reported by Davis (1970) for groups of 15 male ICR mice exposed to oxygen dilfuoride. The lowest exposure tested (4.5 ppm for 15 minutes or 1.0 ppm for 60 minutes) resulted in lethality.

3.2.5. Summary of Nonlethal Toxicity in Animals

Exposures of rats for 5 minutes to10 ppm, 15 minute-exposure to 5-9.5 ppm, 2.2 ppm for 60 minutes were not lethal (assessed after a 14-day post-exposure observation period). Exposure of rhesus monkeys to 16 ppm oxygen dilfuoride for 1 hour or to 60 ppm for 15 minutes was not lethal. As for lethality, nonlethal responses also indicate that smaller species (rats, mice) are notably more sensitive than larger species (monkeys, dogs). Pathology assessments of animals exposed to oxygen difluoride affirm pulmonary involvement (congestion, edema, focal atelectasis, hemorrhage).

3.3. Developmental/Reproductive Effects

Data regarding the developmental/reproductive toxicity of oxygen difluoride following inhalation exposure were not available.

3.4. Genotoxicity

No information was available regarding the genotoxicity of oxygen difluoride.

3.5. Carcinogenicity

There were no data with which to evaluate the carcinogenic potential of inhaled oxygen difluoride.

3.6. Summary

Based upon lethality data in several species, oxygen difluoride appears to be a potent pulmonary toxicant. Gross and microscopic examinations of rats exposed to 20 ppm oxygen difluoride for 5 minutes revealed pulmonary damage (swelling, acute pneumonia, consolidation of lung lobes; focal atelectasis and polymorphonuclear leukocyte infiltration, pulmonary hemorrhage and edema) that progressed with time following cessation of exposure and which did not appear to affect bronchial regions. Based upon lethal response, larger species (dogs and monkeys) appeared to be notably less sensitive than rodents (mice and rats). The overall toxicity data for oxygen difluoride is compromised by an absence of exposure-response data for nonlethal effects.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No data were available regarding the metabolism of oxygen difluoride.

4.2. Mechanism of Toxicity

Data regarding the precise mechanism of action of oxygen difluoride are not available. Its oxidizing potential implies an ability to cause direct-contact tissue damage.

4.3. Structure-Activity Relationships

Because chemical-specific data were available, structure-activity relationships were not used for development of AEGL values for oxygen difluoride. Both fluorine and hydrogen fluoride are present in the reaction mixture producing oxygen difluoride but are less toxic than oxygen difluoride (Lester and Adams, 1965). Other fluorinated compounds (hydrogen fluoride, chlorine pentafluoride, and chlorine trifluoride) also act as direct-contact irritants. Relative toxicity data from Davis(1970) and Darmer et. al. (1972) for several fluorinated compounds are summarized in Table 8. Generally, relative toxicity appears to be oxygen difluoride>chlorine pentafluoride>chlorine trifluoride>hydrogen fluoride.

TABLE 8. Relative Toxicity Of Oxygen Difluoride To Other Fluorinated Compounds[a].

Species	OF_2	ClF_5	ClF_3	HF
Rat	2.6/2.6=1	122/2.6=47	299/2.6=115	1276/2.6=491
Mouse	1.5/1.5=1	57/1.5=38	178/1.5=119	501/1.5=334
Dog	26/26=1	122/26=5	–	–
Monkey	26/26=1	173/26=6.7	230/26=8.8	1774/26=68

[a] 1-hr LC_{50} values expressed in ppm (Davis, 1970; Darmer et al., 1972)

4.4. Species Variability

As shown by the data from Davis, (1970), there is considerable variability in the lethal response to inhaled oxygen difluoride among the species tested (monkeys, dog, rat, and mouse). Specifically, comparison of 1-hr LC_{50} values reveals about a 17-fold difference between the least sensitive and most sensitive species with larger species appearing to be less sensitive. Additionally, the monkey appears to exhibit the least variability in lethal response to other fluorinated compounds (see Tables 3 and 8).

4.5. Concurrent Exposure Issues

Concurrent exposure to other chemicals affecting the respiratory tract will be of concern but can not be readily quantified.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No quantitative data are available regarding AEGL-1 type effects in humans.

5.2. Animal Data Relevant to AEGL-1

No data were available regarding AEGL-1 type effects in animals exposed to oxygen difluoride vapors.

5.3. Derivation of AEGL-1 Values

Exposure-response data for AEGL-1 severity effects was unavailable. Studies in animals primarily focused on lethality. Where nonlethal responses were reported, the severity of the effects was not described or likely involved effects (e.g., pulmonary damage) more severe than those defined for the AEGL-1 tier. Therefore, AEGL-1 values are not recommended for oxygen difluoride due to insufficient data (Table 9).

TABLE 9. AEGL-1 Values for Oxygen Difluoride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	NR	NR	NR	NR	NR

NR: not recommended due to insufficient data; absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No data were available regarding nonlethal adverse effects in humans resulting from inhalation exposure to oxygen difluoride.

6.2. Animal Data Relevant to AEGL-2

Information regarding AEGL-2 severity effects is limited to that obtained from studies focusing on lethality. Specifically, exposure of rats to 10 ppm oxygen difluoride for 5 minutes or 5 ppm for 15 minutes was not lethal (Lester and Adams, 1965). However, the severity of pulmonary damage associated with these exposures is uncertain. In the same study, gross and microscopic examination of rats exposed to 20 ppm for 5 minutes revealed significant progressive pulmonary damage (swelling, acute pneumonia, consolidation of lung lobes; focal atelectasis, polymorphonuclear leukocyte infiltration, pulmonary hemorrhage and edema) post exposure.

Davis (1970) reported nonlethal 1-hour exposures for monkeys (16 ppm), dogs (8.2 ppm), and rats (2.2 ppm), 15-minute nonlethal exposures for monkeys and dogs (60 ppm), and a 15-minute nonlethal exposure for rats (9.5 ppm). Similar to the findings of Lester and Adams, Davis (1970) reported pulmonary involvement in animals surviving oxygen difluoride exposure but definitive exposure-response are not available from these reports.

6.3. Derivation of AEGL-2 Values

Because the exposure-response relationship for AEGL-2 severity effects is not well described by the available animal data and no human exposure data are available, possible PODs for AEGL-2 development are limited to the nonlethal exposure of animals in the Lester and Adams (1965) and Davis (1970) studies. For the Lester and Adams data, the exposures of rats (10 ppm for 5 minutes and 5 ppm for 15 minutes) were nonlethal, but the presence or extent of pulmonary damage was not assessed in these groups. However, a 5-minute exposure of rats to 20 ppm showed serious pulmonary effects (swelling, acute pneumonia, consolidation of lung lobes; focal atelectasis, polymorphonuclear leukocyte infiltration, pulmonary hemorrhage and

edema). Data from Davis (1970) showed survival of rhesus monkeys exposed to 16 ppm oxygen difluoride for 1 hour and observed for 14 days. Hematology and clinical chemistry findings were negative at 14 days post exposure but gross pathology indicated minor to mild pulmonary congestions and edema in all monkeys exposed to oxygen dilfuoride. Although these findings may support the 1-hour exposure to 16 ppm as a point-of-departure (POD) for AEGL-2 derivation, the resulting AEGL values would exceed the AEGL-3 values developed based upon the 1-hr $BMCL_{05}$ derived from the rhesus monkey lethality data. Although clinical chemistry data for the surviving monkeys was not indicative of progressive pulmonary damage, it is unknown if the pulmonary congestion and edema would have resolved. For these reasons and because of the overall uncertainty in identifying a threshold for AEGL-2 severity effects form the available data, the AEGL-2 values were derived by a three-fold reduction of the AEGL-3 values (NRC, 2001).

The AEGL-2 values for oxygen difluoride are shown in Table 10 and their derivation summarized in Appendix A.

TABLE 10. AEGL-2 Values for Oxygen Difluoride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	4.3 ppm	1.6 ppm	0.83 ppm	0.24 ppm	0.13 ppm

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No data were available regarding lethality in humans resulting from inhalation exposure to oxygen difluoride.

7.2. Animal Data Relevant to AEGL-3

Acute lethality data for several animals species are available (Lester and Adams, 1965; Davis, 1970). One-hr LC_{50} values ranged from 1.5 to 26.0 ppm, with larger species (dog, monkey) being less sensitive than rodents (rats and mice) (see Table 7). Based upon gross and microscopic examinations of the lungs of rats serially sacrificed over 29 hours following a single 5-minute exposure to 20 ppm oxygen difluoride (Lester and Adams, 1965), lethality was contingent upon the relationship between pulmonary damage (the primary target of oxygen difluoride) and tissue repair. Three days appeared to define a critical period for determining a lethal versus nonlethal response. Necropsy of animals (rats, mice, dogs, monkeys) receiving sublethal exposures to oxygen difluoride exhibited minor of moderate pulmonary edema and congestion up to 14 days post exposure (Davis, 1970).

7.3. Derivation of AEGL-3 Values

The lethality data (Davis, 1970) for rhesus monkeys exposed to oxygen difluoride for 15 minutes or one hour are the most relevant for derivation of AEGL-3 values. In addition to being a more relevant test species than rodents, hematology, clinical chemistry and gross pathology data were reported out to 14 days post exposure. Analysis of the 1-hour exposure data for monkeys reported by Davis (1970) resulted in a BMC_{05} of 17.2 ppm, a $BMCL_{05}$ of 7.48 ppm and a BMC_{01} of 14.4 ppm (U.S. EPA Benchmark Dose, v.1.3.2; Appendix D). Analysis of these data

by the method of Litchfield and Wilcoxon (1949) resulted in an LC_1 value of -13 ppm and an LC_5 value of -17 ppm (Appendix D). The $BMCL_{05}$ (7.48 ppm) accounts for the variability due to the small number of test animals (4 per group) and is lower than the LC_5 determined by the method of Litchfield and Wilcoxon (1949) but is typically used as the POD for AEGL-3 derivation (NRC, 2001). Extrapolation from the experimental exposure duration to the AEGL-specific exposure durations used an *n* of 1.1 for the $C^n \times t = k$ relationship (Appendix B) derived using the response data of Lester and Adams (1965) and Davis (1970) and the software package of ten Berge. A regression analysis of 5-, 15- and 60-minute LC_{50} values (Lester and Adams (1965) and Davis (1970) resulted in a very similar *n* value of 1.27.

Because the available data indicated that larger species (dog and monkey) were less sensitive (up to 17-fold difference between the rhesus monkey and mice) to the lethal effects of inhaled oxygen difluoride than were smaller species (rats and mice) and because the AEGL-3 derivation is based upon data from a nonhuman primate, the interspecies uncertainty factor was limited to 1. Asthmatics and any individuals with compromised pulmonary function would likely exhibit a more severe response to oxygen difluoride vapor than healthy individuals. Consistent with uncertainty factor application for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride all appear to cause tissue irritation by direct-contact mechanisms) an intraspecies uncertainty factor of 3 was applied to account for greater sensitivity of individuals with compromised respiratory function.

The resulting AEGL-3 values are shown in Table 11 and their derivation summarized in Appendix A.

TABLE 11. AEGL-3 Values for Oxygen Difluoride

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	13 ppm	4.7 ppm	2.5 ppm	0.71 ppm	0.38 ppm

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

Table 12 summarizes the AEGL values for oxygen difluoride. Date were unavailable for assessing AEGL-1 tier effects. Lethality tests in several laboratory species suggests that inhalation exposure to oxygen difluoride results in latent pulmonary damage. Data with which to derive AEGL-2 value were unavailable. Following AEGL Standing Operating Procedures (NRC, 2001), the AEGL-2 values were derived by a three-fold reduction of the AEGL-3 values. Development of AEGL-3 values was based upon an estimated lethality threshold (1-hr $BMCL_{05}$ of 7.48 ppm for rhesus monkeys).

TABLE 12. AEGL Values for Oxygen Difluoride					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-hour**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	4.3 ppm	1.6 ppm	0.83 ppm	0.24 ppm	0.13 ppm
AEGL-3 (Lethality)	13 ppm	4.7 ppm	2.5 ppm	0.71 ppm	0.38 ppm

NR: not recommended due to data deficiencies; absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

8.2. Comparisons with Other Standards and Guidelines

Standard and guidance levels for workplace and community exposures are listed in Table 13.

TABLE 13. Extant Standards and Guidelines for Oxygen Difluoride					
Guideline	**Exposure Duration**				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	4.3ppm	1.6 ppm	0.83 ppm	0.24 ppm	0.13 ppm
AEGL-3	13 ppm	4.7 ppm	2.5 ppm	0.71 ppm	0.38 ppm
REL-TWA (NIOSH)[a]					0.05 ppm
TLV STEL (ACGIH)[b]					0.05 ppm (ceiling)
PEL-TWA (OSHA)[c]					0.05 ppm
MAC[d] (the Netherlands)					0.05 ppm (ceiling)
NRC EEL[e]	0.5 ppm	0.2 ppm	0.1 ppm		
IDLH (NIOSH)[f]		0.5 ppm			

NR: not recommended due to insufficient data.

[a]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.

[b]**ACGIH TLV-STEL (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Short-Term Exposure Limit)** (ACGIH 2005) is a 15-minute TWA exposure that should not be exceeded at any time during the work-day, even if the 8-hour TWA is within the TLV-TWA. The TLV-STEL is the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, 3) dose-rate-dependent toxic effects, or 4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency. The TLV-STEL for oxygen difluoride is a ceiling value.

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

[d]**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.

[e] **NRC (National Research Council)**. Committee on Toxicology. Emergency Exposure Limits (EEL) for military and space agencies; exposure limits are for "rare in the lifetime of the individual" and permit some degree of reversible injury short of incapacitation. (Smyth, 1966).

[f]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1996; 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

8.3. Data Adequacy and Research Needs

Data on human exposure to oxygen difluoride were not available. Results of animal studies in several species were sufficient for identifying lethal concentrations of oxygen difluoride vapor, demonstrating latency in the lethal response, deep pulmonary damage as the probable cause of death and the fact that smaller species exhibited greater sensitivity to the lethal effects of oxygen difluoride vapor exposure. The AEGL values are based data from a studies on a non-human primate (rhesus monkey). Both lethal response data at 14 days post exposure as well as assessment of hematological and clinical chemistry parameters, and gross pathology findings were used to define critical effects. However, data with which to definitively assess the exposure response-exposure duration relationship for nonlethal effects were lacking.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Oxygen Difluoride

AEGL-1 values for oxygen difluoride are not recommended due to insufficient data. The absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.

Derivation of AEGL-2 Values for Oxygen Difluoride

Key study: See AEGL-3 derivation.

Critical effect: Data are unavailable with which to define a point-of-departure for a AEGL-2 derivation. Following the guidelines for AEGL development (NRC, 2001), the AEGL-2 values have been estimated by a three-fold reduction of the AEGL-3 values.

Time scaling: See AEGL-3 derivation

Uncertainty factor: See AEGL-3 derivation

Modifying factor: None applied

Calculation: One third reduction of AEGL-3 values

10-minute AEGL-2	13 ppm/3	=	4.3 ppm
30-minute AEGL-2	4.7 ppm/3	=	1.6 ppm
1-hour AEGL-2	2.5 ppm/3	=	0.83 ppm
4-hour AEGL-2	0.71 ppm/3	=	0.24 ppm
8-hour AEGL-2	0.38 ppm	=	0.13 ppm

Derivation of AEGL-3 Values for Oxygen Difluoride

Key study: Davis, 1970. Acute toxicity of oxygen difluoride. Aerospace Medical Research Laboratory, Aerospace Div., Air Force Systems Command, Wright-Patterson AFB, OH. AMRL-TR-70-102.

Critical effect: 1-hr $BMCL_{05}$ of 7.48 ppm for rhesus monkeys exposed to oxygen difluoride for 1 hour. The $BMCL_{05}$ (7.48 ppm) accounts for the variability due to the small number of test animals (4 per group) and is typically used as the POD for AEGL-3 derivation. The $BMCL_{05}$ is below the nonlethal exposure of 16 ppm for 1 hour reported by Davis (1970) for rhesus monkeys and Beagle dogs, is equivalent to one-third of the 1-hr LC_{50} of 26 ppm determined by the method of Litchfield and Wilcoxon (1949) but more conservative than the 1-hr LC_5 of 17 ppm calculated by this method.

Time scaling: Extrapolation from the experimental exposure duration to the AEGL-specific exposure durations used an n of 1.1 for the $C^n \times t = k$ relationship (Appendix B) derived using the software of ten Berge and the response data from Lester and Adams (1965) and Davis (1979). Regression analysis of 1-hr LC_{50} data from these investigators provided a very similar n value of 1.27.

Uncertainty factors: Total uncertainty factor adjustment was 3
Interspecies: 1; available data indicated larger species (dog and monkey) were less sensitive to the lethal effects of inhaled oxygen difluoride than were smaller species (rats and mice). Because one test species was a nonhuman primate, the interspecies uncertainty factor was limited to 1.
Intraspecies: 3; consistent with uncertainty factor application for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride all appear to cause tissue irritation by direct-contact mechanisms) an intraspecies uncertainty factor of 3 was applied to account for greater sensitivity of individuals with compromised respiratory function.

Modifying Factor: None applied

Calculation: $(7.48 \text{ ppm})^{1.1} \times 1 \text{ hr} = 9.15 \text{ ppm}^{1.1} \cdot \text{hrs}$

10-minute AEGL-3

$C^{1.1} \times 0.1667 \text{ hr} = 9.15 \text{ ppm}^{1.1} \cdot \text{hrs}$
$C = 38.13 \text{ ppm}$
10-min AEGL-3 = 38.13 ppm/3 = 12.7 ppm (13 ppm)

30-minute AEGL-3

$C^{1.1} \times 0.5 \text{ hr} = 9.15 \text{ ppm}^{1.1} \cdot \text{hrs}$
$C = 14.05 \text{ ppm}$
30-min AEGL-3 = 14.05 ppm/3 = 4.68 ppm (4.7 ppm)

1-hour AEGL-3

$C^{1.1} \times 1 \text{ hr} = 9.15 \text{ ppm}^{1.1} \cdot \text{hrs}$

C = 7.48 ppm

1-hr AEGL-3 = 7.48 ppm/3 = 2.49 ppm (2.5 ppm)

4-hour AEGL-3

$C^{1.1} \times 4 \text{ hrs} = 9.15 \text{ ppm}^{1.1} \cdot \text{hrs}$

C = 2.12 ppm

4-hr AEGL-3 = 2.12 ppm/3 = 0.71 ppm

8-hour AEGL-3

$C^{1.1} \times 8 \text{ hrs} = 9.15 \text{ ppm}^{1.1} \cdot \text{hrs}$

C = 1.13 ppm

8-hr AEGL-3 = 1.13 ppm/3 = 0.38 ppm

APPENDIX B: 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, 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.

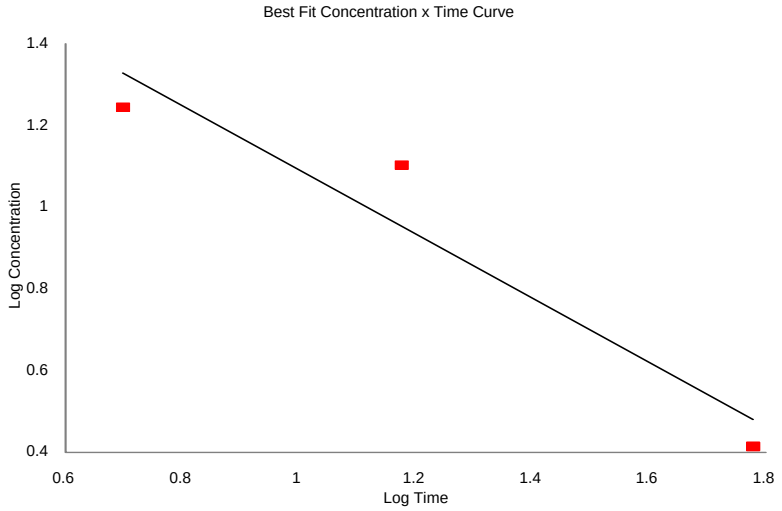
Analysis of data from Davis (1970) and Lester and Adams (1965) with the software of ten Berge provided an n value of 1.1 for the expression $C^n \times t = k$. Regression analysis of lethality data for rats (LC_{50} values for 5 minutes, 15 minutes, and 1 hour) also showed a near linear relationship (n = 1.27) very similar to that of the ten Berge software. The n value of 1.1 was used for deriving the values for AEGL-specific exposure periods.

Oxygen difluoride lethality in rats: Lester and Adams, 1965; Davis, 1970

Time	Conc.	Log Time	Log Conc.
5	17.6	0.6990	1.2455
15	12.7	1.1761	1.1038
60	2.6	1.7782	0.4150

Regression Output:	
Intercept	1.8782
Slope	-0.7857
R Squared	0.9145
Correlation	-0.9563
Degrees of Freedom	1
Observations	3

n = 1.27
k = 245.78



LogProbit_Oxygen difluoride_rat AEGL

Filename: Oxygen difluoride_rat AEGL for Log Probit Model
Date: 09 February 2007 Time: 12:15:08

Seq.Nr Responded	Conc ppm	Minutes	Exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8
14	17	15	10	9
15	2	60	10	0
16	3	60	10	7
17	3	60	15	14
18	4	60	10	10

Filename: Oxygen difluoride_rat AEGL for Log Probit Model
Date: 09 February 2007 Time: 12:18:17

Seq.Nr Responded	Conc ppm	Minutes	Exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8

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LogProbit_Oxygen difluoride_rat AEGL

14	17	15	10	9	
15	2	60	10	0	
16	3	60	10	7	
17	3	60	15	14	
18	4	60	10	10	

Observations 1 through 18 considered!

Seq.nr responded	Conc ppm	Minutes	exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8
14	17	15	10	9
15	2	60	10	0
16	3	60	10	7
17	3	60	15	14
18	4	60	10	10

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = Conc ppm, ln-transformed
X2 = Minutes, ln-transformed

ChiSquare	=	74.27
Degrees of freedom	=	15
Probability Model	=	7.66E-10

Ln(Likelihood) = -56.25

B 0	= -6.6734E+00	Student t	=	-1.5079
B 1	= 2.4596E+00	Student t	=	2.7662
B 2	= 2.2229E+00	Student t	=	2.5684

1

LogProbit_Oxygen difluoride_rat AEGL

variance B 0	0	=	1.9587E+01
covariance B 0	1	=	-3.8663E+00
covariance B 0	2	=	-3.7876E+00
variance B 1	1	=	7.9059E-01
covariance B 1	2	=	7.3042E-01
variance B 2	2	=	7.4905E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)

Point estimate	=	1.106
Lower limit (95% CL)	=	0.817
Upper limit (95% CL)	=	1.396

Filename: Oxygen difluoride_rat AEGL for Log Probit Model
Date: 09 February 2007 Time: 12:41:36

Seq.Nr Responded	Conc ppm	Minutes	Exposed	
1	10	5	10	0
2	20	5	10	7
3	30	5	10	9
4	40	5	10	10
5	5	15	10	0
6	10	15	10	7
7	15	15	10	7
8	10	15	10	0
9	10	15	10	1
10	11	15	10	3
11	12	15	10	1
12	14	15	10	9
13	15	15	10	8
14	17	15	10	9
15	2	60	10	0
16	3	60	10	7
17	3	60	15	14
18	4	60	10	10

Filename: Oxygen difluoride_rat AEGL for Log Probit Model
Date: 09 February 2007 Time: 15:27:10

Seq.Nr	Conc ppm	Minutes	Exposed

1

APPENDIX C: Derivation Summary Tables

ACUTE EXPOSURE GUIDELINE LEVELS FOR OXYGEN DIFLUORIDE DERIVATION SUMMARY

AEGL-1 VALUES FOR OXYGEN DIFLUORIDE				
10 mi	**30 min**	**1 h**	**4 h**	**8 h**
NR	**NR**	**NR**	**NR**	**NR**
Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations: NA				
Effects: NA				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: NA				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: no adjustments				
Time Scaling: NA				
Data Adequacy: AEGL-1 values for oxygen difluoride are not recommended due to insufficient data. The absence of AEGL-1 values does not imply that exposure to concentrations less than the AEGL-2 values is without effect.				

1

AEGL-2 VALUES FOR OXYGEN DIFLUORIDE				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
4.3 ppm	**1.6 ppm**	**0.83 ppm**	**0.24 ppm**	**0.13 ppm**
Reference: Davis, 1970. Acute toxicity of oxygen difluoride. Aerospace Medical Research Laboratory, Aerospace Div., Air Force Systems Command, Wright-Patterson AFB, OH. AMRL-TR-70-102.				
Test Species/Strain/Sex/Number: rhesus monkey; 2/gender/group (See AEGL-3 development)				
Exposure Route/Concentrations/Durations: See AEGL-3 development				
Effects: Not applicable				
Endpoint /Concentration Rationale: Data are unavailable with which to develop AEGL-2 values for oxygen dilfuoride. AEGL-2 values estimated as one third of AEGL-3 values as described in Standing Operating Procedures for developing AEGLs (NRC, 2001)				
Uncertainty Factors/Rationale: See AEGL-3 derivation				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: See AEGL-3 derivation.				
Data Adequacy: The exposure-response relationship for nonlethal effects is not well defined; AEGL-2 values estimated as one third of the AEGL-3 values.				

1

AEGL-3 VALUES FOR OXYGEN DIFLUORIDE				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
13 ppm	**4.7 ppm**	**2.5 ppm**	**0.71 ppm**	**0.38 ppm**

Reference: Davis, 1970. Acute toxicity of oxygen difluoride. Aerospace Medical Research Laboratory, Aerospace Div., Air Force Systems Command, Wright-Patterson AFB, OH. AMRL-TR-70-102.

Test Species/Strain/Sex/Number: rhesus monkey; 2/gender/group

Exposure Route/Concentrations/Durations:15-min. or 1-hr exposure (whole-body inhalation); 60, 100, 120, or 140 ppm for15 minutes; 16, 21, or 32 ppm for 1 hr

Effects:

15 min		1 hr	
Conc. (ppm)	Mortality ratio	Conc. (ppm)	Mortality ratio
60	0/40/4	16	0/4
100	2/4	21	1/4
120	2/4	32	3/4
140	4/4		

Endpoint/Concentration/Rationale: The $BMCL_{05}$ (7.48 ppm) accounts for the variability due to the small number of test animals (4 per group) and is typically used as the POD for AEGL-3 derivation. The $BMCL_{05}$ is below the nonlethal exposure of 16 ppm for 1 hour reported by Davis (1970) for rhesus monkeys and Beagle dogs, is equivalent to one-third of the 1-hr LC_{50} of 26 ppm determined by the method of Litchfield and Wilcoxon (1949) but more conservative than the 1-hr LC_5 of 17 ppm calculated by this method.

Uncertainty Factors/Rationale: Total uncertainty factor adjustment was 3

Interspecies: 1; available data indicated larger species (dog and monkey) were less sensitive to the lethal effects of inhaled oxygen difluoride than were smaller species (rats and mice). Because one test species was a nonhuman primate, the interspecies uncertainty factor was limited to 1.

Intraspecies: 3; consistent with uncertainty factor application for other direct-acting fluorinated compounds (chlorine pentafluoride, chlorine trifluoride, and hydrogen fluoride all appear to cause tissue irritation by direct-contact mechanisms) an intraspecies uncertainty factor of 3 was applied to account for greater sensitivity of individuals with compromised respiratory function

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Extrapolation from the experimental exposure duration to the AEGL-specific exposure durations used an n of 1.1 for the $C^n \times t = k$ relationship (Appendix B) derived using the software of ten Berge and the response data from Lester and Adams (1965) and Davis (1979). Regression analysis of 1-hr LC_{50} data from these investigators provided a very similar n value of 1.27.

Data Adequacy: Lethality data are available for four species (monkey, dog, rat, mouse) and sufficient for deriving AEGL-3 values. Results of experiments indicate larger species to be less susceptible.

APPENDIX D: LETHALITY THRESHOLD AND BMC ANALYSIS FOR OXYGEN DIFLUORIDE

Davis, 1970 rhesus monkeys (4/group; 2 males, 2 females), 1-hr exposure

$BMCL_{05}$

```
==========================================================================
          Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
          Input Data File: C:\BMDS\UNSAVED1.(d)
          Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
        Tue Jan 30 08:44:51 2007


==========================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
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 = 4
  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    =  -9.26036
      slope        =   2.85468

 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        -12.6489           5.97666
        slope            3.8667           1.85849

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                 -4.49868
Fitted model               -4.65729        0.317211            2        0.8533
Reduced model              -8.997368.99736              3          0.02933
```

AIC: 13.3146

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	4	0
16.0000	0.0269	0.108	0	4	-0.3327
21.0000	0.1903	0.761	1	4	0.3039
32.0000	0.7740	3.096	3	4	-0.1148

Chi-square = 0.22 DF = 2 P-value = 0.8975

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95

BMC = 17.216
BMCL = 7.48236

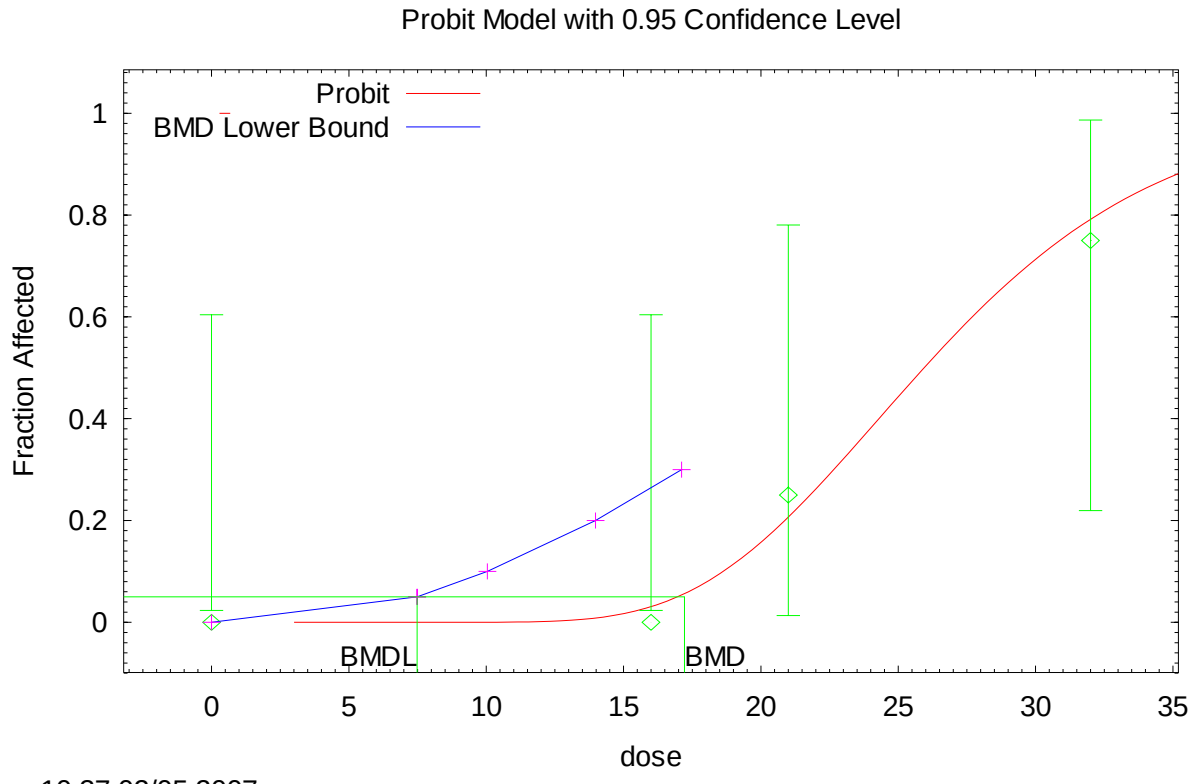

FIGURE 1. Probit model $BMCL_{05}$

Davis, 1970. Rhesus monkey (4/group; 2 males, 2 females), 1-hr exposure.

BMC_{01}

```
 ================================================================
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          Input Data File: C:\BMDS\UNSAVED1.(d)
          Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                Wed Jan 31 10:38:01 2007
 ================================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
 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 = 3
  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   =    -9.26036
                   slope   =     2.85468

  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        -12.6489         5.97666
        slope          3.8667         1.85849

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          -4.49868
  Fitted model         -4.65729       0.317211          1           0.5733
 Reduced model         -7.63817       6.27898           2           0.0433
        AIC:          13.3146


                              Goodness  of  Fit
```

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
16.0000	0.0269	0.108	0	4	-0.3327
21.0000	0.1903	0.761	1	4	0.3039
32.0000	0.7740	3.096	3	4	-0.1148

Chi-square = 0.22 DF = 1 P-value = 0.6420

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 14.4341
BMCL = 4.22764

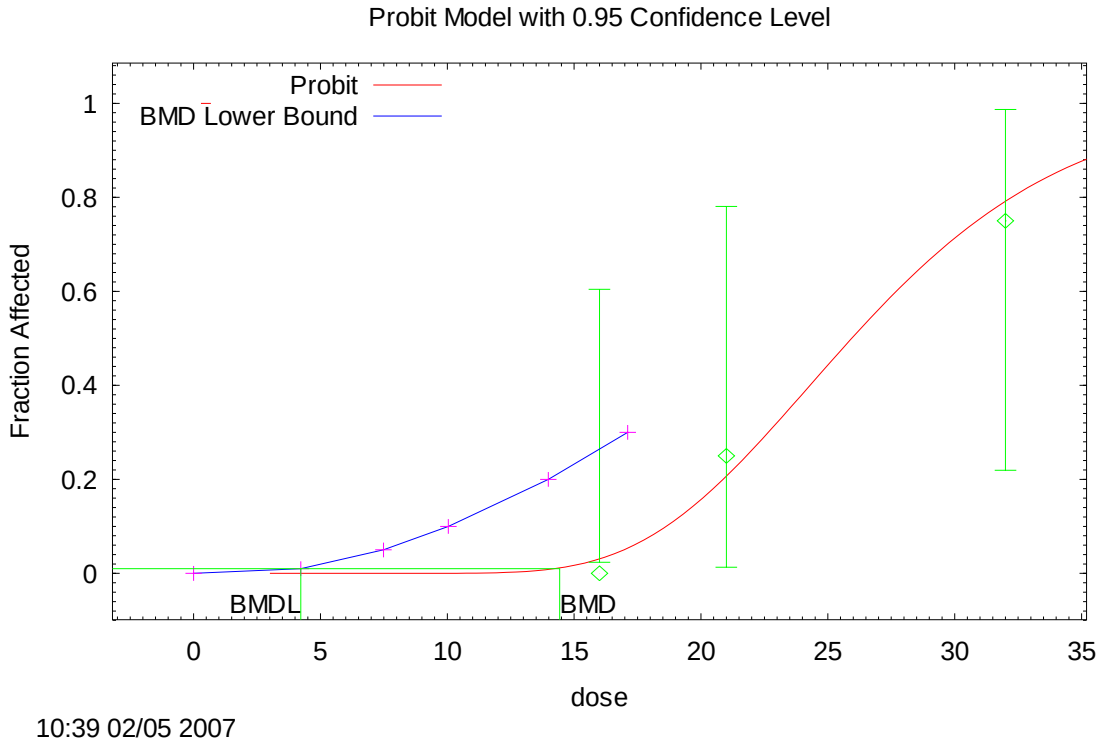

FIGURE 2. Probit model BMC_{01}

LC_{50} and Lethality Threshold- Litchfield-Wilcoxon

Davis, 1970; rhesus monkeys 1-hr exposure to OF_2

	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
16.000	0/ 4	0(2.30)	3.37	-1.07	0.0035
21.000	1/ 4	25.00	18.45	6.55	0.0285
32.000	3/ 4	75.00	80.38	-5.38	0.0183

Values in parentheses are corrected for 0 or 100 percent Total = 0.0503

LC_{50} = 26.067(20.584 - 33.010)*
Slope = 1.27(1.02 - 1.58)*
* These values are 95 percent confidence limits

Total animals = 12 Total doses = 3 Animals/dose = 4.00
Chi-square = total chi-square X animals/dose = 0.2013
Table value for Chi-square with 1 Degrees of Freedom = 3.8400

LC_{84} = 33.175 LC_{16} = 20.481 FED = 1.27 FS = 1.24 A = 1.10

Expected Lethal Dose Values

$LC_{0.1}$	9.545
$LC_{1.0}$	13.360
$LC_{5.0}$	16.986
LC_{10}	18.936
LC_{25}	22.217
LC_{50}	26.067
LC_{75}	30.583
LC_{90}	35.882
LC_{99}	50.857

APPENDIX E: CATEGORY PLOT FOR OXYGEN DIFLUORIDE

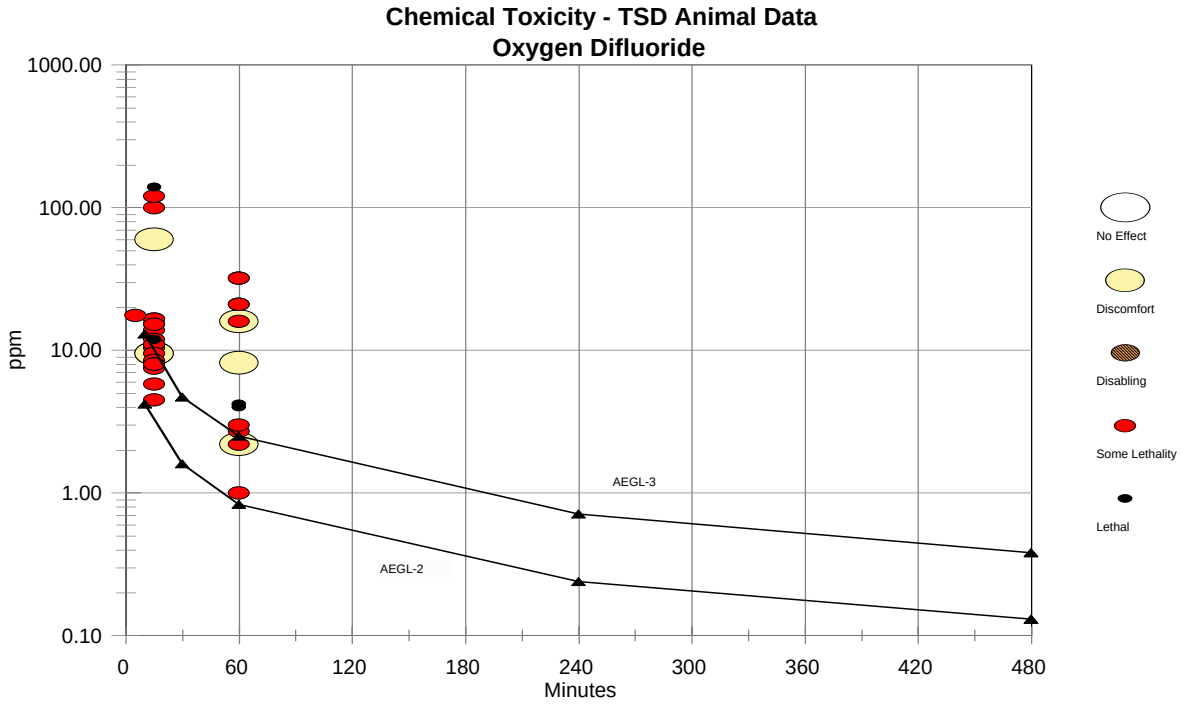

FIGURE 3. Category Plot

Note: the lethality data points at or below the AEGL-2 and AEGL-3 levels are for rats and mice, species shown to be 10-fold to 17-fold more sensitive than the rhesus monkey and beagle dog (Davis, 1970). AEGL-1 values are not recommended.