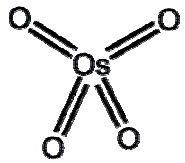
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

OSMIUM TETROXIDE (CAS Reg. No. 20816-12-0)



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

Osmium tetroxide is a colorless to pale yellow solid used as a fixative and stain in cell/tissue procedures such as electronmicroscopy. It is an oxidizing agent and is formed by the heating of finely divided osmium metal in the air. Upon inhalation, osmium tetroxide is assumedly reduced to osmium metal based upon the dark discoloration of tissue upon contact with it.

No quantitative exposure data are available regarding lethal effects of osmium tetroxide in humans. Nonlethal exposure is characterized by extreme irritation of the eyes and respiratory tract similar to that caused by bromine or chlorine. The irritation effects of osmium tetroxide reportedly may persist for up to 12 hours but appear to be reversible upon removal from exposure.

Animal toxicity data for osmium tetroxide are limited to lethality values. Although the values are non-verifiable or come from experiments for which the exposure concentrations are poorly assessed, the available data suggest little species variability.

Data consistent with AEGL-1 tier effects are not available and, therefore, AEGL-1 values for osmium toxicity are not recommended.

Data for developing AEGL-2 values are limited. Animal data specific to AEGL-2 tier effects were limited to the findings of ocular and respiratory tract irritation in rats exposed 2 or 20 ppm for 8 hours (Shell Development Co., 1955). Those exposed to 2 ppm recovered within 10 days post exposure. For those exposed to 20 ppm, most overt signs of toxicity resolved at 10 days post exposure but necropsy findings revealed pulmonary damage (emphysema, bronchopneumatic consolidation) persisting at 10 days post exposure

The most relevant exposure-response data for AEGL-2 development are the occupational exposure data reported by McLaughlin et al. (1946). Exposure concentrations ranged from 133-640 :g osmium/m^3 (equivalent to 177-853 :g osmium tetroxide/m^3 [0.02-0.08 ppm]) based upon sample (2-hr samples at 75 L/hr) analysis with a Spekker absorptiometer. Exposure durations were not specified but were assumed to be about 6 hours/day due to a statement indicating that three 2-hour samples were taken during the reaction and distillation phases of osmiridium refining. Although the report suggested a total exposure time of 6 hours, monitoring intervals were 2 hours. Because it was likely that osmium tetroxide-mediated ocular irritation would occur within the first 2-hour monitoring interval, a 2-hour exposure to 0.02 ppm osmium tetroxide (the lower limit of this concentration range producing reversible ocular irritation) was considered an appropriate point-of-departure (POD) for AEGL-2 derivation.

Because human occupational exposure data were used, the interspecies uncertainty factor was 1. Although most individuals would likely respond similarly to the direct-contact action of osmium tetroxide, those with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability was considered appropriate.

Reliable quantitative data on the lethality of inhaled osmium tetroxide in animals are limited to the studies conducted for Shell Development Company (1955). In this study, an 8-hour exposure to 40 ppm killed 5 of 5 rats while an 8-hour exposure to 20 ppm caused no lethality. A 4-hour exposure of rats to 40 ppm killed 3 of 5 rats. All ten mice exposed for 8 hours to 20 ppm survived, while exposure to 40 ppm for 4 hours killed 9 of 10 mice. The study reported an estimated 8-hr LC_{50} of 28.2 ppm for both species. The 20 ppm (a no-effect level for lethality in two species) exposure for 8 hours was selected as the POD for AEGL-3 development.

Lethality data in rats and mice are similar. Osmium tetroxide is a direct-contact irritant and, therefore, its effects are probably similar across species although dosimetry may vary. Therefore, a factor of 3 is considered sufficient to account for species variability. Although most individuals would likely respond similarly to the direct-contact action of osmium tetroxide, those with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability is considered appropriate.

The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, *n*, for the relationship $C^n \times t = k$ is not possible. Therefore, temporal scaling was performed using n = 3, when extrapolating to shorter time points and n = 1 when extrapolating to longer time points for AEGL values (NRC 2001).

The AEGL values for osmium tetroxide are summarized in the following table.

S 1. AEGL Values for osmium tetroxide (expressed as ppm and [mg/m3])

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data.
AEGL-2 (Disabling)	0.015 [0.16]	0.011 [0.11]	0.0084 [0.087]	0.0033 [0.034]	0.0017 [0.018]	Lower limit of occupational exposure (0.02 ppm for 2 hrs) producing reversible ocular irritation and headache (McLaughlin et al., 1946); UF =3; C^nxt=k, where n = 1 or 3
AEGL-3 (Lethality)	5.0 [52]	5.0 [52]	4.0 [42]	2.5 [26]	2.0 [21]	No-effect level for lethality (20 ppm, 8 hrs) in rats and mice. (Shell Development Co., 1955); UF =3 x 3; C^nxt=k, where n=3.

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.

References

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.

McLaughlin, A.I.G., Milton, R., Perry, K.A. 1946. Toxic manifestations of osmium tetroxide. Br. J. Ind. Med. 3: 183-186.

Shell Development Company. 1955. The acute toxicity of osmium tetroxide and an organic osmium complex. Shell Development Co., Emeryville, CA 29 August, 1955, pp. 1-11.

1. INTRODUCTION

Osmium tetroxide is a colorless to pale yellow solid used as a fixative and stain in cell/tissue procedures such as electronmicroscopy. It is an oxidizing agent especially with respect to converting olefins to glycols. Osmium tetroxide is formed by heating of finely divided osmium metal in the air.

TABLE 1. Chemical and Physical Data for agent osmium tetroxide

Parameter	Value	Reference
Synonyms	osmic acid	Budavari et al., 1989
Chemical formula	OsO_4	Budavari et al., 1989
Molecular weight	254.2	Budavari et al., 1989
CAS Registry No.	20816-12-0	Budavari et al., 1989
Physical state	crystalline solid	Budavari et al., 1989
Solubility in water	7.24g/100g water @ 25°C	Budavari et al., 1989
Vapor pressure	11 mm@22°C	Budavari et al., 1989
Relative vapor density		
Specific gravity	4.91@22°C	ACGIH, 1991
Melting point/boiling point	39.5-41°C/130°C	ACGIH, 1991
Conversion factors in air	1 ppm = 10.38 mg/m^3 1 mg/m^3 = 0.096 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

The only information regarding human fatalities from inhalation exposure to osmium tetroxide is that related by McLaughlin et al. (1946) regarding an individual exposed to osmium tetroxide vapors (concentration unknown) that resulted in severe bronchitis, bronchopneumonia and death.

2.2. Nonlethal Toxicity

Osmium tetroxide has a powerful and disagreeable chlorine-like odor; hence the elemental name which is based upon the Latin “osme” (odor). An odor threshold of 0.0019 ppm has been reported (Amoore and Hautala 1983).

Flury and Zernick (1931) reported that 6-hour exposure of humans to 0.001 mg osmium/m^3 (0.0001 ppm) was without effect.

Osmium tetroxide is reportedly very irritating to the eyes like bromine or chlorine, and has a sudden vigorous irritant effect on the mucosal surfaces of the nose, pharynx, and bronchi (Hunter, 1953). Histologists working with osmium tetroxide have reported headaches when in the presence of osmium tetroxide. Based on the analysis of seven case reports, McLaughlin et al. (1946) characterized the signs and symptoms of workers exposed to osmium tetroxide in the refining of osmiridium. Exposure concentrations ranged from 133-640 :g osmium/m^3

(equivalent to 177-853 :g osmium tetroxide/m^3 [0.02-0.08 ppm]) based upon sample (2-hr samples at 75 L/hr) analysis with a Spekker absorptiometer. Exposure durations were not specified but were assumed to be up to 6 hours/day due to a statement indicating that three 2-hour samples were taken during the reaction and distillation phases of osmiridium refining. The effects of these occupational exposures included intense and sudden smarting of the eyes associated with lacrimation and occasionally orbital headache, occasional gritty feeling in the eyes, conjunctival injection, and a halo effect around bright objects. The irritation effects of osmium tetroxide may persist for up to 12 hours (McLaughlin et al., 1946). Most of the aforementioned symptoms subsided within 24 hours. Clinical data (blood pressure, hematology indices, urinalysis) were not indicative of systemic involvement.

2.3. Developmental/Reproductive Effects

No human developmental/reproductive toxicity data are available regarding inhalation exposure to osmium tetroxide.

2.4. Genotoxicity

No human genotoxicity data were available for osmium tetroxide.

2.5. Carcinogenicity

No data were found in the available literature regarding the carcinogenic potential of osmium tetroxide.

2.6. Summary

No quantitative exposure data are available regarding lethal effects of osmium tetroxide in humans. Nonlethal exposure is characterized by extreme irritation of the eyes and respiratory tract like that caused by bromine or chlorine. Ocular effects include sudden smarting of the eyes associated with lacrimation and occasionally orbital headache, occasional gritty feeling in the eyes, conjunctival injection, and a halo effect around bright objects. The irritation effects of osmium tetroxide reportedly may persist for up to 12 hours. The only quantitative information available is a report of occupational exposure to osmium tetroxide (133-640 :g/m^3 as osmium; equivalent to 177-853 :g osmium tetroxide/m^3) resulting in the aforementioned effects.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

A lethality study in rats was conducted for the Shell Development Co. (1955). In this study, groups of 5 male Long-Evans rats were exposed to osmium tetroxide (2, 20 or 40 ppm) for four or eight hours (Table 2). The osmium tetroxide was metered and volatilized into the effluent air (5-6 L/min.) of a 19L glass chamber. Actual concentrations were not measured. The animals were observed for 10 days after the exposure. Rats exposed to 2 ppm showed signs of very slight irritation of the eyes and respiratory tract within several minutes. These signs of irritation occurred intermittently through the 8-hour exposure period. Although the fur of the

rats was discolored due to the osmium tetroxide, no corneal lesions were detected and all rats appeared normal throughout the observation period. Rats exposed to 20 ppm for 8 hours exhibited moderate ocular and respiratory tract irritation as well as corneal opacities. At the end of the 10-day observation period, no corneal opacities were observed although some rats still exhibited slight dyspnea. Necropsy findings at 10 days revealed emphysematous lungs in 3 of 5 rats and one rat exhibited scattered areas of bronchopneumatic consolidation. Exposure to 40 ppm caused severe irritation and respiratory distress; profuse lacrimation, salivation, gasping, and moderate dyspnea were evident within 15 minutes. Severely eroded and opaque corneas were evident at the end of the 4-hour or 8-hour exposures. Gaseous distention of the abdomen and pronounced respiratory difficulty were evident the day after exposure. Rats that died did so at 1 to 3 days post exposure. Necropsy indicated respiratory tract damage (erosion of the upper respiratory tract, severe mucus accumulation, pulmonary hemorrhage, and emphysema). In rats surviving through the 10-day observation period, corneal opacity resolved but necropsy findings revealed notable pulmonary damage (emphysema and bronchopneumatic consolidation). The investigators estimated the 8-hour LC_{50} to be 28.2 ppm. A $BMCL_{05}$of 16 ppm and a BMC_{01} of 27 ppm were calculated from these data (U.S. EPA, 2007).

TABLE 2. Lethality of osmium tetroxide in male rats

Concentration (ppm)	Exposure time (hrs)	Mortality ratio[a]
2	8	0/5
20	8	0/5
40	8	5/5
40	4	3/5

[a]Deaths occurred at 1-3 days post exposure; 10-day observation period
Shell Chemical Co. (1955)

A 4-hr LC_{50} of 40 ppm (~400 mg/m^3) was also reported for rats (ACGIH, 1991 citing a 1961 report from Shell Chemical Co., 1961). No further details are available. This value is not verifiable and may be estimated based upon the 4-hour response data (3 of 5 lethality ratio) noted for the above study.

3.1.2. Mice

Shell Development Co. (1955) also examined the lethality in mice following 4 or 8-hour inhalation exposure to osmium tetroxide. In these experiments (protocol similar to that described for rats in Section 3.1.1.), groups of 10 male Webster mice were exposed to 20 ppm osmium tetroxide for 8 hours or 40 ppm for 4 hours (Table 3). Mice exposed to 20 ppm for 8 hours showed moderate irritation of the eyes and respiratory tract, corneal opacities, and breathing difficulty. Nine of ten mice exposed to 40 ppm for 4 hours died. Necropsy revealed pulmonary damage as the cause of death. The 4-hour LC_{50} was estimated as 28.2 ppm.

TABLE 3. Lethality of osmium tetroxide in male mice

Concentration (ppm)	Exposure time (hrs)	Mortality ratio[a]
20	8	0/10
40	4	9/10

[a]Deaths occurred at 3-6 days post exposure; 10-day observation period
Shell Chemical Co. (1955)

A 4-hr LC_{50} of 40 ppm (~400 mg/m^3) was reported for mice as it was for rats (ACGIH, 1991 citing a 1961 report from Shell Chemical Co., 1961). No further details are available.

3.1.3. Rabbits

Brunot (1933) reported on experiments in which groups of four white rabbits were exposed to osmium tetroxide for 30 minutes. The rabbits were exposed in air-tight glass boxes of 190-L volume. An ampoule of osmic acid was opened and its contents (250 mg, 500 mg, or 1 g) were placed on a hot plate. A fan was operated to circulate the vapor and the hot plate turned off when vaporization was complete. Peak concentration was achieved within 1-3 minutes, with concentration notably declining thereafter. Sampling of the test atmosphere at the beginning and end of the 30-minute period both with and without animals revealed poor accountability of the osmium tetroxide; 40% with no rabbit in the chamber and only 10% with the rabbit. The investigator assumed that the difference (30%) represented the effective dose including amounts inhaled and deposited on the rabbit. The exposures caused a blackening of the muzzle and other exposed mucosal surfaces (osmium tetroxide blackens upon contact with oil and fat). The lowest amount tested (250 mg) would approximate an exposure concentration of ~1.3 mg/L (1300 mg/m^3 or 125 ppm). Based upon a 30% effective dose assumed by Brunot, the lowest exposure would approximate 390 mg/m^3 (37 ppm). The actual exposure was likely much higher at the beginning of the 30-minute exposure period. Nonetheless, all rabbits died with lethality occurring at about 4 days at the low exposure and within 30 hours for the highest exposure (one rabbit died at 14 hours post exposure). Necropsy affirmed the cause of death as severe damage in the upper respiratory tract and lungs.

3.1.4. Summary of Animal Lethality Data

Data on the lethality in animals following inhalation exposure to osmium tetroxide include an unverifiable unpublished report of 4-hour LC_{50} values of 40 ppm for both rats and mice; a report of 100% lethality in rabbits exposed for 30 minutes to an estimated concentration of 390 mg OsO_4/m^3 (37 ppm); and lethality response data for rats and mice exposed to 20 or 40 ppm osmium tetroxide for 4 or 8 hours (4-hour LC_{50} estimated at 28.2 ppm for both rats and mice). Rat lethality data for 8-hour exposures were used to derive a $BMCL_{05}$ of 16 ppm.

3.2. Nonlethal Toxicity

Data regarding nonlethal effects in animals exposed to osmium tetroxide are limited. Shell Development Co. (1955) reported that rats exposed to 2 ppm for 8 hours exhibited only minor ocular and respiratory irritation which resolved by 10 days post exposure, while rats exposed to 20 ppm for 8 hours exhibited moderate ocular and pulmonary irritation, the latter based upon gross pathology findings, persisted at 10 days post exposure. Mice exposed to 20 ppm for 8 hours also exhibited ocular and respiratory irritation which resolved at 10 days post exposure; unlike the rats, gross pathology findings were negative in the mice.

3.3. Developmental/Reproductive Effects

Data regarding the developmental/reproductive toxicity of osmium tetroxide in animals are not available.

3.4. Genotoxicity

There were no data with which to evaluate the genotoxicity of osmium tetroxide.

3.5. Carcinogenicity

There were no data with which to evaluate the carcinogenic potential of osmium tetroxide.

3.6. Summary

Animal toxicity data for osmium tetroxide are limited to lethality values. Although the values are non-verifiable or come from experiments for which the exposure concentrations are poorly assessed, the available values suggest little species variability.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Osmium tetroxide is assumedly reduced to osmium metal based upon the dark discoloration of tissue upon contact with it (McLaughlin et al., 1946).

4.2. Mechanism of Toxicity

The oxidizing potential of osmium tetroxide is likely the basis for its action on biological tissues. Lethality resulting from osmium tetroxide exposure is ultimately a function of tissue damage leading to pulmonary edema. No definitive mechanistic studies are available.

4.3. Structure-Activity Relationships

No data were available with which to asses structure-activity relationships.

4.4. Species Variability

Limited lethality data in rats, mice, and rabbits suggest little species variability. For both rats and mice, signs of toxicity were similar.

4.5. Concurrent Exposure Issues

Current exposure to any chemical affecting respiratory function would likely exacerbate the effects of osmium tetroxide.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The notable irritation reported by McLaughlin et al. (1946) from occupational exposures to osmium tetroxide were of a severity exceeding that described for AEGL-1 tier effects. The report of a 6-hour no-effect level of 0.001 mg Os/m^3 (0.0001 ppm) by Flury and Zernick (1931) lacks details.

5.2. Animal Data Relevant to AEGL-1

Animal data consistent with AEGL-1 tier effects are not available.

5.3. Derivation of AEGL-1 Values

Data appropriate for developing AEGL-1 are not available. Therefore, AEGL -1 values for osmium tetroxide are not recommended (Table 4).

TABLE 4. AEGL-1 Values for Osmium Tetroxide

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

McLaughlin et al. (1946) reported that occupational exposures to 133-640 **:**g osmium/m^3 (equivalent to 177-853 **:**g osmium tetroxide/m^3 [0.02-0.08 ppm]) produced intense and sudden smarting of the eyes, lacrimation, orbital headache, occasional gritty feeling in the eyes, conjunctival injection, and a halo effect around bright objects. Exposure durations were assumedly about 6 hours based upon atmosphere sample acquisition descriptions. These effects of osmium tetroxide were reportedly reversible but could persist for up to 12 hours.

6.2. Animal Data Relevant to AEGL-2

Animal data specific to AEGL-2 tier effects were limited to the findings of ocular and respiratory tract irritation in rats exposed 2 or 20 ppm for 8 hours. Those exposed to 2 ppm recovered within 10 days post exposure. For those exposed to 20 ppm, most overt signs of toxicity resolved at 10 days post exposure but necropsy findings revealed pulmonary damage (emphysema, bronchopneumatic consolidation) persisting at 10 days post exposure.

6.3. Derivation of AEGL-2 Values

The most relevant exposure-response data for AEGL-2 development are the occupational exposure assessments reported by McLaughlin et al. (1946). Although the report suggested a total exposure time of 6 hours, monitoring intervals were 2 hours. Because it was likely that osmium tetroxide-mediated ocular irritation would occur within the first 2-hour monitoring

interval, 2-hour exposure to 0.02 ppm osmium tetroxide was considered an appropriate point-of-departure (POD) for AEGL-2 derivation. This was the lower limit of the exposure concentration range producing reversible ocular irritation, headache, and visual disturbances in osmium refinery workers.

Because osmium tetroxide is a direct-contact irritant, the mode of action is probably very similar among individuals. Although most would likely respond similarly to the direct-contact action, those with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability was considered appropriate. Because human data were used, the interspecies uncertainty factor was 1.

The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship with any validity and empirical derivation of the exponent, *n*, for the relationship $C^n \times t = k$ was not determined. Therefore, temporal scaling was performed using n = 3 when extrapolating to the 10-minute, 30-minute, 1-hour and 4-hour AEGL-3 durations, and with and an n of 1 for extrapolating to the 8-hour AEGL-3 duration (NRC, 2001). The 30-minute value was adopted as the 10-minute value due to uncertainties in extrapolating from the 6-hour experimental exposure duration to a 10-minute duration.

The AEGL-2 values for osmium tetroxide are shown in Table 5 and their derivation summarized in Appendix A.

TABLE 5. AEGL-2 Values for Osmium Tetroxide

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	0.015 ppm 0.16 mg/m^3	0.011 ppm 0.11 mg/m^3	0.0084 ppm 0.087 mg/m^3	0.0033 ppm 0.034 mg/m^3	0.0017 ppm 0.018 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

The only information regarding human lethality resulting from exposure to osmium tetroxide is that related by McLaughlin et al. 1946) regarding the death of an individual exposed to unknown levels of osmium tetroxide vapor.

7.2. Animal Data Relevant to AEGL-3

Lethality data for animals exposed to osmium tetroxide are limited. ACGIH (1991) referenced non-verifiable 4-hour LC_{50} values of 40 ppm each for rats and mice (Shell Chemical Co., 1961). Brunot (1933) reported100% lethality in rabbits for a 30-minute exposure to an estimated concentration of 390 mg OsO_4/m^3 (37 ppm). A report by Shell Development Co. (1955) provided lethality data for rats exposed to 2, 20, or 40 ppm for 8 hours or 40 ppm for 4 hours, and for mice exposed to 20 ppm for 8 hours or 40 ppm for 4 hours. Although none of the studies provided definitive information on the lethality threshold, the data suggest a steep

exposure-response relationship. The 8-hour exposure of mice and rats to 20 ppm did not result in any deaths.

7.3. Derivation of AEGL-3 Values

The rodent data from experiments conducted for Shell Development Co. (1955) were used to develop AEGL-3 values for osmium tetroxide. This report cited an estimated 8-hour LC_{50} of 28.2 ppm for both rats and mice. Because the rat dataset from the 1955 Shell report represents the best available exposure-response dataset, it was selected as the key study for AEGL-3 derivation. Although a benchmark dose analysis (U.S. EPA, 2007) provided a $BMCL_{05}$ of 16 ppm (Appendix D) and a BMC_{01} of 27 ppm, the 20-ppm exposure for 8 hours (no effect level for lethality) was selected as the POD for AEGL-3 derivation for osmium tetroxide.

Lethality data are available for rats, mice, and rabbits. For both rats and mice, the 4-hour LC_{50} was 40 ppm and 8-hour LC_{50} was 28.2 ppm and 20 ppm was a no-effect level for lethality. Being a direct-contact irritant, the mode of action is probably very similar across species although dosimetry may vary. Therefore, a factor of 3 is considered sufficient to account for species variability. Although most individuals would likely respond similarly to the direct-contact action of osmium tetroxide, those with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability is considered appropriate.

The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, *n*, for the relationship $C^n \times t = k$ is not possible. Therefore, temporal scaling was performed using n = 3, for extrapolating to the shorter AEGL-specific time points (NRC 2001). The 30-minute AEGL-3 value was adopted as the 10-minute value due to uncertainties in extrapolating from the 8-hour experimental exposure duration to 10 minutes.

The resulting AEGL-3 values are shown in Table 6 and their derivation summarized in Appendix A.

TABLE 6. AEGL-3 Values for Osmium Tetroxide

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	5.0 ppm 52 mg/m^3	5.0 ppm 52 mg/m^3	4.0 ppm 42 mg/m^3	2.5 ppm 26 mg/m^3	2.0 ppm 21 mg/m^3

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for osmium tetroxide are summarized in Table 7. Definitive data with which to derive AEGL-1 values were unavailable. The AEGL-2 values were derived based upon occupational exposure data for humans showing that exposures to 133-640 :g osmium/m^3 (equivalent to 177-853 :g osmium tetroxide/m^3 [0.02-0.08 ppm]) produced intense and sudden smarting of the eyes, lacrimation, orbital headache, occasional gritty feeling in the eyes,

conjunctival injection, and a halo effect around bright objects. AEGL-3 values were derived using a no-efefct level for lethality in rats and mice (Shell Development Co., 1955. As shown in the category plot (Appendix D), the AEGL values appear to be consistent with the limited data.

TABLE 7. AEGL Values for Osmium Tetroxide

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.015 ppm 0.16 mg/m^3	0.011 ppm 0.11 mg/m^3	0.0084 ppm 0.087 mg/m^3	0.0033 ppm 0.034 mg/m^3	0.0017 ppm 0.018 mg/m^3
AEGL-3 (Lethality)	5.0 ppm 52 mg/m^3	5.0 ppm 52 mg/m^3	4.0 ppm 42 mg/m^3	2.5 ppm 26 mg/m^3	2.0 ppm 21 mg/m^3

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.

8.2. Comparisons with Other Standards and Guidelines

A summary of currently available standards and guidelines is shown in Table 8.

TABLE 8. Extant Standards and Guidelines for Osmium Tetroxide

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.015 ppm	0.011 ppm	0.0084ppm	0.0033 ppm	0.0017 ppm
AEGL-3	5.0 ppm	5.0 ppm	4.0 ppm	2.5 ppm	2.0 ppm
ERPG-1 (AIHA)[a]					
ERPG-2 (AIHA)					
ERPG-3 (AIHA)					
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					0.002 mg/m^3 (0.0002 ppm)
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]		1 mg/m^3 (.096 ppm)			
REL-TWA (NIOSH)[f]					
REL-STEL (NIOSH)[g]					
TLV-TWA (ACGIH)[h]					0.0002 ppm (0.0016 mg/m^3)
TLV-STEL (ACGIH)[i]	0.0006 ppm (0.0047 mg/m^3) (15 min)				
MAC[j] (the Netherlands)					0.0002 ppm (0.002 mg/m^3)
MAK (Germany)[k]					0.0002 ppm (0.0021 mg/m^3)
MAK Spitzenbegrenzung (Germany)[l]					
Einsaztoleranzwert (Germany)[m]					

NR: Not recommended. Numeric values for AEGL-1 are not recommended because of the lack of available data. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association)** (AIHA, 2006)
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 protective 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.

[b] **EEGL (Emergency Exposure Guidance Levels, National Research Council)** (NRC, 1985)
is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c] **OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA, 1993) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d] **OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** (OSHA, 1993) is defined analogous to the ACGIH-TLV-STEL.

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

[f] **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.

[g] **NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH, 2005) is defined analogous to the ACGIH-TLV-STEL.

[h] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH, 2006) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. Expressed as osmium.

[i] **ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH, 2006) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range. Expressed as osmium.

[j] **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.

[k] **MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany)** (DFG, 2006) is defined analogous to the ACGIH-TLV-TWA.

[l] **MAK Spitzenbegrenzung (Kategorie II,2) [Peak Limit Category II,2]** (DFG, 2006) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes, with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK. Cat. III indicates possible significant contribution to cancer risk.

[m] **Einsatztoleranzwert [Action Tolerance Levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention])** constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 hours without any health risks.

8.3. Data Adequacy and Research Needs

Toxicity data, especially for exposure-response relationships, on osmium tetroxide are limited. Such data would allow for a more definitive assessment of the exposure concentration-time relationship. Additionally, data on nonlethal responses to inhaled osmium tetroxide are lacking.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Osmium Tetroxide

Data appropriate for developing AEGL-1 values are not available. Therefore, AEGL -1 values for osmium tetroxide are not recommended. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Derivation of AEGL-2 Values for Osmium Tetroxide

Key study: McLaughlin, A.I.G., Milton, R., Perry, K.A. 1946. Toxic manifestations of osmium tetroxide. Br. J. Ind. Med. 3: 183-186.

Critical effect: Smarting of the eyes, lacrimation, orbital headache, occasional gritty feeling in the eyes, conjunctival injection, and a halo effect around bright objects; effects were reversible. The lower limit (0.02 ppm osmium tetroxide) of the concentration range (0.02-0.08 ppm) which produced reversible ocular irritation, headache, visual disturbances in osmiridium refinery workers. Although exposure may have been as long as 6 hours, sampling was conducted at 2-hour intervals and reported effects may have been occurring at the initial sampling period. Because ocular effects from osmium tetroxide exposure would likely occur quickly, the 2-hour exposure to 0.02 ppm was considered an appropriate point-of-departure (POD) for AEGL-2 derivation.

Time scaling: The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, *n*, for the relationship $C^n \times t = k$ is not possible. Therefore, temporal scaling was performed using n = 3, when extrapolating to the shorter AEGL-specific time points and an n of 1 for extrapolating to the 8-hour AEGL duration (NRC 2001).

Uncertainty factors: Total uncertainty factor adjustment was 3
Interspecies: 1: Human data (occupational exposure data) were used.
Intraspecies: 3; the mode of action of osmium tetroxide appears to be via direct-contact irritation and its activity as an oxidizer; individuals with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability is considered appropriate.

Modifying factor: None applied

Calculation: $(0.02 \text{ ppm})^3 \times 2 \text{ hrs} = 0.000016 \text{ ppm}^3\text{-hrs}$
$(0.02 \text{ pm})^1 \times 2 \text{ hrs} = 0.04 \text{ ppm}$

10-minute AEGL-2 $C^3 \times 0.1667 \text{ hrs} = 0.000016 \text{ ppm}^3 \text{ - hrs}$
$C^3 = 0.000096 \text{ ppm}$
$C = 0.046 \text{ ppm}$
$C = 0.049 \text{ ppm}/3 = 0.015 \text{ ppm}$

30-minute AEGL-2 $C^3 \times 0.5$ hrs = 0.000016 ppm^3 - hrs
C^3 = 0.00004 ppm
C = 0.034 ppm
C = 0.034 ppm/3 = 0.011 ppm

1-hour AEGL-2 $C^3 \times 1$ hr = 0.0000016 ppm^3 - hrs
C^3 = 0.0000016 ppm
C = 0.025 ppm
C = 0.027ppm/3 = 0.0084 ppm

4-hour AEGL-2 $C^1 \times 4$ hrs = 0.04 ppm^1 - hrs
C = 0.010 ppm
C = 0.010 ppm/3 = 0.0033 ppm

8-hour AEGL-2 $C^1 \times 8$ hrs = 0.04 ppm^1 - hrs
C = 0.005 ppm
C = 0.005 ppm/3 = 0.0017ppm

Derivation of AEGL-3 Values for Osmium Tetroxide

Key study: Shell Development Company. 1955. The acute toxicity of osmium tetroxide and an organic osmium complex. Shell Development Co., Emeryville, CA 29 August, 1955, pp. 1-11.

Critical effect: An 8-hour exposure to 20 ppm was a no-effect level for lethality in rats and mice. This was not inconsistent with the estimated lethality threshold in rats ($BMCL_{05}$ of 16.0 ppm; BMC_{01} of 27 ppm) based upon 8-hour exposure of rats to 2, 20, or 40 ppm with a 10-day observation period.

Time scaling: The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, *n*, for the relationship $C^n \times t = k$ is not possible. Therefore, temporal scaling was performed using n = 3, when extrapolating to the shorter AEGL-specific time points (NRC 2001).

Uncertainty factors: Total uncertainty factor adjustment was 10
Interspecies: 3: LC_{50} values (4 and 8 hours) are identical for rats and mice; being a direct-contact irritant, the mode of action is probably very similar across species although dosimetry may vary. Therefore, a factor of 3 is considered sufficient to account for species variability.
Intraspecies: 3; the mode of action of osmium tetroxide appears to be via direct-contact irritation and its activity as an oxidizer; individuals with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability is considered appropriate.

Modifying Factor: None applied

Calculation: $(20.0 \text{ ppm})^3 \times 8 \text{ hrs} = 64{,}000 \text{ ppm}^3\text{-hrs}$

10-minute AEGL-3: 5.0 ppm; due to uncertainties in extrapolating from an 8-hour experimental exposure duration to 10 minutes, the 10-minute AEGL-3 is equivalent to the 30-minute AEGL-3 value (NRC, 2001).

30-minute AEGL-3:
$C^3 \times 0.5 \text{ hrs} = 64{,}000 \text{ ppm}^3 \text{ - hrs}$
$C^3 = 128{,}000 \text{ ppm}$
$C = 50.4 \text{ ppm}/10 = 5.0 \text{ ppm}$

1-hour AEGL-3

$C^3 \times 1 \text{ hrs} = 64{,}000 \text{ ppm}^3 \text{ - hrs}$
$C^3 = 64{,}000 \text{ ppm}$
$C = 40.0 \text{ ppm}/10 = 4.0 \text{ ppm}$

4-hour AEGL-3

$C^3 \times 4 \text{ hrs} = 64{,}000 \text{ ppm}^3 \text{ - hrs}$
$C^3 = 16{,}000 \text{ ppm}$
$C = 25.2 \text{ ppm}/10 = 2.5 \text{ ppm}$

8-hour AEGL-3

$C^3 \times 8 \text{ hrs} = 64{,}000 \text{ ppm}^3 \text{ - hrs}$
$C^3 = 8000 \text{ ppm}$
$C = 20.0 \text{ ppm}/10 = 2.0 \text{ ppm}$

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.

Data were unavailable with which to empirically determine the exposure concentration-exposure time relationship for osmium tetroxide. In the absence of an empirically derived exponent (n) for the equation $C^n \times t = k$, temporal scaling was performed using $n = 3$ when extrapolating to shorter exposure durations and $n = 1$ when extrapolating to longer exposure durations (NRC 2001).

APPENDIX C: Derivation Summary Tables

ACUTE EXPOSURE GUIDELINE LEVELS FOR OSMIUM TETROXIDE DERIVATION SUMMARY

AEGL-1 VALUES FOR OSMIUM TETROXIDE				
10 min	**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: Insufficient for developing AEGL-1 values				

1

AEGL-2 VALUES FOR OSMIUM TETROXIDE				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.015 ppm	**0.011 ppm**	**0.0084 ppm**	**0.0033 ppm**	**0.0017 ppm**
Reference: McLaughlin, A.I.G., Milton, R., Perry, K.A. 1946. Toxic manifestations of osmium tetroxide. Br. J. Ind. Med. 3: 183-186.				
Test Species/Strain/Sex/Number: humans; occupational exposure				
Exposure Route/Concentrations/Durations: inhalation exposure to 133-640 :g osmium/m^3 (equivalent to 177-853 :g osmium tetroxide/m^3 [0.02-0.08 ppm]); although a 6-hr total exposure duration may be assumed based upon sample analysis description; effects likely occurred within the first 2-hr monitoring interval.				
Effects: smarting of the eyes, lacrimation, orbital headache, occasional gritty feeling in the eyes, conjunctival injection, and a halo effect around bright objects; although persisting up to 12 hours, the effects were reversible				
Endpoint/Concentration/Rationale: lower limit (0.02 ppm) of occupational exposure concentration range (0.02-0.08 ppm) causing reversible ocular effects, visual disturbance, and headache was considered an appropriate POD for AEGL-2.				
Uncertainty Factors/Rationale: 3 Interspecies: 1; human occupational exposure data were used for the assessment Intraspecies: 3; the mode of action of osmium tetroxide appears to be via direct-contact irritation and its activity as an oxidizer; individuals with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability is considered appropriate.				
Modifying Factor: none applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Data were unavailable with which to empirically determine the exposure concentration-exposure time relationship for osmium tetroxide. In the absence of an empirically derived exponent (n) for the equation $C^n \times t = k$, temporal scaling was performed using n = 3 when extrapolating to shorter exposure durations and n = 1 when extrapolating to longer exposure durations (NRC 2001).				
Data Adequacy: Data are considered adequate for AEGL-2 derivation.				

AEGL-3 VALUES FOR OSMIUM TETROXIDE				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
5.0 ppm	**5.0 ppm**	**4.0 ppm**	**2.5 ppm**	**2.0 ppm**
Reference: Shell Development Company. 1955. The acute toxicity of osmium tetroxide and an organic osmium complex. Shell Development Co., Emeryville, CA 29 August, 1955, pp. 1-11.				
Test Species/Strain/Sex/Number: rat/Long-Evans/male/5 per group				
Exposure Route/Concentrations/Durations: inhalation/2, 20, or 40 ppm for 8 hrs				
Effects: mortality ratio of 0/5, 0/5, 5/5 at 2, 20, and 40 ppm, respectively				
Endpoint/Concentration/Rationale: exposure to 20 ppm for 8 hrs was a no-effect level for lethality in rats and mice (consistent with a $BMCL_{05}$ of 16 ppm and BMC_{01} of 27 ppm) was used as the POD for AEGL-3 derivation.				
Uncertainty Factors/Rationale: Total uncertainty factor adjustment was 10 Interspecies: 3; lethality data for rats and mice show similar response. Intraspecies: 3; the mode of action of osmium tetroxide appears to be via direct-contact irritation and its activity as an oxidizer; individuals with compromised respiratory function (e.g., asthmatics and those with other COPD disorders) are considered especially susceptible and, therefore, an uncertainty factor of 3 for intraspecies variability is considered appropriate.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Data were unavailable with which to empirically determine the exposure concentration-exposure time relationship for osmium tetroxide. In the absence of an empirically derived exponent (n) for the equation $C^n \times t = k$, temporal scaling was performed using n = 3 when extrapolating to shorter exposure durations (NRC 2001).				
Data Adequacy: Lethality data for rats and mice indicate little variability in the lethal response. The available data with corresponding uncertainty adjustment were considered adequate for AEGL-3 development.				

1

APPENDIX D: BENCHMARK CONCENTRATION CALULATION FOR OSMIUM TETROXIDE

```
 ================================================================
     Probit Model. (Version: 2.8;  Date: 02/20/2007)
     Input Data File: C:\BMDS\OSO4RATS.(d)
     Gnuplot Plotting File:  C:\BMDS\OSO4RATS.plt
                                                Tue May 29 11:10:06 2007
 ================================================================
```

BMDS MODEL RUN OSMIUM TETROXIDE

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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 = 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 = -2.16142
slope = 0.691439

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

intercept
intercept 1

Parameter Estimates
95.0% Wald Confidence Interval

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-60.2803	3019.01	5977.44	-5856.88
slope	18	NA		
~~~~~~

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)	# Param's	Deviance	Test df.	P-value
Full model	0	3			
Fitted model	-2.86042e-009	1	5.72084e-009	2	1
Reduced model	-9.54771	1	19.0954	2	<0.001
AIC	2				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
2.0000	0.0000	0.000	0	5	0.000
20.0000	0.0000	0.000	0	5	-0.000
40.0000	1.0000	5.000	5	5	0.000

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

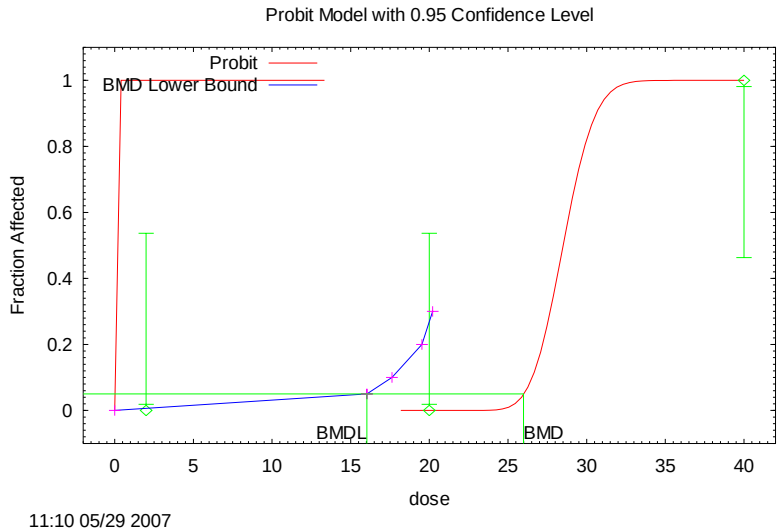
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

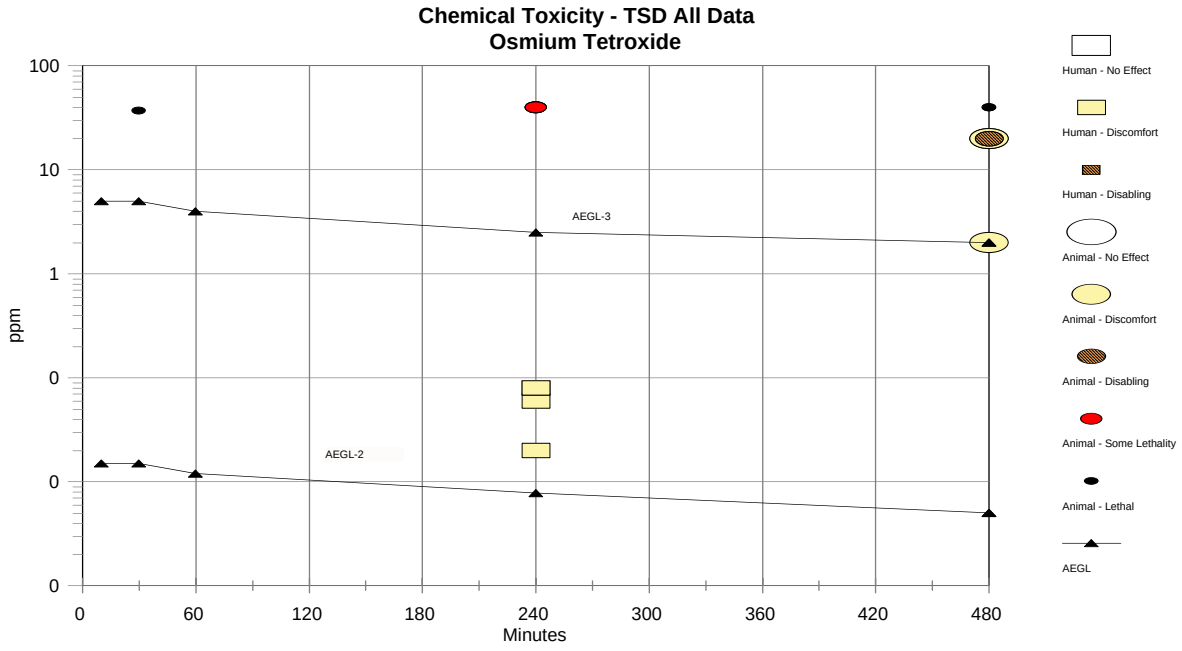
BMC = 25.9852

BMCL = 16.0284



11:10 05/29 2007

APPENDIX E: CATEGORY PLOT FOR OSMIUM TETROXIDE


Chemical Toxicity - TSD All Data
Osmium Tetroxide
100
10
1
0
0
0
ppm
AEGL-3
AEGL-2
0
60
120
180
240
300
360
420
480
Minutes
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL