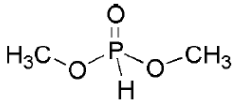
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
DIMETHYL PHOSPHITE
CAS Reg. No. 868-85-9



INTERIM

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FOR
DIMETHYL PHOSPHITE
CAS Reg. No. 868-85-9

PROPOSED

PREFACE

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

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

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m3]) 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/m3) 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/m3) 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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EXECUTIVE SUMMARY

Dimethyl phosphite (DMP) is a colorless liquid with a mild odor; it is a degradation product of trimethyl phosphite (TMP). It is used as an intermediate in the manufacture of insecticides and herbicides. It is also used as a fireproofing agent in the production of textiles. Dimethyl phosphite is manufactured in a closed system by reacting phosphorus trichloride with methanol or sodium methoxide, and is listed as a High Production Volume (HPV) chemical.

Data are insufficient for derivation of AEGL-1 values; therefore AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

Clinical signs (labored breathing and ptosis) in mice exposed to 1575 ppm DMP for 6 hours (Hazleton, 1962) were used as the point-of-departure for AEGL-2 values. Inter- and intraspecies uncertainty factors of 3 each (total 10) were applied because DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. The interspecies uncertainty factor of 3 is also considered sufficient because no clinical signs were noted in rats or guinea pigs exposed to 1575 ppm for 6 hours. A modifying factor of 3 was also applied because of the sparse database and because the point-of-departure is a nominal concentration. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling may be performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The 30-minute AEGL-2 value was adopted as the 10-min value because of the added uncertainty of extrapolating from the 6-hr point-of-departure.

The highest concentration causing no mortality in rats (843 ppm for 6 hr) was used as the point-of-departure for AEGL-3 (Biodymanics, 1980a). Excessive lacrimation, partially closed eyes, red nasal discharge, red-brown material around the nares, labored breathing, and unresponsiveness to sound stimuli were noted in rats exposed to 843 ppm DMP 6 hr/day for 5 days. Death was noted at the next concentration tested (934 ppm) essentially after one exposure because one rat was killed *in extremis* after day 1 of the study. Inter- and intrapsecies uncertainty factors of 3 each (total 10) were applied because DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling may be performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The 30-minute AEGL-3 value will also be adopted as the 10-min value because of the added uncertainty of extrapolating from the 6-hr point-of-departure.

The calculated values are listed in Table 1 below.

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Table 1. Summary of AEGL Values for Dimethyl Phosphite

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL–2 (Disabling)	120 ppm (540 mg/m^3)	120 ppm (540 mg/m^3)	95 ppm (430 mg/m^3)	60 ppm (270 mg/m^3)	39 ppm (180 mg/m^3)	Labored breathing and ptosis in mice (Hazleton, 1962)
AEGL–3 (Lethal)	190 ppm (850 mg/m^3)	190 ppm (850 mg/m^3)	150 ppm (670 mg/m^3)	96 ppm (430 mg/m^3)	63 ppm (240 mg/m^3)	NOEL for mortality in rats (Biodynamics, 1980a)

2 NR: Not Recommended due to insufficient data. Absence of AEGL-1 values does not imply that concentrations
3 below AEGL-2 are without effect.
4
5
6

1. INTRODUCTION

Dimethyl phosphite (DMP) is a colorless liquid with a mild odor; it is a degradation product of trimethyl phosphite (TMP). It is used as an intermediate in the manufacture of insecticides and herbicides. It is also used as a fireproofing agent in the production of textiles. Dimethyl phosphite is manufactured in a closed system by reacting phosphorus trichloride with methanol or sodium methoxide, and is listed as a High Production Volume (HPV) chemical. HPV chemicals were produced or imported into the U.S. in quantities of > 1 million pounds in 1990 and/or 1994; estimated US manufacturing capacity was 1000-5000 tons/year in 2002 (UNEP, 2004). Chemical and physical properties are presented in Table 2.

Table 2. Chemical and physical properties for dimethyl phosphite

Parameter	Value	References
Synonyms	Dimethyl phosphonate; dimethylhydrogen phosphite; DMPH; DMP; Phosphonic acid, dimethyl ester; Dimethyl phosphonus acid; Phosphorus acid dimethyl ester; Hydrogen dimethyl phosphite	UNEP, 2004
Chemical formula	$C_2H_7O_3P$	HSDB, 2009
Molecular weight	110.05	HSDB, 2009
CAS Reg. No.	868-85-9	HSDB, 2009
Physical state	Colorless liquid	HSDB, 2009
Solubility in water	Soluble; >10 g/100 ml at 25ºC; Decomposes to monomethyl phosphite and methanol	UNEP, 2004
Vapor pressure	1.5 mm Hg at 20ºC	HSDB, 2009
Vapor density (air =1)	7.9	HSDB 2009
Specific gravity	1.2002 g/cm^3 at 20ºC	HSDB, 2009
Melting point	-60ºC	HSDB, 2009
Boiling point	170.5ºC	UNEP, 2004
Flash point	70ºC	HSDB, 2009
Explosive limits	Lower: 5.8%; Upper: 38.1%	UNEP, 2004
Conversion factors	1 ppm = 4.49 mg/m^3 1 mg/m^3 = 0.22 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No information concerning acute lethality was located.

2.2. Nonlethal Toxicity

Albright and Wilson, Inc. (1985) reported the results of an air and health monitoring study on DMP conducted in a manufacturing facility in Charleston, South Carolina. The maximum partial shift (approximately 3- to 4-hours) employee exposure to DMP was 1.9 ppm and the average exposure was 0.22 ppm. The maximum 8-hour TWA concentration was 1.1 ppm and the average exposure was 0.16 ppm. A single maximum area sample of 3 ppm DMP was reported in

the immediate production area. The report did not describe the duration of the monitoring, but noted that exposure information had been obtained on an "ongoing basis." It was also stated that standard practice was to obtain separate employee samples in the morning and afternoon from which an eight hour time weighted average was determined. Albright and Wilson, Inc. (1985) reported that medical surveillance of the workers did not indicate any significant adverse health effects related to historical exposures to DMP at this facility. The report states that respiratory protection is provided to employees during operations with highest exposure potential, to reduce actual exposure.

2.3. Developmental/Reproductive Toxicity

No human developmental/reproductive data were located.

2.4. Genotoxicity

No human genotoxicity data were located.

2.5. Carcinogenicity

No human carcinogenicity data were located.

2.6. Summary

Human data are limited to one workplace monitoring report where an average exposure of 0.22 ppm did not show health effects. No other human data were located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

A 1-hour rat LC_{50} of >5112 ppm was reported (Albright and Wilson, Inc., 1985). No other details were reported.

3.2. Non-lethal Toxicity

Groups of ten male Swiss albino mice, ten male Wistar rats, and ten male English short-hair guinea pigs were exposed to a "mean theoretical concentration" of 1575 ppm DMP for 6 hours (Hazleton, 1962). Concentrations were calculated from air flow and net loss of test material. Exposures were conducted in a 500 liter stainless steel chamber with one or two fritted-disc glass bubblers at the inlet containing the DMP. A glass trap was placed between the vapor generator and chamber to collect liquid. Air flow was 18 L/minute with one bubbler and 35 L/min with two bubblers. Animals were observed continually during exposure for signs of toxicity and mortality. At the end of the seven day observation period, animals were sacrificed and necropsies were performed. There were no deaths during exposure or during the 7-day observation period. There were no clinical signs in rats or guinea pigs. Two mice had labored breathing after 1 hr- 50 min of exposure, and all mice had ptosis after 5 hours exposure. No other clinical signs were noted. Necropsies showed only lung congestion with pulmonary hemorrhage in rats and small hemorrhagic areas on the lungs of two guinea pigs.

3.3. Repeated-Exposure Studies

In a range-finding study, groups of five male and five female Sprague-Dawley rats were repeatedly exposed to 0, 431, 843, or 934 ppm DMP for six hours per day for five consecutive days (Biodymanics, 1980a). Animals were exposed in one cubic meter stainless steel and glass dynamic chambers, with an airflow of 83 L/min. The test atmosphere was generated by passing a nitrogen stream through a bubbler containing the DMP, varying the amount of nitrogen to volatilize the appropriate amount of test material. Test atmospheres were sampled four times per exposure (at 1, 2.5, 4, and 5.5 hours) for infrared analysis. Mortality was observed only in the 934 ppm group. None of the female rats in the 934 ppm group survived beyond day three of exposure (1 was killed *in extremis* on day one, 3 died on day two, and 1 died on day three). Two males died and one was killed *in extremis* on day three, while one died and another was killed *in extremi*s on day 4 prior to exposure. Clinical signs were observed in all DMP-exposed animals at all exposure levels. Excessive lacrimation, partially closed eyes, red nasal discharge, labored breathing, and unresponsiveness to sound stimuli were recorded during exposure in all treated groups. The time to observation of effects decreased with exposure concentration; effects were noted on day 1 for the 934 ppm group, day 2 for the 843 ppm group, and day 4 for the 431 ppm group. On day 3, swelling of the limbs with red discoloration, fresh or dried ocular or nasal discharge, and dull, dry and/or cloudy corneal surfaces were observed in animals exposed to 431 and 843 ppm, with the incidence of these effects increasing until termination. The authors suggested that the degradation of DMP to phosphorus acid was likely responsible for the irritant effects observed. Body weight loss or decreased body weight gain were noted in both sexes in the 843 and 934 ppm groups. Increased absolute and relative lung weights were noted in males from all treatment groups. Lung discoloration was noted in both sexes at all treatment levels, and congestive changes were noted only in high-concentration animals.

Groups of twenty male and twenty female Sprague-Dawley rats were exposed to 0, 12, 35, 119, or 198 ppm DMP 6 h/d, 5 d/wk, for up to 4 wks, followed by a 4-week follow-up period (Biodymanics, 1980b). Exposure methods were similar to those described above (Biodymanics, 1980a). Up to five rats/sex/concentration were sacrificed 2, 4, and 6 weeks after the start of exposure, with the remaining survivors being sacrificed after 8 weeks. Lethality occurred at concentrations of 119 and 198 ppm. In the 198-ppm group, 13 males and 14 females died or were killed *in extremis* before day 27; in the 119-ppm group, one male died on day 23 and one female died on day 14. Neurological impairment, which was usually reversed by the following morning, was noted in the rats exposed to 119 and 198 ppm. Physical signs of irritation of the skin, mucous membranes, eyes, eyelids, and conjunctiva, and inflammation of the cornea (keratitis) were noted at concentrations of 35 ppm and above during clinical observation periods, and signs of respiratory irritation (rales) occurred at 119 ppm and above. Body weight reduction (8%) was reported for both male and female rats at concentrations of 119 and 198 ppm for much of the study period. Hemoglobin and hematocrit were decreased in males at 119 and 198 ppm and in females at 198 ppm. Increased SGPT, alkaline phosphatase, and urea levels were noted in males and females at 198 ppm, and increased SGPT (males) and decreased glucose concentration (males and females) were also noted at 119 ppm. Irritation of superficial ocular structures was observed in all treatment groups, and was associated with inflammatory changes of intraocular structures. Lenticular opacities were observed at concentrations of 35 ppm and above, and progressed to cataracts in the 119 and 198 ppm groups during the post-exposure period.

Increased absolute and relative kidney weights were observed in all treatment groups. Red discoloration of the lungs and nasal turbinates and involution of the thymus were seen in decedents at 198 ppm. An increased incidence of hypospermatogenesis (decreased epididymal sperm content) was also reported in the two highest concentration groups.

3.4. Developmental/Reproductive Toxicity

No inhalation studies designed specifically to look at reproductive or developmental toxicity in animals were located. However, hypospermatogenesis was observed in 3/20 and 4/19 rats exposed via inhalation to 119 and 198 ppm DMP, respectively, for 6 hr/d, 5 d/wk for 4 weeks (Biodymanics, 1980b).

3.5. Genotoxicity

Dimethyl phosphite was not mutagenetic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or abcence of exogenous metabolic activation (NTP, 1985). DMP was positive with metabolic activation and negative without metabolic activation in the L5178Y tk+/- mouse lymphoma cell forward mutation assay (McGregor et al., 1988). DMP caused chromosomal aberrations and sister chromatid exchanges in the Chinese hamster ovary assay with and without metabolic activation (Tennant et al., 1987). DMP was positive in a mouse bone marrow micronucleus test (Shelby et al., 1993). DMP did not induce sex linked recessive lethals in *Drosophila melanogaster* (NTP, 1995; Woodruff, 1985).

3.6. Chronic Toxicity/Carcinogenicity

No inhalation data were located. Dimethyl phosphite was administered for 103 weeks by gavage in corn oil to groups of 50 male F344/N rats and groups of 50 male and 50 female B6C3F1 mice at doses of 0, 100, or 200 mg/kg (NTP, 1985; Dunnick et al., 1986). Groups of 50 female F344/N rats were administered 0, 50, or 100 mg/kg. Dose-related toxicity was noted in the lungs of treated male and female rats, with lung lesions being most prevalent in high-dose male rats. Lung lesions included alveolar epithelial hyperplasia, chemical pneumonia, alveolar/bronchiolar adenoma and carcinoma, and squamous cell carcinoma. Neoplastic and non-neoplastic lesions were noted in the forestomachs of male and female rats, with males more severely affected. Mineralization of the cerebellum in male rats and focal calcification of the testes in male mice were also noted.

3.7. Summary

Animal inhalation data are limited. Clinical signs from both acute and repeated-exposure studies suggest that DMP is an irritant; effects included lacrimation, exophthalmos, respiratory distress, ocular opacities, cataracts, and pulmonary congestion. Genotoxicity testing yielded both positive and negative results. Hypospermatogenesis was noted in rats repeatedly exposed to DMP for 4-weeks. No inhalation data on chronic toxicity/carcinogenicity were located.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Studies in rats and mice suggest that DMP is oxidatively demethylated to monomethyl hydrogen phosphite and the methanol formed is further oxidized via formaldehyde to CO_2. Nomeir and Matthews (1997) administered 10-200 mg/kg 14^C-labeled DMP to male F-344/N rats and male B6C3F1 mice. The compound was readily and essentially completely absorbed from the GI tract of both rats and mice and was eliminated primarily as expired CO_2 (44-57%) and urine (28-49%). Only 1-2% was collected from feces and only 2-3% as volatile organics. Radioactivity was primarily distributed to the liver, kidneys, spleen, lungs and forestomach. Absorption, metabolism, and disposition were linear in both species. The clearance rate was two times faster in the mouse than in the rat. The monomethyl hydrogen phosphite metabolite was excreted in the urine of both species and suggests that DMP is demethylated *in vivo*. In vitro studies suggest that DMP is metabolized to formaldehyde in the liver, lung, kidney, forestomach and stomach of rats (Nomeir and Matthews, 1997).

4.2. Mechanism of Toxicity

Information concerning the mechanism of toxicity of DMP was not located; however, repeated-exposure studies in rats suggest that it is an irritant when inhaled. Clinical signs noted in rat inhalation studies include lacrimation, exophthalmos, respiratory distress, ocular opacities, cataracts, and pulmonary congestion.

4.3. Structure Activity Relationships

DMP is structurally similar to organophosphate insecticides that inhibit cholinesterase activity; however, DMP does not appear to be a cholinesterase inhibitor. Repeated-exposure inhalation studies in rats (Biodymanics, 1980a,b) did not indicate systemic or cumulative toxic effects suggesting cholinesterase inhibition, but suggested the effects were indicative of local irritation.

4.4. Other Relevant Information

4.4.1. Species Variability

Data are not sufficient for determining species sensitivity. However, because DMP is an irritant via the inhalation route, little interspecies variability is expected.

4.4.2. Susceptible Populations

No information was available on populations especially sensitive to DMP toxicity. However, because DMP is an irritant via the inhalation route, little intraspecies variability is expected.

4.4.3. Concentration-Exposure Duration Relationship

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 ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

4.4.4. Concurrent Exposure Issues

No concurrent exposure issues were identified.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values were identified.

5.2. Summary of Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values were identified.

5.3. Derivation of AEGL-1

Data are insufficient to derive AEGL-1 values for dimethyl phosphite. Therefore, AEGL-1 values are not recommended (Table 3).

TABLE 3. AEGL-1 values for dimethyl phosphite

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

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

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values were identified.

6.2. Summary of Animal Data Relevant to AEGL-2

Mice exposed to 1575 ppm DMP for 6 hrs exhibited labored breathing and ptosis. No clinical signs were noted in rats and guinea pigs similarly exposed (Hazleton, 1962).

Irritation of superficial ocular structures associated with inflammatory changes of intraocular structures was observed in rats exposed to 12 ppm DMP 6 hr/day, 5 days/week for 4-weeks (Biodynamics, 1980b).

6.3. Derivation of AEGL-2

The clinical signs (labored breathing and ptosis) in mice exposed to 1575 ppm DMP for 6

hours (Hazleton, 1962) will be used as the point-of-departure for AEGL-2 values. Inter- and intraspecies uncertainty factors of 3 each (total 10) will be applied because DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. The interspecies uncertainty factor of 3 is also considered sufficient because no clinical signs were noted in rats or guinea pigs exposed to 1575 ppm for 6 hours. A modifying factor of 3 will also be applied because of the sparse database and because the point-of-departure is a nominal concentration. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling may be performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The 30-minute AEGL-2 value will also be adopted as the 10-min value because of the added uncertainty of extrapolating from the 6-hr point-of-departure. AEGL-2 values are presented in Table 4, and calculations are presented in Appendix A.

TABLE 4. AEGL-2 values for dimethyl phosphate

10-minute	30-minute	1-hour	4-hour	8-hour
120 ppm (540 mg/m^3)	120 ppm (540 mg/m^3)	95 ppm (430 mg/m^3)	60 ppm (270 mg/m^3)	39 ppm (180 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were identified.

7.2. Summary of Animal Data Relevant to AEGL-3

A 1-hr rat LC_{50} of >5112 ppm was reported (Albright and Wilson Inc., 1985).

Excessive lacrimation, partially closed eyes, red nasal discharge, labored breathing, and unresponsiveness to sound stimuli were noted in rats exposed to 843 ppm DMP 6 hr/day for 5 days (Biodymanics, 1980a). Swelling of the limbs with red discoloration, fresh or dried ocular or nasal discharges, and dull, dry and/or cloudy corneal surfaces were also noted as was decreased body weight gain. Death was noted at the next highest concentration tested (934 ppm) as one rat was killed *in extremis* after day 1 of exposure.

7.3. Derivation of AEGL-3

The highest concentration causing no mortality in rats (843 ppm for 6 hr) will be used as the point of departure for AEGL-3 (Biodymanics, 1980a). Excessive lacrimation, partially closed eyes, red nasal discharge, red-brown material around the nares, labored breathing, and unresponsiveness to sound stimuli were noted in rats exposed to 843 ppm DMP 6 hr/day for 5 days. Death was noted at the next concentration tested (934 ppm) essentially after one exposure because one rat was killed *in extremis* after day 1 of the study. Inter- and intraspecies

uncertainty factors of 3 each (total 10) will be applied because DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. 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). To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling may be performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The 30-minute AEGL-3 value will also be adopted as the 10-min value because of the added uncertainty of extrapolating from the 6-hr point-of-departure. AEGL-3 values are presented in Table 5, and calculations are presented in Appendix A.

TABLE 5. AEGL-3 values for dimethyl phosphate

10-minute	30-minute	1-hour	4-hour	8-hour
190 ppm (850 mg/m^3)	190 ppm (850 mg/m^3)	150 ppm (670 mg/m^3)	96 ppm (430 mg/m^3)	63 ppm (240 mg/m^3)

The AEGL-3 values are considered protective. Dividing the 1-hr rat LC_{50} of >5112 ppm (Albright and Wilson Inc., 1985) by 3, yields an estimated 1-hr lethality threshold of >1701 ppm. Applying a total uncertainty factor of 10, yields a value of 170 ppm; this concentration is consistent with the derived 1-hr AEGL-3 value.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 6. AEGL-1 values are not recommended due to insufficient data. AEGL-2 values are based on labored breathing and ptosis in mice exposed to DMP for 6-hr. AEGL-3 values are based on the highest concentration causing no mortality in rats exposed to DMP for 6-hr.

TABLE 6. Summary of AEGL values

Classification	Exposure Duration				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	120 ppm (540 mg/m^3)	120 ppm (540 mg/m^3)	95 ppm (430 mg/m^3)	60 ppm (270 mg/m^3)	39 ppm (180 mg/m^3)
AEGL-3 (Lethal)	190 ppm (850 mg/m^3)	190 ppm (850 mg/m^3)	150 ppm (670 mg/m^3)	96 ppm (430 mg/m^3)	63 ppm (240 mg/m^3)

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

8.2. Comparison with Other Standards and Guidelines

No other standards or guidelines were located for dimethyl phosphite.

8.3. Data Adequacy and Research

Human and animal data are both limited. Human data are limited to one workplace monitoring report. Acute animal inhalation data are limited to studies with nominal concentrations. Repeated-exposure analytical data are available. Additional acute inhalation toxicity studies would be helpful.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

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

Derivation of AEGL-2

Key Study: Hazleton, 1962. Initial Submission: Letter submitting acute inhalation exposure in mice, rat, and guinea pigs, on hexachloro-2-cyclopentanone (final report) with attachments. Hazelton Laboratories, Inc. Falls Church, VA. November 1, 1962. OTS0537047.

Toxicity endpoint: Labored breathing and ptosis in mice exposed to 1575 ppm DMP for 6 hours.

Uncertainty factors: Interspecies: 3, DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species. The interspecies uncertainty factor of 3 is also considered sufficient because no clinical signs were noted in rats or guinea pigs exposed to 1575 ppm for 6 hours.

Intraspecies: 3, DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly among individuals.

Modifying factor: 3: Sparse data base and nominal concentration for point-of-departure

Time scaling: $C^3 \times t = k$ (30-min, 1-hr, 4-hr)
$1575\ ppm^3 \times 6\ hr = 2.34 \times 10^{10}\ ppm^3\text{-hr}$

$C^1 \times t = k$ (8-hr)
$1575\ ppm \times 6\ hr = 9450\ ppm\text{-hr}$

10-minute AEGL-2: 30-min value adopted as 10-min value = 120 ppm

30-minute AEGL-2: $C^3 \times 0.5\ hr = 2.34 \times 10^{10}\ ppm^3 \cdot hr$
$C^3 = 4.68 \times 10^{10}\ ppm$
$C = 3604 \div 30 = 120\ ppm$

1-hour AEGL-2: $C^3 \times 1\ hr = 2.34 \times 10^{10}\ ppm^3 \cdot hr$
$C^3 = 5.85 \times 10^9\ ppm$
$C = 2860 \div 30 = 95\ ppm$

4-hour AEGL-2: $C^3 \times 4\ hr = 2.34 \times 10^{10}\ ppm^3 \cdot hr$
$C^3 = 5.85 \times 10^9\ ppm$
$C = 1802 \div 30 = 60\ ppm$

8-hour AEGL-2: $C^1 \times 8\ hr = 9450\ ppm^3 \cdot hr$
$C^1 = 1181\ ppm$
$C = 1181 \div 30 = 39\ ppm$

Derivation of AEGL-3

Key Study:	Biodynamics, 1980a. A five day inhalation toxicity study of MCTR-174-79 in the rat. Project No. 79-7344. March 4, 1980.
Toxicity endpoint:	Highest concentration causing no mortality in rats (843 ppm for 6 hr). Excessive lacrimation, partially closed eyes, red nasal discharge, red-brown material around the nares, labored breathing, and unresponsiveness to sound stimuli were noted in rats exposed to 843 ppm DMP 6 hr/day for 5 days. Death was noted at the next concentration tested (934 ppm) essentially after one exposure because one rat was killed *in extremis* after day 1 of the study.
Uncertainty factors:	Interspecies: 3, DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species. Intraspecies: 3, DMP is irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly among individuals.
Modifying factor:	None
Time scaling:	$C^3 \times t = k$ (30-min, 1-hr, 4-hr) $843\ ppm^3 \times 6\ hr = 3.59 \times 10^9\ ppm^3\text{-hr}$ $C^1 \times t = k$ (8-hr) $843\ ppm \times 6\ hr = 5058\ ppm\text{-hr}$
10-minute AEGL-3:	190 ppm: 30-min value adopted as 10-min value
30-minute AEGL-3:	$C^3 \times 0.5\ hr = 3.59 \times 10^9\ ppm^3 \cdot hr$ $C^3 = 7.18 \times 10^9\ ppm$ $C = 1929 \div 10 = 190\ ppm$
1-hour AEGL-3:	$C^3 \times 1\ hr = 3.59 \times 10^9\ ppm^3 \cdot hr$ $C^3 = 3.59 \times 10^9\ ppm$ $C = 1531 \div 10 = 150\ ppm$
4-hour AEGL-3:	$C^3 \times 4\ hr = 3.59 \times 10^9\ ppm^3 \cdot hr$ $C^3 = 8.98 \times 10^8\ ppm$ $C = 964 \div 10 = 96\ ppm$
8-hour AEGL-3:	$C^1 \times 8\ hr = 5058\ ppm^3 \cdot hr$ $C^1 = 632\ ppm$ $C = 632 \div 10 = 63\ ppm$

APPENDIX B: Derivation Summary for Dimethyl Phosphite AEGLs

AEGL-1 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

Key Reference:

Test Species/Strain/Number:

Exposure Route/Concentrations/Durations:

Effects:

Endpoint/Concentration/Rationale:

Uncertainty Factors/Rationale:
Total uncertainty factor:
Interspecies:
Intraspecies:

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling:

Data Adequacy: Not Recommended due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

AEGL-2 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
120 ppm (540 mg/m^3)	120 ppm (540 mg/m^3)	95 ppm (430 mg/m^3)	60 ppm (270 mg/m^3)	39 ppm (180 mg/m^3)

Key Reference: Hazleton, 1962. Initial Submission: Letter submitting acute inhalation exposure in mice, rat, and guinea pigs, on hexachloro-2-cyclopentanone (final report) with attachments. Hazelton Laboratories, Inc. Falls Church, VA. November 1, 1962. OTS0537047.

Test Species/Strain/Number: Mouse/Swiss albino/10 males

Exposure Route/Concentrations/Durations: Inhalation/1575 ppm/6-hr

Effects: Labored breathing (2/10) and ptosis (10/10).

Endpoint/Concentration/Rationale: Labored breathing and ptosis/1575 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
DMP is highly irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals. The interspecies uncertainty factor of 3 is also considered sufficient because no clinical signs were noted in rats and guinea pigs exposed to 1575 ppm for 6 hr.

Modifying Factor: 3: Sparse data base and nominal concentration point-of-departure

Animal to Human Dosimetric Adjustment: NA

Time Scaling: $C^n \times t = k$. To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The 30-min AEGL-2 value was adopted as the 10-min value because the point-of-departure is 6-hr.

Data Adequacy: Sparse data set.

AEGL-3 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
190 ppm (850 mg/m^3)	190 ppm (850 mg/m^3)	150 ppm (670 mg/m^3)	96 ppm (430 mg/m^3)	63 ppm (240 mg/m^3)

Key Reference: Biodynamics, 1980a. A five day inhalation toxicity study of MCTR-174-79 in the rat. Project No. 79-7344. March 4, 1980.

Test Species/Strain/Number: Rat/Sprague-Dawley/ 5/sex/group

Exposure Route/Concentrations/Durations: Inhalation/ 431, 843, 934 ppm/6-hr for up to five days

Effects: All Concentration Groups: Excessive lacrimation, partially closed eyes, red nasal discharge, red-brown material around the nares, labored breathing, and unresponsiveness to sound.

934 ppm: Mortality. One rat killed *in extremis* on day 1, 8/9 remaining rats died before study termination.

Endpoint/Concentration/Rationale: Highest concentration causing no mortality in rats. Death was noted at the next concentration tested (934 ppm) essentially after one exposure because one rat was killed *in extremis* after day 1 of the study. /843 ppm for 6-hr

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
DMP is highly irritating, and much of the toxicity is likely caused by a direct chemical effect on the tissue; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

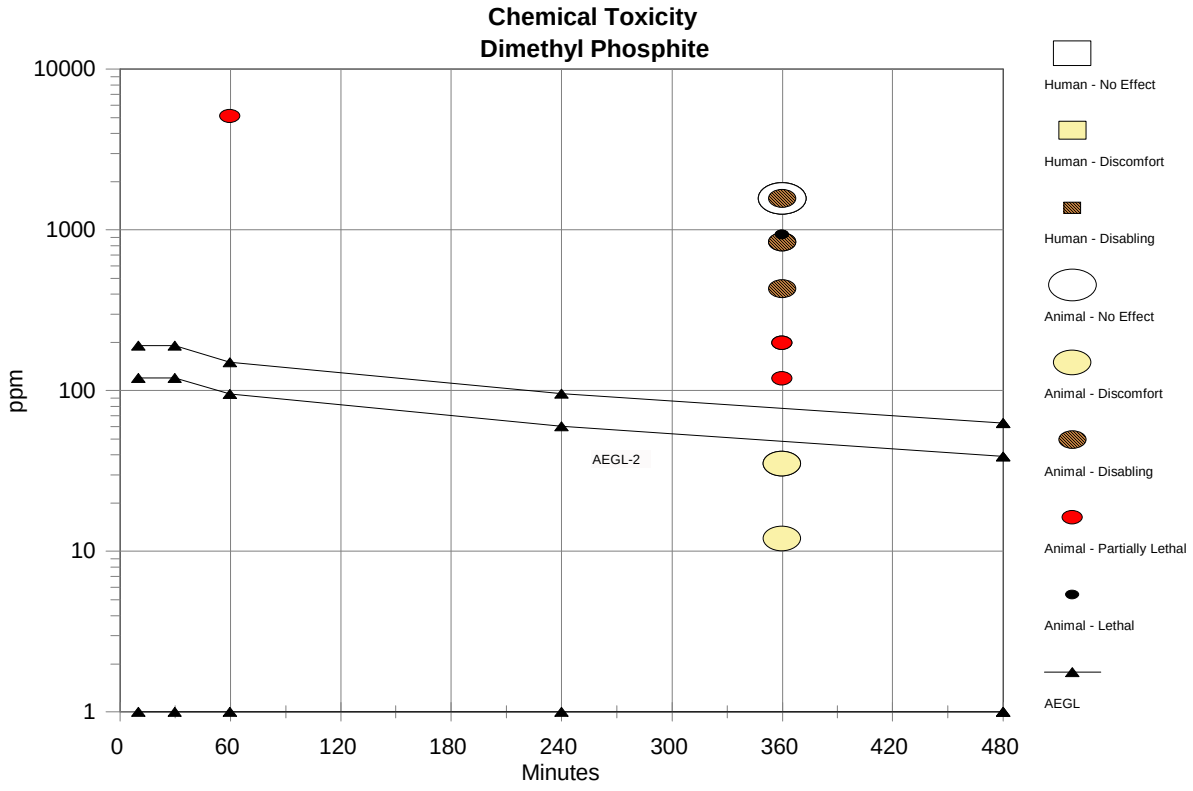
Modifying Factor: NA:

Animal to Human Dosimetric Adjustment: NA

Time Scaling: $C^n \times t = k$. To obtain conservative and protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The 30-min AEGL-3 value was adopted as the 10-min value because the point-of-departure is 6-hr.

Data Adequacy: Sparse data set. However, the AEGL-3 values are considered protective. Dividing the 1-hr rat LC_{50} of >5112 ppm (Albright and Wilson Inc., 1985) by 3, yields an estimated 1-hr lethality threshold of >1701 ppm. Applying a total uncertainty factor of 10, yields a value of 170 ppm; this concentration is consistent with the derived 1-hr AEGL-3 value.

APPENDIX C: Category Plot for Dimethyl Phosphite



Note: Animal partially lethal data points at 360 minutes are from repeated exposure studies. Lethality was not noted until after 14-27 days of exposure.

Category Plot Data

Source	Species	Sex	# Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				NR	10	AEGL	
NAC/AEGL-1				NR	30	AEGL	
NAC/AEGL-1				NR	60	AEGL	
NAC/AEGL-1				NR	240	AEGL	
NAC/AEGL-1				NR	480	AEGL	
NAC/AEGL-2				120	10	AEGL	
NAC/AEGL-2				120	30	AEGL	
NAC/AEGL-2				95	60	AEGL	
NAC/AEGL-2				60	240	AEGL	
NAC/AEGL-2				39	480	AEGL	
NAC/AEGL-3				190	10	AEGL	
NAC/AEGL-3				190	30	AEGL	
NAC/AEGL-3				150	60	AEGL	
NAC/AEGL-3				96	240	AEGL	
NAC/AEGL-3				63	480	AEGL	
	Rat		1	5112	60	pl	free standing LC50 >5112 ppm
	Rat		1	1575	360	0	no clinical signs
	Gp		1	1575	360	0	no clinical signs
	Mouse		1	1575	360	2	labored breathing (1/10), ptosis (10/10)
	Rat		5	431	360	2	lacrimation, nasal discharge, labored breathing, unresponsive to sound, corneal effects
	Rat		5	843	360	2	lacrimation, nasal discharge, labored breathing, unresponsive to sound, corneal effects, increased lung weight
	Rat		5	934	360	3	10/10 mortality, days 1-4 of 5 day exposure protocol
	Rat		20	12	360	1	Irritation of superficial ocular structure
	Rat		20	35	360	1	skin, mucous membrane, ocular irritation
	Rat		20	119	360	pl	2/40 mortality days 14-23; signs of irritation, rales, decreased BW, hematological effects, ocular opacity, cataract
	Rat		20	198	360	pl	27/40 mortality before day 27; signs of irritation, rales, decreased BW, hematological effects, ocular opacity, cataract