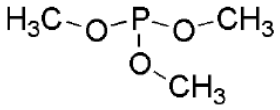
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
TRIMETHYL PHOSPHITE
CAS Reg. No. 121-45-9



INTERIM

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FOR
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CAS Reg. No. 121-45-9

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

Trimethyl phosphite (TMP) is a colorless liquid with an irritating, pungent, oily, pyridine-like odor. Its primary use is as an intermediate in the manufacture of pesticides. It is also used as a fireproofing agent in the production of textiles, as an intermediate in the production of flame-retardant polymers for polyurethane foams, and as a catalyst (HSDB, 2009).

The no-effect-level for clinical signs in rats (10 ppm) exposed to TMP 6 hr/day, 5 days/week for 4 weeks (Biodynamics, 1979) was used as the point-of-departure for AEGL-1 values. An intraspecies uncertainty factor of 3 was applied because the point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. An interspecies uncertainty factor of 1 was applied. Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-1 values that are not compatible with human occupational exposure data (AEGL-1 values derived with a total UF of 10 are 3.3, 2.3, 1.8, 1.1, and 0.60 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991). 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 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). Extrapolation was used to derive the 10-minute value because the 6-hour point-of-departure is from a repeated exposure study.

The lens opacities in rats exposed to 101 ppm TMP 6 hours/day, 5 days/week for 4 weeks (Biodynamics, 1979) were used as the point-of-departure for AEGL-2 values. This endpoint was still present in some animals at 2-weeks post-exposure. An intraspecies uncertainty factor of 3 was applied because the point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. The lens opacities observed in rats repeatedly exposed to 101 ppm TMP were noted after 2 weeks and continued to increase in frequency and severity after 4 weeks exposure, suggesting a cumulative effect. An interspecies uncertainty factor of 1 was applied. Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-2 values that are not compatible with human occupational exposure data (AEGL-2 values derived with a total UF of 10 are 33, 23, 18, 12, and 6.0 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991). Time scaling is as described above for AEGL-1.

Up to 50% lethality was observed in mice exposed to 6450 ppm TMP for approximately 3 hours (Hazleton, 1962). In the absence of other appropriate data for deriving AEGL-3 values, this exposure concentration was divided by 3 to estimate a threshold for lethality (Rusch et al., 2009) (point-of-departure 2150 ppm). Inter- and intraspecies uncertainty factors of 3 each (total 10) were applied because TMP is highly irritating, and much of the toxicity resulting from an acute exposure 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. 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 calculated values are listed in Table 1 below.

1
2

Table 1. Summary of AEGL Values for Trimethyl Phosphite

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	11 ppm (56 mg/m^3)	7.6 ppm (39 mg/m^3)	6.1 ppm (31 mg/m^3)	3.8 ppm (19 mg/m^3)	2.5 ppm (13 mg/m^3)	NOEL for clinical signs in rats (Biodynamics, 1979)
AEGL–2 (Disabling)	110 ppm (560 mg/m^3)	77 ppm (390 mg/m^3)	61 ppm (310 mg/m^3)	38 ppm (190 mg/m^3)	25 ppm (128 mg/m^3)	Lens opacities in rats (Biodynamics, 1979)
AEGL–3 (Lethal)	560 ppm (2900 mg/m^3)	390 ppm (2000 mg/m^3)	310 ppm (1600 mg/m^3)	160 ppm (820 mg/m^3)	81 ppm (410 mg/m^3)	Estimated 3-hr lethality threshold in mice (Hazleton, 1962)

3
4
5

1. INTRODUCTION

Trimethyl phosphite (TMP) is a colorless liquid with an irritating, pungent, oily, pyridine-like odor. Its primary use is as an intermediate in the manufacture of pesticides. It is also used as a fireproofing agent in the production of textiles, as an intermediate in the production of flame-retardant polymers for polyurethane foams, and as a catalyst (HSDB, 2009). It is produced by reaction of phosphorus trichloride and methyl alcohol in the presence of a tertiary amine. Trimethyl phosphite is manufactured primarily overseas and is imported into the US for domestic use; manufacture is in closed systems (HPV, 2005). No current quantitative manufacturing information was located. Chemical and physical properties are presented in Table 2.

Table 2. Chemical and physical properties for trimethyl phosphite

Parameter	Value	References
Synonyms	Methyl phosphite; Phosphorus acid trimethyl ester; TMP; Trimethoxyphosphine	ACGIH, 1991
Chemical formula	$C_3H_9O_3P$	HSDB, 2009
Molecular weight	124.08	HSDB, 2009
CAS Reg. No.	121-45-9	HSDB, 2009
Physical state	Colorless liquid	HSDB, 2009
Solubility in water	Insoluble- Decomposes to dimethyl phosphite and methanol	ACGIH, 1991
Vapor pressure	24 torr at 25ºC (saturates in air at 32,000 ppm)	HSDB, 2009
Vapor density (air =1)	4.3	HSDB 2009
Specific gravity	1.046 at 20ºC	HSDB, 2009
Melting point	-78ºC	HSDB, 2009
Boiling point	111.5ºC	ACGIH 1991
Flash point	37.8ºC, open cup	HSDB, 2009
Conversion factors	1 ppm = 5.1 mg/m^3 1 mg/m^3 = 0.20 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No information concerning acute lethality was located.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

An odor threshold of 0.0001 ppm was reported from a laboratory test panel. No further information was available (Mobil Oil, 1979).

ACGIH (1991) reported that in an occupational setting, the odor of TMP was not generally considered objectionable until concentrations approached 20 ppm. No further information was available.

2.2.2. Case Reports

ACGIH (1991) reported that analyses of air in a TMP manufacturing plant from 1969 to 1971 showed an average concentration of up to 8 ppm. ACGIH (1991) also reported that average workplace exposures in another TMP plant in 1979 usually ranged from 0.3 to 4 ppm, with occupational exposures up to 15 ppm. Monitoring of 179 employees in these plants showed no ocular effects or other adverse effects associated with occupational exposure to TMP. No further details were provided.

2.3. Developmental/Reproductive Toxicity

No human developmental/reproductive data were located.

2.4. Genotoxicity

No human data were located.

2.5. Carcinogenicity

No human data were located.

2.6. Summary

Human data are limited to odor threshold and occupational monitoring data, both of which are available only from secondary sources. An odor threshold of 0.0001 ppm was reported, and odor was not considered objectionable until concentrations approached 20 ppm. No effects were reported from occupational exposure concentrations ranging from 0.3 to 15 ppm.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

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 6450 ppm TMP for 6 hours, followed by a 24-hour observation period (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 TMP. 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 24-hour observation period, surviving animals were sacrificed and necropsies were performed; necropsies were also performed on animals that died during exposure. Both clinical signs and lethality data suggest that mice are more sensitive than rats, and rats may be more sensitive than guinea pigs. Clinical signs included an initial increase in activity, followed by progressive depression. At 30 minutes, all mice were prostrate and rats and guinea pigs were depressed. Lacrimation and ptosis were observed in most animals, and after 3-hours, mice exhibited increasing exophthalmos. Signs remained unchanged until the death of the animal or cessation of exposure after 6 hours. No guinea pigs died during exposure; whereas ten mice and six rats died during

exposure; times to death for mice and rats dying during exposure are summarized in Table 3. Additionally, one rat died the day after exposure. Animals dying during exposure showed a foamy fluid in the stomachs and lungs and liver congestion. Four rats also exhibited congestion of the spleen and two rats had adrenal congestion. Mice all had distention of the large intestine. Guinea pigs sacrificed at study termination had lung and liver congestion and gaseous distention of the gastrointestinal tract. Necropsies of surviving rats showed only lung congestion with hemorrhage and kidney congestion.

Table 3. Time to death in mice and rats exposed to 6450 ppm TPM for 6 hours

Time to death (hrs: mins)	Number dead/Number exposed (cumulative)	
	Mice	Rats
2:55	2/10	-
2:58	4/10	-
3:01	5/10	-
3:02	-	2/10
3:05	6/10	-
3:11	-	3/10
4:03	8/10	5/10
4:07	9/10	-
4:20	-	6/10
4:44	10/10	-
LT_{50} (hrs: mins) (95%CI)	3:08 (2:51-3:27)	4:03 (3:27-4:47)

Hazleton, 1962

A nominal 1-hr rat LC_{50} of 35,885 ppm was reported by Mobil Oil (1979); no further details were provided.

A nominal 4-hr rat LC_{50} of > 10,000 ppm has also been reported (Levin and Gabriel, 1973). Animals showed a high degree of irritation, discomfort, and respiratory distress. No further details were provided.

3.2. Repeated-Exposure Studies

Groups of Sprague-Dawley rats were repeatedly exposed to 0 (20 rats/sex), 105 (20 rats/sex), or 600 ppm (36 rats/sex) TMP (Biodynamics, 1978). Control and 105 ppm group animals were exposed 6 hours/day, 5 days/week for four weeks. Animals in the 600 ppm group were exposed 6 hours/day, 5 days/week for three weeks and received three 6-hour exposures during the fourth week. Animals were exposed in one cubic meter stainless steel and glass dynamic chambers, with an airflow of 132 L/min. The test atmosphere was generated by passing a nitrogen stream through a bubbler containing the TMP, varying the amount of nitrogen to volatilize the appropriate amount of test material. Test atmospheres were sampled four times per exposure for infrared analysis. Additionally, periodic samples were taken from the chambers each exposure day and analyzed via gas chromatography. The purpose of the study was to determine if lenticular cataracts would develop from TMP exposure. No treatment-related mortality was reported in the control or 105 ppm groups; however, 30/36 males and 19/36 females in the 600 ppm group died during the study. One male and one female in the 600 ppm group were

sacrificed in extremis. Deaths occurred between days 15 and 31 of the study. All rats in both treatment groups showed concentration-related signs of irritation during the 4-week exposure. Additionally, animals exposed to 600 ppm exhibited decreased activity, poor condition, excessive salivation, and ocular abnormalities. Ophthalmoscopic examinations revealed grooved lens opacities in 7 of 30 rats exposed to 105 ppm; these lesions were reversible within 8 weeks post exposure. At 600 ppm, almost all rats developed mature (severe), irreversible cataracts. Body weight in the 105 ppm group was comparable to controls throughout the study. Body weight in the 600 ppm group was significantly decreased from week 1 through 5; body weights then increased and became comparable with controls, thereafter. No treatment-related necropsy findings were noted in rats in the 105 ppm group. However, there was an increase in absolute and relative lung weights in the 600 ppm group, and gross necropsy revealed lung congestion and discoloration.

In another study, Biodynamics (1979) groups of twenty male and twenty female Sprague-Dawley rats were exposed to 0, 10, 51, or 101 ppm TMP 6 hours/day, 5 days/week for up to four weeks. Five rats/sex were sacrificed after two and four weeks exposure, and after two and eight weeks post-exposure. Exposure methods are similar to those described above (Biodynamics, 1978). No treatment-related deaths occurred at any concentration, and no clinical signs were observed during the exposure period. Body and lung weights for all treatment groups were similar to those of controls. No lens effects were noted at 10 ppm. Ocular surface irregularities were noted at the end of 4 weeks in rats exposed to 51 or 101 ppm, with females affected more than males. Two weeks after exposure, lens opacities were noted only in females in the 51 ppm group (2/10), and 101 ppm group (6/10).

Albino rats were administered 100, 300, or 600 ppm TMP 6 hours/day, 5 days/week for four weeks (Mobil Oil, 1979). There were no treatment-related deaths at 100 ppm. Approximately 10% mortality occurred in the 300 ppm group, and mortality exceeded 70% in the 600 ppm group over the 4 week exposure period. No respiratory effects were noted at 100 or 300 ppm; however, gross histological evidence of lung inflammation was noted at 600 ppm. Clinical signs of ocular irritation were noted in all treatment groups. A few rats exposed to 100 ppm had mild and reversible striate opacities of the lenses; however, these lesions were similar to those occurring spontaneously in untreated rats. Mild cataracts were noted at 300 ppm, and severe cataracts were reported at 600 ppm. No other experimental details were available.

Groups of five rats were exposed to 0 (5 males) or 500 ppm (nominal concentration; 4 males, 1 female) TMP 7.5 hours/day, 5 days/week for 8 weeks (Levin and Gabriel, 1973). Histopathological changes in the lungs were noted; however, a later review of this study deemed the results unreliable because the effects were likely related to chronic lung disease in the laboratory rats (HPV, 2005).

3.3. Developmental/Reproductive Toxicity

No inhalation data were located.

3.4. Genotoxicity

Trimethyl phosphite was negative for bacterial mutagenicity in a series of *S. typhimurium* Ames tests both with and without activation. Trimethyl phosphite was positive both with and

without metabolic activation in the mouse lymphoma assay and was also positive in a battery of *Drosophila melanogaster* mutagenicity assays. It gave both positive and negative results in DNA damage and repair assays *in vitro* in *E. coli* and *S. typhimurium* strains, both with and without exogenous metabolic activation and was negative for cell transformation in C3H/T10½ cells *in vitro* (HSDB, 2009; HPV, 2005).

3.5. Chronic Toxicity/Carcinogenicity

No data were located.

3.6. Summary

Limited acute inhalation data suggest that trimethyl phosphite is of low acute toxicity with regard to lethality. Clinical signs from both acute and repeated-exposure studies suggest that TMP is an irritant; effects included lacrimation, exophthalmos, respiratory distress, ocular opacities, cataracts, and pulmonary congestion. Cumulative effects were also noted; lens opacities observed in rats repeatedly exposed to approximately 100 ppm TMP were noted after 2 weeks and continued to increase in frequency and severity after 4 weeks exposure. Genotoxicity testing yielded both positive and negative results. No data on developmental/ reproductive toxicity or chronic toxicity/carcinogenicity were located.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Little information was located concerning the metabolism and disposition of trimethyl phosphite. However, trimethyl phosphite may be hydrolyzed in the moist respiratory tract to dimethyl phosphite and methanol (ACGIH, 1991).

4.2. Mechanism of Toxicity

TMP is an acute irritant to the skin, eyes, and upper respiratory tract (ACGIH, 1991). Clinical signs noted in rat inhalation studies include lacrimation, exophthalmos, respiratory distress, ocular opacities, cataracts, and pulmonary congestion. Cumulative effects were also noted. Lens opacities observed in rats repeatedly exposed to approximately 100 ppm TMP were noted after 2 weeks and continued to increase in frequency and severity after 4 weeks exposure (Biodynamics, 1979).

4.3. Structure Activity Relationships

TMP is structurally similar to organophosphate insecticides that inhibit cholinesterase activity. However, a study of cholinesterase inhibition following intravenous administration of TMP in rats, rabbits, and dogs and *in vitro* studies of cholinesterase inhibition potential showed that TMP does not inhibit cholinesterase activity (HPV, 2005). Repeated-exposure inhalation studies in rats (Biodymanics, 1978, 1979; Mobil Oil, 1979; Levin and Gabriel, 1973) did not indicate systemic or cumulative toxic effects suggesting cholinesterase inhibition.

4.4. Other Relevant Information

4.4.1. Species Variability

Data are not sufficient for determining species sensitivity.

4.4.2. Susceptible Populations

No information was available on populations especially sensitive to TMP toxicity.

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 clinical signs during exposure or ocular effects at study termination were noted in rats exposed to 10 ppm TMP 6 hr/day, 5 days/week for 4 weeks (Biodymanics, 1979). Two weeks after exposure, lens opacities were noted only in females in the 51 ppm group (next highest concentration tested) (2/10), and 101 ppm group (6/10). Corneal surface irregularities were noted at the end of 4 weeks in rats exposed to 51 or 101 ppm, with both males and females affected.

5.3. Derivation of AEGL-1

The no-effect-level for clinical signs in rats (10 ppm) exposed to TMP 6 hr/day, 5 days/week for 4 weeks (Biodynamics, 1979) will be used as the point-of-departure for AEGL-1 values. An intraspecies uncertainty factor of 3 will be applied because the point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. An interspecies uncertainty factor of 1 will be applied. Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-1 values that are not compatible with human occupational exposure data (AEGL-1 values derived with a total UF of 10 are 3.3, 2.3, 1.8, 1.1, and 0.60 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991). 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). Extrapolation will be used to derive the 10-minute value because the 6-hr point-of-departure is from a repeated exposure study. The AEGL-1 values are presented in Table 4, and calculations are presented in Appendix A.

Table 4. AEGL-1 values for trimethyl phosphite

10-minute	30-minute	1-hour	4-hour	8-hour
11 ppm (56 mg/m^3)	7.6 ppm (39 mg/m^3)	6.1 ppm (31 mg/m^3)	3.8 ppm (19 mg/m^3)	2.5 ppm (13 mg/m^3)

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

Lens surface irregularities were noted after 2 and of 4 wk in rats exposed to 101 ppm TMP 6 hr/day, 5 days/week. Two weeks after exposure, lens opacities were still noted in some animals.

6.3. Derivation of AEGL-2

The lens opacities in rats exposed to 101 ppm TMP 6 hr/day, 5 days/week for 4 weeks (Biodynamics, 1979) will be used as the point-of-departure for AEGL-2 values. An intraspecies uncertainty factor of 3 will be applied because the point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. The lens opacities observed in rats repeatedly exposed to 101 ppm TMP were noted after 2 weeks and continued to increase in frequency and severity after 4 weeks exposure, suggesting a cumulative effect. An interspecies uncertainty factor of 1 will be applied. Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-2 values that are not compatible with human occupational exposure data (AEGL-2 values derived with a total UF of 10 are 33, 23, 18, 12, and 6.0 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991). 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). Extrapolation will be used to derive the 10-minute value because the 6-hr point-of-departure is from a repeated exposure study. AEGL-2 values are presented in Table 5, and calculations are presented in Appendix A.

Table 5. AEGL-2 values for trimethyl phosphite

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

110 ppm (560 mg/m^3)	77 ppm (390 mg/m^3)	61 ppm (310 mg/m^3)	38 ppm (190 mg/m^3)	25 ppm (128 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 35, 885 ppm (nominal) was reported by Mobil Oil (1979), and a 4-hr rat LC_{50} of >10,000 ppm (nominal) was reported by Levin and Gabriel (1973). In a time-to-death study, up to 50% mortality was reported in mice exposed to 6450 ppm (nominal) TMP for approximately 3 hours (Hazleton, 1962); mortality was 2/10 at 2 hr 55 min, 4/10 at 2 hr 58 min, and 5/10 at 3 hr 1 min.

7.3. Derivation of AEGL-3

Up to 50% lethality was observed in mice exposed to 6450 ppm TMP for approximately 3 hours (Hazleton, 1962). In the absence of other appropriate data for deriving AEGL-3 values, this exposure concentration will be divided by 3 to estimate a threshold for lethality (Rusch et al., 2009) (point-of-departure 2150 ppm). Inter- and intraspecies uncertainty factors of 3 each (total 10) will be applied because TMP is highly irritating, and much of the toxicity resulting from an acute exposure 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). AEGL-3 values are presented in Table 6, and calculations are presented in Appendix A.

Table 6. AEGL-3 values for trimethyl phosphite

10-minute	30-minute	1-hour	4-hour	8-hour
560 ppm (2900 mg/m^3)	390 ppm (2000 mg/m^3)	310 ppm (1600 mg/m^3)	160 ppm (820 mg/m^3)	81 ppm (410 mg/m^3)

The AEGL-3 values are supported by the 4-hr rat LC_{50} of >10,000 ppm (Levin and Gabriel, 1973). Dividing 10,000 ppm by three yields an estimated 4-hr lethality threshold of 3000 ppm; applying a total uncertainty factor of 10, yields a 4-hr AEGL-3 value of 300 ppm. Also, no deaths were noted in rats exposed to approximately 100 ppm TMP 6 hr/day, 5 days/week for 4 weeks (Biodymanics, 1978, 1979; Mobil Oil, 1979). These data suggest that the AEGL-3 values are protective.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 7. AEGL-1 values are based on a no-effect-level for clinical signs in rats repeatedly exposed to TMP. AEGL-2 values are based on lens opacities in rats repeatedly exposed to TMP, and AEGL-3 values are based on an estimated lethality threshold in mice.

Table 7. Summary of AEGL values

Classification	Exposure Duration				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	11 ppm (56 mg/m^3)	7.6 ppm (39 mg/m^3)	6.1 ppm (31 mg/m^3)	3.8 ppm (19 mg/m^3)	2.5 ppm (13 mg/m^3)
AEGL-2 (Disabling)	110 ppm (560 mg/m^3)	77 ppm (390 mg/m^3)	61 ppm (310 mg/m^3)	38 ppm (190 mg/m^3)	25 ppm (128 mg/m^3)
AEGL-3 (Lethal)	560 ppm (2900 mg/m^3)	390 ppm (2000 mg/m^3)	310 ppm (1600 mg/m^3)	160 ppm (820 mg/m^3)	81 ppm (410 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

AEGL values for trimethyl phosphite are compared to other guidelines and standards for this compound are listed in Table 8.

Table 8. Extant standards and guidelines for trimethyl phosphate

Guideline	**Exposure Duration**				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	11 ppm (56 mg/m^3)	7.6 ppm (39 mg/m^3)	6.1 ppm (31 mg/m^3)	3.8 ppm (19 mg/m^3)	2.5 ppm (13 mg/m^3)
AEGL-2	110 ppm (560 mg/m^3)	77 ppm (390 mg/m^3)	61 ppm (310 mg/m^3)	38 ppm (190 mg/m^3)	25 ppm (128 mg/m^3)
AEGL-3	560 ppm (2900 mg/m^3)	390 ppm (2000 mg/m^3)	310 ppm (1600 mg/m^3)	160 ppm (820 mg/m^3)	81 ppm (410 mg/m^3)
TLV-TWA (ACGIH)[a]					2 ppm
MAC-Peak Category (The Netherlands)[b]					2 ppm

[a] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2008) 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. Basis is ocular nd skin irritation.

[b] MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration - Peak Category]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-Ceiling

8.3. Data Adequacy and Research

There are no quantitative human data, and animal data are limited. 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

Key Study:	Biodynamics, 1979. A repeated (4-week) inhalation study of MCTR-74-79 in the rat. Project No. 79-7279. OTS 88-7900291.
Toxicity endpoint:	NOEL for clinical signs in rats exposed to 10 ppm TMP 6 hr/day, 5 days/week for 4 weeks. Ocular effects were noted at the next highest concentration tested (51 ppm).
Uncertainty factors:	Intraspecies: 3, the point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure Interspecies: 1, A UF of 3 might normally be applied. However use of a total uncertainty factor of 10 yields AEGL-1 values that are not compatible with human worker exposure data (no effects with occupational exposures up to 15 ppm).
Modifying factor:	NA
Time scaling:	$C^3 \times t = k$ (10- min, 30-min, 1-hr, 4-hr) $10\ ppm^3 \times 6\ hr = 6000\ ppm^3\text{-hr}$ $C^1 \times t = k$ (8-hr) $10\ ppm \times 6\ hr = 60\ ppm\text{-hr}$
10-minute AEGL-1:	$C^3 \times 0.167\ hr = 6000\ ppm^3 \cdot hr$ $C^3 = 35928\ ppm$ $C = 32.9 \div 3 = 11\ ppm$
30-minute AEGL-1:	$C^3 \times 0.5\ hr = 6000\ ppm^3 \cdot hr$ $C^3 = 12{,}000\ ppm$ $C = 22.8 \div 3 = 7.6\ ppm$
1-hour AEGL-1:	$C^3 \times 1\ hr = 6000\ ppm^3 \cdot hr$ $C^3 = 6000\ ppm$ $C = 18.2 \div 3 = 6.1\ ppm$
4-hour AEGL-1:	$C^3 \times 4\ hr = 6000\ ppm^3 \cdot hr$ $C^3 = 1500\ ppm$ $C = 11.4 \div 3 = 3.8\ ppm$
8-hour AEGL-1:	$C^1 \times 8\ hr = 60\ ppm \cdot hr$ $C^1 = 7.5\ ppm$ $C = 7.5 \div 3 = 2.5\ ppm$

Derivation of AEGL-2

Key Study:	Biodynamics, 1979. A repeated (4-week) inhalation study of MCTR-74-79 in the rat. Project No. 79-7279. OTS 88-7900291.
Toxicity endpoint:	Lens opacities in rats exposed to 101 ppm TMP 6 hr/day, 5 days/week for 4 weeks. Ocular effects were still noted 2-weeks post-exposure.
Uncertainty factors:	Intraspecies: 3, The point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. The lens opacities observed in rats repeatedly exposed to 101 ppm TMP were noted after 2 weeks and continued to increase in frequency and severity after 4 weeks exposure, suggesting a cumulative effect. Interspecies: 1, A UF of 3 might normally be applied. However use of a total uncertainty factor of 10 yields AEGL-2 values that are not compatible with human worker exposure data (no effects with occupational exposures up to 15 ppm).
Modifying factor:	NA
Time scaling:	$C^3 \times t = k$ (10- min, 30-min, 1-hr, 4-hr) 101 $ppm^3 \times 6$ hr = 6,181,806 ppm^3-hr $C^1 \times t = k$ (8-hr) 101 ppm x 6 hr = 606 ppm-hr
10-minute AEGL-2:	$C^3 \times 0.167$ hr = 6,181,806 $ppm^3 \cdot hr$ C^3 = 37016802 ppm C = 333 ÷ 3 = 110 ppm
30-minute AEGL-2:	$C^3 \times 0.5$ hr = 6,181,806 $ppm^3 \cdot hr$ C^3 = 12363612 ppm C = 231 ÷ 3 = 77 ppm
1-hour AEGL-2:	$C^3 \times 1$ hr = 6,181,806 $ppm^3 \cdot hr$ C^3 = 6,181,806 ppm C = 183 ÷ 3 = 61 ppm
4-hour AEGL-2:	$C^3 \times 4$ hr = 6,181,806 $ppm^3 \cdot hr$ C^3 = 1545452 ppm C = 115 ÷ 3 = 38 ppm
8-hour AEGL-2:	$C^1 \times 8$ = 606 ppm-hr C = 76 ÷ 3 = 25

Derivation of AEGL-3

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:	3-hr estimated lethality threshold in mice (2150 ppm)
Uncertainty factors:	Interspecies: 3, TMP is highly irritating, and much of the acute 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, TMP is highly irritating, and much of the acute 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:	NA
Time scaling:	$C^3 \times t = k$ (10- min, 30-min, 1-hr) 2150 ppm ^{3} x 3 hr = 2.98×10^{10} ppm^3-hr $C^1 \times t = k$ (4-hr, 8-hr) 2150 ppm x 3 hr = 6450 ppm-hr
10-minute AEGL-3:	$C^3 \times 0.167$ hr = 2.98×10^{10} ppm^3-hr $C^3 = 1.78 \times 10^{11}$ ppm C = 5630 ÷ 10 = 560 ppm
30-minute AEGL-3:	$C^3 \times 0.5$ hr = 2.98×10^{10} ppm^3-hr $C^3 = 5.96 \times 10^{10}$ ppm C = 3906 ÷ 10 = 390 ppm
1-hour AEGL-3:	$C^3 \times 1$ hr = 2.98×10^{10} ppm^3-hr $C^3 = 2.98 \times 10^{10}$ ppm C = 3100 ÷ 10 = 310 ppm
4-hour AEGL-3:	$C^1 \times 4$ hr = 6450 ppm·hr C = 1613 ppm ÷ 10 = 160 ppm
8-hour AEGL-3:	$C^1 \times 8$ hr = 6450 ppm·hr C = 806 ppm ÷ 10 = 81 ppm

APPENDIX B: Derivation Summary for Trimethyl Phosphite AEGLs

AEGL-1 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
11 ppm (56 mg/m^3)	7.6 ppm (39 mg/m^3)	6.1 ppm (31 mg/m^3)	3.8 ppm (19 mg/m^3)	2.5 ppm (13 mg/m^3)

Key Reference: Biodynamics, 1979. A repeated (4-week) inhalation study of MCTR-74-79 in the rat. Project No. 79-7279. OTS 88-7900291.

Test Species/Strain/Number: Rat/Sprague-Dawley/20/sex/group

Exposure Route/Concentrations/Durations: Inhalation/0, 10, 51, 101 ppm/ 6 hr/day, 5 days/week, up to 4 weeks

Effects:
10 ppm: No effects
51 ppm: Lens irregularities and opacities (2/10 females still affected at two weeks post-exposure)
101 ppm: Lens irregularities and opacities (6/10 females still affected at two weeks post-exposure)

Endpoint/Concentration/Rationale: NOEL for clinical signs/ 10 ppm/ Ocular effects seen at next highest concentration tested

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 1
Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-1 values that are not compatible with human occupational exposure data (AEGL-1 values derived with a total UF of 10 are 3.3, 2.3, 1.8, 1.1, and 0.60 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991).
Intraspecies: 3
The point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure.

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). Extrapolation was used to derive the 10-minute value because the 6-hr point-of-departure is from a repeated exposure study.

Data Adequacy: Poor data set necessitated use of a NOEL from a repeated-exposure study.

AEGL-2 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
110 ppm (560 mg/m^3)	77 ppm (390 mg/m^3)	61 ppm (310 mg/m^3)	38 ppm (190 mg/m^3)	25 ppm (128 mg/m^3)

Key Reference: Biodynamics, 1979. A repeated (4-week) inhalation study of MCTR-74-79 in the rat. Project No. 79-7279. OTS 88-7900291.

Test Species/Strain/Number: Rat/Sprague-Dawley/20/sex/group

Exposure Route/Concentrations/Durations: Inhalation/0, 10, 51, 101 ppm/ 6 hr/day, 5 days/week, up to 4 weeks

Effects:
10 ppm: No effects
51 ppm: Lens irregularities and opacities (2/10 females still affected at two weeks post-exposure)
101 ppm: Lens irregularities and opacities (6/10 females still affected at two weeks post-exposure)

Endpoint/Concentration/Rationale: Lens opacities/ 101 ppm/ lens effects still present 2-weeks post-exposure

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 1
Although an interspecies UF of 3 might normally be applied, use of a total uncertainty factor of 10 yields AEGL-2 values that are not compatible with human occupational exposure data (AEGL-2 values derived with a total UF of 10 are 33, 23, 18, 12, and 6.0 ppm for 10-min, 30-min, 1-hr, 4-hr, and 8-hr, respectively). No effects were noted in workers repeatedly exposed up to 15 ppm (ACGIH, 1991).
Intraspecies: 3
The point-of-departure is from a repeated exposure study and the endpoint is not likely the result of a single exposure. The lens opacities observed in rats repeatedly exposed to 101 ppm TMP were noted after 2 weeks and continued to increase in frequency and severity after 4 weeks exposure, suggesting a cumulative effect.

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). Extrapolation was used to derive the 10-minute value because the 6-hr point-of-departure is from a repeated exposure study.

Data Adequacy: Poor data set necessitated use of a repeated-exposure study.

AEGL-3 VALUES

10-minute	30-minute	1-hour	4-hour	8-hour
560 ppm (2900 mg/m^3)	390 ppm (2000 mg/m^3)	310 ppm (1600 mg/m^3)	160 ppm (820 mg/m^3)	81 ppm (410 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: Mice/Swiss albino/10 males; Rats/Wistar/10 males; Guinea pigs/English short hair/10 males

Exposure Route/Concentrations/Durations: Inhalation/6450 ppm/up to 6-hr (time to death study)

Effects:
Clinical signs: Initial increased activity, followed by progressive depression; lacrimation; ptosis;exophthalmos

Mortality:
Guinea pigs: No mortality

Mice and Rats:

Time to death (hrs:min)	Cumulative Mortality	
	Mice	Rats
2:55	2/10	-
2:58	4/10	-
3:01	5/10	-
3:02	-	2/10
3:05	6/10	-
3:11	-	3/10
4:03	8/10	5/10
4:07	9/10	-
4:20	-	6/10
4:44	10/10	-

Endpoint/Concentration/Rationale: Estimated lethality threshold in mice/ One-third the concentration: time exposure causing up to 50% lethality in mice (6450 ppm ÷ 3 = 2150 ppm)

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
TMP is highly irritating, and much of the acute 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

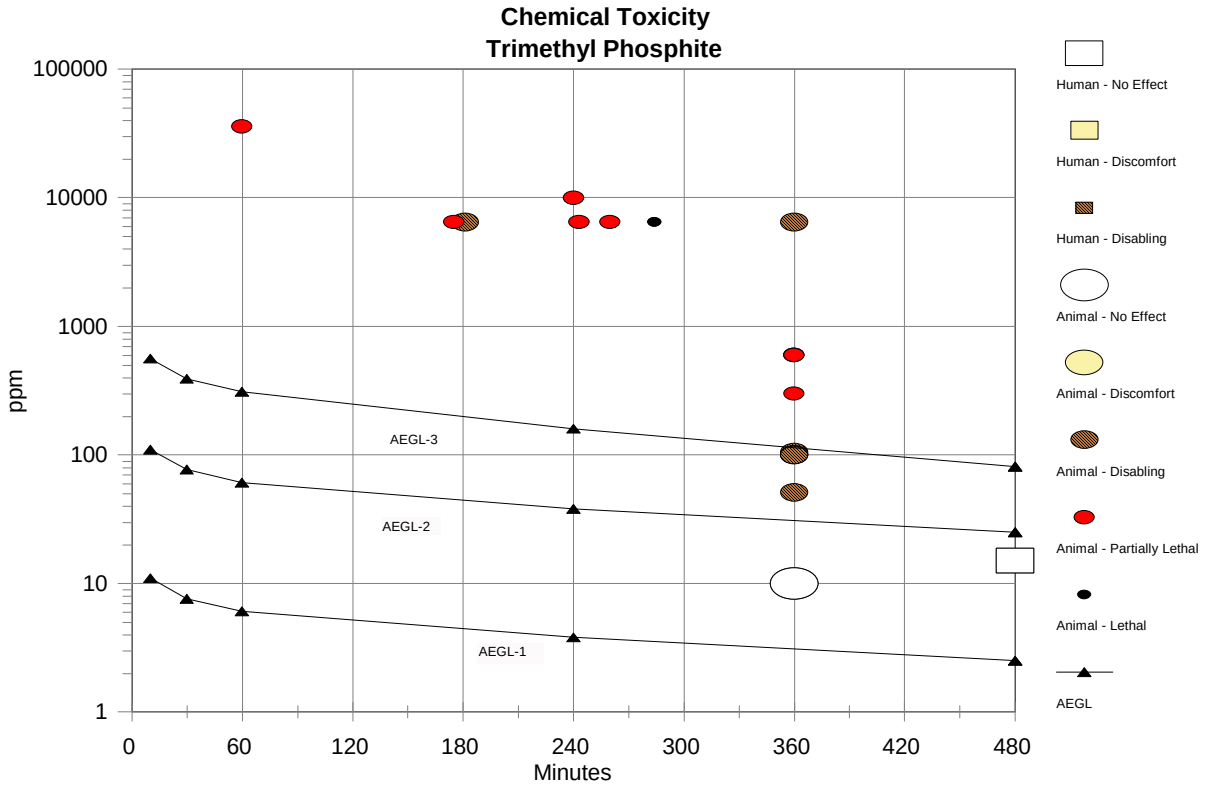
Modifying Factor: NA

Animal to Human Dosimetric Adjustment: none

Time Scaling: $c^n \times t = k$, where the exponent, n=3 when extrapolating to shorter time points (30, 60 min, 1-hr) and n = 1 when extrapolating to longer time (4- and 8-hr). (NRC, 2001)

Data Adequacy: Sparse data set. AEGL-3 values are supported by the 4-hr rat LC_{50} of >10,000 ppm (Levin and Gabriel, 1973). Dividing 10,000 ppm by three yields an estimated 4-hr lethality threshold of 3000 ppm; applying a total uncertainty factor of 10, yields a 4-hr AEGL-3 value of 300 ppm. Also, no deaths were noted in rats exposed to approximately 100 ppm TMP 6 hr/day, 5 days/week for 4 weeks (Biodymanics, 1978, 1979; Mobil Oil, 1979). These data suggest that the AEGL-3 values are protective.

APPENDIX C: Category Plot for Trimethyl Phosphite



1 **Category Plot Data**
2
3

Source	Species	Sex	# Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				11	10	AEGL	
NAC/AEGL-1				7.6	30	AEGL	
NAC/AEGL-1				6.1	60	AEGL	
NAC/AEGL-1				3.8	240	AEGL	
NAC/AEGL-1				2.5	480	AEGL	
NAC/AEGL-2				110	10	AEGL	
NAC/AEGL-2				77	30	AEGL	
NAC/AEGL-2				61	60	AEGL	
NAC/AEGL-2				38	240	AEGL	
NAC/AEGL-2				25	480	AEGL	
NAC/AEGL-3				560	10	AEGL	
NAC/AEGL-3				390	30	AEGL	
NAC/AEGL-3				310	60	AEGL	
NAC/AEGL-3				160	240	AEGL	
NAC/AEGL-3				81	480	AEGL	
	rat		1	6450	181	2	Clinical signs, depression, lacrimation; no mortality
	rat		1	6450	243	pl	5/10 mortality
	rat		1	6450	260	pl	6/10 mortality
	mouse		1	6450	175	pl	2/10 mortality
	mouse		1	6450	284	3	10/10 mortality
	gp		1	6450	360	2	Clinical signs, depression, lacrimation
	rat		1	35885	60	pl	LC50
	rat		1	10000	240	pl	LC50
	rat		20	105	360	2	Lens opacity
	rat		20	600	360	pl	Corneal opacity, partial mortality
	rat		20	10	360	0	No effects
	rat		20	51	360	2	Lens opacity
	rat		20	101	360	2	Lens opacity
	rat		20	100	360	2	Lens opacity
	rat		20	300	360	pl	partial mortality
	rat		20	600	360	pl	partial mortality
	human			15	480	0	No effect in worker exposures

4