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ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

BIPHENYL

(CAS Reg. No. 92-52-4)

$C_{12}H_{10}$

INTERIM

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

Biphenyl (CAS 92-52-4) is a colorless to white solid at ambient temperature and pressure. The chemical is an aromatic hydrocarbon and has a peculiar, strong odor similar to that of geraniums. Biphenyl is used in industry as a heat-transfer agent and a fungistat for citrus crops. Biphenyl inhalation or dermal contact can cause headaches, eye and throat irritation and nausea. Production and use of biphenyl have decreased due to restrictions now in place on the use of polychlorinated biphenyls (PCBs) which biphenyl was used in the derivation of.

AEGL-1 or AEGL-3 values were not derived for this chemical due to inadequate data.

AEGL-2 values were derived from a chronic inhalation study in mice exposed to 316 mg/m^3 (50 ppm) biphenyl 7 hours/day, 5 days/week for 13 weeks. The report states some adverse clinical signs were observed but they are not stated. Upon histopathological examination, tracheal hyperplasia was recorded.(Cannon Laboratories 1977). An acute inhalation study exposing mice to 271 mg/m^3 (43 ppm) for 4 hours was considered for derivation; however, the higher exposure in the chronic study was used because of the delayed effects possible with biphenyl exposures. Extrapolation to different exposure durations was performed using the equation $C^n \times t = k$ (ten Berge et al. 1986), where n=3 for extrapolation to 30-min, 1 hour and 4 hours and n=1 for extrapolation to 8 hours. A total uncertainty factor of 10 was applied for the AEGL-2 values with 3 for interspecies variability because the mouse was the most sensitive species and had clinical signs similar to other species; and 3 for intraspecies variability. Application of a higher uncertainty factor leads to unrealistically low values when compared to existing occupational standards. According to Section 2.7 of the AEGL SOP (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of $4 hours. Therefore, the 30-minute AEGL-2 value was also adopted as the 10-minute value. The AEGL-1, AEGL-2 and AEGL-3 derived values are listed in the table below.

Summary of AEGL Values for Biphenyl						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to inadequate data
AEGL-2 (Disabling)	12 ppm (76 mg/m ^{3})	12 ppm (76 mg/m ^{3})	9.6 ppm (61 mg/m ^{3})	6.0 ppm (38 mg/m ^{3})	4.4 ppm (28 mg/m ^{3})	Cannon Laboratories, 1977
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Not recommended due to inadequate data

NR = not recommended, ppm - parts per million, m/m^3 = milligrams per cubic meter

References:

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1. INTRODUCTION

Biphenyl is a colorless to white solid with a peculiar, strong odor. The National Fire Protection Association classifies biphenyl as a combustible solid. Biphenyl is used as a heat-transfer agent and as a fungistat for citrus fruits.(ACGIH 1991). Biphenyl was originally used in the production of polychlorinated biphenyls (PCBs); however, the production and use of PCB compounds in many countries, including the USA, is either restricted or prohibited thus making the levels of biphenyl in the production workplace much lower.

Biphenyl is currently produced commercially in the United States primarily by three chemical companies. Biphenyl is produced by either the hydrodealkylation of toluene to benzene or by direct dehydrocondensation of benzene. In the 1990's, the estimated volume of production was in the range of 10-14 million kg/year. (Thompson 1992).

Potential symptoms of overexposure include: eye/throat irritation, headaches, and nausea. The most common routes of exposure are through inhalation or dermal absorption. (NIOSH 2004)

Selected chemical and physical properties of biphenyl are listed in Table 1.

Table 1. Chemical and Physical Data

Characteristic/Property	Data	Reference
Common name	Biphenyl	O'Neil et al. 2001
Synonyms	Diphenyl, 1,1'- Diphenyl, Phenylbenzene	O'Neil et al. 2001
CAS Registry No.	92-52-4	O'Neil et al. 2001
Chemical formula	$C_{12}H_{10}$	O'Neil et al. 2001
Molecular weight	154.2 g/mol	O'Neil et al. 2001
Physical state	colorless to white solid with pleasant odor	O'Neil et al. 2001
Vapor pressure	.0005 mm Hg at 20 ºC	NIOSH 2004
Density (water = 1)	1.04	O'Neil et al. 2001
Specific Gravity	0.991	NIOSH 2004
Melting point	70 ºC	IPCS 1994
Boiling point	256 ºC	O'Neil et al. 2001
Flash point	113 ºC	IPSC 1994
Explosive limits (volume % in air)	Upper limit- 5.8 (166 ºC) Lower limit- 0.6 (111ºC)	IPSC 1994
Solubility (in water)	Insoluble	O'Neil et al. 2001
Conversion factors	1 mg/m^3 = 0.158 ppm 1ppm= 6.31 mg/m^3	NIOSH 2004

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of human fatalities from acute biphenyl exposure were found.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold

The odor threshold for biphenyl is 0.0095 ppm or 0.06 mg/m^3 . The characteristic odor is pleasant and butter-like. (AIHA 1995). Data were not adequate to derive a LOA.

2.2.2. Experimental Studies

Insufficient data were available concerning case reports in humans with biphenyl.

2.2.3. Epidemiologic Studies/Occupational Exposures

No epidemiologic studies were found concerning human exposure to biphenyl.

Occupational exposure at a factory producing biphenyl-impregnated paper for fruit wrapping resulted in a fatality due to liver necrosis/cirrhosis in a worker regularly exposed to biphenyl. (Hakkinen et al. 1973). Exposure came from biphenyl-impregnated paper produced under poor hygienic conditions. Average air concentrations of biphenyl ranged from 4.4- 128 mg/m^3 (0.7- 20.3 ppm) in 1959 to 0.6-123 mg/m^3 (0.1- 20 ppm) in 1970. Other workers consistently exposed to these concentrations exhibited clinical signs of headaches, gastrointestinal symptoms, fatigue and numbness/aching of limbs. Liver biopsies through fine-needle aspirates were done on eight workers and changes were found on three, including incipient liver cirrhosis and fatty changes. Neurological tests were conducted on twenty-four workers. (Seppalainen 1975). Ten men showed electroencephalographic (EEG) abnormalities of a diffuse nature and nine had electromyographic (EMG) abnormalities in the peripheral nervous system.

2.2.4. Clinical Studies

Some clinical studies reported on dermal exposure to copying paper but specific amounts of biphenyl in the paper were not included. Most reactions were minimal.

2.3. Neurotoxicity

As stated above, long-term exposure to biphenyl via inhalation can result in central and peripheral nervous system signs.

2.4. Developmental/Reproductive Toxicity

Human developmental or reproductive toxicity studies with biphenyl are not available.

2.5. Genotoxicity

Studies on genotoxic effects of biphenyl in humans are not available.

2.6. Carcinogenicity

Biphenyl is currently listed as a Classification D- not classifiable as a human carcinogen, and

there is no carcinogenic data reported in humans. (U.S. EPA 2000).

2.7. Summary

Studies using biphenyl in humans are limited. Most of the data collected are through incidental occupational exposures like those witnessed in employees working at the paper impregnation factory. These effects appear to be via inhalation and/or dermal contact. At lower levels, clinical signs range from headache, fatigue, and gastrointestinal symptoms to those associated with the central/peripheral nervous system. Chronic high-dose exposure appear to contribute to hepatic changes. No data were found on genotoxic, developmental or reproductive toxicity in humans. The current EPA listing on biphenyl is Classification D, not classifiable as a human carcinogen.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

No single exposures clearing showing lethality in experimental animals are available.

3.2. Acute Nonlethal Toxicity

Animal studies for acute nonlethal and repeat exposures are summarized below in Table 2.

3.2.1. Rats

In an acute inhalation study, six Sprague-Dawley albino rats were exposed to 5 or 19 mg/m^3 (0.8 or 3.0 ppm) biphenyl vapor for six hours with no reported abnormalities in appearance or behavior during the exposure. (Younger Laboratories 1959). Rats were exposed in a metal chamber of 75 liter capacity. In the 5 mg/m^3 (0.8 ppm) biphenyl exposure, the chamber temperature was maintained at 80 EF by a 120 watt light bulb. Biphenyl was placed on a petri dish placed inside the chamber with no air added to the chamber. In the 19 mg/m^3 (3.0 ppm) exposure, the chamber temperature was maintained at 100 EF by adding another light bulb. Ten liters of air were added to the chamber in this exposure by adding five liters twice. Sacrifices were not performed for gross or histopathological examinations.

In another acute inhalation study, four Sprague-Dawley rats were exposed to biphenyl at a nominal concentration of 3.02 mg/L for seven hours. (Dow Chemical Co. 1974). Rats were placed in a 28.3 liter chamber. Air was added to chamber at a rate of 3 liters/minute through a bubbler containing the biphenyl. The biphenyl was heated to 85 EC. Rats exhibited no change in appearance, demeanor, food consumption, or survival although no documentation was included in the study report.

Six CFE female albino rats were exposed eight hours to 95% pure grade biphenyl. Fifty milliliters of the material was contained in a bubbler submerged in a silicone bath held at 176 EC. Air was added at a rate of 2.5 liters/minute through the mist, and the temperature within the nine liter chamber was maintained at 27 EC. No actual concentration numbers were provided. Rats showed no clinical signs during exposure and for 14 days post-exposure. Weight gain was normal. Rats were sacrificed at day 14, no gross abnormal pathology was reported. (Mellon Institute 1961).

3.2.2. Mice

In an acute inhalation study, 10 male and 10 female mice per group were exposed to 88, 240 or 271 mg/m^3 (14, 38 or 43 ppm) biphenyl for 4 hours. (Cannon Laboratories 1977). A flask containing test material submerged in a heated water bath provided the vapor. Air passed through the flask at 5.0 liters/min into a 40 liter glass chamber. At least four samples were taken per exposure to determine biphenyl concentration. These samples were taken through two in-series impingers containing 20 ml cylcohexane each and the resulting solution was analyzed by UV absorption. One mouse in the 271 mg/m^3 (43 ppm) group died during the exposure (after 2 hours). The report stated this was not considered to be compound-related; however, no evidence to support this was included in the report. In the 88 mg/m^3 (14 ppm) dose group, mice had shallow respiration. Every dose group exhibited clinical signs of hyperactivity during exposure with the 240 mg/m^3 (38 ppm) and 271 mg/m^3 (43 ppm) dose groups also showing rapid respiration and nasal discharge. On Day 1 post-exposure, moderate weight loss was noted in the 240 mg/m^3 (38 ppm) and 271 mg/m^3 (43 ppm) dose groups but this trend reversed to normal. No weight gain tables were provided. Five females were sacrificed for gross pathological examination on Day 2 post-exposure, and five males on Day 3 post-exposure in the 240 mg/m^3 (38 ppm) and 271 mg/m^3 (43 ppm) dose groups, respectively. The remaining animals were observed daily for 14 days post-exposure and then sacrificed. Slight lung congestion was reported in gross pathological examination but was not dose dependent. The author concluded the LC_{50} for biphenyl is greater than 271 mg/m^3 (43 ppm) in mice.

3.3. Repeat Exposure Studies

Animal studies for acute nonlethal and repeat exposures are summarized below in Table 2.

3.3.1. Rats

Ten rats (sex and species not identified) were exposed to 50% biphenyl dust on zeolite at an average concentration of 300 mg/m^3 (48 ppm). (Monsanto Co. 1946). The exposure was 7 hours/day for 64 sessions. Animals were exposed in a 160 liter capacity inhalation chamber. Air was introduced into the chamber at a rate of 10 to 20 L/min. The biphenyl was dispersed into the stream of air by a “dustshaker” . This is a spring-activated rotating drum fitted with a sieve to hold the compound. This constantly shakes by tightening and loosening of the spring. This

motion causes the compound to fall from the sieve into the airstream. Concentrations of the material were controlled by varying the temperature and the flow of air through the chamber. Air concentration of biphenyl were determined based on a reaction with butanone; however, information on the frequency of checking the air concentration was not included. All rats exhibited a nasal serosanguinous discharge indicative of nasal mucosa irritation. Five of the ten rats exposed died. Deaths occurred after the 29th, 30th, 34th, 46th and 49th exposure. Survivors exhibited an average weight loss of 20 grams. Subsequent exposures to the same material at concentrations of 40 mg/m^3 (6.0 ppm) and 5 mg/m^3 (0.8 ppm) were reported. Six rats were exposed to the 40 mg/m^3 for 7 hours/day for 46 days and four to the 5 mg/m^3 for 7 hours/day for 62 days. At the 40 mg/m^3 concentration, one rat died after the 29th exposure and the rest exhibited nasal mucosa irritation and normal weight gain. No clinical signs or fatalities were reported at the 5 mg/m^3 concentration

3.3.2. Mice

Twelve mice (sex and species not identified) were exposed to 5 mg/m^3 (0.8 ppm) of 50% biphenyl dust on zeolite for seven hours/day for 62 days. Two mice died after the 33rd and 62nd exposure and all exhibited upper respiratory irritation. (Monsanto Co. 1946). Animals were exposed in a 160 liter capacity inhalation chamber. Air was introduced into the chamber at a rate of 10 to 20 L/min. The biphenyl was dispersed into the stream of air by a “dust-shaker” as described in rat study above. Concentrations of the material were controlled by varying the temperature and the flow of air through the chamber. Air concentrations of biphenyl were determined based on a reaction with butanone; however, information on the frequency of checking the air concentration was not included.

In a subacute inhalation study, 10 male and 10 female mice per group were exposed to 0, (controls) , 156 or 345 mg/m ^{3} (24.8 or 54.75 ppm) biphenyl 7 hours/day, 5 days/week for 2 weeks. (Cannon Laboratories 1977). A flask containing test material was placed in a submerged heated oil bath. Air was passed through the flask at 5.0 liters/min into a 40 liter exposure chamber. At least four samples were taken per exposure to determine biphenyl concentration. Samples were taken through two in-series impingers containing 20 ml cylcohexane each with the resulting solution analyzed by UV absorption. During exposure, no abnormal signs were observed in the control group, although 1/10 females was found dead prior to exposure #10. Mice exposed to 156 mg/m ^{3} (24.8 ppm) showed hyperactivity (exposures 1-3), closed eyes (all exposures) and 1/10 females was found dead prior to exposure #3. The 345 mg/m ^{3} (54.7 ppm) dose group showed hyperactivity (exposures 1-5), mild hyperemia (exposures 1-5) and closed eyes (all exposures). One-half of each dose group was sacrificed after the last exposure and the remaining after a 14-day recovery. During the 14-day recovery period, no abnormal clinical signs were noted. Gross and histopathological examination of the trachea, lung, spleen, liver and kidney reported no findings in any group except for severe lung congestion in the female found dead in the 156 mg/m ^{3} (24.8 ppm) group.

In a subchronic inhalation study, 50 male and 50 female CD-1 mice per group were exposed to 0 (controls), 0, 158 or 316 mg/m^3 (25 or 50 ppm, respectively) biphenyl for 7 hours/day, 5 days/week for 13 weeks. (Cannon Laboratories 1977). The inhalation chamber was a ½ cubic meter stainless steel Rochester type with glass windows on all four sides. Two ports (3 and 7 mm) were located on opposite sides of the chamber. The animals' position within the chamber was rotated daily. A flask containing test material was submerged in a hot oil bath. Air was introduced into the flask, into a heated connecting tube and then into the chamber via the 7 mm port. A vacuum pump provided air flow at a positive 2 liters/min. Samples to confirm concentration levels of biphenyl were taken twice daily. Samples were taken through two in-series impingers containing 20 ml cylcohexane each and the resulting solution was analyzed by UV absorption with a spectrophotometer. A standard curve of biphenyl in cylcohexane was developed each week. No adverse clinical signs during exposure were reported. Mice were weighed weekly and no significant weight losses occurred in any dose groups. During the exposure period, forty-six mice died as a consequence of accidental overheating of the animal room. They were replaced. At the end of the exposures, ten mice of each sex from each dose group were held for a 30 day recovery period while the rest were sacrificed immediately. Immediate sacrifice animals were placed in a metabolism cage for urine collection. Blood was collected for clinical chemistry and hematology prior to sacrifice. Urinalysis and blood collection were also done on the 30 day recovery group prior to their sacrifice. Urinalysis, clinical chemistries and hematology results showed no remarkable changes between controls and treated groups nor between the immediate and 30 day post-exposure sacrifice groups. Histopathological examination did reveal some differences in the dose groups. In the animals immediately sacrificed, microscopic exam resulted in diagnoses of tracheal hyperplasia and inflammation in 70/71 (99%) of the high-dose group, 80/98 (82%) of the low-dose group and 0/80 of the controls. In the 30 day recovery groups, tracheal hyperplasia and inflammation were reported in 5/19 (26%) for the 316 mg/m^3 (50 ppm) group; 2/15 (13%) for the 158 mg/m^3 (25 ppm) group and 3/20 (15%) in the controls. This suggests recovery of the damage with time. Lung congestion seen in all groups was thought to be from the anesthetic used at sacrifice as stated by the pathologist. From this study, there appears to be a dose related increase in tracheal hyperplasia and inflammation with inhalation exposure to biphenyl.

3.3.3. Rabbits

Three rabbits were exposed to concentrations of 300 mg/m^3 or 40 mg/m^3 (48 or 6.0 ppm) of 50% biphenyl dust on zeolite for 7 hours/day for 64 periods and 46 periods, respectively, with no clinical signs reported.(Monsanto Co. 1946). Animals were exposed in a 160 liter capacity inhalation chamber. Air was introduced into the chamber at a rate of 10 to 20 L/min. As described earlier, the biphenyl was dispersed into the stream of air by a "dust-shaker". Concentrations of the material were controlled by varying the temperature and the flow of air through the chamber. Air concentrations of biphenyl were determined based on a reaction with butanone; however, information on the frequency of checking the air concentration was not included.

Table 2. Biphenyl animal studies

Concentration	Exposure Time	Species	Effects	References
5.0 mg/m ^{3} (0.8 ppm)	6 hours	Rat	no abnormalities noted	Younger Labs 1959
19 mg/m ^{3}(3.0 ppm)	6 hours	Rat	no abnormalities noted	Younger Labs 1959
Nominal concentration of 3.02 mg/L	7 hours	Rat	no abnormalities noted in appearance, demeanor, food consumption or survival	Dow Chemical Co. 1974
None given- only 95% purity	8 hours	Rats	no clinical signs, fatalities or gross autopsy results normal weight gain.	Mellon Institute 1961
88.3 mg/m ^{3} (14 ppm)	4 hours	Mice	hyperactivity and shallow respiration during exposure gross path. examination- sl. lung congestion	Cannon Labs. 1977
240 mg/m ^{3}(38 ppm)	4 hours	Mice	hyperactivity, rapid respiration and nasal discharge during exposure wt. loss on Day 1 post-exposure only gross path. examination- sl. lung congestion	Cannon Labs. 1977
271 mg/m ^{3} (43 ppm)	4 hours	Mice	death (1/10 @ 2 hrs- not cmpd related) hyperactivity, rapid respiration and nasal discharge during exposure wt. loss on Day 1 post-exposure only gross path. examination- sl. lung congestion	Cannon Labs. 1977
5 mg/m^3 (0.8 ppm)	7 hrs/day x 62 days	Rat	no clinical signs or fatalities	Monsanto Co. 1946
40 mg/m^3 (6.0 ppm)	7 hrs/day x 46 days	Rat	nasal serosanguineous discharge (6/6) death (1/6) normal wt. gain in survivors	Monsanto Co. 1946
300 mg/m^3 (48 ppm)	7 hrs/day X 64 days	Rat	nasal serosanguineous discharge (10/10) death (5/10) wt. loss in survivors	Monsanto Co. 1946
5 mg/m^3 (0.8 ppm)	7 hrs/day x 62 days	Mice	upper respiratory irritation (12/12) death (2/12)	Monsanto Co. 1946

0 (control)	7 hrs/day x 5 days/wk x 2 wks	Mice	death (1/10) no gross/histopath abnormalities	Cannon Labs. 1977
156 mg/m ^{3} (24.8 ppm)	7 hrs/day x 5 days/wk x 2 wks	Mice	death-lung congestion noted (1/10) hyperactivity (all exposures) eyes closed (all exposures) no gross/histopath abnormalities	Cannon Labs. 1977
345 mg/m ^{3} (54.75 ppm)	7 hrs/day x 5 days/wk x 2 wks	Mice	hyperactivity (exp. 1-5) eyes closed (all exposures) mild hyperemia (exp. 1-5) no gross/histopath abnormalities	Cannon Labs. 1977
0 (controls)	7 hrs/day x 5 days/wk x 13 wks	Mice	no clinical signs seen in exposure Immediate sacrifice: tracheal hyperplasia (histopath) (0/80**)** 30 day sacrifice: tracheal hyperplasia (histopath) (3/20)	Cannon Labs. 1977
158 mg/m ^{3} (25 ppm)	7 hrs/day x 5 days/wk x 13 wks	Mice	No clinical signs seen in exposure Immediate sacrifice: tracheal hyperplasia (histopath) (80/98) 30 day sacrifice:tracheal hyperplasia (histopath) (2/15**)**	Cannon Labs. 1977
316 mg/m ^{3} (50 ppm)	7 hrs/day x 5 days/wk x 13 wks	Mice	No clinical signs seen in exposure Immediate sacrifice: tracheal hyperplasia (histopath) (70/71) 30 day sacrifice: tracheal hyperplasia (histopath) (5/19)	Cannon Labs. 1977
40 mg/m^3 (6.0 ppm)	7 hrs/day x 46 days	Rabbits	No signs of toxicity noted	Monsanto Co. 1946
300 mg/m^3 (48 ppm)	7 hrs/day x 64 days	Rabbits	No signs of toxicity noted	Monsanto Co. 1946

3.4. Neurotoxicity

There is no evidence of neurotoxic effects reported in the animal studies examined.

3.5. Developmental/Reproductive Toxicity

The only developmental/reproductive toxicity studies found on biphenyl were oral feeding studies, not inhalation. In one example, biphenyl was administered to Long Evans rats in the diet with concentrations of 0%, 0.01% (100 ppm), 0.1 % (1,000 ppm) or 1.0% (10,000 ppm) biphenyl for 3 generations (Dow Chemical Co. 1953). Offspring in each generation were fed the same diet as their parents. Rats receiving the control, 0.01% and 0.1% diets exhibited no

differences in fertility, lactation, size of litter or growth/mortality of the offspring. The 1% diet, however, caused effects including decreased fertility, smaller litter sizes and statistically smaller growth rates for the pups. No evidence of cumulative toxicity appeared on autopsy examination. Although body weight and food consumption data were not given, the author concluded that the adverse effects on fertility in the high-dose group can be attributed to the unpalatability of the diet rather than an effect of the chemical.

3.6. Genotoxicity

Biphenyl did not cause a positive reaction in mutagenicity testing in *Salmonella typhimurium* strains TA100, TA98, TA1535, TA1537, TA1538, TA1532 and TA2636 assays with and without metabolic activation at dose levels of 0.1 to 500 Fg/plate. Metabolic activation was performed by rat and hamster liver microsomal fraction (S-9) and phenobarbitol-induced mouse liver S-9 fraction. Positive controls dosed at the same time exhibited appropriate responses. (Pagano et al. 1983).

Yeast, *Saccharomyces cerevisiae* strain D7, exposed to biphenyl exhibited mutagenic changes with and without mouse liver S-9 metabolic activation. (Pagano et al. 1983). The addition of the S-9 fraction enhanced the effects.

In a study of bone-marrow chromosome abberations, five male rats per group were exposed by inhalation to 0 (control group), 64 or 320 mg/m^3 (10 or 50 ppm, respectively) biphenyl for 7 hours/day, 5 days/week for 30 days (20 exposures). The control group was held unexposed. Inhalation occurred by aerosolizing molten compound at a controlled rate with a positive pressure spray nozzle entering the chambers. At the end of the 30 days, bone marrow cell slides were prepared. In the 50 metaphase spreads per animal examined, no increased frequency of chromosome aberrations were noted in the treated group. (Dow Chemical Co. 1976).

3.7. Chronic Toxicity/Carcinogenicity

There is no data on chronic inhalation studies using biphenyl. Many oral feeding studies have been conducted and none found biphenyl increased any type of tumor production.

3.8. Summary

The toxicity of biphenyl has been studied in three mammalian species. All studies located, however, were lacking in details and used dated methodology. Based on those reviewed, the mouse appears to be the most sensitive species and the rabbit the least. The most common toxic side effects reported were those related to the respiratory tract with eye irritation to a mild degree noted also. A lack of inhalation studies in the reproductive, developmental and carcinogenicity areas makes correlation between animals and human more difficult. Animal feeding studies showed chronic toxic effects in the kidney rather than the liver necrosis/cirrhosis that was

reported in a human with chronic exposure.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Absorption of biphenyl occurs with inhalation, gastrointestinal and dermal exposure as seen in results of human occupational exposure and laboratory animal testing. Exact distribution of biphenyl after absorption is unclear, however, it travels to the liver where it undergoes hydroxylation and conjugation.

Studies providing quantitative data on the metabolism of biphenyl in humans were not identified. However, in laboratory animals, different metabolites have been identified following dosing and absorption of biphenyl (Meyer and Scheline, 1976). Rats were administered 100 to 400 mg biphenyl/kg via stomach tube or intracecal injection. Urine and feces were collected for 24 hrs periods. Bile samples were also obtained. The main route of excretion was in the urine and most of the biphenyl metabolites were recovered in the first 24 hours. Total urine recovery of metabolites after biphenyl administration (96 hours) was 29.5% of the dose. The prevalent metabolites found in the urine were conjugates of mono-, di-, and tri-hydroxybiphenyl derivatives of biphenyl. The main ones were 4-hydroxybiphenyl and 4,4'-dihydroxybiphenyl. These metabolites were identified in the feces as well but at much lower levels. The prominent biliary metabolites of biphenyl are conjugates and were 4-hydroxybiphenyl, 4-4'-dihydroxybiphenyl and 3,4,4'-trihydroxybiphenyl and were 5.2% of the dose. Biphenyl forms these metabolites by undergoing hydroxylation and conjugation in the liver prior to excretion.

4.2. Mechanism of Toxicity

In human exposure, the most common toxic effects reported are nausea, eye and nasal irritation at lower acute doses and hepatic changes at chronic doses. The acute effects can be accounted for biphenyls' characteristic odor and its affinity for inhalation absorption through mucous membranes**.** Chronic toxic effects through inhalation and/or dermal contact result from biphenyl being absorbed and then metabolized by the liver into the water-soluble hydroxy derivatives. (Bingham et al. 2001)

4.3. Structure Activity Relationships

No data on the structure activity relationships of biphenyl were available.

4.4. Other Relevant Information

4.4.1. Species Variability

Species differences were observed in inhalation studies of rats, rabbits and mice. Rabbits appeared to be the least affected out of three species tested with no adverse effects seen upon exposure to biphenyl in the form of dust (50% biphenyl in zeolite) at concentrations of 40 or 300 mg/m^3 for 7 hours/day for at least 46 days. Rats in these dose groups exhibited increased mortality and mucus membrane irritation. Mice exposed to a much lower concentration 5 mg/m^3 exhibited slightly increased mortality and all had upper respiratory tract irritation. Based on this data, mice appear to be the most sensitive species.(Monsanto Co. 1946).

4.4.2. Susceptible Populations

No information on susceptible populations was identified.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases can be described by the relationship $c^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data were unavailable for an empirical derivation of *n* in the equation, $C^n \times t = k$. In the absence of chemical specific data, an *n* of 3 will be applied to extrapolate to shorter time periods, and an *n* of 1 will be applied to extrapolate to longer time periods, to provide AEGL values that would be protective of human health (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

While the U.S. Department of Labor states that exposure to 5. 0 mg/m^3 (0.8 ppm) or greater can cause throat and eye irritation, no formal data has been collected. Therefore, human data were not used for AEGL-1 determination.

5.2. Summary of Animal Data Relevant to AEGL-1

Adequate data for the derivation of AEGL-1 are not available therefore no recommended levels are set.

5.3. Derivation of AEGL-1

Due to insufficient data available on biphenyl in either animal or human studies, AEGL-1 levels could not be established.

Table 3. AEGL-1 Values for Biphenyl				
10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Human data relevant for deriving AEGL-2 levels were not found.

6.2. Summary of Animal Data Relevant to AEGL-2

Effects in animals which are applicable to the AEGL-2 definition were identified. Some clinical signs recorded in an acute inhalation study exposing mice to 271 mg/m ^{3} (43 ppm) were nasal discharge and rapid respiration. One mortality occurred in this study at this dose range but the study stated it was not compound related. Two additional studies by this same laboratory for longer time periods, 2 weeks/13 weeks, exposing mice to 345 mg/m ^{3} (57.5 ppm) and 316 mg/m ^{3} (50 ppm), respectively showed no mortalites. Animals did have treatment-related histopathological changes in the trachea in a dose-related trend in the 13 week study but no clinical signs during the exposures. Due to biphenyl's affinity for chronic toxicity, the 13 week study shall be utilized in the AEGL-2 value derivation.

6.3. Derivation of AEGL-2

The chronic inhalation study exposing mice to 316 mg/m ^{3} (50 ppm) biphenyl 7 hrs/day, 5 days/week for 13 weeks will be utilized in deriving AEGL-2 levels (Cannon Laboratories, 1977). No mortalities or clinical signs occurred during the exposure. An acute 4 hour inhalation study exposing mice to 271 mg/m ^{3} (43 ppm) biphenyl was not utilized in creating the AEGL-2 values because of biphenyl's affinity for delayed side effects. Another Cannon Laboratories' study exposed mice to 345 mg/m ^{3} (54.75 ppm) biphenyl for 7 hrs/day, 5 days/week for 2 weeks with no mortalities. In the chronic study used, tracheal hyperplasia was recorded in a dose-related trend. The incidence rate of the hyperplasia lessened in those rats allowed a 30 day recovery suggesting a reversibility to the finding. Extrapolation to different exposure durations was performed using $C^n \times t = k$. (ten Berge et al. 1986) where n=3 for extrapolation to 30-min, 1 hour and 4 hour and n=1 for extrapolation to 8 hour. A total uncertainty factor of 10 was applied for the AEGL-2 values. An interspecies variability of 3 was utilized because the mouse was the most sensitive and had clinical signs similar to other species, and an intraspecies variability of 3 because defaulting to 10 makes values too close to occupational standards. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental

exposure time of $4 hours. Therefore, the 30-minute AEGL-2 value was also adopted as the 10-minute value. AEGL-2 values are presented in Table 5 and calculations described in Appendix A.

Table 4. AEGL-2 Values for Biphenyl

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
12 ppm (76 mg/m ^{3})	12 ppm (76 mg/m ^{3})	9.6 ppm (61 mg/m ^{3})	6.0 ppm (38 mg/m ^{3})	4.4 ppm (28 mg/m ^{3})

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human data included a fatal liver episode in an individual continually exposed to a biphenyl concentration of at least 120 mg/m^3; however, no additional contributing factors were reported. The exact concentration causing the fatality was never quantified making human data unsuitable for deriving AEGL-3 levels.

7.2. Summary of Animal Data Relevant to AEGL-3

Adequate data for the derivation of AEGL-3 are not available therefore no recommended levels are set.

7.3. Derivation of AEGL-3

Due to insufficient data available on biphenyl in either animal or human studies, AEGL-3 levels could not be established.

Table 5. AEGL-3 Values for Biphenyl

10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
NR	NR	NR	NR	NR

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

The derived values for AEGL levels of biphenyl are presented in Table 6. No values were derived for AEGL-1 or AEGL-3. A subchronic inhalation study with a biphenyl concentration

causing no mortality in mice was used for the derivation of AEGL-2.

Table 6. Summary of AEGL Values for Biphenyl

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	76 mg/m^3 (12 ppm)	76 mg/m^3 (12 ppm)	61 mg/m^3 (9.6 ppm)	38 mg/m^3 (6.0 ppm)	28 mg/m^3 (4.4 ppm)
AEGL-3 (Lethality)	NR	NR	NR	NR	NR

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for the workplace are summarized in Table 5. The OSHA PEL-TWA is 0.2 ppm for an 8 hour period. (OSHA 1999). The IDLH was revised by NIOSH in 1996 to 16 ppm. The ACGIH established 0.2 ppm as the TLV-TWA for 8 hours with the lung being the most susceptible organ. (ACGIH 2003). German, Dutch and Swedish occupational exposure levels are concurrent with the United States at 0.2 ppm for an 8 hour period. Occupational exposure limits found are presented in Table 7.

Table 7. Extant Standards and Guidelines for Biphenyl

Guideline	Exposure Duration				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	12 ppm 76 mg/m^3	12 ppm 76 mg/m^3	9.6 ppm 61 mg/m^3	6.0 ppm 38 mg/m^3	4.4 ppm 28 mg/m^3
AEGL-3	NR	NR	NR	NR	NR
PEL-TWA (OSHA)[a]					0.2 ppm
IDLH (NIOSH)[b]		16 ppm (100 mg/m^3)			
REL-TWA (NIOSH)[c]					0.2 ppm (10 hour TWA)
TLV-TWA (ACGIH)[d]					**0.2 ppm (lung)**
MAK (Germany)[e]					0.2 ppm
MAC (Dutch)[f]					0.2 ppm
LLV (Sweden)[g]					0.2 ppm
STV (Sweden)[h] (15-min)	0.4 ppm				

a- OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA 1999) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

b- IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH 2004) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

c- NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average) (NIOSH 2004) Recommended exposure level to diphenyl.

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d- ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2003) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect**.**

e- MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA.

f- MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) Nationale MAC list 2000. The Hague, SDU Uitgevers (under the auspices of the Ministry of Social Affairs and Employment) The Netherlands. Defined analogous to the ACGIH-TLV-TWA.

g- LLV (Level Limit Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health. Defined as an occupational exposure limit value for exposure during one working day.

h- STV (Short-Term Value) Swedish Occupational Exposure Limits. 2000. By Ordinance of the Swedish National Board of Occupational Safety and Health. Defined as a recommended value consisting of a time-weighed average for exposure during a reference period of 15 minutes.

8.3. Data Adequacy and Research Needs

Data on biphenyl inhalation studies, primarily acute, are lacking in mammalian species. No study adequately defines a LC_{50} to be used to derive AEGL values. This makes setting appropriate levels applicable to human exposure difficult. Human data are sparse and based on historical concentrations in one work-place instead of controlled exposures. If industry requires appropriate AEGL levels to be determined, additional LC_{50} studies should be performed following current animal study guidelines.

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APPENDIX A: Time Scaling Calculations for Biphenyl

DERIVATION OF AEGL-1 VALUES

Key Study: Due to inadequate data, it is not recommended that AEGL-1 values be derived.

DERIVATION OF AEGL-2 VALUES

Key Study:	Cannon Laboratories, 1977
Toxicity Endpoint:	Subchronic inhalation study causing no mortality
Scaling:	$C^n \times t = k$ n = 3 for extrapolating to the 30-min, 1-hour and 4-hour time-points $(50 \text{ ppm})^3 \times 7 \text{ hours} = 875{,}000 \text{ ppm} \cdot \text{hr}$ (30 min, 1 hr, 4 hrs AEGL) n = 1 for extrapolating to the 8 hr. time-point $(50 \text{ ppm})^1 \times 7 \text{ hrs} = 350 \text{ ppm} \cdot \text{hr}$ (8 hrs AEGL) 10-minute values are not to be scaled from an experimental exposure time of $ 4 hours. Therefore, the 30-minute AEGL-2 value was also adopted as the 10-minute value
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability
<u>10-min.AEGL-2:</u>	Use the 30 minute value for the 10 minute value 10-min AEGL-2 = 120 ppm/10 = 12 ppm or 76 mg/m ^{3}
<u>30-min. AEGL-2:</u>	$C^3 \times 0.5 \text{ hr.} = 875{,}000 \text{ ppm} \cdot \text{hr}$ $C^3 = 1{,}750{,}000 \text{ ppm}$ C = 120 ppm 30-min. AEGL-2 = 120 ppm/10 = 12 ppm or 76 mg/m ^{3}
<u>1-hr. AEGL-2:</u>	$C^3 \times 1 \text{ hr} = 875{,}000 \text{ ppm} \cdot \text{hr}$ $C^3 = 875{,}000 \text{ ppm}$ C = 96 ppm 1 hr AEGL-2 = 96 ppm/10 = 9.6 ppm or 61 mg/m ^{3}
<u>4-hr. AEGL-2:</u>	$C^3 \times 4 \text{ hr} = 875{,}000 \text{ ppm} \cdot \text{hr}$ $C^3 = 218{,}750 \text{ ppm}$ C = 60 ppm

4 hr. AEGL-2 = 60 ppm/10 = 6 ppm or 38 mg/m ^{3}

8-hr. AEGL-2: C^1 x 8 hr = 350 ppm • hr
C^1 = 44 ppm
8 hr AEGL-2 = 44 ppm/10 = 4.4 ppm or 28 mg/m ^{3}

DERIVATION OF AEGL-3 VALUES

Key Study: Due to inadequate data, it is not recommended that AEGL-3 values be derived.

APPENDIX B: Derivation Summary for Biphenyl

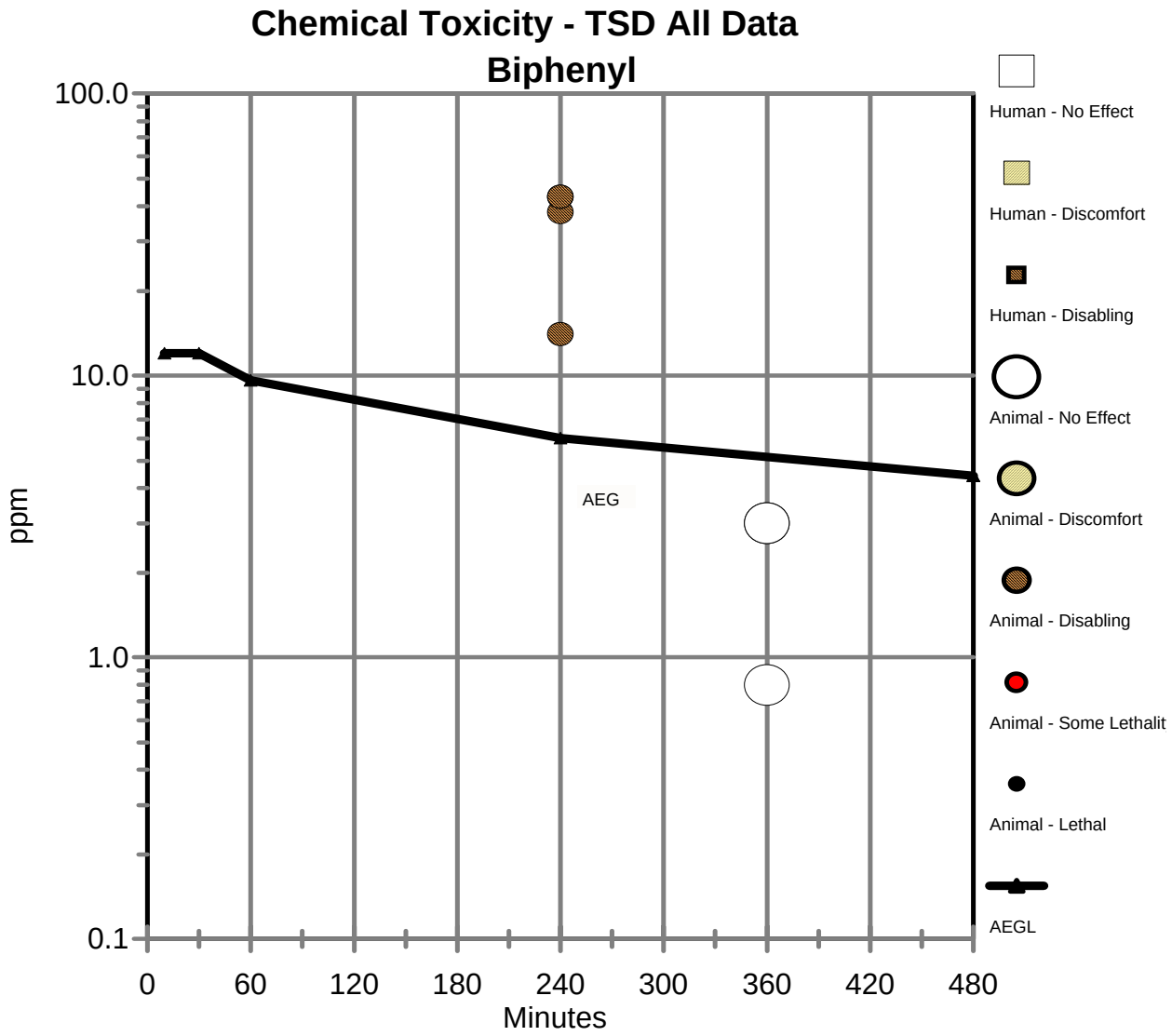
ACUTE EXPOSURE GUIDELINE LEVELS FOR BIPHENYL (CAS Reg. No. 92-52-4) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
Not Recommended	**Not Recommended**	**Not Recommended**	**Not Recommended**	**Not Recommended**
Key Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Adequacy: Numeric values for AEGL-1 were not recommended because of inadequate data. Absence of an AEGL-1 number does not ensure that exposure below AEGL-2 is safe.				

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
12 ppm	**12 ppm**	**9.6 ppm**	**6.0 ppm**	**4.4 ppm**
Key Reference: Cannon Laboratories, Inc. 1977. Final report: 90-day inhalation toxicity study of biphenyl (99+% purity) in CD-1 mice. Sponsored by Sun Company Lab. EPA Doc. No. 878213532; Fiche No. OTS0206401.				
Test Species/Strain/Number: Mice/CD-1/50 Male and 50 Female				
Exposure Route/Concentrations/Durations: Inhalation: 25 or 50 ppm, 7 hrs/day**,** 5 days/week for 13 weeks				
Effects: Histopathology: dose dependent tracheal hyperplasia				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3, clinical signs similar among different species Intraspecies: 3, using UF of 10 would produce levels too close to occupational levels				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Extrapolation to time points was done: n =3 for 30-min, 1 hr and 4 hr and n = 1 for 8 hr. The 30-minute AEGL-3 value was also adopted as the 10-minute value because 10-minute values are not to be scaled from an experimental exposure time of $4 hours.				
Data Adequacy: Insufficient human data were available. Animal studies were not thorough and a true LC_{50} was not established. Additional animal inhalation studies are recommended for more accurate guidelines to be established.				

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference: None utilized				
Test Species/Strain/Number/Sex: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling:Extrapolation to time points was not done.				
Data Adequacy: In-adequate data in humans or animals are available for AEGL-3 value derivations.				

APPENDIX C: Time-Scaling Category Plot for Biphenyl



No effect= No effect or mild discomfort
Discomfort= Notable transient discomfort/irritation
Disabling= Irreversible/long lasting effects or impaired ability to escape
Some lethality= Some, but not all, exposed animals died
Lethal= All exposed animals died