

TABLE 10.—SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHORUS TRICHLORIDE—Continued

Classification	10-minutes	30-minutes	1-hour	4-hours	8-hours	Endpoint (Reference)
AEGL-3 (Lethal)	7.0 ppm	7.0 ppm	5.6 ppm	3.5 ppm	1.8 ppm	Estimated lethality threshold based upon 3-fold reduction of guinea pig 4-hour LC ₅₀ (50.1 ppm/3 = 16.7 ppm) (Weeks et al., 1964) ^a

^aBased upon animal data, lethality may be delayed.

ii. *References.* a. Hazleton Laboratories. 1983. Subacute inhalation toxicity study in rats—phosphorus trichloride. Final Report. Project No. 241–141. Hazleton Laboratories America, Inc. Unpublished.

b. Weeks, M.H.; Mussleman, N.P.; Yevich, P.P.; Jacobson, K.H.; and Oberst, F.W. 1964. Acute vapor toxicity of phosphorus oxychloride, phosphorus trichloride and methyl phosphonic dichloride. *American Industrial Hygiene Journal*. 25:470–475.

10. *Xylenes*—i. *Description.* Xylene is found in a number of consumer products, including solvents, paints, or coatings, and as a blend in gasoline. Mixed xylenes are comprised of 3 isomers: m-xylene, o-xylene, and p-xylene, with the m-isomer predominating. Ethyl benzene is also present in the technical product formulation. Absorbed xylene is rapidly metabolized and is excreted almost exclusively in the urine as methylhippuric acid isomers in humans and as methylhippuric acid isomers and toluic acid glucuronides in animals. In both humans and animals, xylene causes irritation and effects the central nervous system following acute inhalation exposure. No consistent developmental or reproductive effects were observed in the studies found in the available literature. Commercial xylene and all 3 isomers have generally tested negative for genotoxicity. Xylenes are currently not classifiable as to its carcinogenicity by the International Agency on Research for Cancer (IARC) or the EPA because of inadequate evidence.

The AEGL-1 is based upon slight eye irritation noted during a 30-minute exposure to 400 ppm mixed xylenes (Hastings et al., 1986). An interspecies uncertainty factor was not applied because the key study used human data. An intraspecies uncertainty factor of 3 was applied because the toxic effect (slight irritation) was less severe than that defined for the AEGL-1 tier (notable discomfort). The resulting value of 130 ppm is supported by several other studies, including: A 150 ppm p-xylene exposure resulting in eye irritation in a contact lens wearer (Hake et al., 1981);

a 15-minute exposure to 230 ppm mixed xylenes resulting in mild eye irritation and dizziness in one individual; and a 3-hour exposure to 200 ppm m- or p-xylene (Ogata et al., 1970), a 4-hour exposure to 200 ppm m-xylene (Savolainen et al., 1981), and a 5.5 hour exposure to 200 ppm m-xylene (Laine et al., 1993) all representing no-effect levels.

The AEGL-2 is based upon poor coordination resulting when rats were exposed to 1,300 ppm mixed xylenes for 4 hours (Carpenter et al., 1975). This concentration represents the threshold for reversible equilibrium disturbances. This concentration and endpoint are consistent with the preponderance of available data for 4-hour exposures in rats: The EC₅₀ for decreased rotarod performance was 1982 ppm (Korsak et al., 1993); the minimum narcotic concentrations for m-, o-, and p-xylene ranged from 1,940–2,180 ppm (Molnár et al., 1986); and exposure to 1,600 ppm p-xylene resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell, 1989), induced flavor aversion (Bushnell and Peele, 1988), and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al., 1988). In dogs, exposure to 1,200 ppm for 4 hours represented a threshold for eye irritation (Carpenter et al., 1975). An interspecies uncertainty factor of 1 was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans. An intraspecies uncertainty factor of 3 was applied because the minimum alveolar concentration (MAC) for volatile anesthetics should not vary by more than a factor of 2–3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

The AEGL-3 derivation is based upon prostration occurring in all 10 rats exposed for 4 hours to 2,800 ppm mixed xylenes, with recovery occurring within 1 hour of exposure (Carpenter et al., 1975). Although coordination initially remained poor, it returned to normal the following day. This concentration also represents a no-effect level for lethality. An interspecies uncertainty factor of 1

was applied because rats receive a greater systemic dose of inhaled xylene as compared to humans. An intraspecies uncertainty factor of 3 was applied because the MAC for volatile anesthetics should not vary by more than a factor of 2–3-fold among humans. A 3-fold factor is also adequate to account for moderate physical activity during exposure, which would result in greater uptake of the chemical.

The two primary effects of concern for xylene are those of irritation and central nervous system effects. Irritation is considered a threshold effect and therefore should not vary over time. The AEGL-1 value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

Data indicate that once steady state is reached, concentration, not duration, is the prime determinant in xylene-induced central nervous system toxicity. Pharmacokinetic modeling in both humans and rats indicate that venous blood concentrations rapidly increase during the first 15 minutes of exposure, followed by minimal increases in blood concentrations with continuing exposure (i.e., increases follow a hyperbolic curve). Likewise, available human data indicate that once the initial increase in blood xylene concentration is reached, blood concentrations level off with increasing exposure duration. Conversely, available human and animal data demonstrate that increasing exposure concentrations correlate with increases in venous blood xylene concentrations. Therefore, the AEGL 2- and -3 values are set equal across time once steady state is approached (starting at approximately 1 hour), while pharmacokinetic modeling was used to extrapolate to exposure durations of 10- and 30-minutes.

The AEGL values should be protective of human health. The AEGL-1 values are consistent with other human studies, and represent a value consistent with exposure concentrations that might result in mild eye irritation. The AEGL-2 levels are protective, especially when considering numerous human studies investigating the effects of exposure to