急性曝露ガイドライン濃度 (AEGL)

Xylenes (1330-20-7)
キシレン

Table　AEGL 設定値

Xylenes　1330-20-7　(Final)					
ppm					
	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	130	130	130	130	130
AEGL 2	2,500*	1,300*	920*	500	400
AEGL 3	**	3,600*	2,500*	1,300*	1,000*

爆発下限界濃度 (LEL) = 9,000 ppm
* = ≥10% LEL
** = ≥50% LEL
AEGL 3 – 10 min = **7,200 ppm
* を付した値については、爆発災害を考慮して安全性を検討する必要がある。
** を付した値については、爆発災害を考慮して厳しく安全性を検討する必要がある。

技術サポート文書

本文書は、米国オークリッジ国立研究所の Claudia Troxel と、有害物質の急性曝露ガイドラインレベル(AEGL)に関する米国諮問委員会(NAC)の化学部主任(Chemical Manager)である Loren Koller によって構成された、AEGL 策定チーム(AEGL Development Team)が作成した。NAC は、必要があると認めたときは、本文書および AEGL 値の見直しと改訂を行った。その後、本文書、AEGL 値ともに、米国学術研究会議(NRC)の AEGL に関する委員会によって、見直しが行われた。NRC 委員会は、本文書の中で導出されている AEGL 値が、NRC によって見直されたデータに基づいた科学的に妥当な判断であり、NRC のガイドライン報告書(NRC 1993, 2001)と整合性が取れていると結論づけている。

設定根拠(要約):

キシレンは、溶剤、塗料、被覆剤など、多くの消費者製品に使用されており、ガソリンにも混合されている。混合キシレンは、*m*-キシレン、*o*-キシレン、*p*-キシレンの 3 種類の異性体からなり、このうち、*m*-キシレンの割合が一番高い。工業用キシレンには、エチルベンゼンも含まれている。吸収されたキシレンは速やかに代謝され、ヒトではメチル馬尿酸の異性体として、動物ではメチル馬尿酸の異性体およびトルイル酸グルクロニドとして、ほとんどが尿中に排泄される。ヒトおよび動物をキシレンに急性吸入曝露すると、粘膜刺激が起こり、中枢神経系(CNS)が冒される。高濃度で急性吸入曝露されたヒトと、亜慢性経口(または吸入)曝露されたラットで、肝臓への影響が認められている。得られた文献を見る限り、各試験に一貫して認められる発生・生殖への影

響はない。市販キシレンおよびキシレンの 3 種類の異性体はいずれも、遺伝毒性試験は一般的に陰性である。国際がん研究機関(IARC)においても米国環境保護庁(EPA)においても、キシレンは、現時点では発がん性に関して未分類である。

AEGL-1 値の導出は、ヒトにおける著しい不快感に関する無影響濃度に基づいた。Hastings et al.(1984)の試験では、被験者を混合キシレンに 400 ppm の濃度で 30 分間曝露したが、軽度の眼刺激しか認められなかった。導出の根拠とした試験がヒトを対象としたものであるため、種間不確実係数は適用しなかった。軽微な眼刺激は、化学物質の直接作用によって引き起こされることと、この反応の個人差は、それほど大きくないと予想されることから、種内不確実係数 3 を適用した。刺激は閾値のある影響であり、経時変化がないと考えられるため、時間スケーリングを行わず、各曝露時間の AEGL-1 値はすべて同じ値とした。AEGL-1 値を 130 ppm としたことの妥当性は、他のいくつもの試験によって支持されている。例えば、Hake et al.(1981)の試験では、150 ppm の *p*-キシレンへの曝露によってコンタクトレンズ使用者に眼刺激が起こり、Carpenter et al.(1975b)の試験では、230 ppm の混合キシレンへの 15 分間曝露によって被験者 1 名に軽度の眼刺激と浮動性めまい(運動協調性の消失を伴わない)が起こったことが報告されている。また、著しい不快感に関する無影響濃度として、Ogata et al.(1970a)の試験では 200 ppm の *m*-キシレンまたは *p*-キシレンへの 3 時間曝露、Savolainen et al.(1981)の試験では 200 ppm の *m*-キシレンへの 4 時間曝露、Laine et al.(1993)の試験では 200 ppm の *m*-キシレンへの 5.5 時間曝露が示されている。

AEGL-2 値の導出は、危険回避能力阻害に関する無影響濃度に基づいた。Carpenter et al.(1975b)の試験では、ラットを混合キシレンに 1,300 ppm の濃度で 4 時間曝露したところ、曝露開始から 2 時間で運動協調性の低下(わずかな消失)が起こり、曝露後に正常な状態に回復した。導出の出発点とした 1,300 ppm の濃度での 2 時間曝露は、したがって、可逆的な平衡障害の閾値であり、危険回避能力阻害に関する無影響濃度である。この濃度と評価項目は、ラットにおける 4 時間曝露濃度について得られたほとんどのデータと整合している。例えば、ロータロッドテストの成績低下に関する半数影響濃度(EC_{50})は 1,982 ppm であり(Korsak et al. 1993)、*m*-、*o*-、および *p*-キシレンの最小麻酔濃度は 1,940～2,180 ppm である(Molnár et al. 1986)。また、1,600 ppm の *p*-キシレンへの曝露によって、自発運動亢進、微小振戦、不安定や(Bushnell 1989)、覚醒の増高を示唆するフラッシュ誘発電位の変化(Dyer et al. 1988)がみられたことが報告されている。キシレンの曝露後に認められた CNS 反応は、脳に到達した親物質の濃度と直接関連していること、また、静脈血中濃度(CV)は、脳内濃度と相関していることが推測されている。したがって、1,300 ppm のキシレンに 2 時間曝露した場合のキシレンの CV を用いて、運動協調性低下の臨床徴候と相関する内部曝露量を算出できるものと思われる。生理学的薬物動態(PBPK)モデルを用いて(Appendix C を参照)、ラットにおける運動協調性を阻害する内部曝露量（CV）を算出した。次に、ヒトの PBPK モデルを、設定された AEGL の各曝露時間に適用して、目標 CV 値への到達に相当する曝露濃度を算出した。

AEGL-3 値の導出は、Carpenter et al.(1975b)の試験で、ラットに可逆性の虚脱が認められ、かつ、死亡に関する無影響濃度(NOEL)であった 2,800 ppm での 4 時間曝露に基づいた。運動協調性は最

初のうちは低下したままであったが、翌日には正常な状態に回復した。この 2,800 ppm という濃度は、死亡に至る可能性のある顕著な CNS 抑制の閾値である。AEGL-2 値に関しては、キシレンへの曝露後にみられた CNS への影響が、脳に到達した親物質の濃度と直接関連していることが推定されている。したがって、ラットにおいて虚脱を生じた 2,800 ppm の濃度での 4 時間曝露量と相関する内部曝露量(CV)を、再度、PBPK モデル(Appendix C を参照)を用いて算出した。設定された AEGL の各曝露時間にヒトの PBPK モデルを適用して、目標 CV 値への到達に相当する曝露濃度を算出した。

AEGL-2 値と AEGL-3 値には、総不確実係数 3 を適用した。揮発性麻酔薬の最小肺胞内濃度(MAC)については、個人差が 2〜3 倍以下であると考えられるため(NRC 2002)、薬物動態学的・薬力学的不確実性を考慮して、種内不確実係数 3 を適用した。種間不確実係数は通例、3 が適用される。PBPK モデルを用いたため、不確実係数の毒物動態学的要素を 1 に減らしたが、薬力学的要素は通常、保持されるため、3 を割り当てた(ヒトと動物では、CNS に同様の影響が起こると思われるが、同じ組織用量で起こるかどうかは不明である)。ただし、総不確実係数として 10 を適用すると、8 時間 AEGL-2 値が 180 ppm、4 時間 AEGL-3 値が 447 ppm となる。この 2 つの曝露濃度では、ヒトは有害な影響をほとんど受けないか、まったく受けずに耐えられることが知られている。8 時間 AEGL-2 値の 180 ppm に関しては、Hake et al.(1981)の試験において、ヒトを *p*-キシレンに 150 ppm の濃度で 7.5 時間曝露しても、作業能力試験で影響が認められず、軽度の眼刺激しか認められなかったことが報告されている。4 時間 AEGL-3 値の 447 ppm に関しては、ヒトを対象とした多数の試験によって、*m*-キシレンへの曝露の影響が調べられており(Savolainen and Linnavuo 1979; Savolainen et al. 1984, 1985a,b; Seppalainen et al. 1989, 1991; Laine et al. 1993)、130〜200 ppm の濃度で 4〜6 時間曝露した場合、20 分間での最高濃度は、運動の有無に関係なく 400 ppm であり、CNS への影響はみられないか、わずかであったことが報告されている。したがって、種間不確実係数を 1 に減らし、よって総不確実係数 3 を AEGL-2 値と AEGL-3 値に適用した(NRC 2002)。

ここに設定したキシレンの AEGL 値は、キシレンの 3 種類の異性体のいずれにも、また混合物にも適用される。異性体の作用強度は、経口曝露と吸入曝露で大きな差はないことが確認されており、また、各異性体とも同じ代謝経路を辿る。PBPK モデル予測によって、曝露後の内部曝露量(CV)に異性体間で大きな差はないことが示唆されている。

Table および Table 6-1 に、導出した AEGL 値をまとめて示す。AEGL-2 値と AEGL-3 値は、爆発下限界の 10%より大きい。

TABLE 6-1 Summary of Proposed AEGL Values for Xylenes

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	Eye irritation in human volunteers exposed to mixed xylenes at 400 ppm for 30 min (Hastings et al. 1984)
AEGL-2 (Disabling)	2,500 ppm[a] (11,000 mg/m^3)	1,300 ppm[a] (5,600 mg/m^3)	920 ppm[a] (4,000 mg/m^3)	500 ppm (2,200 mg/m^3)	400 ppm (1,700 mg/m^3)	Rats exposed to mixed xylenes at 1,300 ppm exhibited poor coordination 2 h into a 4-h exposure (Carpenter et al. 1975b)
AEGL-3 (Lethal)	—[b]	3,600 ppm[a] (16,000 mg/m^3)	2,500 ppm[a] (11,000 mg/m^3)	1,300 ppm[a] (5,600 mg/m^3)	1,000 ppm[a] (4,300 mg/m^3)	Rats exposed to mixed xylenes at 2,800 ppm for 4 h exhibited prostration followed by a full recovery (Carpenter et al. 1975b)

[a]Concentrations are at or higher than 1/10th of the lower explosive limit (LEL) for all forms of xylene (*o*-xylene LEL, 9,000 ppm; *m*- and *p*-xylene LEL, 11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]10-min AEGL-3 = 7,200 ppm is ≥50% of LEL. Therefore, extreme safety considerations against the hazards of explosions must be taken into account.

APPENDIX C

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING OF XYLENE

Summary

Two research groups developed PBPK models for xylene, and both groups modeled the single isomer *m*-xylene. Kaneko et al. (1991ab, 2000) developed a six-compartment model in rats and a seven-compartment model in humans. The other research group developed a four-compartment model in rats and humans (Tardif et al. 1993, 1997; Haddad et al. 1999). The basic model generated by Tardif et al. (1993, 1997) and Haddad et al. (1999) was chosen for the AEGL derivations because it was more data rich. The main difference among the models was in the physiologic parameters used. The model was coupled with additional human data from five publications for verification (see Table 6C-1). Next, the rat model was run to determine CV at the exposure concentration producing the defined AEGL end point. Then the human model was run for each time period to determine the equivalent exposure concentration producing the same CV. The application of PBPK modeling to the derivation of the xylene AEGL values was based on guidance in the PBPK modeling White Paper (Dennison et al. 2009). All PBPK modeling was performed in Berkeley Madonna, version 8.0.2a8, a recent beta version that includes scripting capabilities (Macey and Oster 2002). A glossary of PBPK modeling abbreviations is provided at the end of this appendix.

Rat Model

The basis of the model was a standard four-compartment model that included richly perfused tissue, slowly perfused tissue, fat, and liver (Figure 6C-1), with the rate of change in the concentration in each tissue described by the equation shown below (Ramsey and Andersen 1984):

$$V_i dC_i/dt = Q_i(C_a - CV_i) - RAM,$$

where

V_i = tissue volume (L),
Q_i = tissue perfusion rate (L/h),
C_a = concentration of solvent in the systemic arterial blood (mg/L),
CV_i = concentration of solvent in venous blood leaving tissue, i (mg/L),
RAM = rate of change in the amount metabolized,
RAM = AMS + AML,
$AMS = V_{max} \times C_{VL}/(K_m + C_{VL})$,

AML = KF × C_{VL}, and
KF = first-order rate constant for high-capacity low-affinity enzymes.

It was assumed that metabolism occurred exclusively in the liver. V_{max} was scaled to the body weight by using $V_{max}C \times BW^{0.75}$. The following data were used to develop the rat PBPK model:

Gas-uptake data from rats exposed at 500, 1,000, 2,000, or 4,000 ppm (Tardif et al. 1993).
CV in rats after a 4-h exposure to 100 or 200 ppm (Tardif et al. 1997).
CV in rats after a 4-h exposure to 50 ppm (Haddad et al. 1999).
Partition parameters from Gargas et al. (1989) (in vitro).
Standard parameters for tissue flows and volumes (see Table 6C-2).

TABLE 6C-1 CV in Humans Exposed to *m*-Xylene at 200 ppm

Time (h)	CV (µmol/L)	Reference
0.12	11.6[a]	Seppalainen et al. 1991
0.15	12.6[a]	Seppalainen et al. 1991
0.18	14.3[a]	Seppalainen et al. 1991
0.22	16.4 a	Seppalainen et al. 1991
0.25	16.6 ± 4.8	Laine et al. 1993
0.33	17.3 ± 5.5	Laine et al. 1993
	17.5	Savolainen et al. 1985
0.5	17.5	Savolainen et al. 1984
0.67	21.3 ± 5.4	Laine et al. 1993
1	23.9*	Seppalainen et al. 1991
1.17	24.9 ± 2.1 (6)	Savolainen et al. 1981
1.5	26	Savolainen et al. 1984
2	28.5 ± 5.2	Laine et al. 1993
	29	Savolainen et al. 1984
2.5	26.7 ± 3.4 (6)	Savolainen et al. 1981
	30	Savolainen et al. 1984
	30	Savolainen et al. 1985
3	31	Seppalainen et al. 1989
	31.4	Seppalainen et al. 1991
3.75	28.6 ± 3.5 (6)	Savolainen et al. 1981

[a]These values read from a graph using digiMatic software (Digimatic 2004).

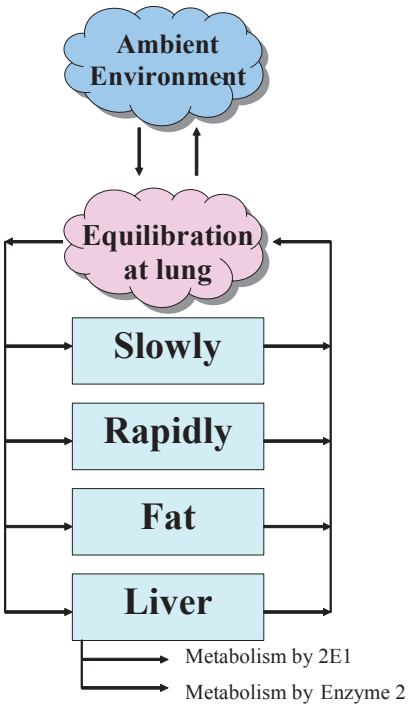


FIGURE 6C-1 Four-compartment rat model.

The rat model from Haddad et al. (1999) was chosen because it was more recent, was more data rich, and had a better fit. However, there was not a large difference among the models. The Haddad et al. (1999) model does have the limitation that it was created with data from Sprague-Dawley rats and had only postexposure data at xylene concentrations up to 200 ppm. In the more recent Haddad et al. (1999) model, slightly different parameters were used for tissue volumes and metabolism compared with the earlier model of Tardif et al. (1993). The 1999 model was run with the 1993 gas uptake data (500, 1,000, 2,000, and 4,000 ppm) (see Figure 6C-2). The results suggest that the 1993 and 1999 models are quite similar as the plot shown here is essentially the same as that in the 1993 paper. At the lower concentrations, the model would actually fit perfectly if the starting concentration were adjusted to the measured concentration. The acute lethality critical study (AEGL-3) is based on an exposure concentration (2,800 ppm) that lies within the range of concentrations used in the gas uptake study.

TABLE 6C-2 Summary of Parameter Values Used in Rat and Human PBPK Model

Variable	Rat[a]	Human[b]	
Body weight (kg) (BW)	0.1678	70	
Alveolar ventilation rate (L/h/kg) (QPC)[c]	15	14.9	
Cardiac output (L/h/kg) (QCC)[c]	15	12.4	
Fraction of body weight (kg/kg BW)			
Fraction fat tissue (VFC)	0.07	0.19[d]	
Fraction liver tissue (VLC)	0.04	0.026[d]	
Fraction rapidly perfused (VRC)	0.05	0.05[d]	
Fraction slowly perfused (VSC)	0.75	0.62[d]	
Fraction of cardiac output corresponding to each compartment ((L/h)/QC)			
Fraction blood flow to fat (QFC)	0.09	0.05	
Fraction to rapidly perfused (QRC)	0.51	0.42	
Fraction to liver (QLC)	0.25	0.32	
Fraction to slowly perfused (QSC)	0.15	0.21	
Partition coefficients			
Blood-air (PB)			
m-xylene	46[e]	32.5[e]; 26.4[f]; 31.9[g];	Average = 30.3
o-xylene	44.3[e]	34.9[e]; 31.1[f]; 35.2[g];	Average = 33.7
p-xylene	41.3[e]	44.7[e]; 37.6[f]; 39.0[g];	Average = 40.4

(Continued)

TABLE 6C-2 Continued

Variable	Rat[a]	Human[b]
Blood-fat (PFA)	1,859	1,859[a]
Slowly perfused-air (PSA)	41.9	41.9[a]
Rapidly perfused-air (PR)]	90.9	90.9[a]
Liver-air (PLA)	90.9	90.9[a]
Scaling coefficient (SF])	0.75	0.75
$V_{max}C$ (mg/h/kg)[g]	6.49	5.5
K_m (mg/L)	0.45	0.45[a]
KFC	0.1	0.1

[a]Haddad et al. 1999.
[b]Astrand 1983.
[c]QPC, QCC, and $V_{max}C$ were scaled to $BW^{0.75}$.
[d]Tardif et al. 1997.
[e]Gargas et al. 1989.
[f]Sato and Nakajima 1979.
[g]Pierce et al. 1996.

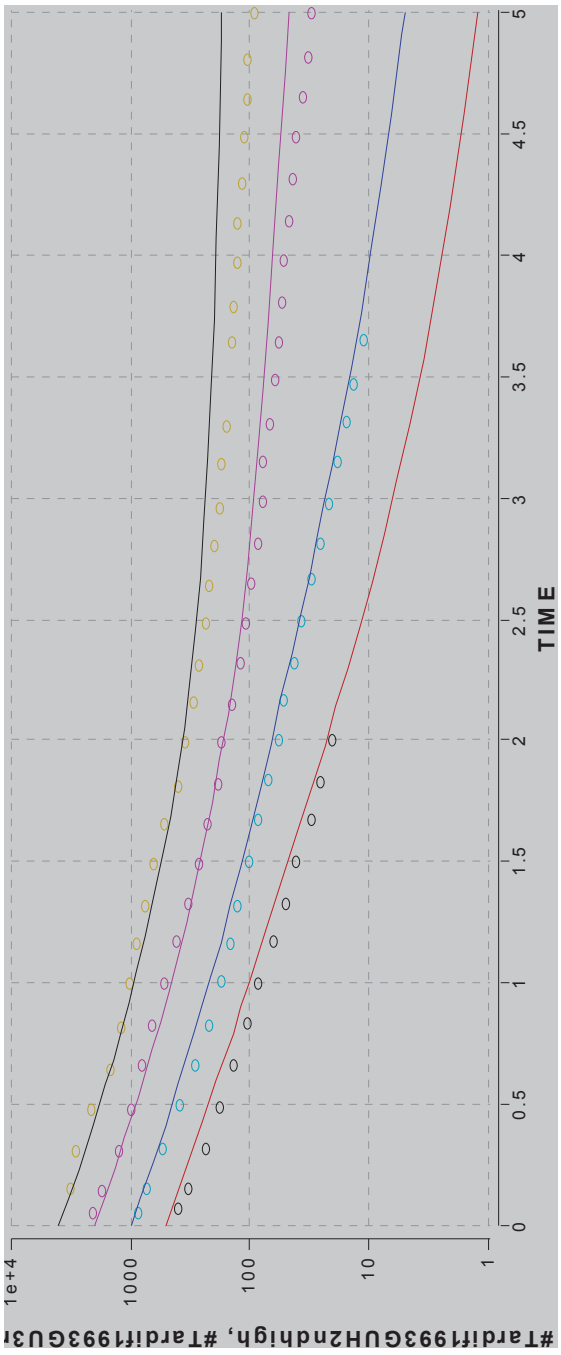


FIGURE 6C-2 The Haddad et al. (1999) model with the Tardif et al. (1993) gas uptake data (500, 1,000, 2,000, and 4,000 ppm).

Using the Haddad et al. (1999) model, the starting concentrations were optimized to reflect the measured concentrations of the first data points. At the high concentrations of interest for xylene, enzymatic saturation of the primary metabolic pathway may have occurred. Therefore, a second pathway of metabolism (lumped metabolism by all the CYPs other than CYP2E1) was added to account for high-capacity low-affinity pathways of metabolism, which would occur at the much higher exposure concentrations (Clewell et al. 2001). The metabolism by the second series of CYPs is given as

$$\text{Rate of metabolism (RAM)} = KF \times C_{VL},$$

where

C_{VL} = concentration of xylenes in the venous blood leaving the liver and
$KF = 0.1/BW^{0.3}$.

The second pathway of metabolism was added and KF (first-order rate constant for high-capacity low-affinity enzymes) was determined. Figure 6C-3 shows the results of optimizing the starting concentrations and adding the second pathway of metabolism. Adding the second metabolic pathway resulted in a very close correspondence between the model and the data.

After optimizing the Haddad model with the Tardif et al. (1993) data, the model was run again with the same parameters against the Haddad data (Figure 6C-4). A good fit is obtained overall, although the 200-ppm experimental data are slightly underpredicted. However, the concern is primarily with estimating CV in rats at very high concentrations (1,000 to 3,000 ppm). Figure 6C-4 shows what the model does without the second metabolic pathway (perfect fit) and with it. There is no real difference at 50 or 100 ppm, but the second line from the top is the new model at 200 ppm.

Application of the Model to Humans

The optimized rat model can now be used to develop a xylene PBPK model for humans. The model was visually reoptimized for *m*- and *p*-xylene with the available human data. Multiple papers were available in which human *m*-xylene CV values were measured during exposure to *m*-xylene at 200 ppm (Savolainen et al. 1981, 1984, 1985; Seppalainen et al. 1989, 1991; Laine et al. 1993) (see Table 6C-1). Postexposure human CV were also reported by Hake et al. (1981) after exposure to *p*-xylene at 20, 100, or 150 ppm for 1, 3, or 7 h and by Tardif et al. (1997) after exposure to *m*-xylene at 33 ppm for 7 h.

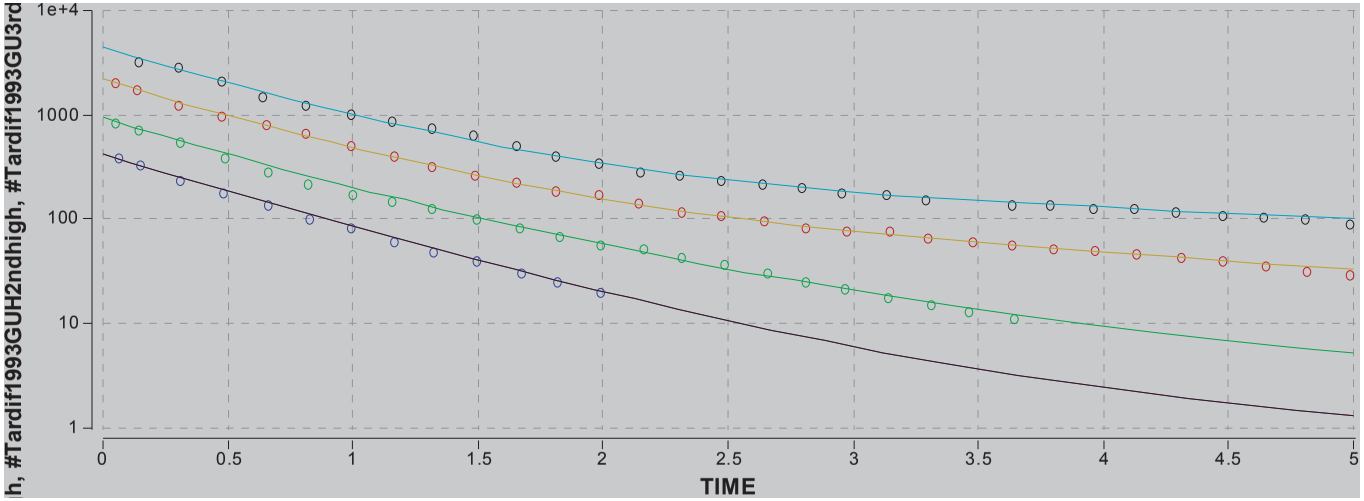


FIGURE 6C-3 The Haddad et al. (1999) model with the Tardif et al. (1993) gas uptake data (500, 1,000, 2,000, and 4,000 ppm), optimized for the starting concentration and inclusion of a second metabolism pathway.

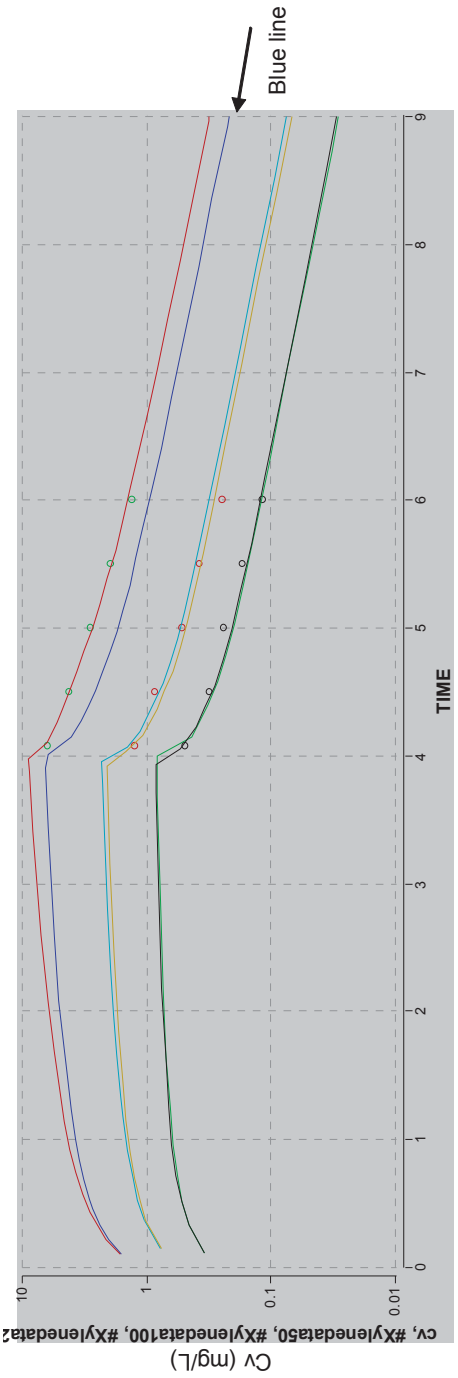
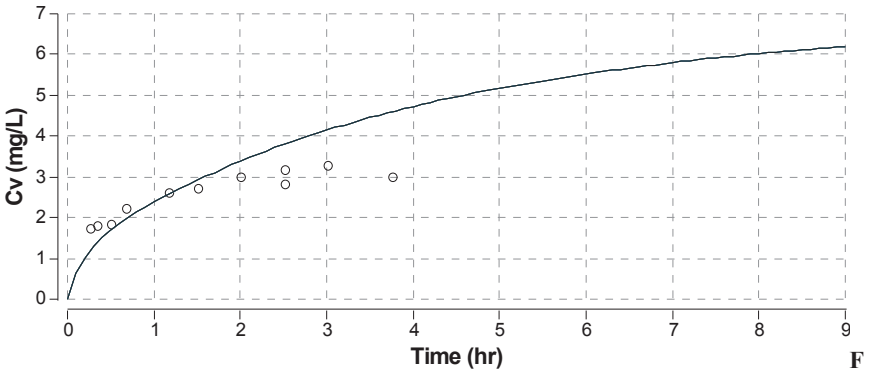


FIGURE 6C-4 Haddad et al. (1999) model after being optimized for the Tardif et al. (1993) gas uptake data.

Human anatomic parameters were generally taken from Astrand (1983) (see Table 6C-2). Kinetics were scaled from the rat model except for $V_{max}C$, which was reoptimized and reduced to 5.5. Without the adjustment, the model tended to underpredict most of the data. Values for QCC or QPC were not optimized because these values came from part of a physiologic parameter set (Astrand 1983). Several human blood-air partition coefficients (PB) for the xylene isomers were reported in the literature and are presented in Table 6C-2. The average PB for the respective xylene isomer was used for modeling data. Figures 6C-5 to 6C-8 show the reoptimized human model predictions for CV for *m*- or *p*-xylene compared with the measured human CV values.



IGURE 6C-5 Model predictions of CV (line; using human input parameters with PB of 30.3) compared with the actual measured human CV values during exposure to *m*-xylene at 200 ppm (open circles; combined data summarized in Table 6C-1).

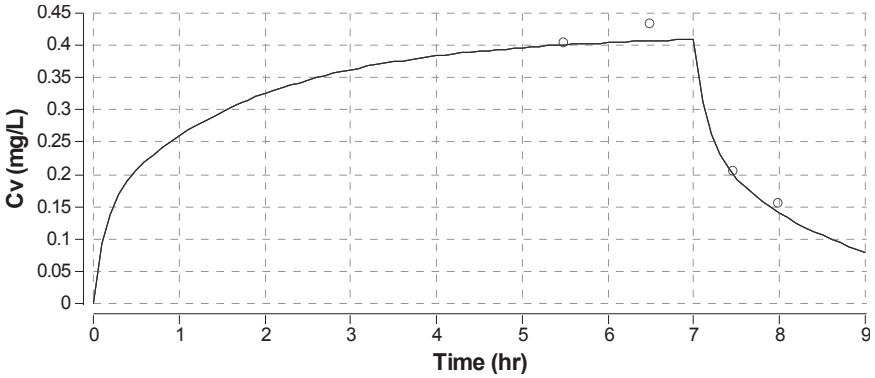


FIGURE 6C-6 Mmodel predictions of CV (line; using human input parameters with PB of 30.3) compared with the actual measured human CV values (open circles) during and after exposure to *m*-xylene at 33 ppm for 7 h (Tardif et al. 1997).

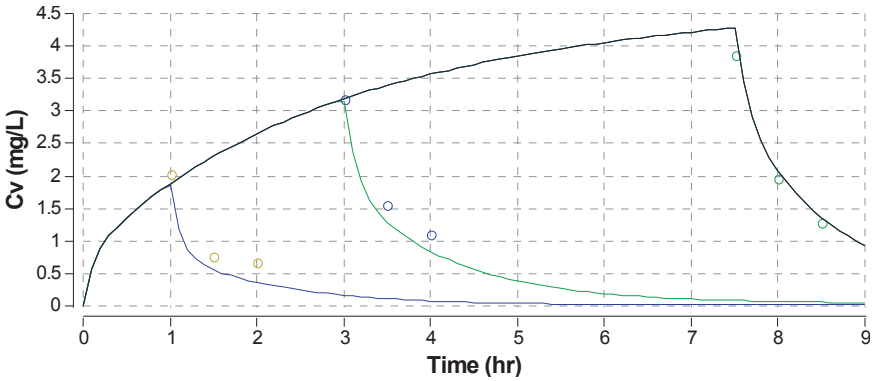


FIGURE 6C-7 Model predictions of CV (line; using male human input parameters with PB of 40.4) compared with the actual measured male human CV values (open circles) after exposure to *p*-xylene at 150 ppm for 1, 3, or 7.5 h (Hake et al. 1981).

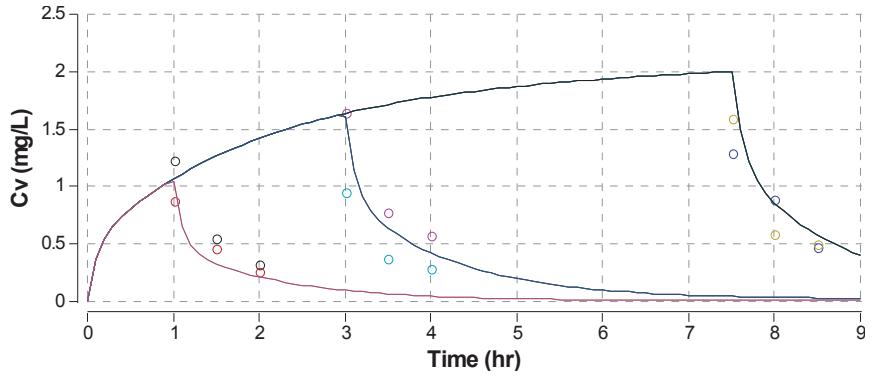


FIGURE 6C-8 Model predictions of CV (lines; using human female input parameters with PB of 40.4) compared with the actual measured human female CV values (open circles) after exposure to *p*-xylene at 100 ppm for 1, 3, or 7.5 h (Hake et al. 1981).

Comparison of Pharmacokinetics in Rats and Humans

Because the AEGL-2 and AEGL-3 key studies are based on rat data, extrapolation to humans is required. PBPK modeling allows a comparison of the internal dose that is received in both species receiving identical external exposures. As shown in Figure 6C-9, rats achieve higher blood *m*-xylene concentrations than humans. This is primarily due to a higher PB in rats (46) compared with humans (26 to 32 in humans). Figure 6C-9 plots CV for rats and humans using the validated models presented earlier at 200, 1,000, and 5,000 ppm.

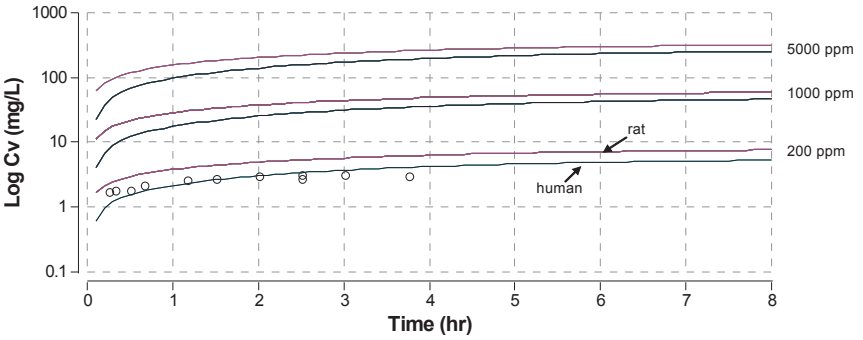


FIGURE 6C-9 Model predictions for CV in rats (top line of each pair of lines) and humans (bottom line of each pair of lines). Open circles are the actual measured human CV values for exposure to xylene at 200 ppm.

The y axis in Figure 6C-9 is on a logarithmic scale. By 8 h, steady state is still slowly increasing.

Application of Modeling to Derive AEGL Values

Because xylene can exist as a mixture or as any of three individual isomers, the question arises as to whether there are any differences in toxicity among the individual isomers and the mixture. No significant differences in the potency of the isomers after oral or inhalation exposure were identified and metabolism of each isomer proceeds via the same pathway. PBPK model predictions indicate that the internal dose (CV) after exposure does not vary significantly among the individual isomers (see Figure 6C-10).

The AEGL-2 and -3 values are based on a study in rats exposed to mixed xylenes for 4 h (Carpenter et al. 1975). The composition of the mixed xylenes used was provided as follows:

Component	Volume Percent
Nonaromatics	0.07
Toluene	0.14
Ethylbenzene	19.27
p-Xylene	7.84
m-Xylene	65.01
o-Xylene	7.63
C_9 + aromatics	0.04
Total	100.00

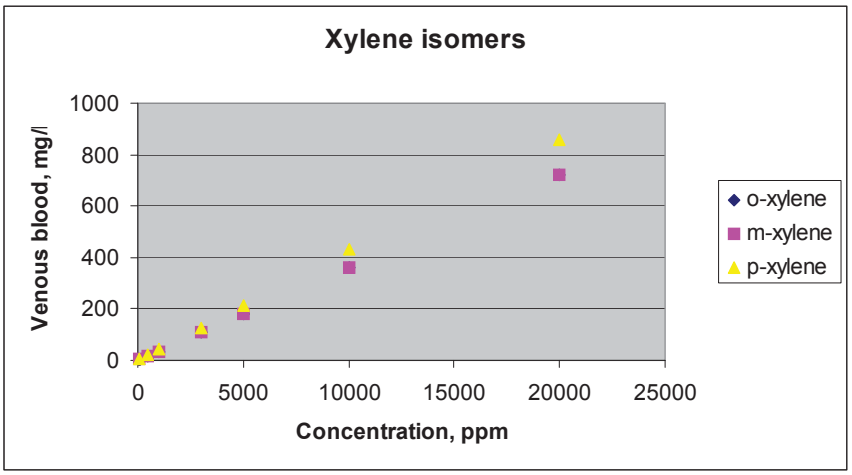


FIGURE 6C-10 The model predictions for CV in humans after exposure to the individual isomers (model parameters remain the same with the exception of PB values specific to the individual isomers; symbol for *m*-xylene is superimposed on symbol for *o*-xylene).

The amount of ethylbenzene is a typical amount seen in a xylene mixture. For the purpose of the modeling, it is known that ethylbenzene has the same spectrum of neurotoxic effects as xylenes, so assuming the exposure is to xylenes alone is reasonable. When considering only the amount of xylene isomers in the mixture and normalizing them to a total of 100%, 80% is the *m*-xylene isomer, while 10% is the *o*-xylene isomer and 10% is the *p*-xylene isomer. Therefore, the PB for *m*-xylene is used in the model.

The AEGL-2 derivation is based on poor coordination exhibited in rats 2 h into a 4-h exposure to mixed xylenes at 1,300 ppm (Carpenter et al. 1975). The rat PBPK model predicts that an exposure to xylenes at 1,300 ppm for 2 h would result in a CV of 48.9 mg/L. It is assumed that this internal dose of 48.9 mg/L is the dose resulting in the clinical sign of poor coordination. Therefore, it is assumed that the same internal dose of 48.9 mg/L would also result in adverse effects in humans. Using the human PBPK model, the model was run for each defined AEGL time point to determine the equivalent exposure concentration producing the same CV.

The AEGL-3 derivation is based on reversible prostration and a NOEL for death in rats exposed to 2,800 ppm for 4 h (Carpenter et al. 1975). The rat PBPK model predicts that an exposure to xylenes at 2,800 ppm for 4 h would result in a CV of 143.8 mg/L. Therefore, it is assumed that the same internal dose of 143.8 mg/L would also result in adverse effects in humans. Using the human PBPK model, the model was run for each defined AEGL time point to determine the equivalent exposure concentration producing the same CV.

Recommended AEGL Values

A total uncertainty factor of 3 was applied to the AEGL-2 and -3 dose metrics.

An intraspecies uncertainty factor of 3 was applied for the pharmacokinetic and pharmacodynamic uncertainty because the MAC for volatile anesthetics should not vary by more than 2- to 3-fold among humans (NRC 2002).

An interspecies uncertainty factor of 3 would usually be applied. PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1, but the pharmacodynamic component would normally be retained and assigned a 3 (although it appears that similar CNS effects occur in humans and animals, it is not known if they occur at the same tissue dose). A total uncertainty factor of 10, however, drives the 8-h AEGL-2 value to 180 ppm and the 4-h AEGL-3 value to 447 ppm. These are exposure concentrations that humans are known to tolerate with minimal or no adverse effects. With regard to the AEGL-2, humans exposed to *p*-xylene at 150 ppm for 7.5 h did not exhibit any effects on performance tests and noted only mild eye irritation (Hake et al. 1981). With regard to the AEGL-3, numerous human studies investigated the effects of exposure to *m*-xylene at 130 to 200 ppm for 4 to 6 h, with 20-min peaks of 400 ppm with or without exercise (Savolainen and Linnavuo 1979; Savolainen et al. 1984, 1985; Seppalainen et al. 1989, 1991; Laine et al. 1993) and found no effect or minimal CNS effects. Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-2 and AEGL-3 values (NRC 2002).

GLOSSARY OF PBPK MODEL TERMS

Most used in the presentation:

CV	venous blood concentration
PB	Blood-air partition coefficient

Physiologic Parameters

BW	Body weight (kg)
QPC	Alveolar ventilation rate (L/h/kg)
QCC	Cardiac output (L/h/kg)
VFC	Fraction fat tissue (kg/(kg/BW))
VLC	Fraction liver tissue (kg/(kg/BW))
VRC	Fraction rapidly perfused (kg/(kg/BW))
QFC	Fractional blood flow to fat ((L/h)/QC)
QLC	Fractional blood flow to liver ((L/h)/QC)
QRC	Fractional blood flow to rapidly perfused ((L/h)/QC)
SF	Scaling coefficient

Chemical-Specific Parameters

PLA =	Liver-air partition coefficient
PFA =	Fat-air partition coefficient
PSA =	Slowly perfused air partition coefficient
PRA =	Rapidly perfused air partition coefficient
PB =	Blood-air partition coefficient
PL = PLA/PB	Liver-blood partition coefficient
PF = PFA/PB	Fat-blood partition coefficient
PS = PSA/PB	Slowly perfused blood partition coefficient
PR = PRA/PB	Rapidly perfused blood partition coefficient
MW =	Molecular weight (g/mol)
$V_{max}C$ =	Maximum velocity of metabolism (mg/h/kg)
K_m =	Michaelis-Menten (mg/L)
KFC =	0.1
CONC =	Inhaled concentration (ppm)

Calculated Parameters

$QC = QCC \times BW^{SF}$	Cardiac output
$QP = QPC \times BW^{SF}$	Alveolar ventilation
$VS = VSC \times BW$	Volume slowly perfused tissue (L)
$VF = VFC \times BW$	Volume fat tissue (L)
$VL = VLC \times BW$	Volume liver (L)
$VR = VRC \times BW$	Volume rapidly perfused (L)
$QF = QFC \times QC$	Blood flow to fat (L/h)
$QL = QLC \times QC$	Blood flow to liver (L/h)
$QS = QC - QF - QL - QR$	Blood flow to non-fat tissue (L/h)
$QR = QRC \times QC$	Blood flow to rapidly perfused (L/h)
$CIX = CONC \times MW/24{,}450$	Exposure concentration (mg/L)
$V_{max} = V_{max}C \times BW^{SF}$	
$KF = KFC/BW^{0.3}$	First-order rate constant for high-capacity low-affinity enzymes

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注：本物質の特性理解のため、参考として国際化学物質安全性カード（ICSC）および急性曝露ガイドライン濃度（AEGL)の原文のURLを記載する。

日本語ICSC

https://www.ilo.org/dyn/icsc/showcard.display?p_lang=ja&p_card_id=0084&p_version=2

https://www.ilo.org/dyn/icsc/showcard.display?p_lang=ja&p_card_id=0085&p_version=2

https://www.ilo.org/dyn/icsc/showcard.display?p_lang=ja&p_card_id=0086&p_version=2

AEGL（原文）

https://www.epa.gov/sites/default/files/2014-11/documents/xylenes_final_volume_9_2010.pdf