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Toxicokinetics of toluene in the rat¹

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REES DC, WOOD RW, McCORMICK JP, COX C. Toxicokinetics of toluene in the rat. *Scand J Work Environ Health* 11 (1985) 301–306. Toxicokinetic experiments with toluene that rely on data pooled from several animals have typically provided estimates of rate constants based on single exponential functions; in the present study a within-subject design was used to describe the time course of toluene in the blood to see if additional exponential terms could be resolved. Each rat was exposed for 2 h to either 1 000, 1 780, or 3 000 ppm of toluene. Blood samples were drawn at different times from indwelling jugular cannulae, and blood toluene concentrations were determined by vapor phase equilibrium chromatography. There was substantial variability between the peak blood values of the animals at each exposure concentration. Nonlinear regression was used to determine regression parameters for data drawn from individual animals. A bi-exponential function was found to minimize significantly the residual sum of squares observed during elimination. However, only a single exponential function could be resolved reliably during uptake. The mean half-time during uptake was approximately 34 min; the two half-times for elimination averaged approximately 6 and 90 min. Because of between-subject variability, a more accurate description of the time course of toluene uptake and elimination can be provided by kinetic studies that use a within-subject design.

Key terms: elimination, kinetics, multicompartmental model, toxicity, volatile solvent.

Despite the economic importance of toluene, the toxicokinetics underlying its acute effects are poorly understood, and thus the selection of exposure parameters for the assessment of its acute and potential chronic neurobehavioral toxicity is complicated (6). Human studies describing uptake and elimination parameters are in disagreement about the time required for blood concentrations to reach equilibrium, estimates ranging between 15 and 60 min (1, 13, 22). Some rodent investigations suggest that equilibrium may not be reached for more than 3 h (8). Others have reported achieving 95 % of the uptake asymptote in 53 min (6). This latter study was performed with single blood samples collected from different animals; formal statistical evaluation indicated that a single-exponential function could characterize the changing blood concentrations.

However, a multicompartment model should best describe the kinetics of most volatile substances (11), including toluene (9, 12). Exponential curve-stripping analysis ("feathering") of the kinetic data suggests that bi- or tri-exponential mathematical func-

tions (suggesting the existence of two or three compartments) should adequately characterize the kinetics of toluene (7, 16, 17, 19, 20).

Since variability of the data may limit the resolution of additional kinetic parameters, our study attempted to eliminate the variability inherent in a between-subjects design, ie, that attributable to differences between individual animals. Our results indicate that a bi-exponential function accounts for the elimination of toluene significantly better than does a single-exponential function, and it provides estimates of elimination parameters that should be useful in future modeling efforts. Large differences in peak blood levels were observed between animals; these large differences suggest that uncontrolled physiological parameters may exert an important influence on solvent uptake and the consequent evaluation of functional impairment.

Subjects and methods

Subjects

Eleven adult Long-Evans (Charles River) rats were separately caged and housed. Purina laboratory chow was used to maintain body weights at 300 (SD 15) g. Water was always available in the home cages.

Cannulation and sampling procedure

The animals were anesthetized with sodium pentobarbital (40 mg/kg). Each animal was prepared with a Tygon catheter [inside diameter (ID) 0.01 inches

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(0.25 mm); outside diameter (OD) 0.03 inches (0.76 mm)] implanted into the external jugular vein (21). The catheter was joined to another piece of Tygon tubing [ID 0.03 inches (0.76 mm); OD 0.09 inches (2.29 mm)]. At least 10 cm from where the catheter emerged from the animal, ethyl cyanoacrylate cement (PermaBond) and heat shrink tubing were used to seal the connection. After surgery, a jacket (Alice King Chatham) was placed on the animal to prevent damage to the cannula; a cannular swivel allowed the animal to move about the cage freely. The catheter was coupled to an infusion pump that delivered heparinized saline [0.1 USP (United States Pharmacopeia) units/ml] at an infusion rate of 3.6 ml/d.

So that the sampling would not disturb atmospheric concentrations during the exposure, the cannula extended out through a small hole in the ex-

posure cylinder (28 × 10 cm) and was connected to a capillary "T." A 44.7- μ l heparinized glass capillary tube was inserted between the "T" and a 20-cc syringe. For occasional hematocrit determinations, a heparinized hematocrit tube was inserted in series with the capillary tube. We could draw blood through the capillary tube by pulling on the syringe. Blood was drawn at least 5 cm past the capillary tube, the tube was disconnected and replaced, and then the blood remaining in the line was returned to the animal. When blood was returned to the animal, air or excess saline in the line could be drawn into a second syringe that was attached to the remaining limb of the capillary "T" that was occluded by a hemostat during the blood sampling.

Toluene exposures

Twenty-four hours after cannula implantation, the animals were exposed for 2 h to either 1 000, 1 780, or 3 000 ppm in a cylinder through which passed approximately 30 l/min of clean compressed air (DelMonox air purifier; Deltec Engineering Inc). Different toluene vapor concentrations were generated by varying the proportion of air that passed through a fritted glass disk in a 500-ml gas-washing bottle containing spectrophotometrically pure toluene (Fisher T330). The bottle sat in an ice bath. Glass wool in the top of the bubbler prevented the delivery of aerosolized toluene. Toluene concentrations were monitored by infrared spectrophotometry (Wilks MIRAN I) and were maintained by adjustment within 5 % of the nominal values.

Analytical technique

A headspace gas chromatographic procedure was used to determine the blood concentrations (5, 26). An aliquot of blood (44.7 μ l) was added to 1 ml of an internal standard solution in a vial, sealed with a Teflon cap, and swirled to insure complete mixing. The internal standard solution consisted of distilled water, sodium citrate (65 mg/l), and propanol (10 μ l/l). The sample was then frozen. At the time of analysis, the sample was defrosted and maintained at 60°C for at least 15 min before an aliquot of the headspace over the sample was injected with a semi-automatic headspace attachment (HS6) to a Sigma 4 chromatograph equipped with a flame ionization detector (Perkin Elmer). The column was a blood alcohol column (Supelco 1—1766): a 1.83-m-by-2-mm ID stainless steel coil containing 60/80 Carbowax B/5 % Carbowax 20 M. These determinations were made under the following conditions: pressurization time 4 min; oven temperature 150°C; zone temperature 175°, carrier gas flow 38 ml/min of nitrogen; hydrogen flow 60 ml/min; combustion air flow 0.5 l/min. Standard curves for blood were developed by the method of addition. A reporting integrator (Hewlett-Packard 3390A) was used to determine

Figure 1. Toluene blood concentrations during and after 2-h exposures to toluene at 1 000, 1 780, and 3 000 ppm. Curves are derived by the nonlinear regression analysis described in the Methods section. Uptake was fit with the use of the formula: $B(t) = C_1(1 - e^{-\lambda_1 t})$. Elimination was fit with the formula $B(t) = C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t}$. Individual animal symbols: 1 000 ppm: 65 (solid circles), 68 (open circles); 1 780 ppm: 70 (open diamonds), 60 (open triangles), 59 (open circles), 63 (open squares); 3 000 ppm: 75 (open squares), 64 (open triangles), 62 (open circles). 1 μ g/ml = 10.85 nmol/ml = 1.154 ppm (v/v).

chromatographic peak heights. Samples with internal standard peak heights which varied by more than 10 % were discarded. Retention times for several solvents, and for the major metabolites of toluene, were ascertained to insure that they did not coelute with toluene.

Data analysis

The following equations were fit to the kinetic data:

Uptake: A. $B(t) = C_1(1 - e^{-\lambda_1 t})$.
 B. $B(t) = C_1(1 - e^{-\lambda_1 t}) + C_2(1 - e^{-\lambda_2 t})$.

Elimination: A. $B(t) = C_3 e^{-\lambda_3 t}$.
 B. $B(t) = C_3 e^{-\lambda_3 t} + C_4 e^{-\lambda_4 t}$.

where $B(t)$ refers to blood concentrations as a function of time (t).

Best estimates for both the uptake and elimination parameters were determined by a nonlinear regression analysis program (BMDP 3R) (10). For three animals, selected data points during elimination were excluded on the following basis: (i) if the residual was very large compared to the other residuals and, in addition, removal resulted in at least a twofold reduction in the residual mean square; and (ii) if the data point was inconsistent with a monotonic trend with time in the data set. Approximate F tests were performed to determine if the amount of variation accounted for by regression (residual mean square)

was significantly different between single- and bi-exponential functions. The denominator mean square for each approximate F ratio was the residual mean square from the larger model. Since it was either not possible to fit a third exponential term to the kinetic data or else the fits did not result in a significant reduction in the residual mean square, the estimates for a tri-exponential function are not presented.

Results

The blood concentrations in individual animals are shown as a function of time for 1 000, 1 780, and 3 000 ppm in figure 1. Lines represent estimates generated by the nonlinear regression analysis. As can be seen, there is good agreement between the fitted lines and the actual values. The toluene blood levels increased throughout the 2-h exposure and did not reach a horizontal asymptote before the exposure was discontinued. Termination of exposure resulted in a reduction in the blood levels that was initially rapid and then became more gradual. This general pattern was observed at all concentrations.

The best estimates of the parameters of toluene elimination for the single and bi-exponential functions are presented in table 1. The goodness of fit for each model was examined, and comparisons between models were expressed as an approximate F statistic. Significant F values suggested that the bi-exponential model best described the elimination kinetics. Signifi-

Table 1. Parameter estimates for one and two exponential elimination functions.^a

Animal	One exponential term				Two exponential terms						F	
	C ₃ (μg/ml)	λ ₃ (min ⁻¹)	t _{1/2} min	RMS	C ₃ (μg/ml)	λ ₃ (min ⁻¹)	t _{1/2} (min)	C ₄ (μg/ml)	λ ₄ (min ⁻¹)	t _{1/2} (min)		RMS
Concentration 3 000 ppm												
75	119 (4.28)	0.007 (0.001)	99	104	41.3 (15.2)	0.063 (0.039)	11.0	90.9 (15.9)	0.004 (0.002)	173	48.0	F _(2,9) = 6.70 p < 0.005
62 ^b	159 (7.57)	0.01 (0.001)	69	224	65.7 (8.09)	0.28 (0.081)	2.5	134 (5.54)	0.008 (0.006)	87	33.8	F _(2,9) = 32 p < 0.0005
64 ^b	90.3 (3.54)	0.007 (0.0008)	99	79.4	31.9 (6.93)	0.22 (0.12)	3.2	77.5 (5.49)	0.005 (0.0007)	139	32.5	F _(2,11) = 10.4 p < 0.005
58 ^c	266 (5.59)	0.017 (0.0006)	41	81.8	..	..	..	..	..	..	..	..
Concentration 1 780 ppm												
70	77.6 (3.18)	0.012 (0.002)	58	40.4	31.3 (4.25)	0.11 (0.03)	6.3	57.4 (4.22)	0.007 (0.0009)	99	5.55	F _(2,6) = 26.1 p < 0.001
59	82.5 (3.85)	0.015 (0.001)	46	31.2	61.7 (26.1)	0.04 (0.02)	17.3	31.9 (28.5)	0.005 (0.007)	139	10.2	F _(2,7) = 11.1 ≅ 0.01
60	107 (3.06)	0.043 (0.003)	16	21.7	44.3 (11.5)	0.14 (0.051)	5.0	72.1 (12.5)	0.027 (0.004)	26	8.47	F _(2,11) = 11.2 p < 0.005
63 ^b	83.6 (2.95)	0.021 (0.002)	33	29.4	40.9 (5.05)	0.13 (0.025)	5.3	58.0 (4.95)	0.014 (0.0012)	50	5.53	F _(2,17) = 42 p < 0.0005
Concentration 1 000 ppm												
67	35.3 (0.69)	0.031 (0.002)	22	1.29	2.37 (1.79)	1.42 (5.58)	0.5	34.5 (1.13)	0.03 (0.002)	23	1.3	Not significant
68	30.0 (0.91)	0.027 (0.002)	26	2.91	9.73 (2.19)	0.16 (0.07)	4.3	23.6 (2.27)	0.018 (0.002)	39	1.12	F _(2,11) = 11.5 p < 0.005
65	59.8 (2.79)	0.009 (0.002)	77	39.7	32.7 (4.69)	0.14 (0.042)	5.0	46.5 (3.01)	0.006 (0.008)	116	8.48	F _(2,11) = 24.9 p < .0005

^a Values are best estimates for the parameters describing the elimination of toluene in the rat, as well as their respective standard deviations (in parentheses). Residual mean squares (RMS) for both single- and bi-exponential functions indicate the relative variability attributable to each ($t_{1/2}$ = half-time). A formal test comparing the variability accounted for by single- and bi-exponential functions was expressed as an F value.

^b Selected data point(s) excluded; see the Methods section.

^c Program would not converge to a solution for the bi-exponential function.

Table 2. Parameter estimates for a single exponential uptake function.^a

Animal	C ₁ (μg/ml)	λ ₁ (min ⁻¹)	t _{1/2} (min)	RMS
<i>Concentration 3 000 ppm</i>				
75	131 (10.5)	0.045 (0.011)	15	163
64	108 (10.9)	0.015 (0.003)	4.6	11.3
<i>Concentration 1 780 ppm</i>				
59	109 (10.2)	0.026 (0.006)	27	111
63	103 (5.85)	0.035 (0.006)	24	62.8
70	69.5 (3.85)	0.029 (0.004)	27	5.86
<i>Concentration 1 000 ppm</i>				
65	68.1 (5.22)	0.026 (0.006)	27	31.2
68	48.4 (13.6)	0.009 (0.04)	77	31.2

^a Table values are the best estimates, standard deviations (in parentheses) and residual mean squares (RMS) for the uptake parameters of a one-compartment fit, as determined by nonlinear regression analysis (t_{1/2} = half-time). Fitting a second uptake exponential term did not account for the data significantly better than a single exponential term for 6 of 7 animals. However, animal 63 showed evidence of a second exponential term:

$$\begin{array}{llll} C_1 = 102 & (10.1) & \lambda_1 = 0.013 & (0.004) & t_{1/2} = 53 \\ C_2 = 27.3 & (5.47) & \lambda_2 = 0.28 & (0.097) & t_{1/2} = 2.5 \\ \text{RMS} = 6.86 & & F_{(2, 6)} = 34.6 & (p < 0.005) & \end{array}$$

Figure 2. Concentration-related changes in estimated peak plasma concentrations and elimination rate constants derived from a nonlinear regression (table 1): peak plasma concentrations (solid inverted triangles) represent sums of the means for C₃ (open squares) and C₄ (open circles). Elimination rate parameters are represented by triangles (λ₃) and diamonds (λ₄). Error bars indicate one standard deviation.

cant evidence for two exponential terms was not found for rats 58 and 67; however, residual plots did show a trend suggesting the existence of an additional exponential term.

The parameter estimates during uptake are presented in table 2. Estimates for a bi-exponential uptake function are not presented, since either the fit could not be performed or the fit did not result in a significant reduction in the residual mean square. Rat 63 was an exception; a significant reduction using two terms was observed ($F_{26} = 34.6$, $p < 0.0005$).

Because we were able to resolve two components during both uptake and elimination for rat 63, we attempted to fit both functions simultaneously using identical parameter values for both the uptake and elimination phases. The four-parameter fit was significantly worse ($F_{(4,23)} = 58.4$, $p < 0.0001$) than that of the eight-parameter fit obtained by combining the separate fits for the two phases. The predicted values and residuals from the four-parameter fit also displayed a systematic lack of fit. We noted a two-fold increase in the rate constant for the rapid component during the uptake phase.

Within a given concentration, the peak plasma toluene levels varied substantially between the animals (figure 2). Concentration-related increases in peak plasma levels were observed although some animals were found to have blood values at lower exposure concentrations that were comparable to those of others exposed to higher concentrations. The obtained peak blood levels were different between the animals exposed to 1 000 or 3 000 ppm. The values obtained at 1 780 ppm were intermediate to, and did not differ appreciably from, the other two groups. No consistent trend was apparent either between animals or across concentrations for either the uptake or the elimination rate estimates.

Half-times (t_{1/2}) were calculated from the parameter estimates. The mean half-time for uptake was 33.7 (range 15.4–77) min. Half-times were also calculated for each of the exponential elimination functions. The more rapid function had a half-time of 6.05 (range 0.49–17.3) min; the slower function had a half-time of 89.7 (range 23.1–173.3) min.

Since we employed a 120-min exposure duration both in this project and in other work (24,25), we were also interested in how close blood levels came to their asymptotic values during exposure. For the seven animals for which single-exponential uptake functions were fit to the data, five achieved greater than 95 % of the calculated plateau; the mean percentage of the asymptote was 90.8 (range 66.0–99.6). For these same animals, we also calculated comparable estimates for elimination. The mean was 74.4 (range 57.4–91.8). Six of these seven animals came closer to a plateau or asymptote during uptake than they did during elimination. To determine if this apparent difference between uptake and elimination functions was attributable to a domination by one ex-

ponential process during the sampling interval, we calculated the mean percentage of the level attained after 120 min of exposure that was attributable to the more rapid function. Since this value was 52.8 %, we conclude that the differences observed between the uptake and elimination functions were not due to an artifactual constraint exerted by the selected duration of exposure.

Discussion

The peak blood concentrations following the reported acute toluene exposure are in relatively good agreement with others reported in the literature. Bruckner & Peterson (8) reported blood concentrations in the mouse of (i) 200 $\mu\text{g/ml}$ following 3-h exposure to 4 000 ppm, (ii) 147 $\mu\text{g/ml}$ following 2-h exposures to 2 600 ppm, and (iii) 97 $\mu\text{g/ml}$ following 2-h exposures at 1 300 ppm. For the rat, Benignus et al (6) reported values of 11 $\mu\text{g/ml}$ following 2-h exposures at 575 ppm. Carlsson & Lindqvist (9) reported 15 $\mu\text{g/ml}$ following 1-h exposures to 500 ppm.

Multicompartmental modeling techniques can be used profitably to describe toluene uptake and elimination processes (7, 9, 16, 17, 19, 20). These investigations typically employed graphic solutions to estimate rate parameters; however, as Sato & Nakajima (19) observed, "The ability to make a three exponential process fit suggests, but does not prove the three-exponential characteristics of the process being fitted." Without a formal test, a conclusion that any particular model is better than another is not defensible. Nonlinear regression techniques, unlike exponential curve-stripping ("feathering") procedures, permit formal model testing. The procedures do not rely on subjective judgments of the investigator about the placement of the function. Furthermore, a systematic application of the procedures can provide further insights. For example, trends in the residuals may provide evidence of additional exponential functions or suggest complications introduced by other physiological processes.

A formal predictive model has been applied previously to the kinetics of toluene (6). Using a between-subject design, these authors indicated that a single-exponential model characterized the kinetics of this compound and that a second compartment could not be resolved. Utilizing a within-subject design, we were able to demonstrate that a bi-exponential equation fit the data significantly better than did a one-exponential equation. These results suggest that the variability inherent in between-group kinetic experiments may reduce the resolution of an experiment sufficiently to prevent adequate description of an agent's toxicokinetics.

We were unable to resolve a second exponential term during uptake in six of the seven animals for whom these data were collected. However, our not resolving an additional term does not preclude its

existence (14, 23). Since a relatively restricted amount of data was collected in this phase of the experiment, it is possible that we were unable to identify outliers and reduce variability sufficiently to resolve a second compartment. This possibility is important because differences in the number of exponential terms required to characterize uptake and elimination could indicate altered dynamics attributable to changes in respiratory rates and tissue perfusion. Alternatively, the diffusion of toluene between compartments across time might favor those tissue groups with greater lipid content.

Physiological modeling techniques can provide estimates of metabolic kinetic constants for a variety of inhaled toxicants (4). Although the equations characterizing compartmental analyses have explicit solutions and are generally less mathematically complex, they do not readily permit extrapolations to unexamined species (2, 3). In addition, compartmental analyses may not adequately describe the process under conditions of metabolic saturation (18). Since toluene metabolism in the rat has been asserted to be saturated at inhaled concentrations of 200 ppm (15), one might expect linear multicompartmental functions to provide an inadequate description of the data obtained at our relatively high exposure concentrations. However, excellent prediction of toluene uptake and elimination was achieved with such functions in the present work.

The present observations have implications for the assessment of functional impairment produced by exposure to volatile solvents. In previous work (24, 25), we have observed orderly concentration-related behavioral impairment in individual animals. However, the animals differed markedly in their sensitivity. Variability between animals in peak blood concentrations may account for these differences in behavioral sensitivity. Additional work that examines both the kinetics of an agent and its behavioral effects within individual subjects should resolve this issue. Furthermore, the variability observed between subjects may result in an overestimation of the minimal solvent concentration needed to impair performance and consequent recommendation of a criterion for occupational exposure that is too high.

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