Supplemental Materials

Quantitative PCR analysis of DNA aptamer pharmacokinetics in mice

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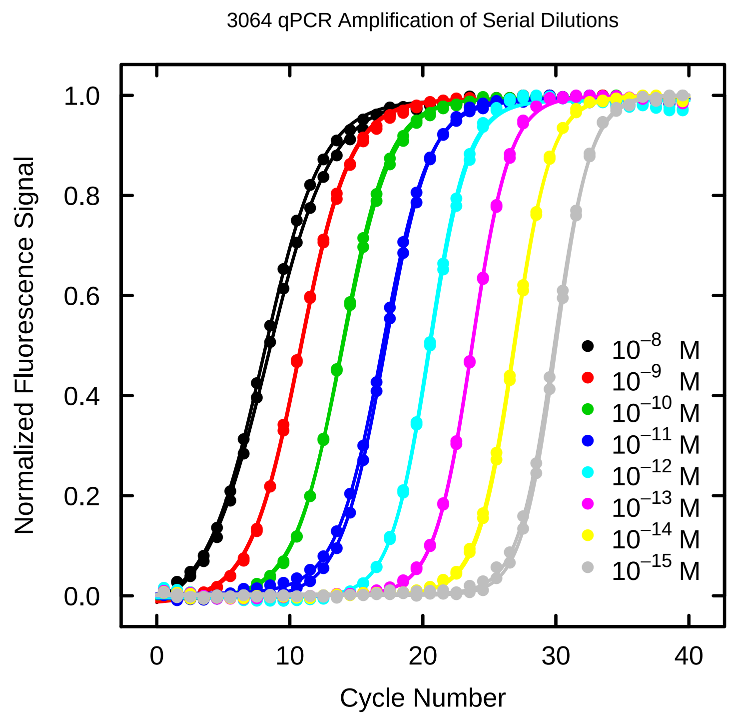
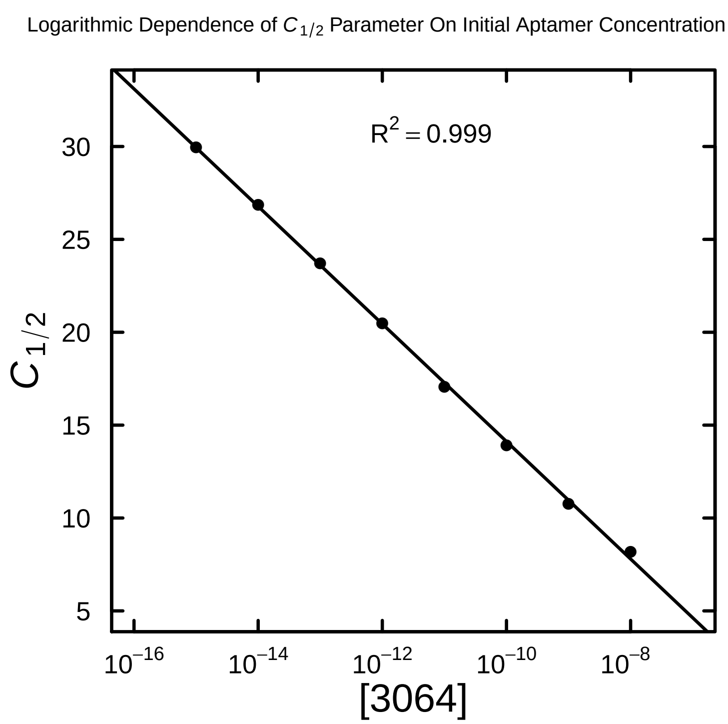
Quantitative PCR

Figure S1: Quantitative PCR assay demonstrating differential amplification of serial dilutions of 3064 aptamer solutions, using a SYBR Green detection system. (Top) Normalized fluorescence data are fit to the sigmoid model given in Equation 1 of Online Methods. (Bottom) The fitted $C_{1/2}$ parameter is plotted as a function of 3064 aptamer concentration. Linear regression gives $R^2 \sim 1$.





From standard curves like the one shown in Figure S1, each $C_{1/2}$ value of the tissue samples is converted into an aptamer concentration using the slope and intercept determined from linear regression. These concentrations are then converted into molecules (using Avogadro's number and the mass of the bare aptamer). Finally, each concentration was divided by 5 mg of tissue (the amount used to seed the qPCR reaction) to arrive at a normalized concentration value. Grubbs test was then performed to determine if any of the 3–7 values represented an outlier, which was removed from the data. The final normalized concentrations (molecules/mg tissue) for each mouse for each tissue at each time point are given in Tables S1–S5. It should be emphasized that at most two digits are significant in the tables that follow, but integer concentrations are shown to allow for computation of means and standard deviations. The mean (and standard deviation) values were used to construct Figures 2–4 of the main text and for pharmacokinetic modeling.

Table S1: 3064BS concentration (molecules/mg tissue)

Tissue	10 minutes	30 minutes	1 hour	4 hours	24 hours	48 hours
Liver	690628138	41570819	1824344639	1033807162	511732	24966
	1146055316	4068976122	5142076435	2051089985	10231810	64774
	1554518131	4626052364	8685232092	2902431497	19450853	203476
	1766135626	7026483427		7786512704	37147797	253926
Spleen	1212328685	892283924	2229615531	483437053	399201	36087
	2199327699	2237994690	2281263647	564122240	19853732	70014
	4206610455	3762435933	3527974975	1729108497	21812908	362566
	5401333247	4507666819	6709622832	2310706313	69198017	1312337
		8173240404				
Kidney	401171766	43307015	2709840	5015137	1084995	1870
	527015476	75934220	9694939	8194079	1128906	31865
	1198596615	80755742	46101564	9485021		89004
	1818182076	104723782	94702740			
Blood	2184375	192505002	65966831	5145631	316291	27584
	28660172	352268556	65970900	9534839	711058	33055
	71408720	836840590		13617897	1066339	57147
	74110545	930682884		28292487		109298
		1095303394				
Spinal Cord	340701	1459900	857423	22587	8996	3080
	5356673	1464795	2037693	758404	19333	4054
	6424052	3860913	2834898	2919474	47239	4708
	11274681	4477161		2979932	150198	
	24732562	6955629				
Brain	270969	500531	670825	150988	22780	100884
	358839	5151538	766317	391954	79642	102554
	752104	15432151	2066911	846104	207984	
	3787195	16057374		1399433	259766	
	7739085					

Table S2: 3064B concentration

Tissue	10 minutes	4 hours	24 hours
Liver	5526294423	601172	9009
	9245183153	618763	11035
	13604781859	901946	20835
	17545692587	916161	
Spleen	4906802752	71496	90056
	8057113780	1085463	179203
	9231517482	1497768	267677
	12999248607	4578226	629207
Kidney	73010802	283307	209826
	76721026	404280	243634
	89337776	494650	320409
		859376	574493
Blood	53755724	3240	4581
	89570070	9258	4963
	218503670	14135	6761
	337785142	18016	
Spinal Cord	8502546	19359	3636
	12452931	24800	3814
	14650901	31909	4502
	31391261		
Brain	6003064	7958	5120
	9012206	9744	8324
	21518483	16639	15117
			21194

Table S3: 3064 concentration

Tissue	10 minutes	4 hours	24 hours
Liver	500028	13016380	5588
	1860294	17277228	14672
	835191796	95811725	25111
	1418827027	230945599	26174
			70724
			132156
			140434
Spleen	840980	29354873	8726
	9031257	36404026	29883
	81492377	51343851	96262
		82475410	229258
			241069
			337458
			351407
Kidney	321033	2260840	7
	586228	13223183	414
	191469570	24885292	6185
	849041755	25237522	85202
			287579
			301458
			441976
Blood	14591	155325	17
	411133	583291	19
	15826802	809136	52
	60608603		72
			658
			691
			1021
Spinal Cord	133347	47317	52
	261683	95161	81
	684845	123438	1435
		231652	2612
			3037
			3278
			4124
Brain	20462	3083	115
	137257	12963	174
	195476	21690	277
	256693	33589	280
			392

Table S4: 3064BS (TMEV) concentration

Tissue	10 minutes	30 minutes	1 hour	4 hours	24 hours	48 hours
Liver	30180457	128327904	1577180	64269	1978	6779
	143152668	249170727	3958304	393927	5604	13161
	319215107	281230428	37189992		13315	31873
	324270676	287612768	130795353		50554	70142
	615311718	498737082	258937468		75611	168923
			537379346		116301	
Spleen	690112261	105234621	2249359	344328	5905	4317
	1286055641	604670795	18052178	2233540	27732	7962
	2019297032	1439433418	74800324		66551	10992
	3009659987	1932352957	232183404		115988	17933
		3862770412	462833319		420640	
					918311	
					935614	
Kidney	303706194	672304841	311608586	2731097	55963	32055
	431702318	791395771	1828795185	17910736	582517	61359
	844887259	856007940	2788185147		729991	176021
	944756477	948309688	3110318185		2618305	224867
			5949598400		6056249	260725
			7969560154		6746747	
Blood	12550	201601	6884235	1140323	1549	36718
	26232	7417344	9763460	3930438	25680	66501
	36993	247990271	12765757		45574	219490
	46639	345160283			83290	294678
		448318729			166583	
					171505	
Spinal Cord	5779813	12770006	308	65658	7	6
	10552411	39807602	344	72037	7	6
	25256133	75936763	22076		15	7
	31233328	76503806	265166		88	
		99024280	1800817		428	
			3180227		916	
					1145	
Brain	59185116	57410561	507187	226241	35473	7044
	74693792	110588692	1865396	756760	56194	13066
	152302349	238584050	5565396	6749846	84603	24097
	317930804	424235500	14212202		98941	43727
			32932611		148878	99186
			62195610		339324	
					471919	

Table S5: 4971 concentration

Tissue	10 minutes	4 hours	24 hours
Liver	888852	1249	41
	1070017	3532	73
	1094008	3575	173
		4690	222
Spleen	876221	479	276
	899544	560	362
		878	375
		1031	449
Kidney	429605	2501	438
	876334	2978	515
	1438972	3988	541
		4371	645
Blood	1141	2996	3336
	5115	3105	3385
	12106	3295	
	12687	4042	
Spinal Cord	1	1	1
	275	1	1
		1	1
		7	9
Brain	1085	52	1
	1962	141	1
	77537	169	2
	80233	283	

Pharmacokinetic modeling

The gamma variate function

Consider a probability density function of the form

$$f(t) = \frac{1}{\beta^{\alpha+1}\Gamma(\alpha+1)} t^{\alpha} e^{-\frac{t}{\beta}} = \frac{C(t)}{A(\infty)} \tag{S1}$$

where α and β are parameters describing the function and $\Gamma(n)$ is the gamma function given by

$$\Gamma(n) = \int_0^{\infty} x^{n-1} e^{-x}\, dx \tag{S2}$$

This density function is equivalent to a concentration-time curve, $C(t)$, in which each time point is divided by the total area under the concentration-time curve, $A(\infty)$, thus transforming each input into a probability measure. Making the substitution

$$\kappa = \frac{A(\infty)}{\beta^{\alpha+1}\Gamma(\alpha+1)} \tag{S3}$$

the concentration-time curve becomes

$$C(t) = \kappa t^{\alpha} e^{-\frac{t}{\beta}} \tag{S4}$$

The area under this concentration-time curve (up to time T) is

$$A(T) = \int_0^T C(t)\,dt \tag{S5}$$

and with the substitutions $t = \beta x$, $dt = \beta dx$, and $\alpha = n - 1$ it follows that

$$\begin{aligned} A(T) = \int_0^T \kappa t^{\alpha} e^{-\frac{t}{\beta}}\,dt &= \int_0^T \kappa(\beta x)^{n-1} e^{-x}\,\beta dx \\ &= \kappa\beta^n \int_0^T x^{n-1} e^{-x}\,dx \\ &= \kappa\beta^n \gamma(n, T) \qquad\qquad = \kappa\beta^{\alpha+1}\gamma(\alpha+1, T) \end{aligned} \tag{S6}$$

where $\gamma(n, T)$ is the lower incomplete gamma function

$$\gamma(n, T) = \int_0^T x^{n-1} e^{-x}\,dx = \Gamma(n) \cdot P(n, T) \tag{S7}$$

which is equal to the product of the gamma function and the gamma distribution function $P(n, T)$ given by

$$P(n, T) = \frac{1}{\Gamma(n)} \int_0^T x^{n-1} e^{-x}\,dx \tag{S8}$$

As $T \to \infty$, it follows that $\gamma(n, T) \to \Gamma(n)$ and the equivalence between Equation S6 at infinite T and Equation S3 becomes clear. Because integration of $C(t)$ (from 0 to ∞) produces a gamma function, this concentration function is known as a gamma variate.

To facilitate interpretation of the parameters α, β, and γ, we rearrange the gamma variate function as follows. First, we make the substitution

$$k = \kappa\beta^{\alpha} \tag{S9}$$

resulting in

$$C(t) = k\left(\frac{t}{\beta}\right)^{\alpha} e^{-\frac{t}{\beta}} \tag{S10}$$

The parameter k has units of concentration (and is related to concentration maximum), β has units of time, and α is dimensionless. Next, we make the substitutions $\alpha = \ln 2/a$ and $\beta = b/\ln 2$ so that $C(t)$ has final form

$$C(t) = k\left(\frac{\ln 2}{b} t\right)^{\frac{\ln 2}{a}} e^{-\frac{\ln 2}{b} t} \tag{S11}$$

In this form, the parameter b represents an effective half-life. Finally, we make substitutions in Equation S6, resulting in the following final form of $A(T)$

$$A(T) = k_1\left(\frac{b_1}{\ln 2}\right)\gamma\left(\frac{\ln 2}{a_1} + 1, T\right) + k_2\left(\frac{b_2}{\ln 2}\right)\gamma\left(\frac{\ln 2}{a_2} + 1, T\right) \tag{S12}$$

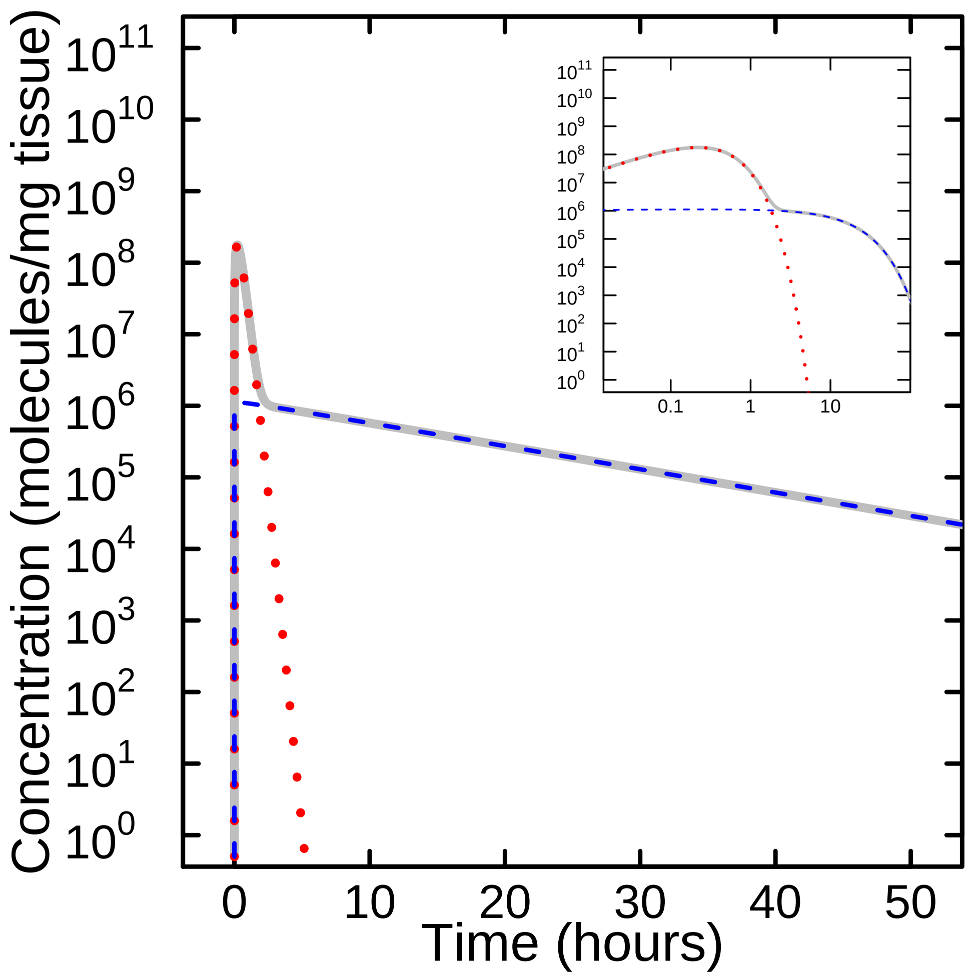
Sum of two gamma variates

Shown in Figure S2, the experimental data sets are modeled as the sum of two gamma variates

$$C(t) = \sum_{i=1}^{2} C_i(t) = \sum_{i=1}^{2} k_i\left(\frac{\ln 2}{b_i} t\right)^{\frac{\ln 2}{a_i}} e^{-\frac{\ln 2}{b_i} t} \tag{S13}$$

Figure S2: Schematic illustration of pharmacokinetic data modeled as the sum of two gamma variates. An example fitting curve expresses recovered aptamer concentration (molecules per mg extracted tissue) on a logarithmic scale as a function of time (in hours) after i.p. injection. Data are well fit by the sum (gray) of two gamma variates (red and blue) describing an initial rapid aptamer accumulation and partial depletion phase, followed by a slow first-order exponential decay phase.

$$C(t) = k_1 \left(\frac{\ln 2}{b_1} t \right)^{\frac{\ln 2}{a_1}} e^{-\frac{\ln 2}{b_1} t} + k_2 \left(\frac{\ln 2}{b_2} t \right)^{\frac{\ln 2}{a_2}} e^{-\frac{\ln 2}{b_2} t}$$



Optimization

A weighted nonlinear least squares method was used to minimize the cost function $Q(\mathbf{p})$ with respect to the free parameters $\mathbf{p} = (k_1, k_2, a_1, a_2, b_1, b_2)$

$$\chi^2 = \min_{\mathbf{p}} Q(\mathbf{p}) = \min_{\mathbf{p}} \sum_{m=1}^{M} \left(\frac{\bar{C}_m - C(t_m; \mathbf{p})}{\sigma_{\bar{C}_m}} \right)^2 \tag{S14}$$

where M is the number of time points being fit, t_m are times in minutes (corresponding to the m-th time point), $\bar{C}_m$ are experimentally determined mean concentrations, $\sigma_{\bar{C}_m}$ are standard deviations of $\bar{C}_m$, and $C(t_m; \mathbf{p})$ are theoretical predictions of the model. Optimizations were performed using a simplex and inductive search hybrid algorithm (SIH).

Monte Carlo estimation of uncertainty

Simulated data sets were generated from the experimental data by adding Gaussian noise, i.e. randomly sampling from the normal distributions $N_m(\mu = \bar{C}_m, \sigma = \sigma_{\bar{C}_m})$. These simulated data sets (N_m^ϵ for $\epsilon = 1, \ldots, \epsilon_{\max}$) were fitted with the pharmacokinetic model to determine $\mathbf{p}_{\min}^\epsilon$

$$\min_{\mathbf{p}^\epsilon} \sum_{m=1}^{M} \left(\frac{N_m^\epsilon - C(t_m; \mathbf{p}^\epsilon)}{\sigma_{N_m^\epsilon}} \right)^2 \tag{S15}$$

For a given parameter p_k, the median was taken and the standard deviation was estimated as

$$\sigma_{p_k} = \sqrt{\frac{1}{\epsilon_{\max} - 1} \sum_{\epsilon=1}^{\epsilon_{\max}} \left(p_{\min,k}^\epsilon - \bar{p}_k \right)^2} \tag{S16}$$

where $\epsilon_{\max}$ was set at 10,000 and $\bar{p}_k$ is the mean value

$$\bar{p}_k = \frac{1}{\epsilon_{\max}} \sum_{\epsilon=1}^{\epsilon_{\max}} p_{\min,k}^\epsilon \tag{S17}$$

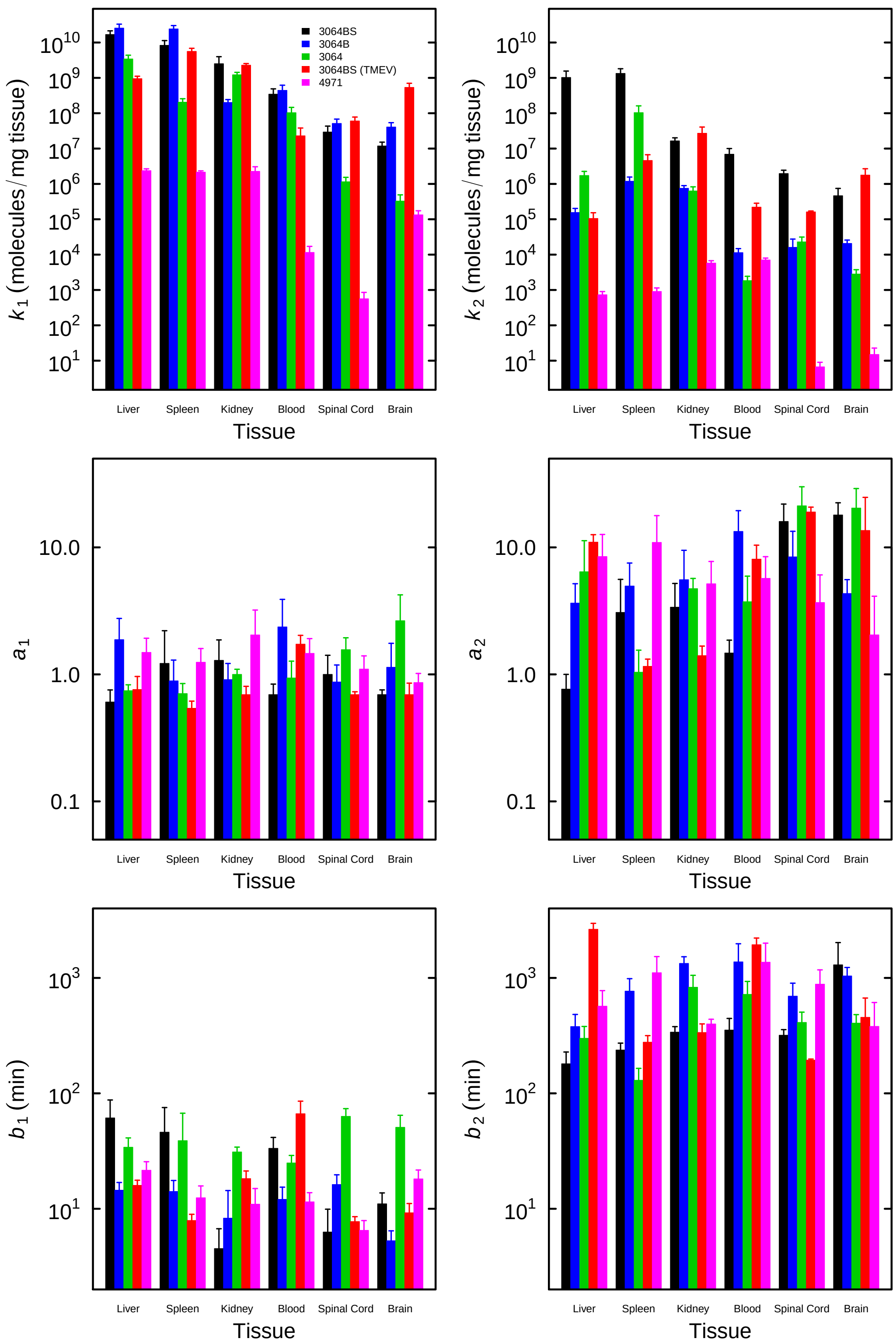
Additionally, the relative bias in the parameter p_k is given by

$$B_k = \frac{|p_{\min,k} - \bar{p}_k|}{p_{\min,k}} \tag{S18}$$

The median relative bias of all parameter estimates was ∼3 percent, giving confidence in the method.

Parameters from concentration-time curves

Figure S3: Parameters from fitting concentration data with pharmacokinetic model. Values of k_1, k_2, a_1, a_2, b_1, and b_2 determined from fitting are given in Table 1 of the main text.



Two additional parameters of interest are time to peak (t_p)

$$t_{p_i} = \alpha_i \beta_i = \frac{b_i}{a_i} \tag{S19}$$

and peak concentration (C_p) achieved at t_p

$$C_{p_i} = k_i \left(\frac{\alpha_i}{e}\right)^{\alpha_i} = k_i \left(\frac{\ln 2}{a_i e}\right)^{\frac{\ln 2}{a_i}} \tag{S20}$$

Since the pharmacokinetic model is a sum of two gamma variates, the observed t_p occurs near but not precisely at t_{p1}. Likewise, the observed C_p reflects the sum of C_{p1} plus the value of C_2 evaluated at the observed t_p. However, as shown in Table S6, in most cases this contribution is negligible as $t_p \approx t_{p1}$ and $C_p \approx C_{p1}$.

Figure S4: The observed t_p and observed C_p from pharmacokinetic modeling.

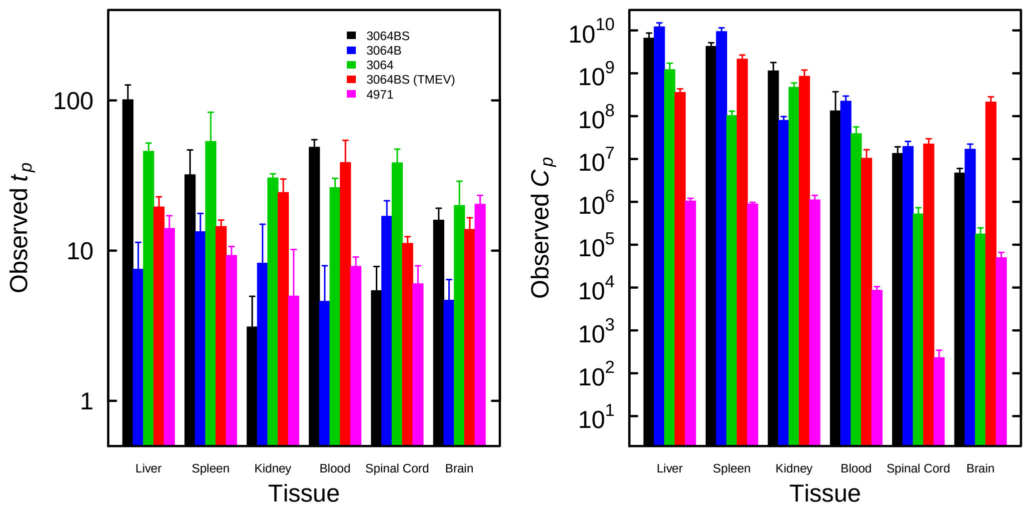


Table S6: Values of t_{p_i}, C_{p_i}, and the observed t_p and observed C_p from the pharmacokinetic model

Tissue	t_{p1} (min)	C_{p1} (molecules/mg tissue)	t_{p2} (min)	C_{p2} (molecules/mg tissue)	observed t_p (min)	observed C_p (molecules/mg tissue)
			3064BS			
Liver	100 ± 30	$6.4 \pm 1.7 \times 10^9$	240 ± 20	$3.8 \pm 1.9 \times 10^8$	100 ± 30	$6.6 \pm 2.1 \times 10^9$
Spleen	32 ± 15	$3.6 \pm 1.0 \times 10^9$	75 ± 66	$7.2 \pm 3.2 \times 10^8$	32 ± 15	$4.3 \pm 0.9 \times 10^9$
Kidney	3.1 ± 1.8	$1.1 \pm 0.6 \times 10^9$	100 ± 60	$9.4 \pm 2.0 \times 10^6$	3.1 ± 1.9	$1.1 \pm 0.6 \times 10^9$
Blood	49 ± 6	$1.3 \pm 2.4 \times 10^8$	240 ± 0	$2.8 \pm 1.2 \times 10^6$	49 ± 6	$1.3 \pm 2.4 \times 10^8$
Spinal Cord	5.4 ± 2.4	$1.2 \pm 0.6 \times 10^7$	23 ± 44	$1.4 \pm 0.4 \times 10^6$	5.4 ± 2.4	$1.3 \pm 0.6 \times 10^7$
Brain	16 ± 3	$4.4 \pm 1.2 \times 10^6$	87 ± 57	$3.8 \pm 1.9 \times 10^5$	16 ± 3	$4.7 \pm 1.3 \times 10^6$
			3064B			
Liver	7.5 ± 3.8	$1.2 \pm 0.3 \times 10^{10}$	110 ± 30	$9.0 \pm 2.8 \times 10^4$	7.5 ± 3.8	$1.2 \pm 0.3 \times 10^{10}$
Spleen	13 ± 4	$9.4 \pm 1.8 \times 10^9$	150 ± 50	$7.9 \pm 2.4 \times 10^5$	13 ± 4	$9.4 \pm 2.1 \times 10^9$
Kidney	8.3 ± 6.7	$7.9 \pm 1.6 \times 10^7$	240 ± 70	$5.4 \pm 1.1 \times 10^5$	8.3 ± 6.7	$8.0 \pm 1.8 \times 10^7$
Blood	4.6 ± 3.3	$2.2 \pm 0.7 \times 10^8$	100 ± 60	$9.3 \pm 2.6 \times 10^3$	4.6 ± 3.3	$2.2 \pm 0.7 \times 10^8$
Spinal Cord	17 ± 5	$2.0 \pm 0.6 \times 10^7$	84 ± 44	$1.2 \pm 0.6 \times 10^4$	17 ± 5	$2.0 \pm 0.6 \times 10^7$
Brain	4.7 ± 1.7	$1.7 \pm 0.5 \times 10^7$	240 ± 20	$1.3 \pm 0.3 \times 10^4$	4.7 ± 1.7	$1.7 \pm 0.5 \times 10^7$
			3064			
Liver	46 ± 6	$1.3 \pm 0.3 \times 10^9$	47 ± 56	$1.3 \pm 0.4 \times 10^6$	46 ± 6	$1.2 \pm 0.5 \times 10^9$
Spleen	53 ± 30	$7.7 \pm 2.1 \times 10^7$	120 ± 30	$4.0 \pm 2.1 \times 10^7$	53 ± 30	$1.0 \pm 0.3 \times 10^8$
Kidney	30 ± 2	$4.7 \pm 0.8 \times 10^8$	220 ± 30	$4.1 \pm 1.0 \times 10^5$	31 ± 2	$4.7 \pm 1.2 \times 10^8$
Blood	26 ± 4	$4.0 \pm 1.5 \times 10^7$	180 ± 40	$1.1 \pm 0.3 \times 10^3$	26 ± 4	$3.9 \pm 1.7 \times 10^7$
Spinal Cord	39 ± 9	$5.2 \pm 1.6 \times 10^5$	23 ± 65	$1.8 \pm 0.8 \times 10^4$	38 ± 9	$5.2 \pm 2.1 \times 10^5$
Brain	20 ± 9	$1.8 \pm 0.6 \times 10^5$	20 ± 24	$2.3 \pm 0.8 \times 10^3$	20 ± 9	$1.8 \pm 0.7 \times 10^5$
			3064BS (TMEV)			
Liver	20 ± 3	$3.6 \pm 0.6 \times 10^8$	240 ± 10	$8.3 \pm 2.6 \times 10^4$	20 ± 3	$3.6 \pm 0.7 \times 10^8$
Spleen	14 ± 1	$2.2 \pm 0.5 \times 10^9$	240 ± 0	$1.9 \pm 0.8 \times 10^6$	14 ± 1	$2.1 \pm 0.5 \times 10^9$
Kidney	24 ± 6	$8.5 \pm 3.2 \times 10^8$	240 ± 10	$1.2 \pm 0.5 \times 10^7$	24 ± 6	$8.5 \pm 3.4 \times 10^8$
Blood	39 ± 16	$1.1 \pm 0.5 \times 10^7$	240 ± 20	$1.6 \pm 0.5 \times 10^5$	39 ± 16	$1.0 \pm 0.6 \times 10^7$
Spinal Cord	11 ± 1	$2.2 \pm 0.7 \times 10^7$	10 ± 15	$1.4 \pm 0.1 \times 10^5$	11 ± 1	$2.2 \pm 0.7 \times 10^7$
Brain	14 ± 3	$2.1 \pm 0.7 \times 10^8$	38 ± 76	$1.1 \pm 0.7 \times 10^6$	14 ± 3	$2.1 \pm 0.7 \times 10^8$
			4971			
Liver	14 ± 3	$1.0 \pm 0.1 \times 10^6$	70 ± 42	$5.3 \pm 1.4 \times 10^2$	14 ± 3	$1.0 \pm 0.2 \times 10^6$
Spleen	9.3 ± 1.4	$8.9 \pm 0.1 \times 10^5$	110 ± 70	$6.9 \pm 1.5 \times 10^2$	9.3 ± 1.4	$8.9 \pm 0.8 \times 10^5$
Kidney	5.0 ± 5.2	$1.1 \pm 0.3 \times 10^6$	78 ± 30	$3.9 \pm 0.6 \times 10^3$	5.0 ± 5.2	$1.1 \pm 0.3 \times 10^6$
Blood	7.8 ± 1.2	$5.0 \pm 1.8 \times 10^3$	240 ± 0	$4.8 \pm 0.4 \times 10^3$	7.9 ± 1.2	$8.7 \pm 1.8 \times 10^3$
Spinal Cord	6.0 ± 1.9	$2.3 \pm 1.1 \times 10^2$	240 ± 20	$4.1 \pm 1.4 \times 10^0$	6.0 ± 1.9	$2.3 \pm 1.1 \times 10^2$
Brain	20 ± 3	$5.0 \pm 1.4 \times 10^4$	180 ± 90	$6.9 \pm 5.2 \times 10^0$	20 ± 3	$5.0 \pm 1.6 \times 10^4$

Figure S5: Tissue exposure to aptamer (at various time points) was estimated as the area under the fitted concentration-time curves, Equation S6. Values of A_T (T in minutes) are given in Table S7. The areas under the dashed line and gray shaded region from Figures 2-4 of the main text are shown for a sense of background.

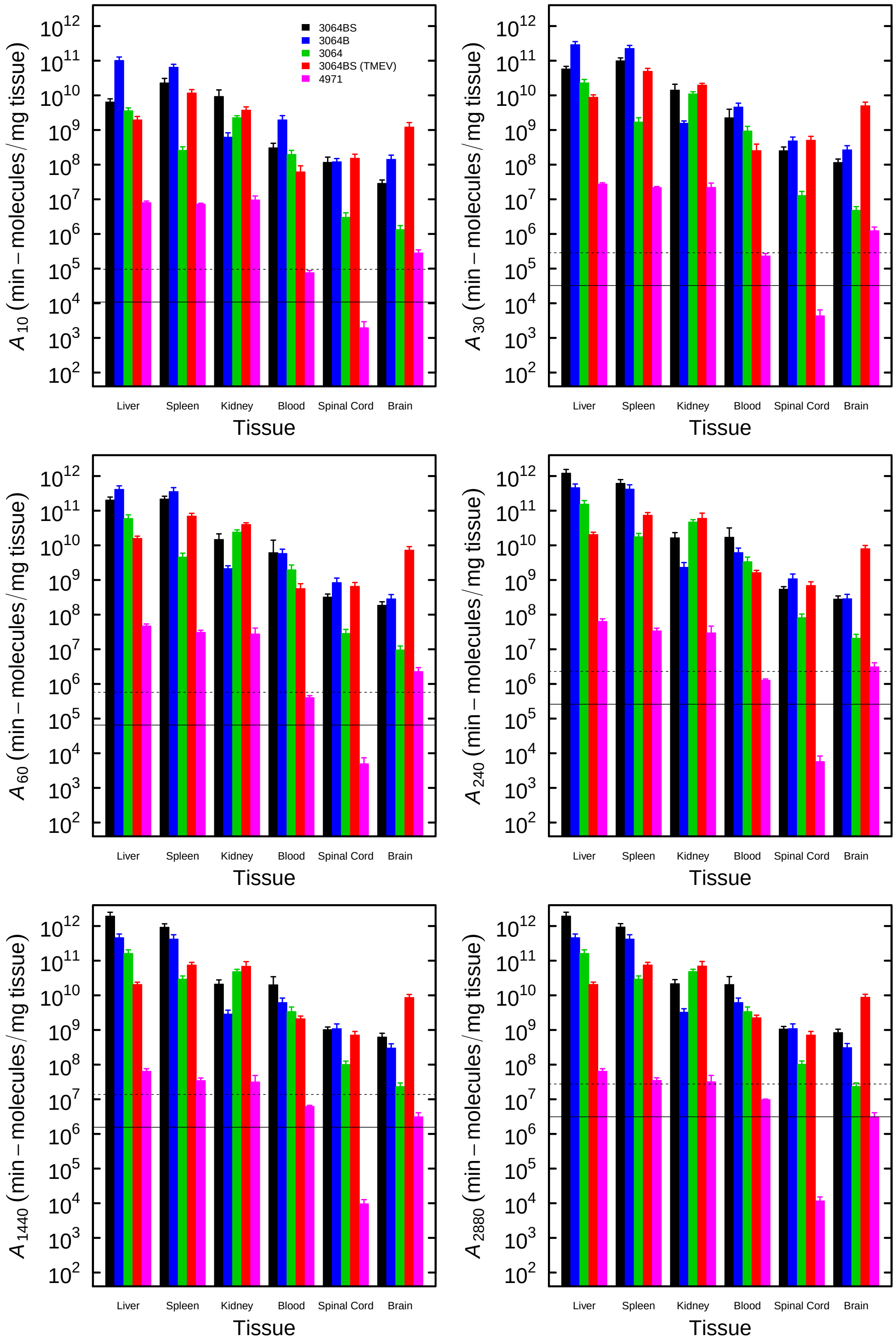


Table S7: Tissue exposure to aptamer (at various time points) was estimated as the area under the fitted concentration-time curves

Tissue	A (min-molecules/mg tissue)						
	10 min	30 min	1 hr	4 hr	24 hr	48 hr	∞
				3064BS			
Liver	$6.5 \pm 1.5 \times 10^{9}$	$5.8 \pm 1.1 \times 10^{10}$	$2.0 \pm 0.4 \times 10^{11}$	$1.2 \pm 0.3 \times 10^{12}$	$1.9 \pm 0.6 \times 10^{12}$	$1.9 \pm 0.6 \times 10^{12}$	$1.9 \pm 0.6 \times 10^{12}$
Spleen	$2.3 \pm 0.8 \times 10^{10}$	$1.0 \pm 0.2 \times 10^{11}$	$2.2 \pm 0.4 \times 10^{11}$	$6.2 \pm 1.7 \times 10^{11}$	$9.3 \pm 2.3 \times 10^{11}$	$9.4 \pm 2.3 \times 10^{11}$	$9.4 \pm 2.3 \times 10^{11}$
Kidney	$9.3 \pm 5.0 \times 10^{9}$	$1.4 \pm 0.7 \times 10^{10}$	$1.5 \pm 0.7 \times 10^{10}$	$1.7 \pm 0.7 \times 10^{10}$	$2.1 \pm 0.7 \times 10^{10}$	$2.2 \pm 0.7 \times 10^{10}$	$2.2 \pm 0.7 \times 10^{10}$
Blood	$3.1 \pm 1.1 \times 10^{8}$	$2.3 \pm 1.7 \times 10^{9}$	$6.2 \pm 7.9 \times 10^{9}$	$1.7 \pm 1.5 \times 10^{10}$	$2.0 \pm 1.4 \times 10^{10}$	$2.1 \pm 1.4 \times 10^{10}$	$2.1 \pm 1.4 \times 10^{10}$
Spinal Cord	$1.2 \pm 0.5 \times 10^{8}$	$2.5 \pm 0.7 \times 10^{8}$	$3.2 \pm 0.7 \times 10^{8}$	$5.5 \pm 1.0 \times 10^{8}$	$1.0 \pm 0.2 \times 10^{9}$	$1.1 \pm 0.2 \times 10^{9}$	$1.1 \pm 0.2 \times 10^{9}$
Brain	$2.9 \pm 0.7 \times 10^{7}$	$1.2 \pm 0.3 \times 10^{8}$	$1.9 \pm 0.5 \times 10^{8}$	$2.8 \pm 0.6 \times 10^{8}$	$6.3 \pm 1.8 \times 10^{8}$	$8.5 \pm 2.1 \times 10^{8}$	$1.1 \pm 0.1 \times 10^{9}$
				3064B			
Liver	$1.0 \pm 0.3 \times 10^{11}$	$2.9 \pm 0.6 \times 10^{11}$	$4.1 \pm 1.1 \times 10^{11}$	$4.6 \pm 1.3 \times 10^{11}$	$4.6 \pm 1.3 \times 10^{11}$	$4.6 \pm 1.3 \times 10^{11}$	$4.6 \pm 1.3 \times 10^{11}$
Spleen	$6.5 \pm 1.4 \times 10^{10}$	$2.3 \pm 0.5 \times 10^{11}$	$3.6 \pm 1.0 \times 10^{11}$	$4.2 \pm 1.4 \times 10^{11}$	$4.2 \pm 1.4 \times 10^{11}$	$4.2 \pm 1.4 \times 10^{11}$	$4.2 \pm 1.4 \times 10^{11}$
Kidney	$6.2 \pm 2.0 \times 10^{8}$	$1.6 \pm 0.2 \times 10^{9}$	$2.1 \pm 0.4 \times 10^{9}$	$2.3 \pm 0.8 \times 10^{9}$	$2.9 \pm 0.8 \times 10^{9}$	$3.3 \pm 0.8 \times 10^{9}$	$3.7 \pm 0.8 \times 10^{9}$
Blood	$2.0 \pm 0.6 \times 10^{9}$	$4.6 \pm 1.3 \times 10^{9}$	$5.9 \pm 1.9 \times 10^{9}$	$6.2 \pm 2.1 \times 10^{9}$	$6.2 \pm 2.1 \times 10^{9}$	$6.2 \pm 2.1 \times 10^{9}$	$6.2 \pm 2.1 \times 10^{9}$
Spinal Cord	$1.2 \pm 0.3 \times 10^{8}$	$4.9 \pm 1.4 \times 10^{8}$	$8.5 \pm 2.9 \times 10^{8}$	$1.1 \pm 0.4 \times 10^{9}$	$1.1 \pm 0.4 \times 10^{9}$	$1.1 \pm 0.4 \times 10^{9}$	$1.1 \pm 0.4 \times 10^{9}$
Brain	$1.4 \pm 0.5 \times 10^{8}$	$2.7 \pm 0.8 \times 10^{8}$	$2.9 \pm 0.9 \times 10^{8}$	$2.9 \pm 1.0 \times 10^{8}$	$3.0 \pm 1.0 \times 10^{8}$	$3.1 \pm 1.0 \times 10^{8}$	$3.2 \pm 1.0 \times 10^{8}$
				3064			
Liver	$3.6 \pm 0.7 \times 10^{9}$	$2.3 \pm 0.6 \times 10^{10}$	$6.0 \pm 1.6 \times 10^{10}$	$1.6 \pm 0.4 \times 10^{11}$	$1.6 \pm 0.4 \times 10^{11}$	$1.6 \pm 0.4 \times 10^{11}$	$1.6 \pm 0.4 \times 10^{11}$
Spleen	$2.6 \pm 0.7 \times 10^{8}$	$1.7 \pm 0.5 \times 10^{9}$	$4.6 \pm 1.3 \times 10^{9}$	$1.8 \pm 0.4 \times 10^{10}$	$3.0 \pm 0.7 \times 10^{10}$	$3.0 \pm 0.7 \times 10^{10}$	$3.0 \pm 0.7 \times 10^{10}$
Kidney	$2.3 \pm 0.3 \times 10^{9}$	$1.1 \pm 0.2 \times 10^{10}$	$2.4 \pm 0.4 \times 10^{10}$	$4.7 \pm 0.8 \times 10^{10}$	$4.9 \pm 0.8 \times 10^{10}$	$4.9 \pm 0.8 \times 10^{10}$	$4.9 \pm 0.8 \times 10^{10}$
Blood	$2.0 \pm 0.6 \times 10^{8}$	$9.4 \pm 3.3 \times 10^{8}$	$2.0 \pm 0.7 \times 10^{9}$	$3.4 \pm 1.2 \times 10^{9}$	$3.4 \pm 1.2 \times 10^{9}$	$3.4 \pm 1.2 \times 10^{9}$	$3.4 \pm 1.2 \times 10^{9}$
Spinal Cord	$3.0 \pm 1.0 \times 10^{6}$	$1.3 \pm 0.4 \times 10^{7}$	$2.9 \pm 0.9 \times 10^{7}$	$8.2 \pm 2.2 \times 10^{7}$	$1.0 \pm 0.2 \times 10^{8}$	$1.0 \pm 0.2 \times 10^{8}$	$1.0 \pm 0.2 \times 10^{8}$
Brain	$1.3 \pm 0.4 \times 10^{6}$	$4.8 \pm 1.3 \times 10^{6}$	$9.6 \pm 2.8 \times 10^{6}$	$2.1 \pm 0.6 \times 10^{7}$	$2.4 \pm 0.6 \times 10^{7}$	$2.4 \pm 0.6 \times 10^{7}$	$2.4 \pm 0.6 \times 10^{7}$
				3064BS (TMEV)			
Liver	$2.0 \pm 0.5 \times 10^{9}$	$8.9 \pm 1.5 \times 10^{9}$	$1.6 \pm 0.2 \times 10^{10}$	$2.1 \pm 0.3 \times 10^{10}$	$2.1 \pm 0.3 \times 10^{10}$	$2.1 \pm 0.3 \times 10^{10}$	$2.1 \pm 0.3 \times 10^{10}$
Spleen	$1.2 \pm 0.3 \times 10^{10}$	$5.0 \pm 1.0 \times 10^{10}$	$7.0 \pm 1.4 \times 10^{10}$	$7.4 \pm 1.4 \times 10^{10}$	$7.5 \pm 1.4 \times 10^{10}$	$7.6 \pm 1.4 \times 10^{10}$	$7.6 \pm 1.4 \times 10^{10}$
Kidney	$3.8 \pm 0.9 \times 10^{9}$	$2.0 \pm 0.2 \times 10^{10}$	$4.0 \pm 0.5 \times 10^{10}$	$6.1 \pm 2.4 \times 10^{10}$	$6.9 \pm 2.5 \times 10^{10}$	$7.0 \pm 2.4 \times 10^{10}$	$7.1 \pm 2.4 \times 10^{10}$
Blood	$6.2 \pm 3.0 \times 10^{7}$	$2.6 \pm 1.4 \times 10^{8}$	$5.7 \pm 2.1 \times 10^{8}$	$1.6 \pm 0.3 \times 10^{9}$	$2.1 \pm 0.4 \times 10^{9}$	$2.3 \pm 0.4 \times 10^{9}$	$2.5 \pm 0.4 \times 10^{9}$
Spinal Cord	$1.5 \pm 0.5 \times 10^{8}$	$5.1 \pm 1.5 \times 10^{8}$	$6.6 \pm 1.9 \times 10^{8}$	$7.0 \pm 1.9 \times 10^{8}$	$7.2 \pm 1.9 \times 10^{8}$	$7.2 \pm 1.9 \times 10^{8}$	$7.2 \pm 1.9 \times 10^{8}$
Brain	$1.2 \pm 0.4 \times 10^{9}$	$5.0 \pm 1.3 \times 10^{9}$	$7.3 \pm 1.9 \times 10^{9}$	$8.0 \pm 1.9 \times 10^{9}$	$8.7 \pm 1.9 \times 10^{9}$	$8.8 \pm 1.9 \times 10^{9}$	$8.9 \pm 1.9 \times 10^{9}$
				4971			
Liver	$8.1 \pm 0.8 \times 10^{6}$	$2.8 \pm 0.2 \times 10^{7}$	$4.7 \pm 0.7 \times 10^{7}$	$6.4 \pm 1.2 \times 10^{7}$	$6.4 \pm 1.2 \times 10^{7}$	$6.5 \pm 1.2 \times 10^{7}$	$6.5 \pm 1.2 \times 10^{7}$
Spleen	$7.2 \pm 0.5 \times 10^{6}$	$2.2 \pm 0.1 \times 10^{7}$	$3.1 \pm 0.4 \times 10^{7}$	$3.4 \pm 0.6 \times 10^{7}$	$3.5 \pm 0.6 \times 10^{7}$	$3.5 \pm 0.6 \times 10^{7}$	$3.5 \pm 0.6 \times 10^{7}$
Kidney	$9.6 \pm 2.9 \times 10^{6}$	$2.2 \pm 0.7 \times 10^{7}$	$2.8 \pm 1.3 \times 10^{7}$	$3.0 \pm 1.7 \times 10^{7}$	$3.2 \pm 1.7 \times 10^{7}$	$3.2 \pm 1.7 \times 10^{7}$	$3.2 \pm 1.7 \times 10^{7}$
Blood	$7.7 \pm 1.1 \times 10^{4}$	$2.3 \pm 0.4 \times 10^{5}$	$4.1 \pm 0.5 \times 10^{5}$	$1.3 \pm 0.1 \times 10^{6}$	$6.3 \pm 0.4 \times 10^{6}$	$9.8 \pm 0.4 \times 10^{6}$	$1.3 \pm 0.3 \times 10^{7}$
Spinal Cord	$2.0 \pm 1.0 \times 10^{3}$	$4.4 \pm 2.1 \times 10^{3}$	$5.0 \pm 2.4 \times 10^{3}$	$5.8 \pm 2.5 \times 10^{3}$	$9.7 \pm 3.0 \times 10^{3}$	$1.2 \pm 0.3 \times 10^{4}$	$1.3 \pm 0.4 \times 10^{4}$
Brain	$2.8 \pm 0.6 \times 10^{5}$	$1.2 \pm 0.3 \times 10^{6}$	$2.3 \pm 0.7 \times 10^{6}$	$3.1 \pm 0.9 \times 10^{6}$	$3.1 \pm 0.9 \times 10^{6}$	$3.1 \pm 0.9 \times 10^{6}$	$3.1 \pm 0.9 \times 10^{6}$