Comparison of PBPK Model Results with Measured Data

by

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Available Data

- Rats: Measured serum AA and GA concentrations during subchronic AA administration in drinking water in relevant dose range
- Humans:
  - Measured serum AAVal and GAVAL following oral administration of ^{13}C-labeled AA
  - Hemoglobin binding kinetics in humans which allows back-calculation to serum AA and GA AUC
  - Equation available for converting serum AA and GA AUC to daily oral dose

Rat Subchronic DW Study

Doerge et al. 2005; Tareke et al. 2006

- DW administration
- 1 mg AA/kg/d, 7 wks and single dose studies
- Measured serum AA and GA concentrations, males and females
- AA avg. conc: 0.65 µM
- GA avg. conc: 0.65 µM

- **24 hr AUC: 15.6 µM•hr per mg/kg/d; same for both AA and GA**

Doerge et al. 2005

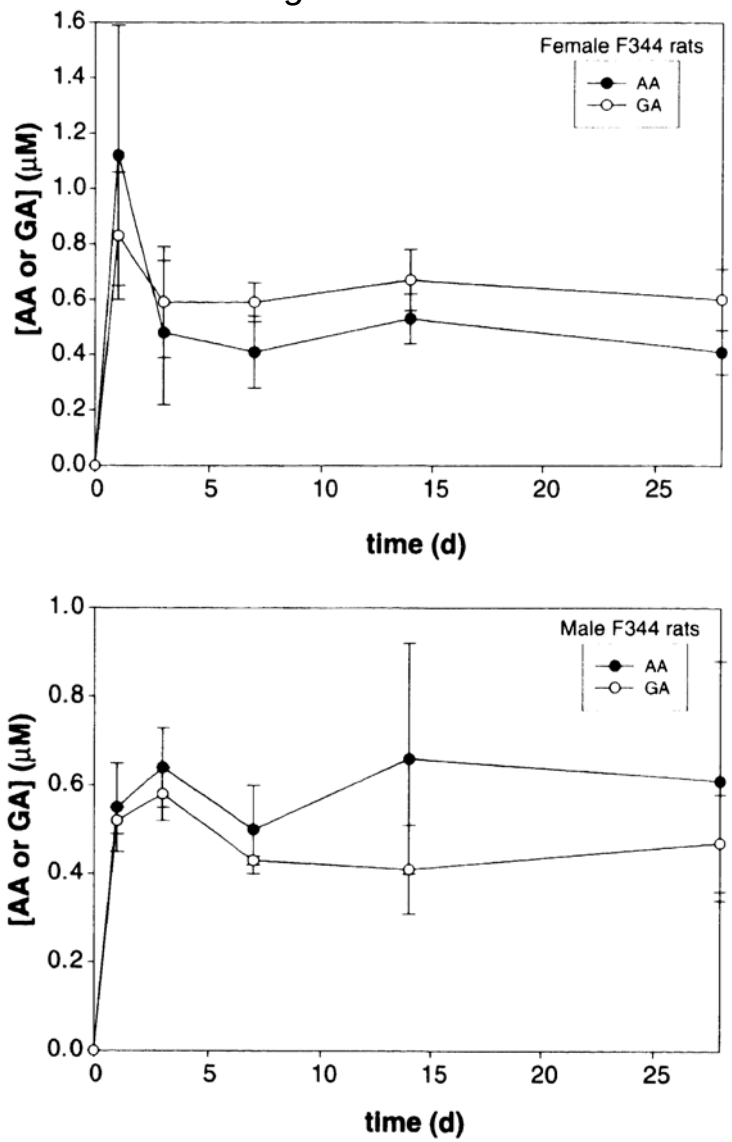
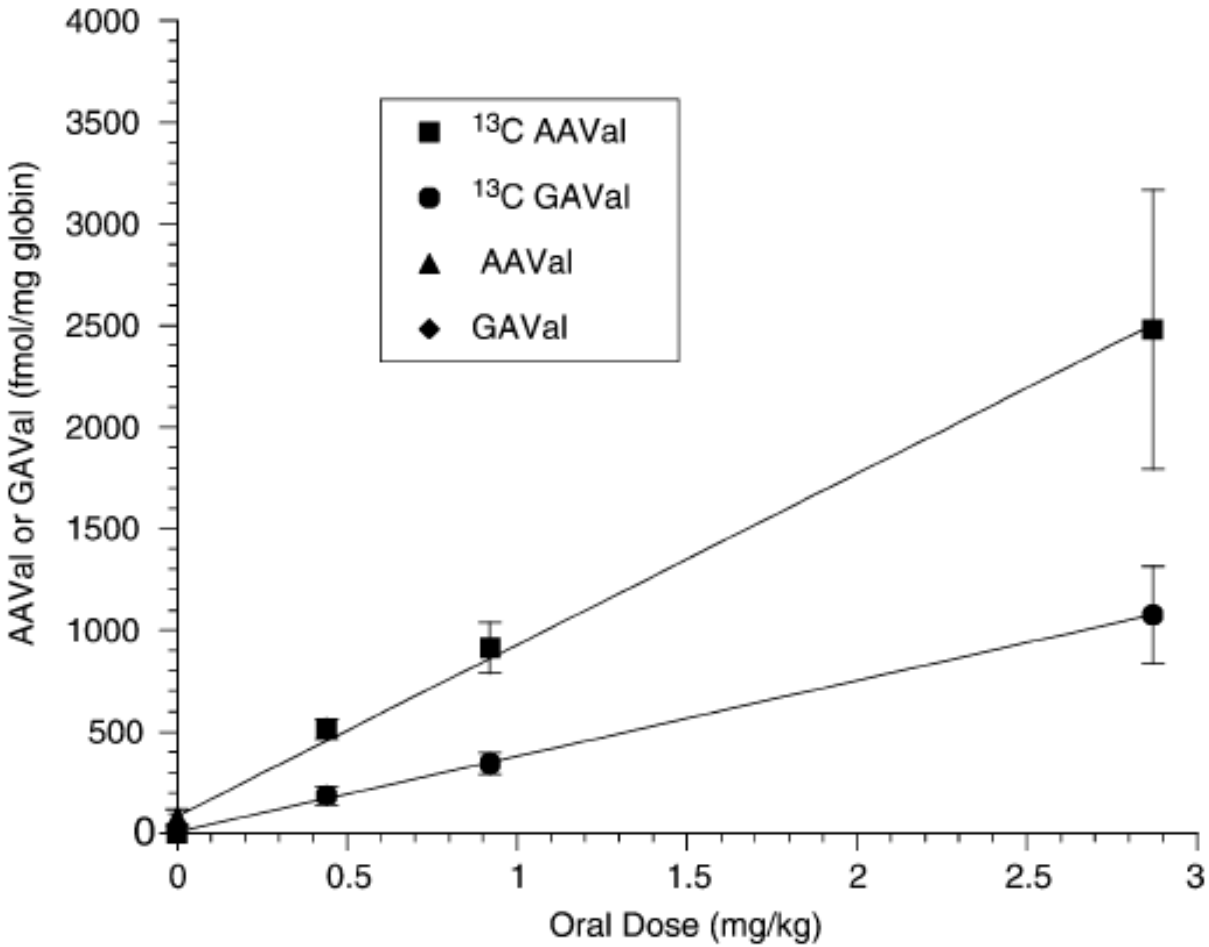


Fig. 8. Serum concentrations of acrylamide and glycidamide in Fischer 344 rats from repeat dosing. Male and female rats were exposed to acrylamide in drinking water (7 mM, approximately 1 mg/kg/day) and at various times, serum was collected for analysis. Data represent means ± S.D. ($n = 4$).

Fennell – Linearity in Humans at doses near BMDLs



Measured AUC in Humans

Fennell et al. 2005

TABLE 9
Comparison of AUC Normalized by Actual Dose (mmol/kg) in Rats and Humans

Dose (Route) (mg/kg)	Measured dose[a] (μmol/kg)	$^{13}C_3$ AM (mM.h/mmol AM/kg)	$^{13}C_3$-GA (mM.h/mmol AM/kg)
Human[b]			
0.5 (oral)	5.8 ± 1.3[b]	20.2 ± 1.8	4.6 ± 1.1
1 (oral)	12.0 ± 0.2	17.2 ± 2.3	4.1 ± 0.6
3 (oral)	37.2 ± 0.5	15.0 ± 4.1	4.1 ± 0.9
Combined (oral)		17.5 ± 3.5	4.3 ± 0.9
1 × 3 (dermal)	27.3 ± 2.0	1.0 ± 0.1[c]	0.30 ± 0.06[c]
2 × 3 (dermal)	55.2 ± 2.5	1.2 ± 0.3[c]	0.45 ± 0.13[c]
3 × 3 (dermal)	83.9 ± 2.4	1.2 ± 0.3[c]	0.52 ± 0.16[c]
Combined (dermal)		1.1 ± 0.2[c]	0.42 ± 0.15[c]
1 × 3 (dermal)	11.6 ± 1.8	2.4 ± 0.6[d]	0.73 ± 0.22[d]
2 × 3 (dermal)	21.4 ± 1.6	3.2 ± 0.6[d]	1.1 ± 0.3[d]
3 × 3 (dermal)	31.8 ± 6.7	3.4 ± 1.0[d]	1.4 ± 0.4[d]
Combined (dermal)		3.0 ± 0.8[d]	1.1 ± 0.4[d]
Rat[e]			
3 (Oral)		5.7 ± 1.1	3.7 ± 0.5
50 (Oral)		6.9 ± 1.3	2.0 ± 0.3

Human AUC as a Function of Administered Dose

- From Fennell et al. (2005):
  - AA_AUC

$$17.5\frac{mM \bullet hr\ AA}{\left(mM\ AA/kg\ BW\right)} * \frac{1\,mM\ AA}{77.1\,mg\ AA} = 0.227\frac{mM \bullet hr\ AA}{mg\ AA/\ kg\ BW} = 227\frac{\mu M \bullet hr\ AA}{mg\ AA/\ kg\ BW}$$

  - GA_AUC

$$4.3\frac{mM \bullet hr\ GA}{\left(mM\ AA/kg\ BW\right)} * \frac{1\,mM\ GA}{87.1\,mg\ GA} = 0.049\frac{mM \bullet hr\ GA}{mg\ AA/\ kg\ BW} = 49\frac{\mu M \bullet hr\ GA}{mg\ AA/\ kg\ BW}$$

Comparing PBPK Results to Measured Data Approach

			EPA PBPK Model Estimated		Tareke/Doerge Measured	Fennell Measured
Endpoint	**POD in Rats BMDL (mg/kg/d)**	**Critical Dose Metric**	**Rat POD Internal dose (uM-hr)**	**HED (mg/kg/d)**	**Rat POD Internal dose (uM-hr)**	**HED (mg/kg/d)**
Neurological Effects	0.27	AA_AUC	18.1	0.076	4.2	0.019
Cancer	0.3	GA_AUC	15.1	0.22	4.7	0.095

Measured Hemoglobin Adduct Levels In Humans

Fennell et al. 2005

TABLE 7
Comparison of Hemoglobin Adducts Normalized by Dose (μmol/kg) in Rats and Humans

Dose (route) (mg/kg)	Dose (μmol/kg)	$^{13}C_3$-AAVal (nmol/g globin/mmol AM/kg)	$^{13}C_3$-GAVal (nmol/g globin/mmol AM/kg)	$^{13}C_3$-GAVal: $^{13}C_3$-AAVal
Human[a]				
0.5 (oral)	5.9 ± 0.2	86.4 ± 7.5[b]	31.2 ± 7.4[b]	0.36 ± 0.06
1 (oral)	12.5 ± 0.2	73.4 ± 9.8[b]	27.6 ± 4.3[b]	0.38 ± 0.03
3 (oral)	38.7 ± 0.5	64.2 ± 17.7[b]	27.8 ± 6.2[b]	0.44 ± 0.06
Combined (oral)		74.7 ± 14.9[b]	28.9 ± 5.9[b]	0.39 ± 0.06

Conversion of AUC to Hemoglobin Adducts

Study	k_{AA} L g^{-1} globin hr^{-1}	k_{GA} L g^{-1} globin hr^{-1}
Bergmark et al. (1993)	4.4×10^{-6}	11×10^{-6}
Fennell et al. (2005)	4.27×10^{-6}	6.72×10^{-6}