

**Experiment Number:** S0312  
**Route:** IV, Gavage  
**Species/Strain:** Mice/B6C3F1

**Toxicokinetics Data Summary**  
**Compound:** Salicylazosulfapyridine/ **Analyte:** Salicylazosulfapyridine  
**CAS Number:** 599-79-1

**Request Date:** 7/11/2023  
**Request Time:** 10:03:16  
**Lab:** University of Arizona

**Male**

**Treatment Group (mg/kg)**

**675 Multi Dose Gavage Plasma<sup>a,d</sup>    1350 Multi-Dose Gavage Plasma<sup>a,e</sup>    2700 Multi-Dose Gavage Plasma<sup>a,f</sup>**

Cmax_obs (M)	35.3	60.8	48.7
Tmax_obs (hour)	0.5	0.5	1
Half-life (hour)	1.2	3.4	3.0
k10 (hour <sup>-1</sup> )	0.605	0.205	0.234
AUCinf_pred (M*hour)	68	149	210
F (percent)	5.45	5.99	4.23

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Female

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Treatment Group (mg/kg)

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675 Multi Dose Gavage Plasma<sup>a,m</sup>    1350 Multi-Dose Gavage Plasma<sup>a,n</sup>    2700 Multi-Dose Gavage Plasma<sup>a,o</sup>

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Cmax_obs (M)	49.7	149.9	157.5
Half-life (hour)	1.6	2.1	1.5
k10 (hour <sup>-1</sup> )	0.444	0.334	0.464
AUCinf_pred (M*hour)	109	401	556
F (percent)	3.78	6.95	4.82

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CAS Number: 599-79-1

Request Date: 7/11/2023  
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Male

Treatment Group (mg/kg)

675 Multi Dose Gavage Plasma<sup>a,g</sup>

1350 Multi-Dose Gavage Plasma<sup>a,h</sup>

2700 Multi-Dose Gavage Plasma<sup>a,i</sup>

C <sub>max_</sub> obs (M)	314.0	385.7	385.2
Half-life (hour)	8.6	9.2	14.5
k <sub>10</sub> (hour <sup>-1</sup> )	0.081	0.075	0.048
AUC <sub>inf_</sub> pred (M*hour)	3190	4634	6157

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Female

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Treatment Group (mg/kg)

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675 Multi Dose Gavage Plasma<sup>a,p</sup>    1350 Multi-Dose Gavage Plasma<sup>a,q</sup>    2700 Multi-Dose Gavage Plasma<sup>a,r</sup>

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Cmax_obs (M)	597.0	617.1	604.5
Half-life (hour)	6.4	10.6	16.5
AUCinf_pred (M*hour)	6308	4490	10601

Experiment Number: S0312  
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Toxicokinetics Data Summary  
Compound: Salicylazosulfapyridine/ Analyte: N-acetylsulfapyridine  
CAS Number: 599-79-1

Request Date: 7/11/2023  
Request Time: 10:03:16  
Lab: University of Arizona

Male

Treatment Group (mg/kg)

675 Multi Dose Gavage Plasma<sup>a,j</sup> 1350 Multi-Dose Gavage Plasma<sup>a,k</sup> 2700 Multi-Dose Gavage Plasma<sup>a,l</sup>

Cmax_obs (M)	20.5	21.1	20.2
Half-life (hour)	9.5	11.5	10.0
k10 (hour <sup>-1</sup> )	0.073	0.060	0.069
AUCinf_pred (M*hour)	197	273	290

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Request Date: 7/11/2023  
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Female

Treatment Group (mg/kg)

675 Multi Dose Gavage Plasma<sup>a,s</sup>

1350 Multi-Dose Gavage Plasma<sup>a,t</sup>

2700 Multi-Dose Gavage Plasma<sup>a,u</sup>

	675 Multi Dose Gavage Plasma <sup>a,s</sup>	1350 Multi-Dose Gavage Plasma <sup>a,t</sup>	2700 Multi-Dose Gavage Plasma <sup>a,u</sup>
Cmax_obs (M)	23.0	24.2	17.4
Half-life (hour)	7.6	11.2	13.3
k10 (hour <sup>-1</sup> )	0.091	0.062	0.052
AUCinf_pred (M*hour)	228	189	232

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Male

Treatment Group (mg/kg)

5.0 Single Dose IV Plasma<sup>b,v</sup>

67.5 Single Dose Gavage Plasma<sup>a,w</sup>

675 Single Dose Gavage Plasma<sup>a,x</sup>

Cmax_obs (M)		15.6	31.0
Tmax_obs (hour)			0.5
Half-life (hour)	0.54	0.9	1.7
k10 (hour <sup>-1</sup> )	1.278	0.802	0.402
Cl (L/hr*kg)	1.36		
V1 (L/kg)	1.07		
MRT (hour)	0.45		
AUCinf_pred (uM*hour)	9.21		
AUCinf_pred (M*hour)		21	97
F (percent)		16.6	7.82

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CAS Number: 599-79-1

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Male

Treatment Group (mg/kg)

1350 Single-Dose Gavage Plasma<sup>a,y</sup>

2700 Single-Dose Gavage Plasma<sup>a,z</sup>

Cmax_obs (M)	40.1	42.3
Tmax_obs (hour)	0.5	1
Half-life (hour)	2.3	1.8
k10 (hour <sup>-1</sup> )	0.304	0.379
AUCinf_pred (M*hour)	135	127
F (percent)	5.44	2.56



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CAS Number: 599-79-1

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Lab: University of Arizona

Female

Treatment Group (mg/kg)

5.0 Single Dose IV Plasma<sup>b,ij</sup> 67.5 Single Dose Gavage Plasma<sup>a,kk</sup> 675 Single Dose Gavage Plasma<sup>a,ll</sup>

Cmax_obs (M)		39.5	127.0
Half-life (hour)	1.19	1.3	1.0
k10 (hour <sup>-1</sup> )	0.581	0.520	0.672
Cl (L/hr*kg)	0.59		
V1 (L/kg)	1.01		
MRT (hour)	0.64		
AUCinf_pred (uM*hour)	21.39		
AUCinf_pred (M*hour)		52	250
F (percent)		18.2	8.66

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CAS Number: 599-79-1

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Treatment Group (mg/kg)

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1350 Single-Dose Gavage Plasma<sup>a,mm</sup>      2700 Single-Dose Gavage Plasma<sup>a,nn</sup>

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Cmax_obs (M)	167.5	212.5
Half-life (hour)	1.4	1.7
k10 (hour <sup>-1</sup> )	0.483	0.401
AUCinf_pred (M*hour)	385	845
F (percent)	6.67	7.32

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Toxicokinetics Data Summary  
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CAS Number: 599-79-1

Request Date: 7/11/2023  
Request Time: 10:03:16  
Lab: University of Arizona

Male

Treatment Group (mg/kg)

5.0 Single Dose IV Plasma<sup>b,aa</sup> 67.5 Single Dose Gavage Plasma<sup>a,bb</sup> 675 Single Dose Gavage Plasma<sup>a,cc</sup>

Cmax_obs (M)		91.4	240.6
Tmax_obs (hour)	3		
Half-life (hour)	1.90	2.2	11.1
k10 (hour <sup>-1</sup> )	0.364	0.318	0.063
MRT (hour)	4.66		
AUCinf_pred (uM*hour)	42.2		
AUCinf_pred (M*hour)		430	3134

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Male

Treatment Group (mg/kg)

1350 Single-Dose Gavage Plasma<sup>a,dd</sup> 2700 Single-Dose Gavage Plasma<sup>a,ee</sup>

Cmax_obs (M)	237.7	258.6
Half-life (hour)	7.4	7.3
k10 (hour <sup>-1</sup> )	0.094	0.094
AUCinf_pred (M*hour)	2995	2811

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Female

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Treatment Group (mg/kg)

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5.0 Single Dose IV Plasma<sup>b,oo</sup> 67.5 Single Dose Gavage Plasma<sup>a,pp</sup> 675 Single Dose Gavage Plasma<sup>a,qq</sup>

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Cmax_obs (M)		111.0	483.7
Half-life (hour)	4.80	3.3	7.9
k10 (hour <sup>-1</sup> )	0.144	0.210	0.088
MRT (hour)	8.31		
AUCinf_pred (uM*hour)	52.65		
AUCinf_pred (M*hour)		540	6261

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Female

Treatment Group (mg/kg)

1350 Single-Dose Gavage Plasma<sup>a,rr</sup>

2700 Single-Dose Gavage Plasma<sup>a,ss</sup>

Cmax_obs (M)	320.3	237.0
Tmax_obs (hour)		
Half-life (hour)	8.3	9.8
k10 (hour <sup>-1</sup> )	0.084	0.071
AUCinf_pred (M*hour)	3464	4082

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Toxicokinetics Data Summary  
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CAS Number: 599-79-1

Request Date: 7/11/2023  
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Male

Treatment Group (mg/kg)

5.0 Single Dose IV Plasma<sup>c</sup> 67.5 Single Dose Gavage Plasma<sup>a,ff</sup> 675 Single Dose Gavage Plasma<sup>a,gg</sup>

Cmax_obs (M)		11.9	21.5
Half-life (hour)		1.6	5.8
k10 (hour <sup>-1</sup> )		0.440	0.119
AUCinf_pred (M*hour)		44	239

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Male

Treatment Group (mg/kg)

1350 Single-Dose Gavage Plasma<sup>a,hh</sup>

2700 Single-Dose Gavage Plasma<sup>a,ii</sup>

Cmax_obs (M)	19.8	18.2
Half-life (hour)	6.2	10.1
k10 (hour <sup>-1</sup> )	0.112	0.068
AUCinf_pred (M*hour)	260	271



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Female

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Treatment Group (mg/kg)

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5.0 Single Dose IV Plasma<sup>c</sup>

67.5 Single Dose Gavage Plasma<sup>a,tt</sup>

675 Single Dose Gavage Plasma<sup>a,uu</sup>

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Cmax_obs (M)		4.2	20.5
Half-life (hour)		3.4	8.7
k10 (hour <sup>-1</sup> )		0.206	0.080
AUCinf_pred (M*hour)		17	234

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Female

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Treatment Group (mg/kg)

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1350 Single-Dose Gavage Plasma<sup>a,vv</sup> 2700 Single-Dose Gavage Plasma<sup>a,ww</sup>

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Cmax_obs (M)	20.5	22.9
Half-life (hour)	8.7	8.3
k10 (hour <sup>-1</sup> )	0.080	0.083
AUCinf_pred (M*hour)	234	224

**Experiment Number:** S0312

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**Toxicokinetics Data Summary**

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LEGEND

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MODELING METHOD & BEST FIT MODEL

<sup>a</sup>Unknown. Data were computed from the plasma concentration-time curves where each point represents the mean of 5-7 mice. first-order kinetics

<sup>b</sup>Unknown. Data were computed from the plasma concentration-time curves where each point represents the mean of 4-6 mice. first-order kinetics

<sup>c</sup>No modeling. N-acetylsulfapyridine was not detected in plasma.

EXCEPTION

<sup>d</sup>Mean absorbance time (MAT) is 1.3 hours. K is 0.602 hour<sup>-1</sup>

<sup>e</sup>Mean absorbance time (MAT) is 2.9 hours. K is 0.205 hour<sup>-1</sup>

<sup>f</sup>Mean absorbance time (MAT) is 4.5 hours. K is 0.234 hour<sup>-1</sup>

<sup>g</sup>Graphed time course 0-24 hours. K is 0.081 hour<sup>-1</sup>

<sup>h</sup>Graphed time course 0-24 hours. K is 0.075 hour<sup>-1</sup>

<sup>i</sup>Graphed time course 0-24 hours. K is 0.048 hour<sup>-1</sup>

<sup>j</sup>Graphed time course 0-24 hours. K is 0.073 hour<sup>-1</sup>

<sup>k</sup>Graphed time course 0-24 hours. K is 0.060 hour<sup>-1</sup>

<sup>l</sup>Graphed time course 0-24 hours. K is 0.069 hour<sup>-1</sup>

<sup>m</sup>Mean absorbance time (MAT) is 2.75 hours. Tmax for the three female groups administered multiple doses for SASP ranged from 0.5-1 hour. K is 0.444 hour<sup>-1</sup>

<sup>n</sup>Mean absorbance time (MAT) is 1.94 hours. Tmax for the three female groups administered multiple doses for SASP ranged from 0.5-1 hour. K is 0.334 hour<sup>-1</sup>

<sup>o</sup>Mean absorbance time (MAT) is 3.53 hours. Tmax for the three female groups administered multiple doses for SASP ranged from 0.5-1 hour. K is 0.464 hour<sup>-1</sup>

<sup>p</sup>Graphed time course 0-24 hours. K is 0.108 hour<sup>-1</sup>

<sup>q</sup>Graphed time course 0-24 hours. K is 0.066 hour<sup>-1</sup>

<sup>r</sup>Graphed time course 0-24 hours. K is 0.042 hour<sup>-1</sup>

<sup>s</sup>AcSP appeared in the plasma at times later than SASP. The AcSP AUC values were much lower than those of SP and did not change linearly with dose. Graphed time course 0-24 hours. K is 0.091 hour<sup>-1</sup>

<sup>t</sup>Graphed time course 0-24 hours. K is 0.062 hour<sup>-1</sup>

<sup>u</sup>Graphed time course 0-24 hours. K is 0.052 hour<sup>-1</sup>

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EXCEPTION (cont'd)

<sup>v</sup>Cl is systemic clearance, V1 is apparent volume of distribution was calculated by Vd equals systemic Clearance over K. Graphed time course 0-4 hours. K is 1.278 hour<sup>-1</sup>

<sup>w</sup>Mean absorbance time (MAT) is 0.4 hours. Graphed time course 0-8 hours. Maximum plasma concentrations of SASP reached within 0.5-1 hour.

<sup>x</sup>Mean absorbance time (MAT) is 2.0 hours. Graphed time course 0-24 hours. Maximum plasma concentrations of SASP reached within 0.5-1 hour.

<sup>y</sup>Mean absorbance time (MAT) is 2.8 hours. Graphed time course 0-24 hours. Maximum plasma concentrations of SASP reached within 0.5-1 hour.

<sup>z</sup>Mean absorbance time (MAT) is 2.4 hours. Graphed time course 0-24 hours. Maximum plasma concentrations of SASP reached within 0.5-1 hour.

<sup>aa</sup>Graphed time course 2-8 hours. K is 0.364 hour<sup>-1</sup>. Sulfapyridine appeared in plasma 2 hour after dosing and reached Cmax at 3 hours (graph).

<sup>bb</sup>Graphed time course 24 hours. K is 0.318 hour<sup>-1</sup>

<sup>cc</sup>Graphed time course 0-24 hours. K is 0.063 hour<sup>-1</sup>

<sup>dd</sup>Graphed time course 0-24 hours. K is 0.094 hour<sup>-1</sup>

<sup>ee</sup>Graphed time course 0-24 hours. K is 0.094 hour<sup>-1</sup>

<sup>ff</sup>Graphed time course 0-12 hours. K is 0.440 hour<sup>-1</sup>

<sup>gg</sup>Graphed time course 0-24 hours. K is 0.119 hour<sup>-1</sup>

<sup>hh</sup>Graphed time course 0-24 hours. K is 0.112 hour<sup>-1</sup>

<sup>ii</sup>Graphed time course 0-24 hours. K is 0.068 hour<sup>-1</sup>

<sup>jj</sup>Cl is systemic clearance, V1 is apparent volume of distribution was calculated by Vd equals systemic Clearance over K. the apparent K was estimated by linear least squares regression of the data in the terminal phase. Graphed time course 0-4 hours. K is 0.581 hour<sup>-1</sup>

<sup>kk</sup>Mean absorbance time (MAT) is 0.73 hours. Tmax for the four female single dose studies for SASP ranged from 0.5-2.0 hours. Graphed time course 0-8 hours. K is 0.520 hour<sup>-1</sup>

<sup>ll</sup>Mean absorbance time (MAT) is 0.72 hours. Tmax for the four female single dose studies for SASP ranged from 0.5-2.0 hours. K is 0.672 hour<sup>-1</sup>

<sup>mm</sup>Mean absorbance time (MAT) is 1.2 hours. Tmax for the four female single dose studies for SASP ranged from 0.5-2.0 hours. K is 0.483 hour<sup>-1</sup>

<sup>nn</sup>Mean absorbance time (MAT) is 2.03 hours. Tmax for the four female single dose studies for SASP ranged from 0.5-2.0 hours. K is 0.401 hour<sup>-1</sup>

<sup>oo</sup>Graphed time course 2-8 hours. K is 0.144 hour<sup>-1</sup>. Sulfapyridine appeared in plasma 2 hour after dosing and reached Cmax at 3 hours (graph).

<sup>pp</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.210 hour<sup>-1</sup>

<sup>qq</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.088 hour<sup>-1</sup>

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<sup>r</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.084 hour<sup>-1</sup>

<sup>s</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.071 hour<sup>-1</sup>

<sup>t</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.206 hour<sup>-2</sup>

<sup>u</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.080 hour<sup>-3</sup>

<sup>v</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.080 hour<sup>-4</sup>

<sup>w</sup>Tmax for the four female single SASP dose studies for metabolite SP and AcSP ranged from 4-6 hours. Graphed time course 0-24 hours. K is 0.083 hour<sup>-5</sup>

**ANALYTE**

Salicylazosulfapyridine

Sulfapyridine

N-acetylsulfapyridine

**TK PARAMETERS**

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration

Tmax = Time at which Cmax predicted or observed occurs

Half-Life = Lambda z Half life, t 1/2, the terminal elimination half-life based on non-compartmental analysis

k10 = Elimination rate constant from the central compartment also ke or kelim

V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies

MRT = Mean residence time

AUCinf\_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

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TK PARAMETERS PROTOCOL

ANALYSIS METHOD

The supernatant from plasma sample extraction was analyzed by HPLC with UV detection (at 360 nm for SASP because it represents specifically the integrity of azo linkage and at 254 nm for its metabolites). The detection limit in plasma for SASP was 0.32 nmol/mL, for SP, 0.5 nmol/mL, and for N-acetylsulfapyridine (AcSP), 1.0 nmol/mL. Values of C<sub>max</sub> and T<sub>max</sub> were obtained directly from plasma concentration-time profiles. The apparent K (Lambda\_Z) was estimated by linear least squares regression of the data in the terminal phase. From these values, the half-lives were calculated (t<sub>1/2</sub> equals 0.693/K) AUC was calculated using the linear trapezoidal rule and extrapolating to time infinity. For multiple doses, the steady-state AUC (0-24) was used.

TK\_GAVAGE PLASMA

675 mg/kg, 1350 mg/kg, 2700 mg/kg Multiple Dose Male and Female (Analytes Salicylazosulfapyridine, Sulfapyridine)

Mice received salicylazosulfapyridine (SASP) by oral gavage daily for 3 days. After the last oral gavage, the blood samples were collected at appropriate time points. Following oral administration of SASP, both Sulfapyridine (SP) and N-acetylsulfapyridine (AcSP) were identified in plasma and had similar plasma profiles to their single dose counterparts. The T<sub>max</sub> values of SASP in the multiple dose studies were the same as those obtained in the single dose studies, although K values varied slightly. T<sub>max</sub> for multiple doses (SASP) was 0.5-1 hour in females. Blood samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours. n=5-7 mice per timepoint.

675 mg/kg, 1350 mg/kg, 2700 mg/kg Multiple Dose Male (Analyte N-acetylsulfapyridine)

Mice received salicylazosulfapyridine (SASP) by oral gavage daily for 3 days. After the last oral gavage, the blood samples were collected at appropriate time points. Following oral administration of SASP, both Sulfapyridine (SP) and N-acetylsulfapyridine (AcSP) were identified in plasma and had similar plasma profiles to their single dose counterparts. The T<sub>max</sub> values of AcSP in the multiple dose studies like in the single dose studies were delayed relative to SASP. In females AcSP. T<sub>max</sub>s were 4-6 hours. Blood samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours. n=5-7 mice per timepoint.

**Experiment Number:** S0312

**Route:** IV, Gavage

**Species/Strain:** Mice/B6C3F1

**Toxicokinetics Data Summary**

**Compound:** Salicylazosulfapyridine

**Analyte:** Salicylazosulfapyridine, Sulfapyridine, N-acetylsulfapyridine

**CAS Number:** 599-79-1

**Request Date:** 7/11/2023

**Request Time:** 10:03:16

**Lab:** University of Arizona

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TK PARAMETERS PROTOCOL (cont'd)

675 mg/kg, 1350 mg/kg, 2700 mg/kg Multiple Dose Female (Analyte N-acetylsulfapyridine)

Mice received salicylazosulfapyridine (SASP) by oral gavage daily for 3 days. After the last oral gavage, the blood samples were collected at appropriate time points. Following oral administration of SASP, both Sulfapyridine (SP) and N-acetylsulfapyridine (AcSP) were identified in plasma and had similar plasma profiles to their single dose counterparts. The Tmax values of AcSP in the multiple dose studies were delayed compared to SASP. In females AcSP Tmaxs were 4-6 hours. Blood samples were collected at 0 (predose), 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours. n=5-7 mice per timepoint. Percentages of acetylated SP(AUC\_AcSP) were about 2.2-8.8 percent of total free plasma SP assayed (AUC\_SP plus AUC\_AcSP)

TK\_INTRAVENOUS PLASMA

5.0 mg/kg Single Dose Male and Female (Analytes Salicylazosulfapyridine, Sulfapyridine, N-acetylsulfapyridine)

A single intravenous dose was administered in the tail vein. Blood samples were collected from the inferior vena cava following euthanasia at 0 (pre-dose), 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose. n= 4-6 mice. The only metabolite of salicylazosulfapyridine (SASP) found in plasma after an intravenous dose was sulfapyridine (SP). Plasma concentration declined rapidly during first hour, followed by an elimination phase with a half-life of 0.5 hour for male mice given a single intravenous dose and by six hours, no detectable amount of parent SASP was found in plasma. Plasma concentration of SASP also rapidly declined in female mice with a half-life of 1.2 hour. In females, SP appeared in plasma 2 hours after dosing and reached Cmax at 3 hours. The AUC of SP was 4.5 fold higher (males) or 2.5 fold higher (females) than that of SASP.

5.0 mg/kg Single Dose Female (Analyte N-acetylsulfapyridine)

A single intravenous dose was administered in the tail vein. Blood samples were collected from the inferior vena cava following euthanasia at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 hours post-dose. The only metabolite of salicylazosulfapyridine (SASP) found in plasma after an intravenous dose was sulfapyridine (SP). Plasma concentration declined rapidly during first hour, followed by an elimination phase with a half life of 0.5 hour for male mice given a single intravenous dose and by six hours, no detectable amount of parent SASP was found in plasma. Plasma concentration of SASP also rapidly declined in female mice with a half-life of 1.2 hour. In females, SP appeared in plasma 2 hours after dosing and reached Cmax at 3 hours.