

Mortality in the Noncomparative *Aspergillus* Study and the Historical Control Study

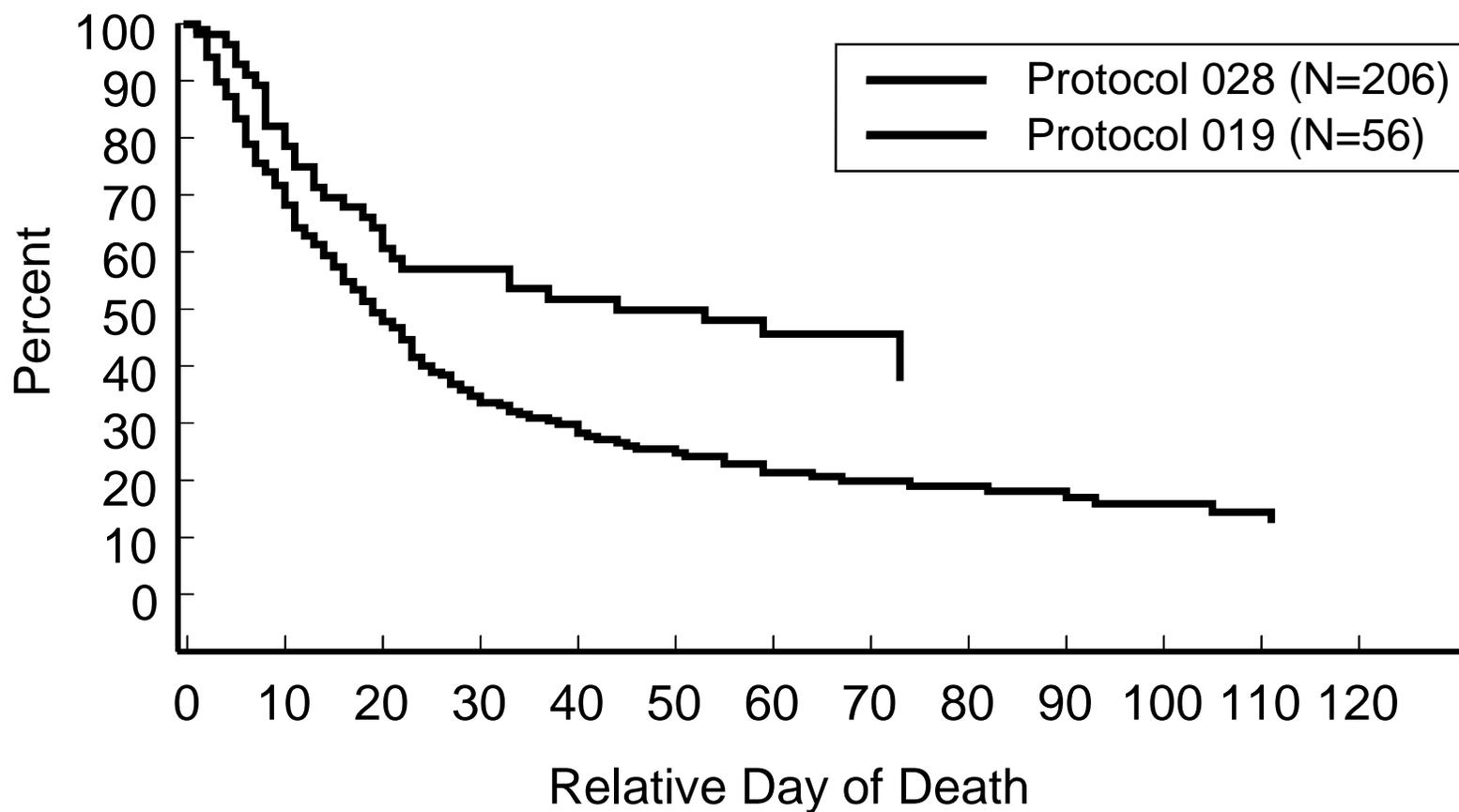
- Deaths during therapy and follow-up were collected in both studies
 - In the caspofungin *Aspergillus* study, patients were seen at a follow-up visit 4 weeks after the end of study therapy. Deaths reported post study are also included.
 - In the Historical Control Study, available information was collected at 4 weeks after the end of antifungal therapy (window of 14 to 42 days). No follow-up data available for some patients.

Mortality in the Noncomparative *Aspergillus* Study and the Historical Control Study (Cont'd)

Study	Deaths Reported	
	n/N	%
Caspofungin <i>Aspergillus</i> Study	30/56	53.6
Historical Control Study	162/206	78.6

Time to Death

R/I Population With Indeterminates Excluded



Outcome by Refractory Reason

Protocol 019

Favorable Response

Reason	N=54		N=63		N=73	
	<u>n/m</u>	<u>%</u>	<u>n/m</u>	<u>%</u>	<u>n/m</u>	<u>%</u>
Progression of disease	9/34	(26.5)	10/40	(25.0)	14/47	(29.8)

Outcome by Refractory Reason

Protocol 019

Reason	Favorable Response					
	N=54		N=63		N=73	
	n/m	%	n/m	%	n/m	%
Progression of disease	9/34	(26.5)	10/40	(25.0)	14/47	(29.8)
Failure to improve	6/9	(66.7)	9/12	(75.0)	10/14	(71.4)

Favorable Response by Immunosuppression Protocol 019 Expert Panel Assessment (N=54)

	<u>n/m</u>	<u>(%)</u>
● Neutropenia at baseline	2/11	(18.2)
– Resolved	2/6	(33.3)
– Persisted	0/5	(0.0)
● Neutropenic at end but not at start of therapy	1/1	(100.0)
● Corticosteroids (≥ 20 mg/day) at baseline	7/22	(31.8)
– Discontinued	3/6	(50.0)
– Continued	4/16	(25.0)

Favorable Response by Immunosuppression Protocol 019 Expert Panel Assessment (N=54)(Cont'd)

	<u>n/m</u>	<u>(%)</u>
● Corticosteroids at end but not at start of therapy	2/3	(66.7)
● Tacrolimus	5/16	(31.3)
● Mycophenolate mofetil	3/8	(37.5)
● Other Immunosuppressives	2/5	(40.0)
● Chemotherapy	4/5	(80.0)

HCS Comparison to Literature

	<u>MRL HCS</u>	<u>White, et al.*</u>
Number of sites (overlap 3)	10	6
Duration of study period	4 years 1/1/95 to 12/31/98	4.5 years 1/1/90 to 6/30/94
Potential patients	1,734	1,204
Met criteria (virtually identical)	229	261
Overall favorable response	21.4%	23.4%

* *Clin Inf Dis*, 1997;24:635-42.

Favorable Response by Neutropenia Protocols 019 vs. 028/029

	Protocol 019 N=54		Protocol 028/029 N=206	
	<u>n/m</u>	<u>(%)</u>	<u>n/m</u>	<u>(%)</u>
Neutropenia at baseline	2/11	(18.2)	4/57	(7.0)
● Resolved	2/6	(33.3)	3/16	(18.8)
● Persisted	0/5	(0.0)	0/36	(0.0)
● No ANC data at end	---	---	1/5	(20.0)
Neutropenia at end but not at start of therapy	1/1	(100.0)	0/8	(0.0)

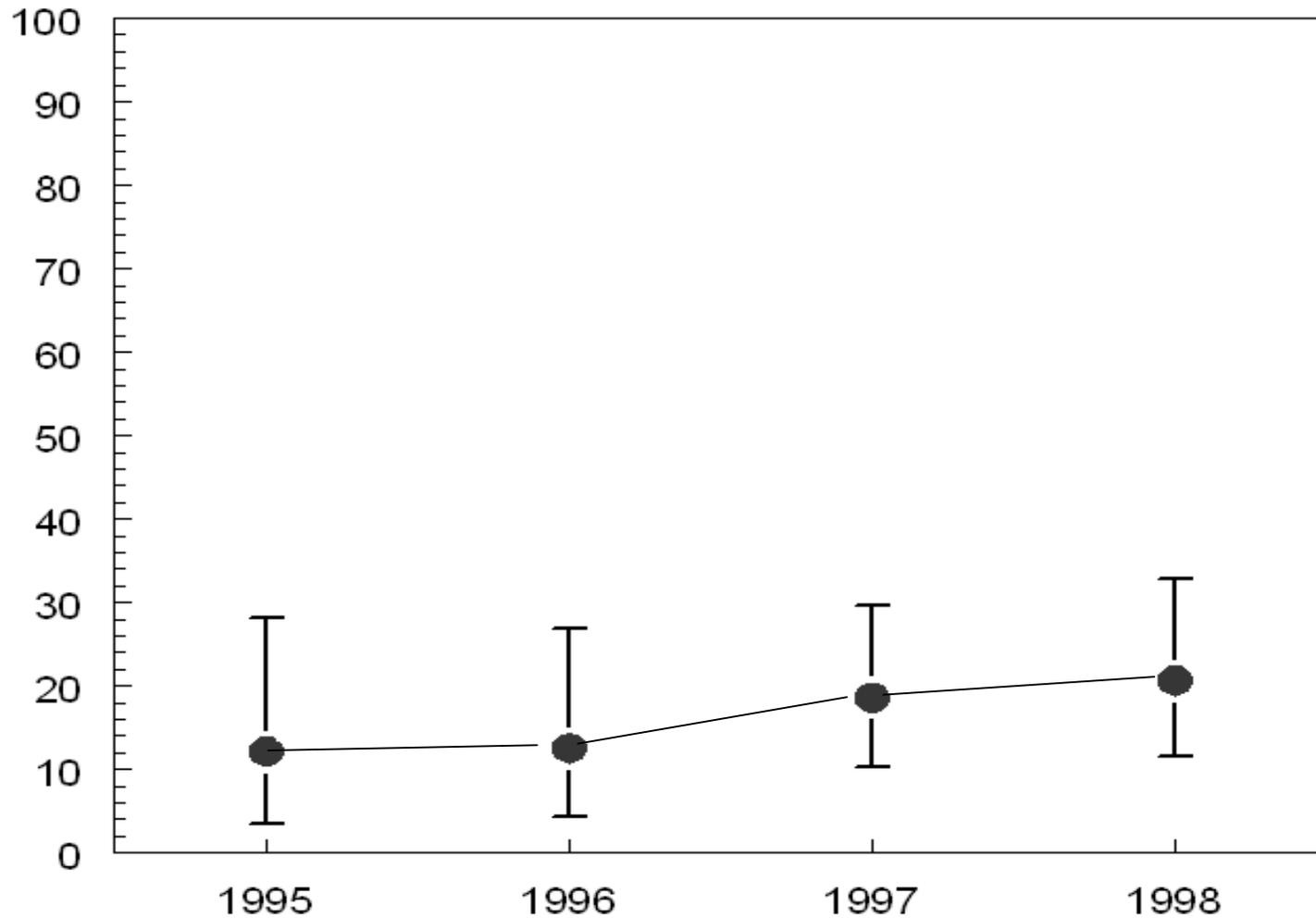
Favorable Response by Immunosuppressives Protocols 019 vs. 028/029

	<u>Protocol 019</u>		<u>Protocol 028/029</u>	
	<u>n/m</u>	<u>%</u>	<u>n/m</u>	<u>%</u>
Corticosteroids (≥ 20 mg/day) at baseline	7/22	(31.8)	8/74	(10.8)
● Discontinued	3/6	(50.0)	5/10	(50.0)
● Continued	4/16	(25.0)	3/64	(4.7)
Corticosteroids at end but not at start of therapy	2/3	(66.7)	7/53	(13.2)
Tacrolimus	5/16	(31.3)	4/28	(14.3)
Mycophenolate mofetil	3/8	(37.5)	1/8	(12.5)
Other immunosuppressants	2/5	(40.0)	12/65	(18.5)
Chemotherapy	4/5	(80.0)	2/13	(15.4)

Outcome Excluding Early Deaths RI Population (Indeterminates Excluded)

<u>Subpopulation</u>	<u>Favorable Response</u>	
	<u>n/m</u>	<u>(%)</u>
Refractory or Intolerant (R/I)	35/206	(17.0)
RI excluding deaths at < 14 days therapy	35/153	(22.9)

Response Rate (95% CI) by Year of Inclusion Refractory or Intolerant Population (N=206)

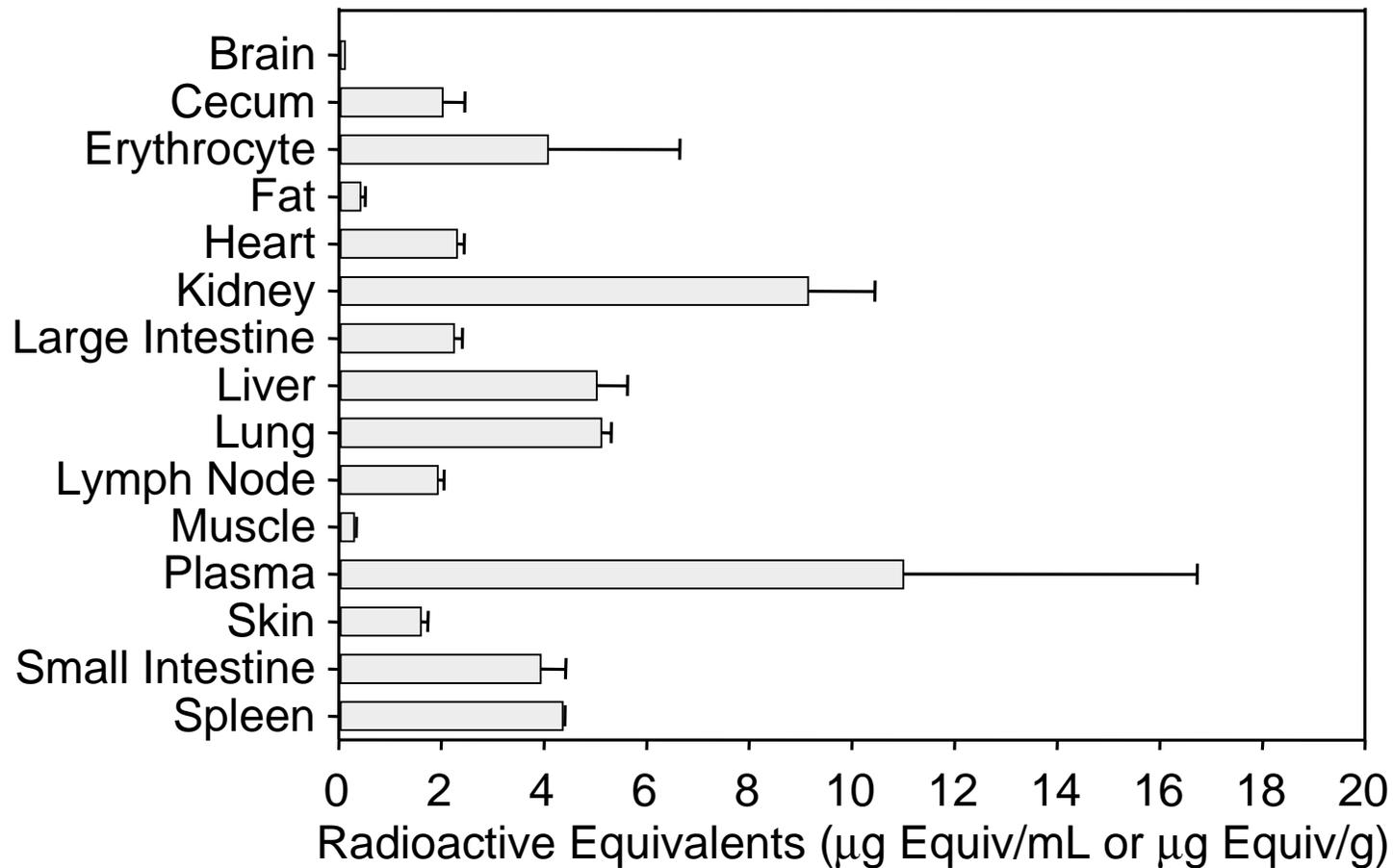


Outcomes in Protocol 019 vs. Protocol 028/029 Patients Included in 1997-1998 in the HCS

Population	Favorable Response			
	Caspofungin Protocol 019		Standard Therapy Protocol 028/029	
	<u>n/m</u>	<u>(%)</u>	<u>n/m</u>	<u>(%)</u>
Refractory or Intolerant	22/54	(40.7)	26/133	(19.5)
Refractory	15/44	(34.1)	20/121	(16.5)
Intolerant	7/10	(70.0)	2/3	(66.7)

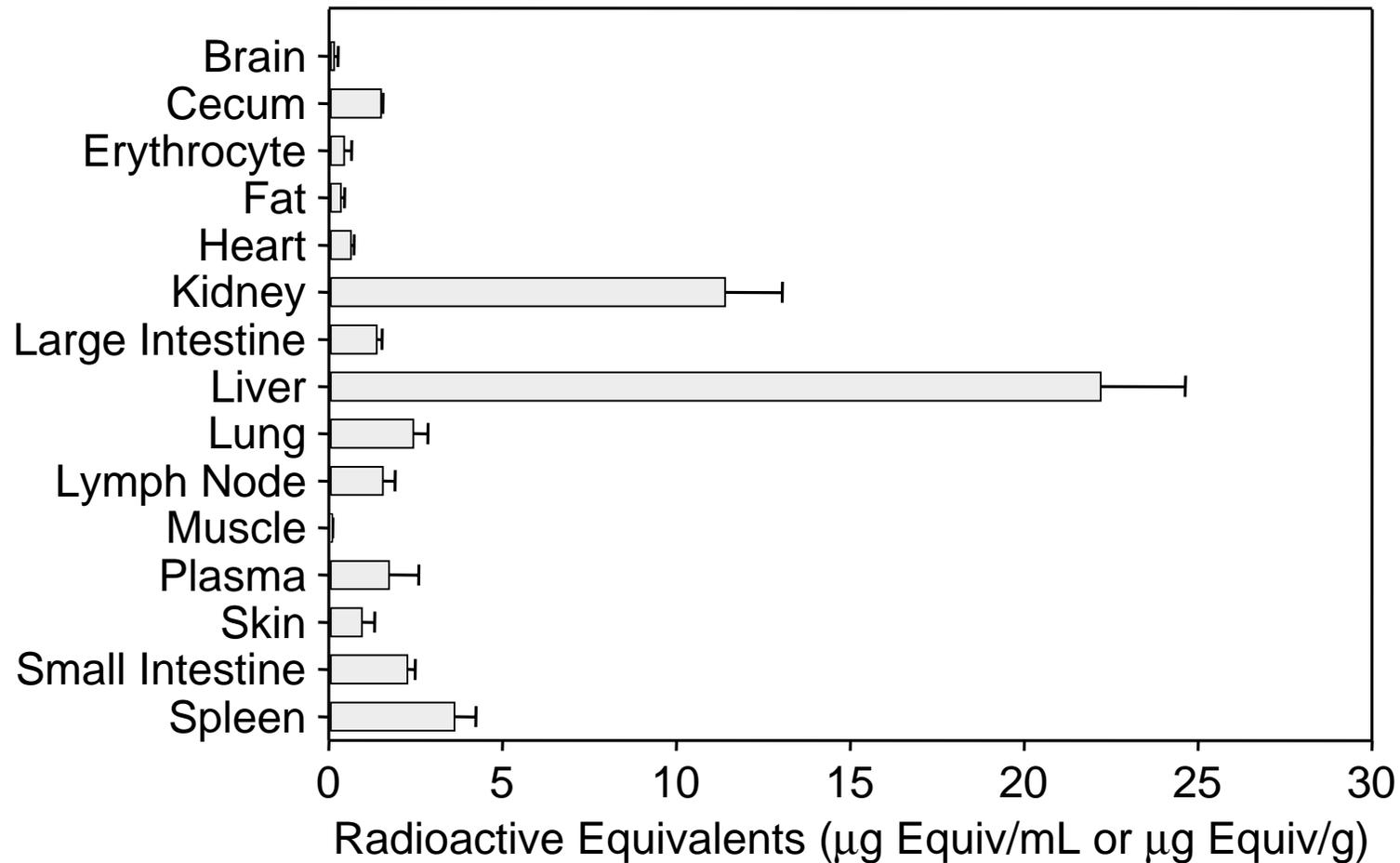
Radioactivity in Rat Tissues

0.5 hr Postdose (2 mg/kg, I.V.)



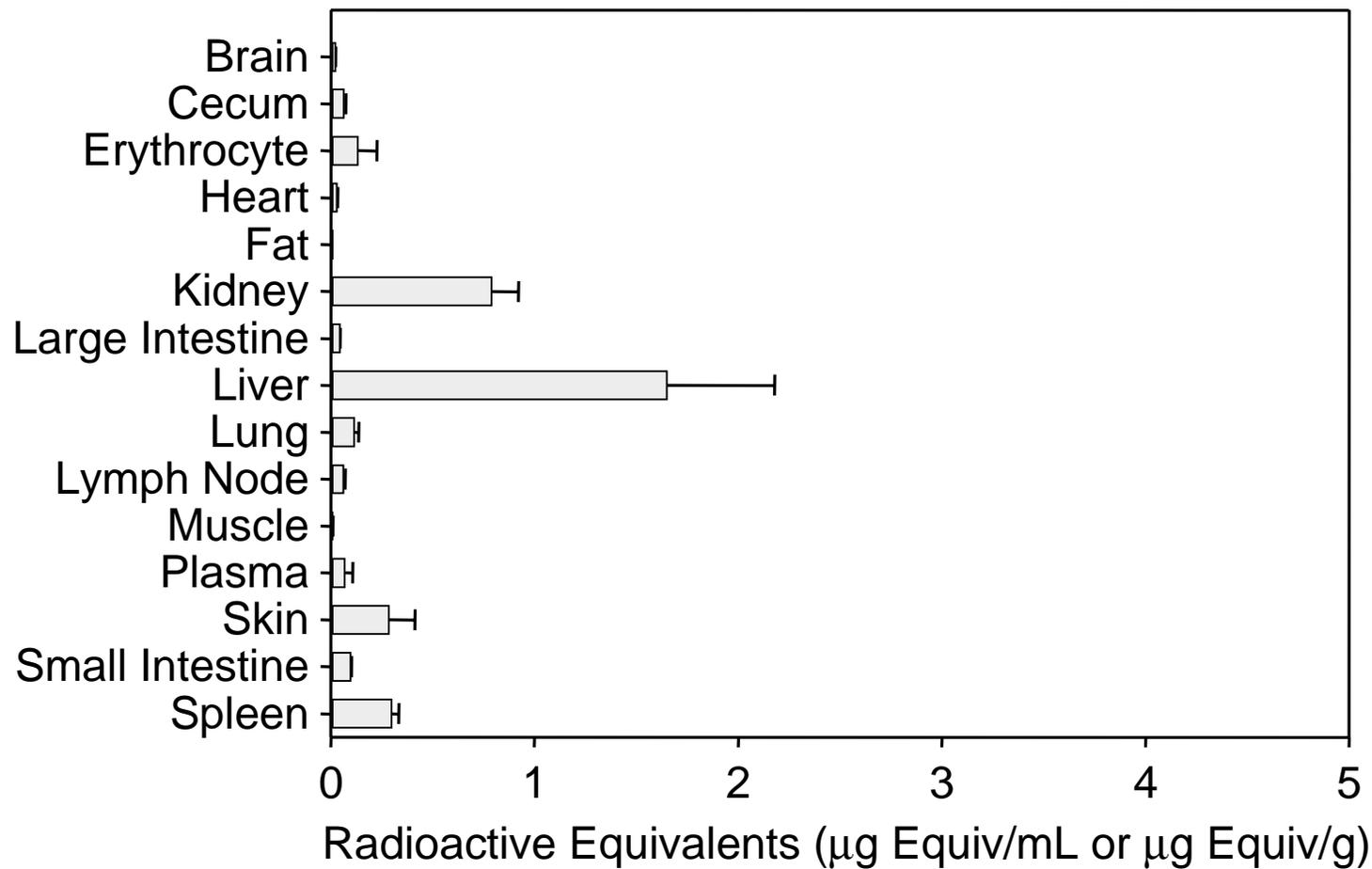
Radioactivity in Rat Tissues

24 hr Postdose (2 mg/kg, I.V.)



Radioactivity in Rat Tissues

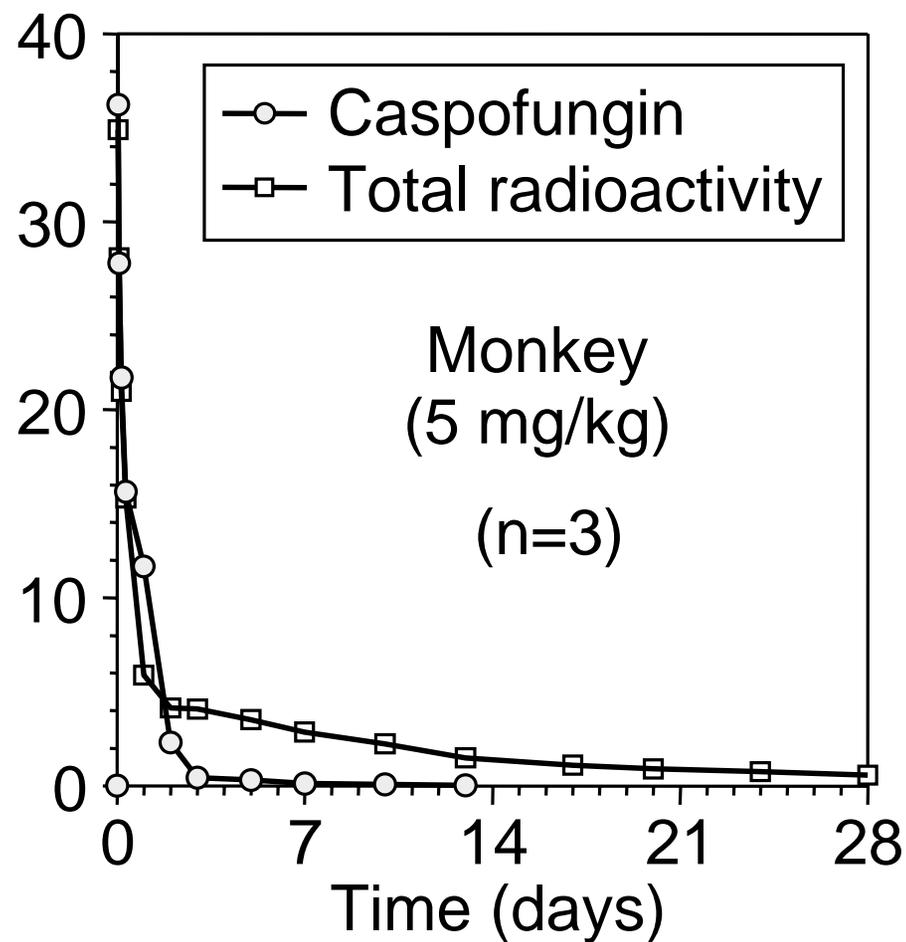
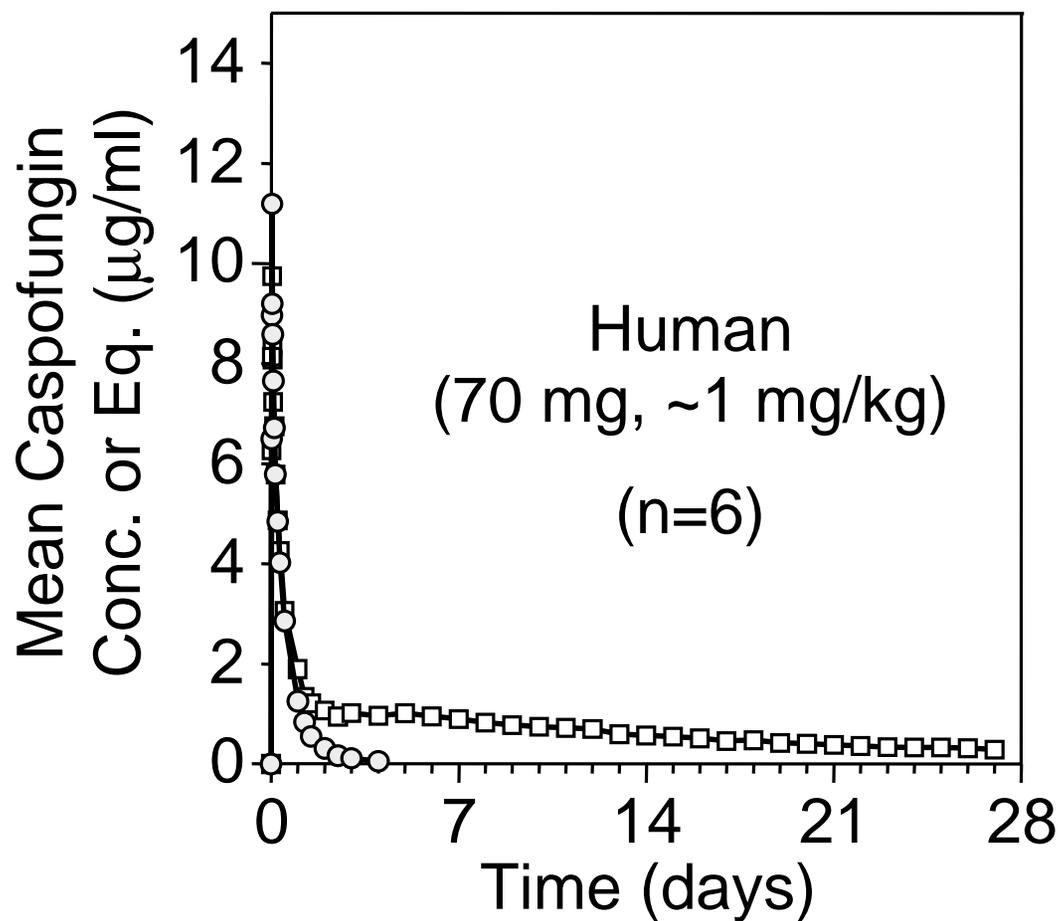
Day 12 Postdose (2 mg/kg, I.V.)



Long Half-Life of Radioactivity in Plasma

- Following I.V. administration of [³H]caspofungin, the half-life of radioactivity in plasma was prolonged relative to that of parent drug in humans, monkeys, and rats
- The long half-life is attributed to low levels of covalent binding of caspofungin-derived radioactivity to plasma proteins
- In humans, the level of covalent binding in plasma was low (≤ 7 pmol/mg protein or ≤ 1.3 % of administered single dose) and declined with time
- At comparable time points, the covalent binding in monkeys was about 3 to 5 times higher than that in humans

Plasma Profiles from [³H]Caspofungin ADME Studies



Covalent Binding of Radioactivity to Plasma Proteins

<u>Species</u>	<u>Dose (mg/kg)</u>	<u>Time (Day)</u>	<u>Covalent Binding (pmol/mg Protein) (Mean±S.D.)</u>
Monkey (n=3)	5	Day 5-7	33±1
		Day 10-13	15±6
		Day 17-20	9±4
Human (n=6)	1	Day 5-6	7±1
		Day 11-12	5±1
		Day 19-20	3±1

Mechanism of Covalent Binding of Caspofungin to Plasma Proteins

- Spontaneous chemical degradation of caspofungin to L-747969 involves the reversible formation of reactive imine and aldehyde intermediates
- The reactive aldehyde intermediate may covalently modify plasma proteins
- L-747969 is the major circulating metabolite in human, rat and monkey
- Spontaneous nature of the proposed mechanism suggests that covalent binding should occur in all animal safety species and humans