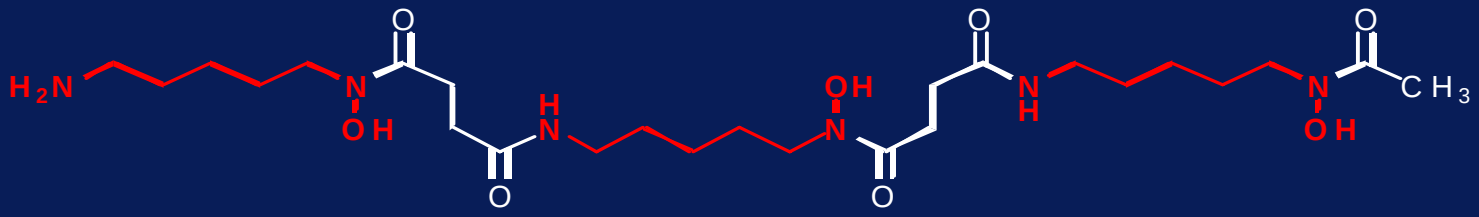
Desferrithiocin Analogues As Actinide Decorporation Agents

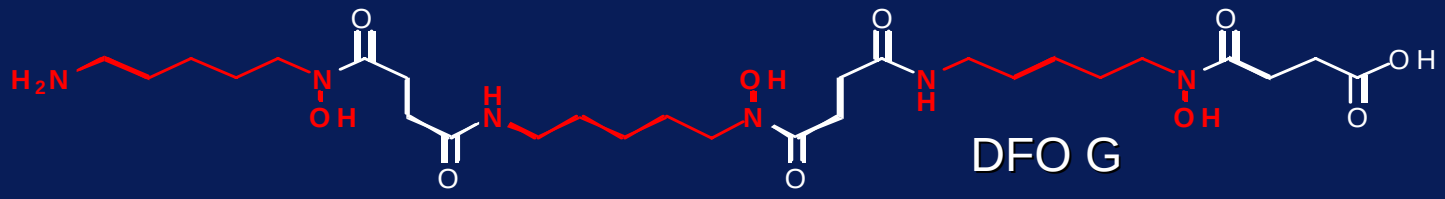
Siderophores


Fe(II) ⇌ Fe(III) + e -

HYDROXAMATE CHELATORS

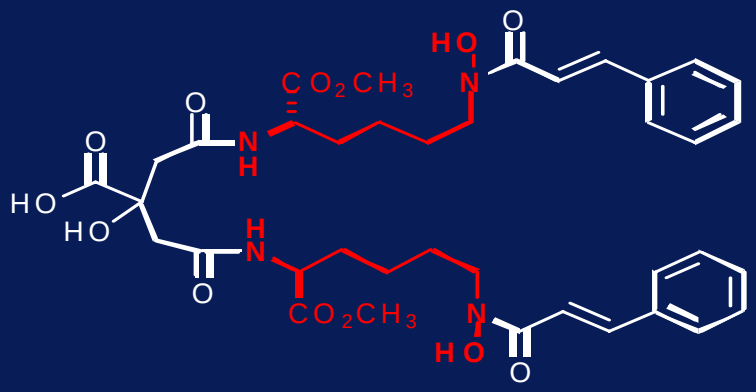


Desferrioxamine B (DFO)



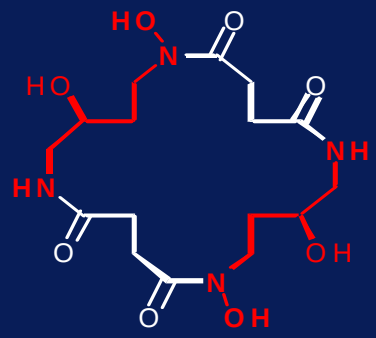
DFO G

Bisucaberin



Nannochelin A

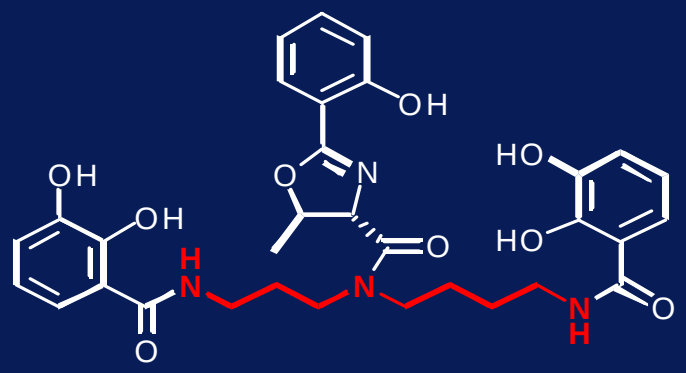
DFO E (Nocardamine)



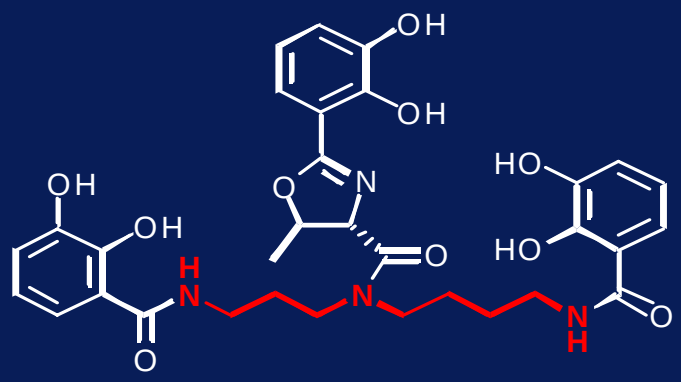
Alcaligin

Rhodotorulic Acid

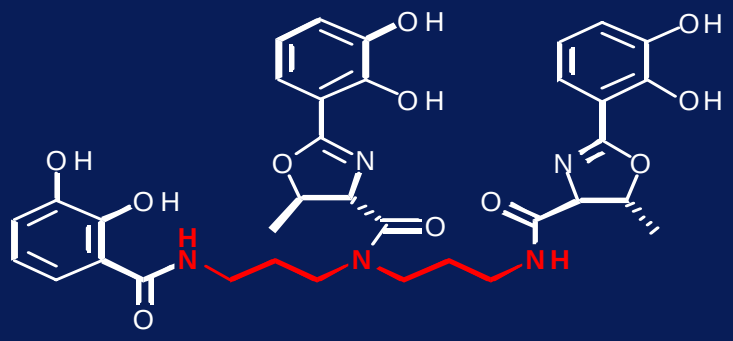
CATECHOLAMIDE CHELATORS



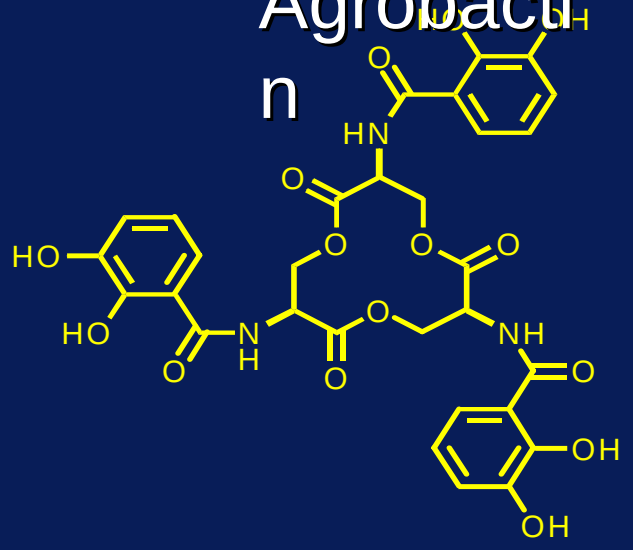
L-Parabactin



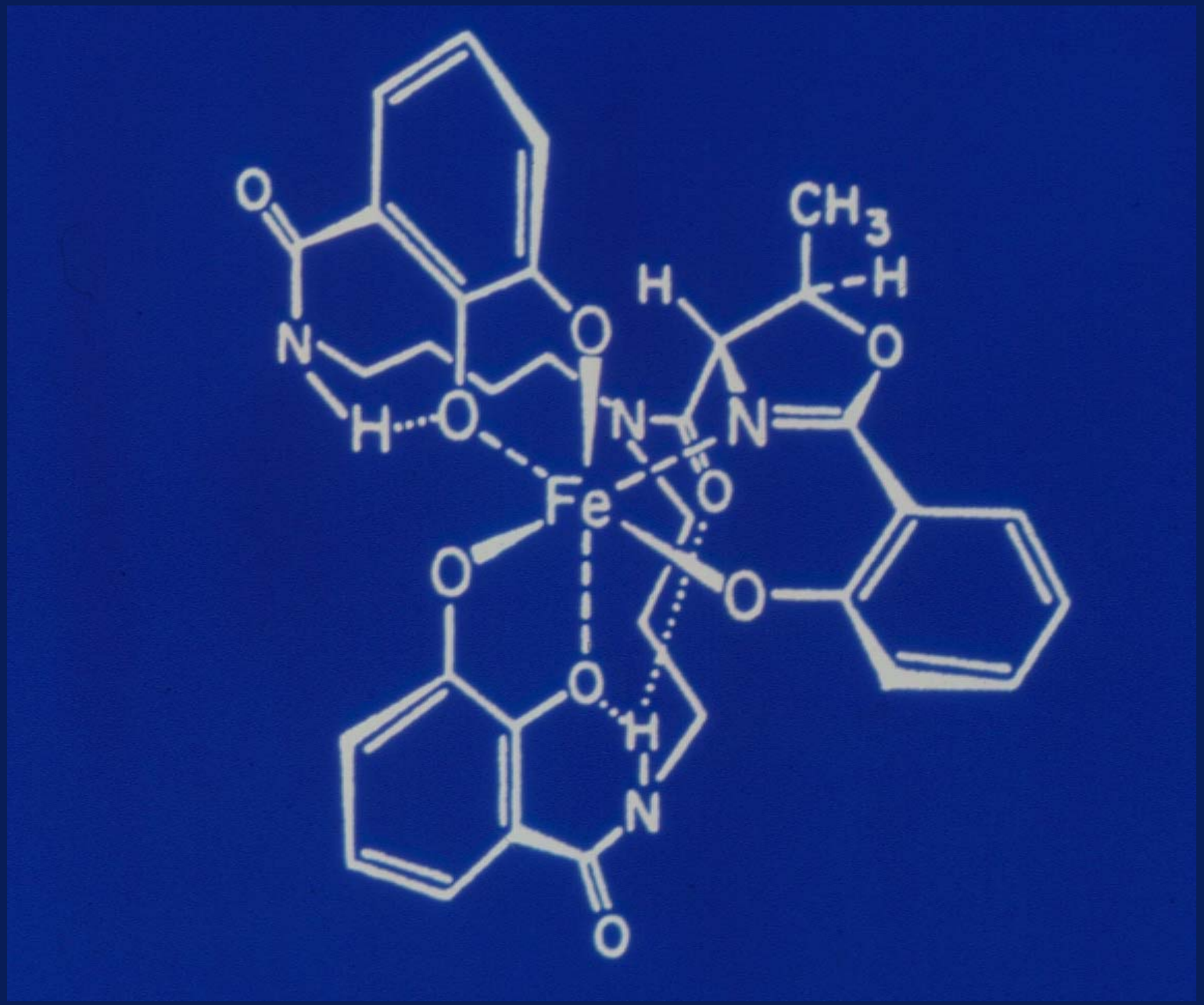
L-Agrobactin



Vibriobactin

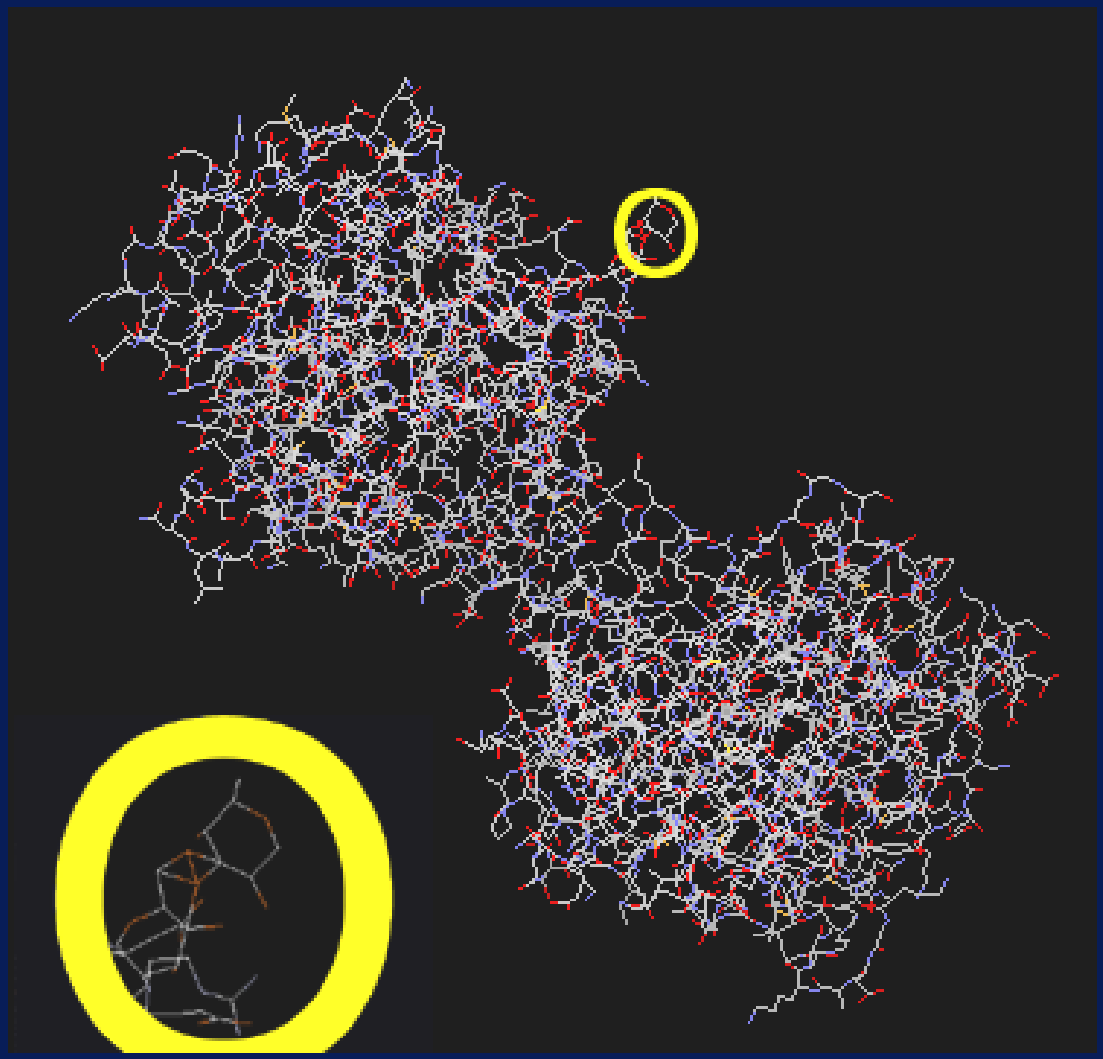


Enterobactin

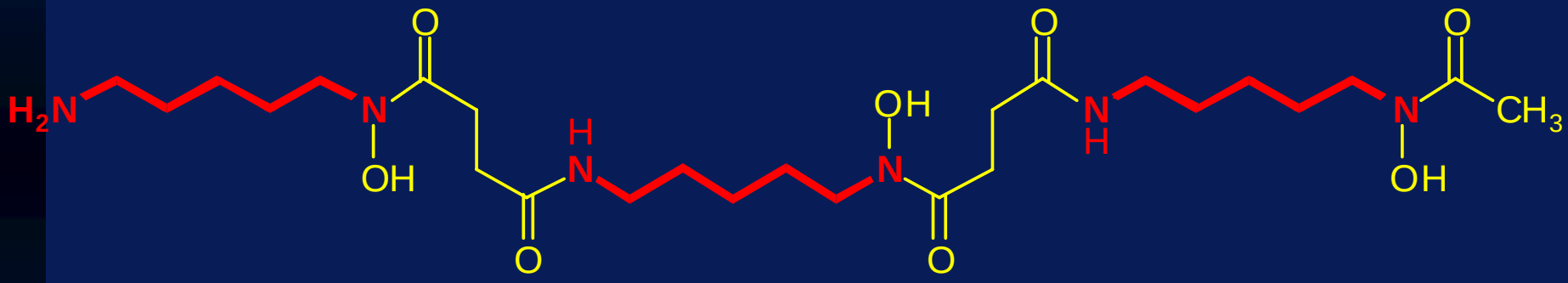

O
N
H
O
O
N
N
O
Fe
O
O
O
H
N
O
H
CH3
H
O

Mammalian Iron Transport

Transferrin



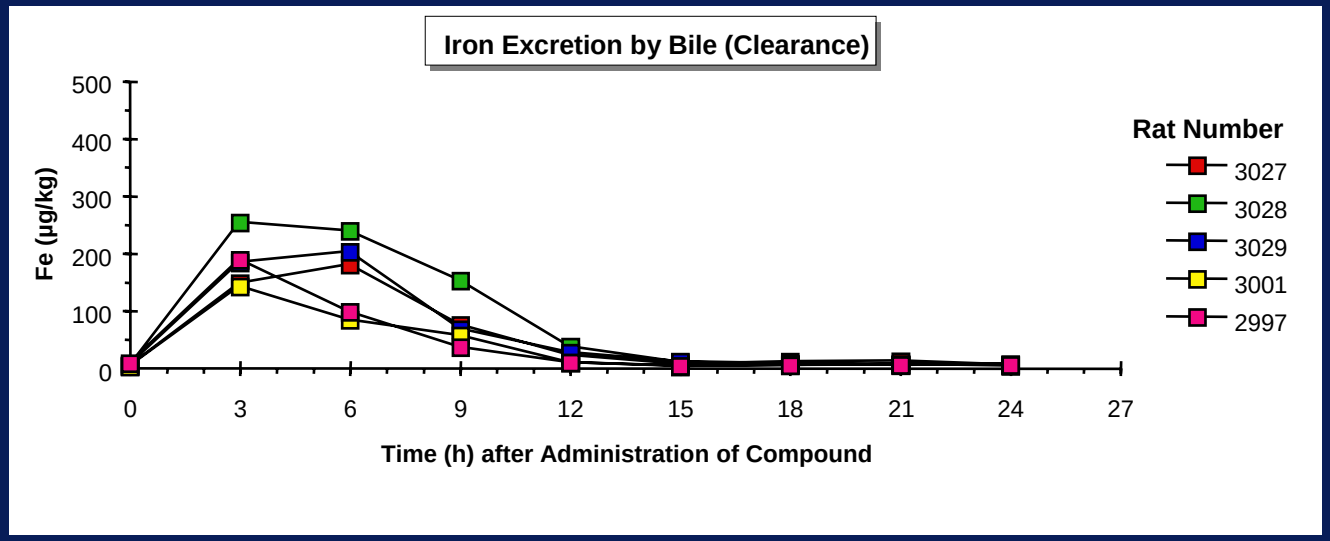
Desferrioxamine B (DFO)

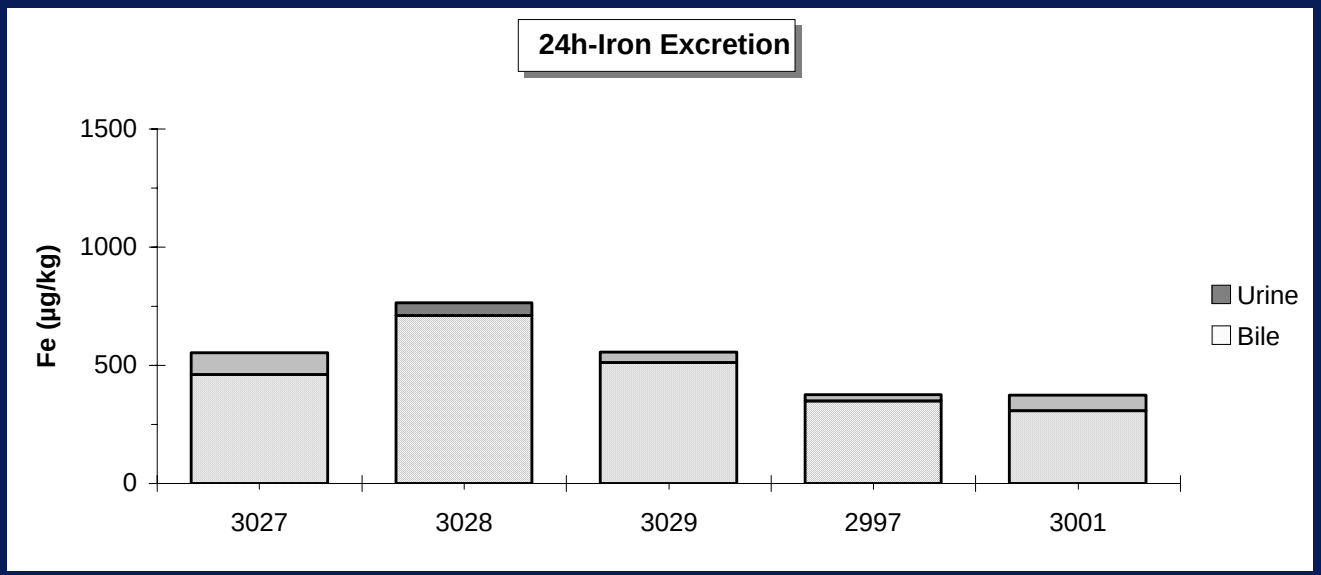


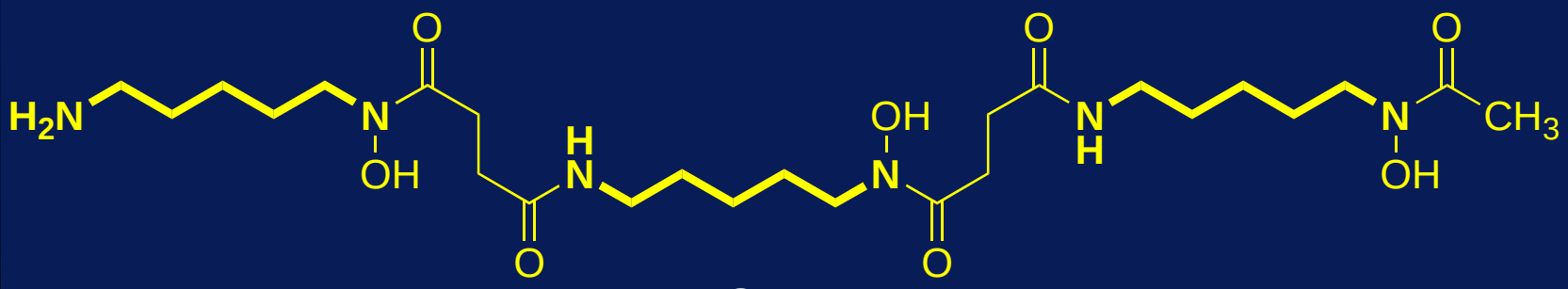
Animal Models

- Non-Iron-Overloaded Bile Duct-Cannulated Roden
- Iron-Overloaded *Cebus apella* Primate

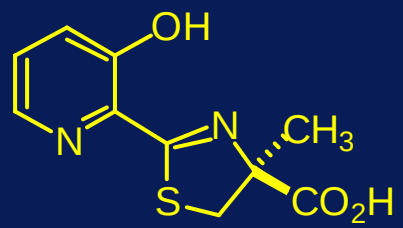
(*S*)-4'-(HO)-DADFT-PE
300 µmol/kg PO



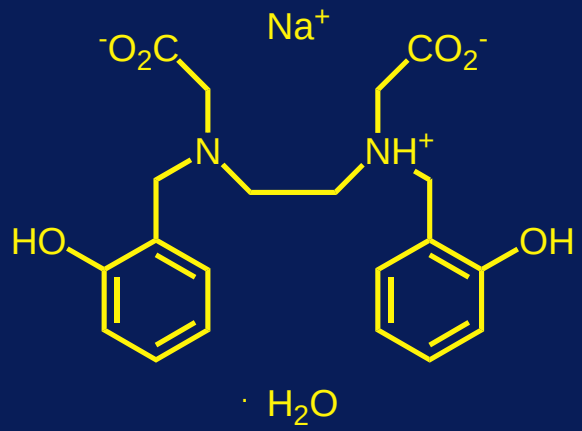




DFO



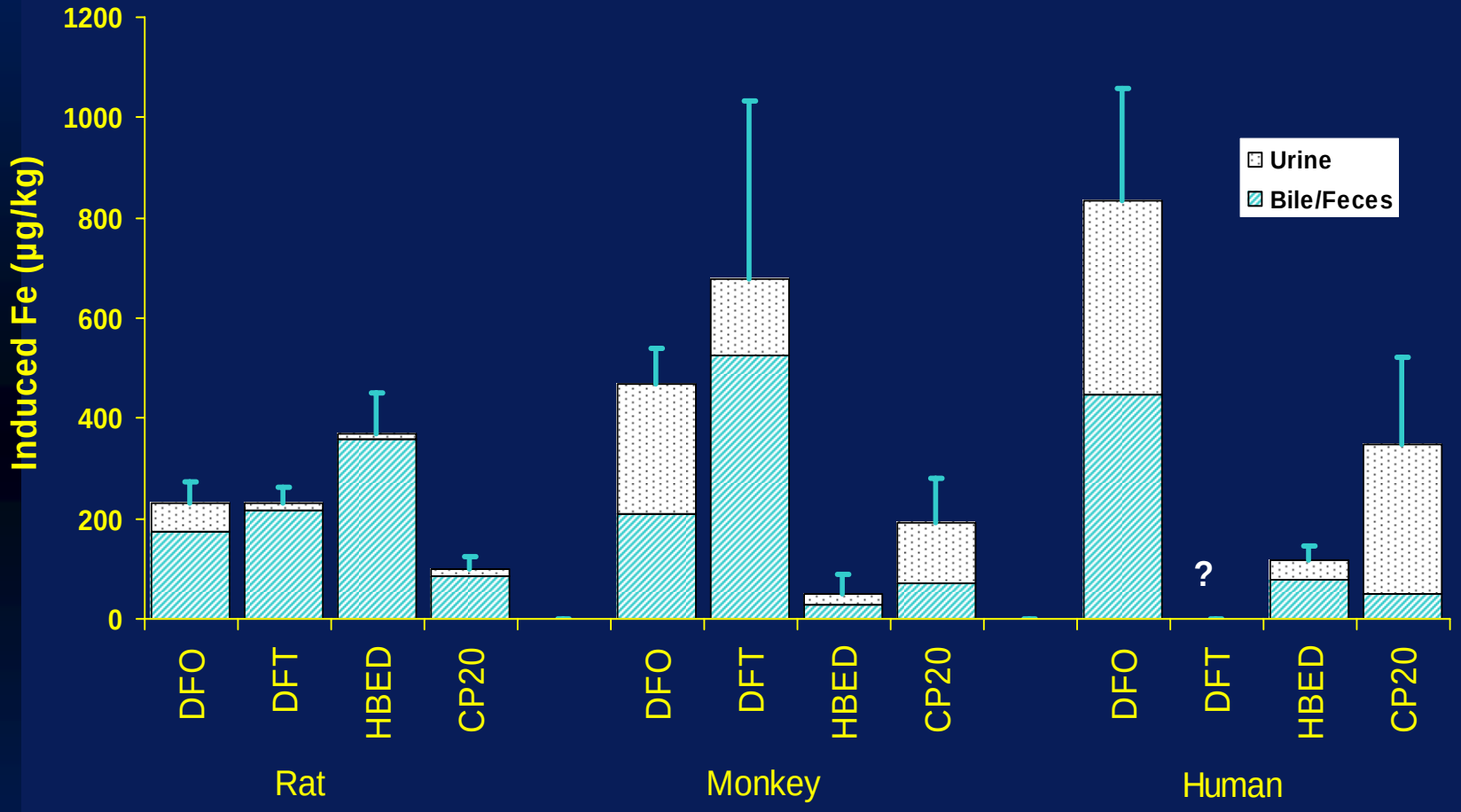
DFT



HBED

CP20

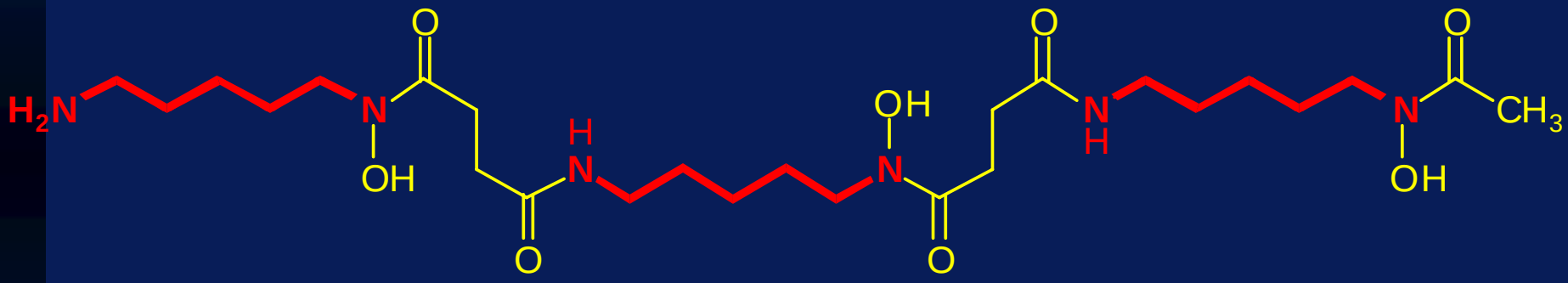
Comparison of Animal Models



Chelator-induced iron excretion in rats, monkeys, and humans.

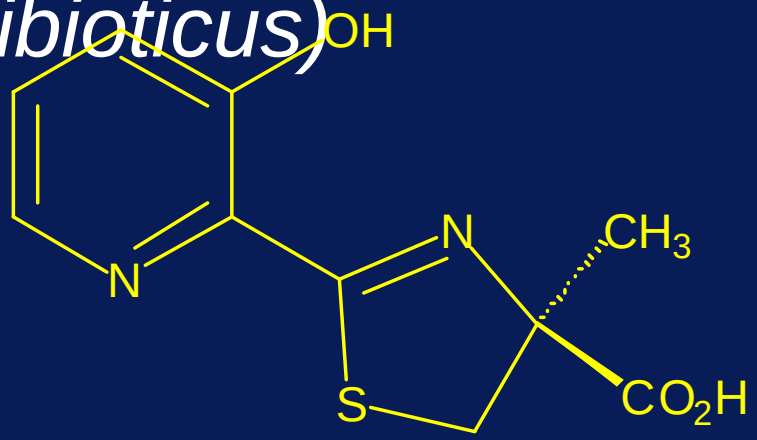
Iron-Clearing Efficiency

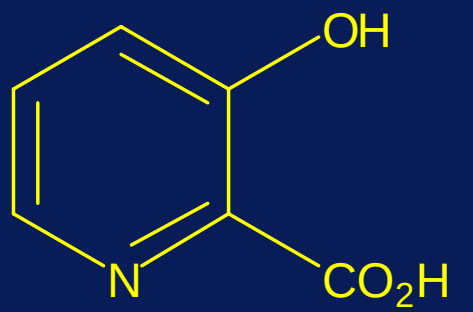
Desferrioxamine B (DFO)



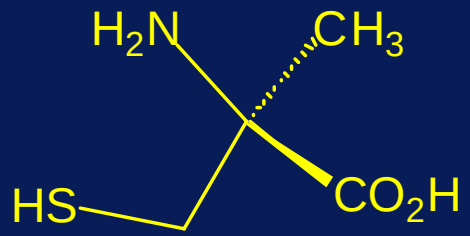
Desferrithiocin (DFT)

(*Streptomyces antibioticus*)

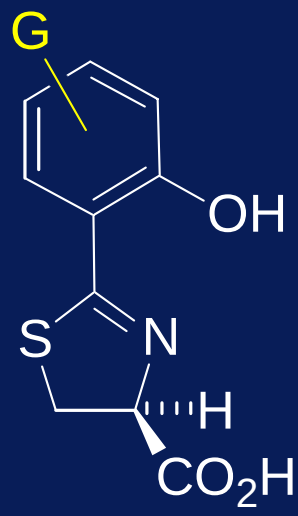




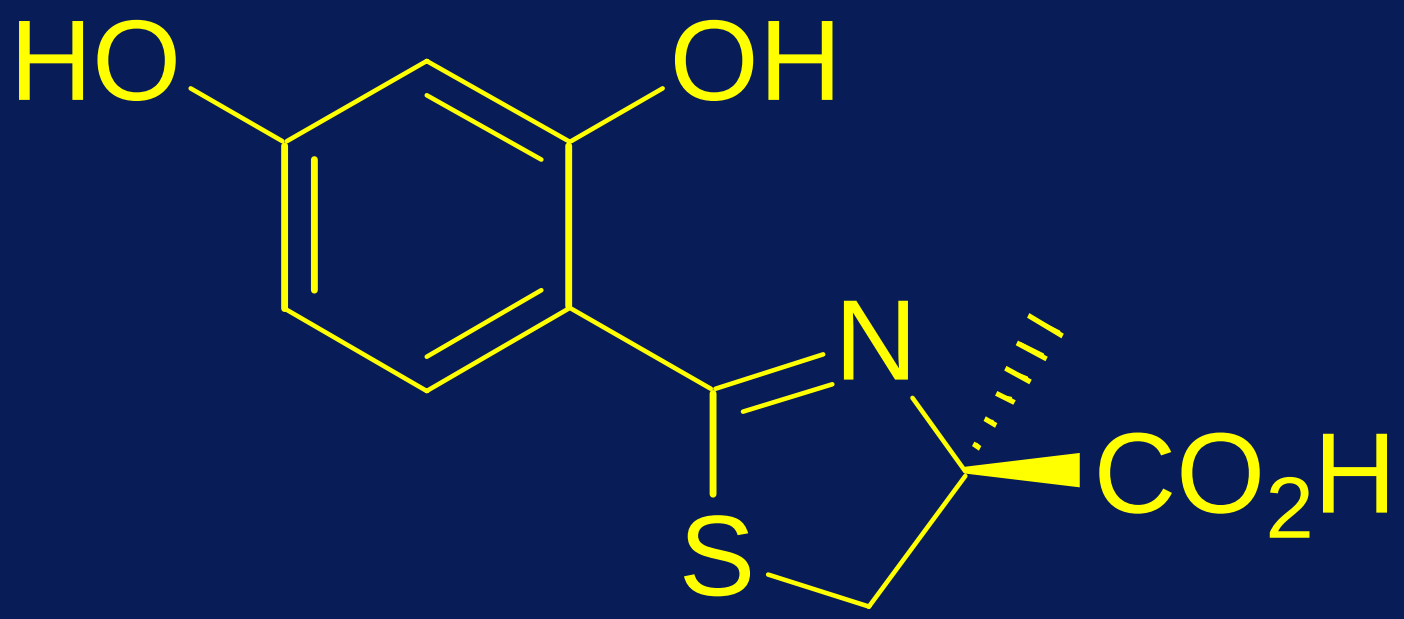
+

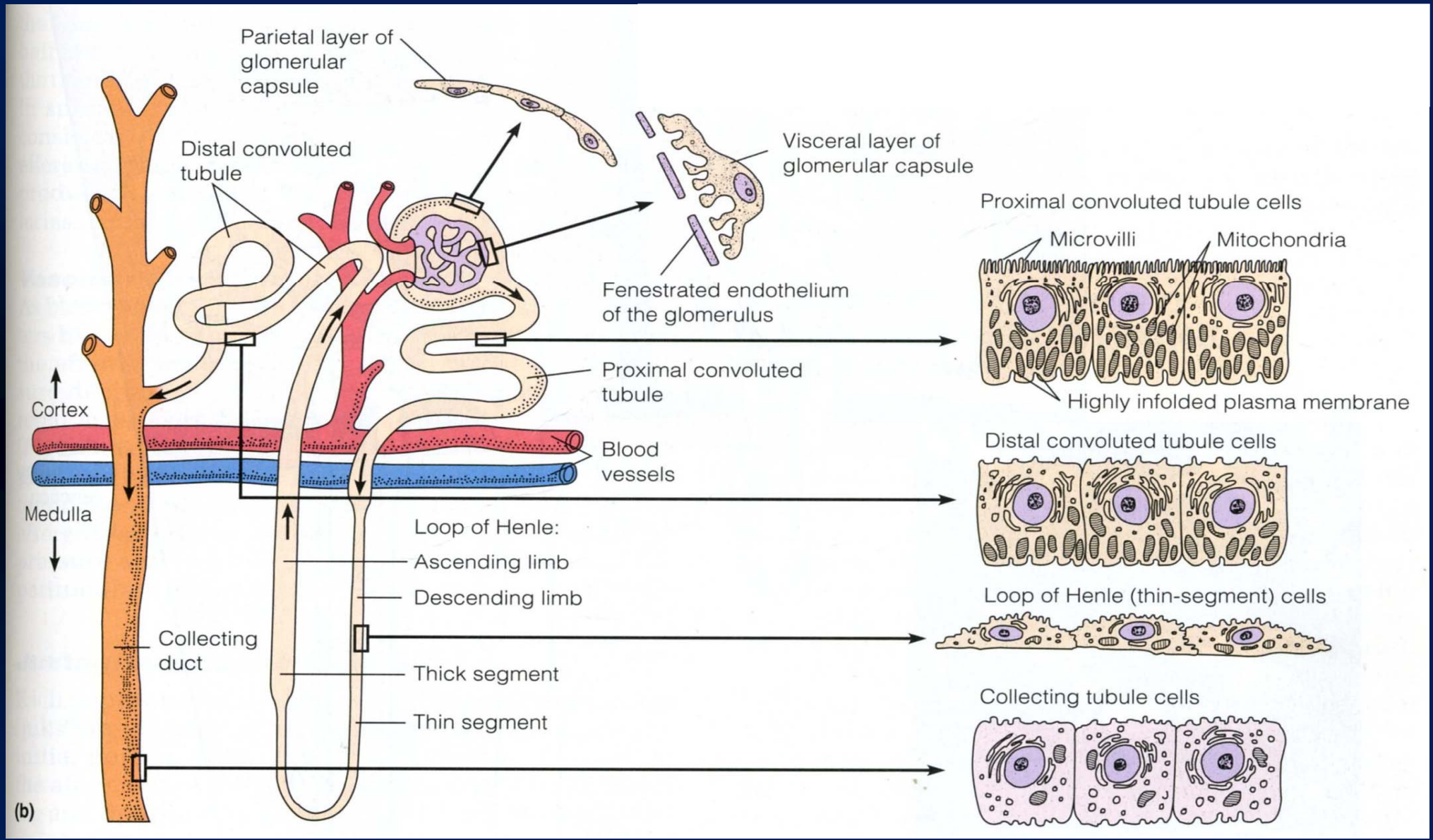


Modifications to the DFT Pharmacophore

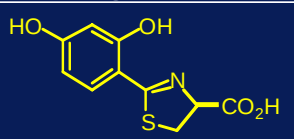
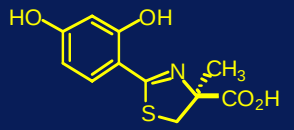
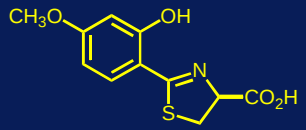
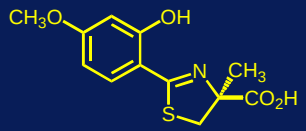
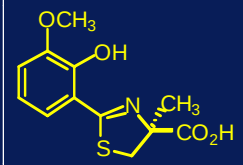


(*S*)-4'-(HO)-DADFT (Deferitrin)

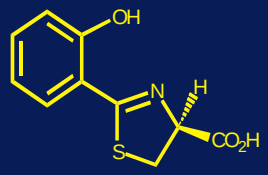
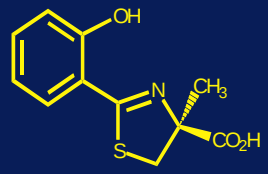


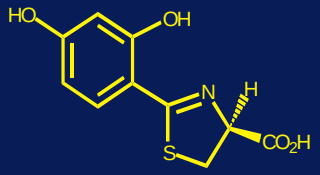
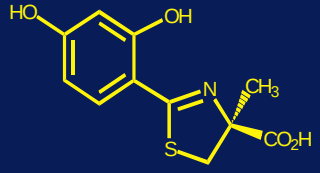

Parietal layer of glomerular capsule
Distal convoluted tubule
Visceral layer of glomerular capsule
Fenestrated endothelium of the glomerulus
Proximal convoluted tubule
Cortex
Blood vessels
Medulla
Loop of Henle:
Ascending limb
Descending limb
Collecting duct
Thick segment
Thin segment
(b)
Proximal convoluted tubule cells
Microvilli
Mitochondria
Highly infolded plasma membrane
Distal convoluted tubule cells
Loop of Henle (thin-segment) cells
Collecting tubule cells

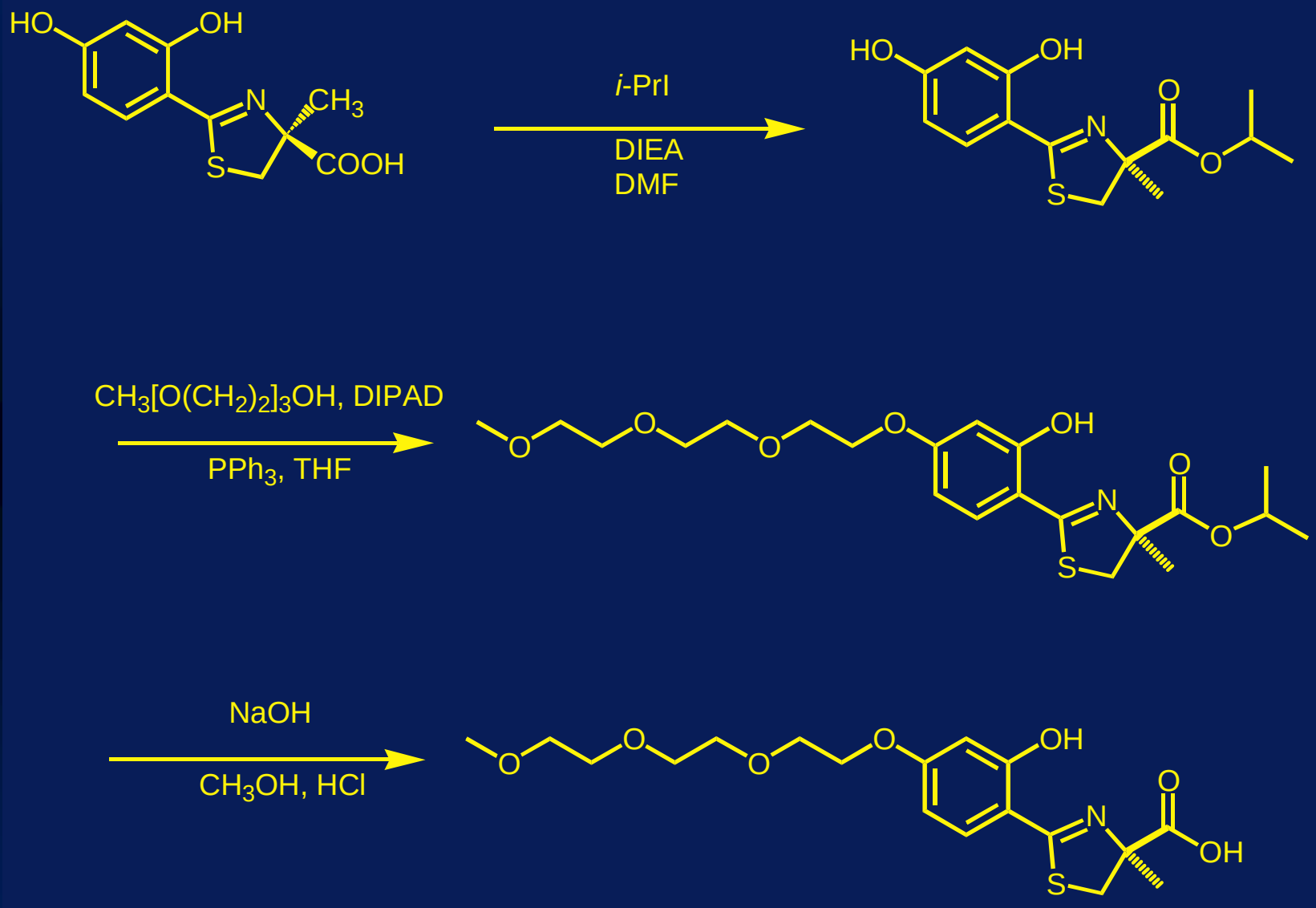
Desferrithiocin Analogues' Iron Clearing Activity when Administered Orally to *Cebus apella* Primates and the Partition Coefficients of the Compounds

Desferrithiocin analogue	Iron clearing efficiency (%) [% stool/% urine]	log *P*	Desferrithiocin analogue	Iron clearing efficiency (%) [% stool/% urine]	log *P*
	4.2 ± 1.4 [70/30]	–1.33		5.8 ± 3.4 [91/9]	–1.67
	13.4 ± 5.8 [86/14]	–1.05		23.1 ± 5.9 [83/17]	–1.17
	16.2 ± 3.2 [81/19]	–0.89		15.5 ± 7.3 [87/13]	–1.52
	24.4 ± 10.8 [91/9]	–0.70		22.5 ± 7.1 [91/9]	–1.12
	12.3 ± 2.7 [64/36]	–0.91			

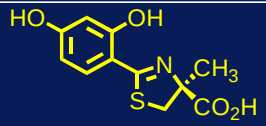
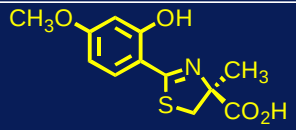
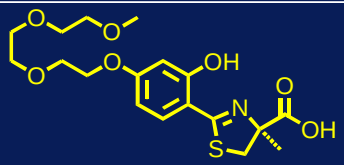
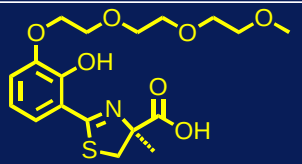
Partition Coefficients and Tolerability of DFT Analogues

Number	Structure	Log Papp	Tolerability
3	 (S)-DADMDFT	-0.93	All rats dead by day 6.
2	 (S)- DADFT	-0.34	All rats dead by day 5.
6	 (S)-4'-(CH_3O)-DADFT	-0.7	All rats dead by day 6.
12	 (S)-5,5-Me$_2$-DADMDFT	-0.34	All rats dead by day 6.

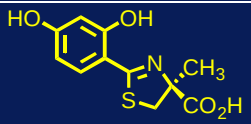
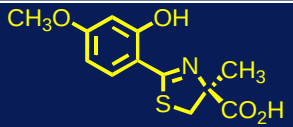
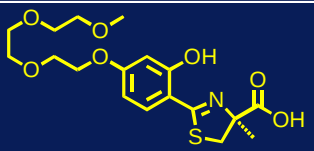
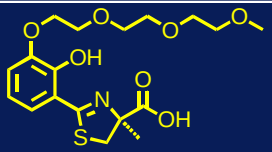
Number	Structure	Log Papp	Tolerability
4	 (S)-4'-(HO)-DADMDFT	-1.33	All rats survived.
1	 (S)-4'-(HO)-DADFT	-1.05	All rats survived.
11	 (S)-4'-(HO)-DADFT-PE	-1.1	All rats survived.
13	 (S)-5,5-Me$_2$-4'-(HO)-DADMDFT	-0.91	All rats survived.


HO
OH
N
CH3
S
COOH
i-PrI
DIEA
DMF
O
O
CH3[O(CH2)2]3OH, DIPAD
PPh3, THF
NaOH
CH3OH, HCl

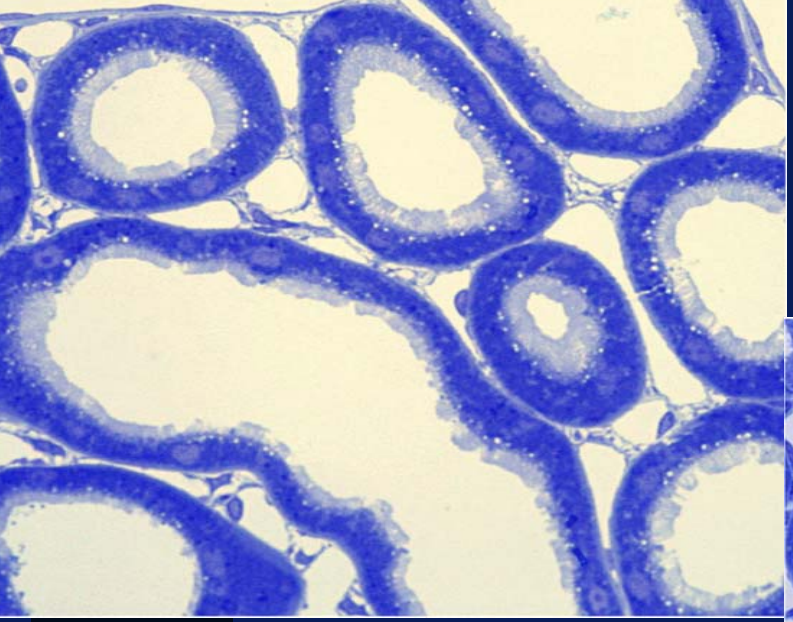
Iron-Clearing Activity of Desferrithiocin Analogues When Administered Orally to Rodents and the Partition Coefficients of the Compounds

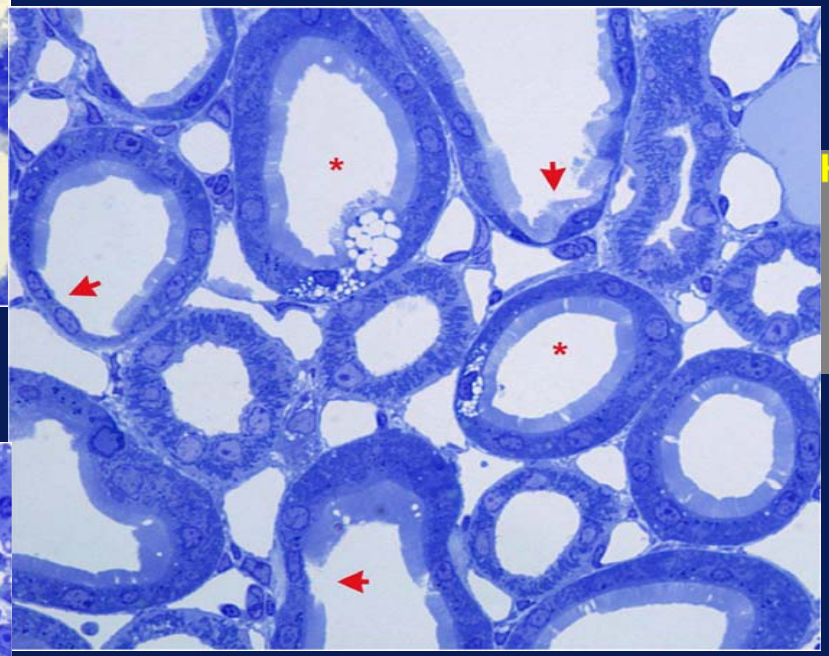
Desferrithiocin Analogue	Iron-Clearing Efficiency (%)	log P_{app}
 (*S*)-4'-(HO)-DADFT, **1**	1.1 ± 0.8 [100/0]	–1.05
 (*S*)-4'-(CH_3O)-DADFT, **2**	6.6 ± 2.8 [98/2]	–0.70
 (*S*)-4'-(HO)-DADFT-PE, **3**	5.5 ± 1.9 [90/10]	–1.10
 (*S*)-3'-(HO)-DADFT, **4**	4.6 ± 0.9 [98/2]	–1.17
 (*S*)-3'-(CH_3O)-DADFT, **5**	12.4 ± 3.5 [99/1]	–1.12
 (*S*)-3'-(HO)-DADFT-PE, **6**	10.6 ± 4.4 [95/5]	–1.22

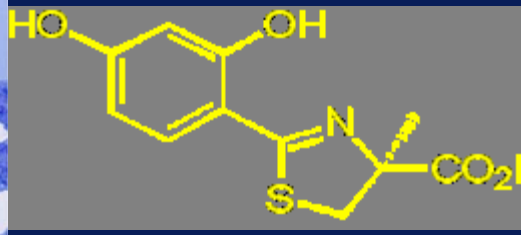
Iron-Clearing Activity of Desferrithiocin Analogues When Administered Orally to *Cebus apella* Primates and the Partition Coefficients of the Compounds

Desferrithiocin Analogue	Iron-Clearing Efficiency (%)	log P_{app}
 (*S*)-4'-(HO)-DADFT, **1**	16.8 ± 7.2 [88/12]	–1.05
 (*S*)-4'-(CH_3O)-DADFT, **2**	24.4 ± 10.8 [91/9]	–0.70
 (*S*)-4'-(HO)-DADFT-PE, **3**	25.4 ± 7.4 [96/4]	–1.10
 (*S*)-3'-(HO)-DADFT, **4**	23.1 ± 5.9 [83/17]	–1.17
 (*S*)-3'-(CH_3O)-DADFT, **5**	22.5 ± 7.1 [91/9]	–1.12
 (*S*)-3'-(HO)-DADFT-PE, **6**	24.5 ± 7.6 [72/28]	–1.22

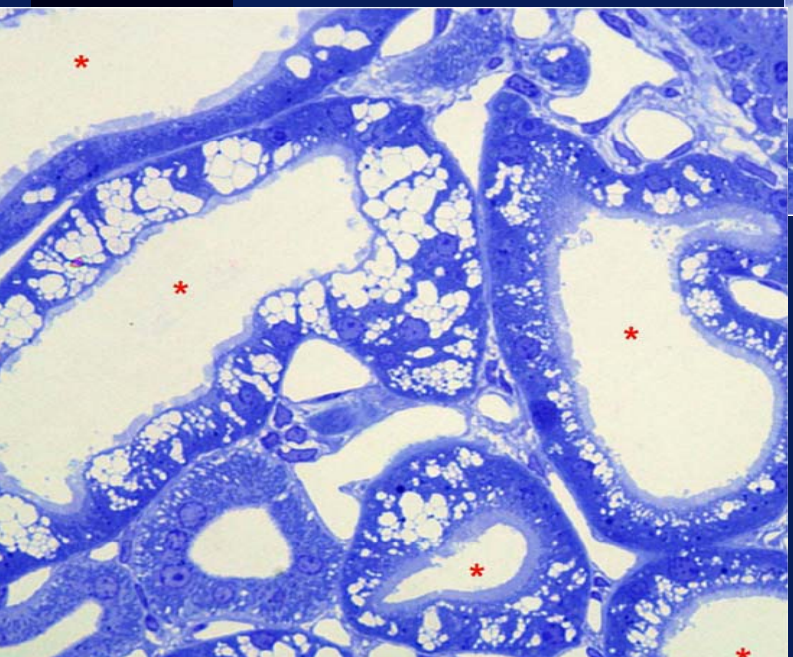
CONTROL







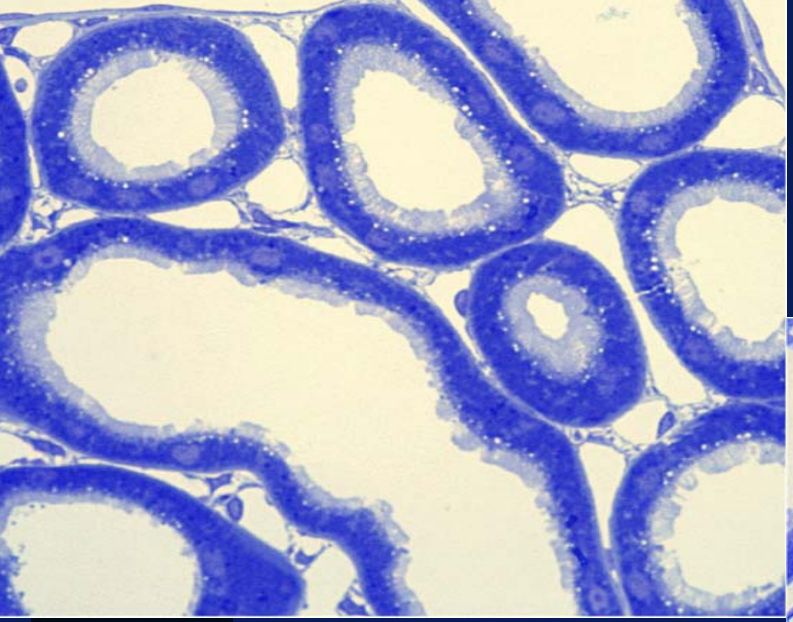
(*S*)-4'-(HO)-DADFT
474 µmol SID x 7 days

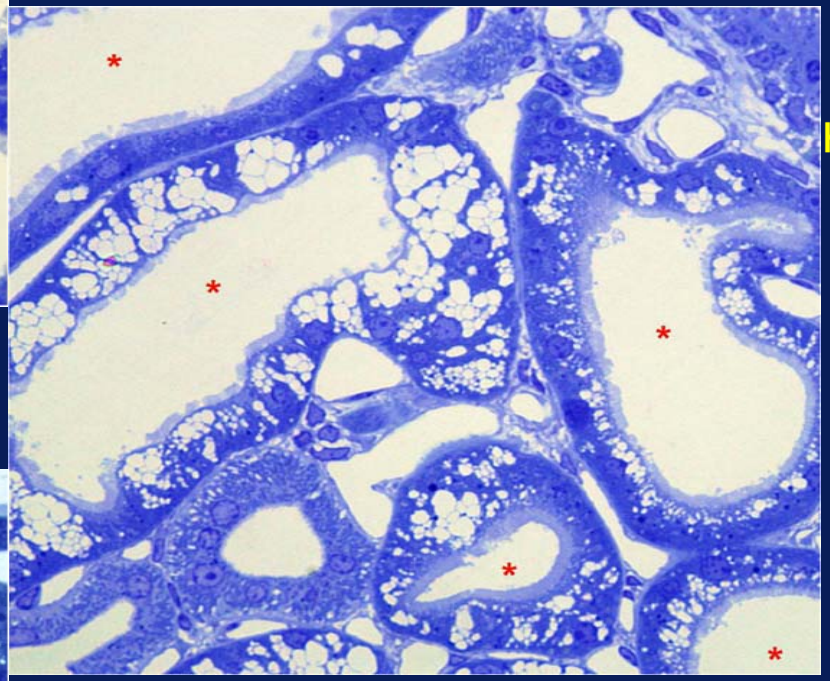


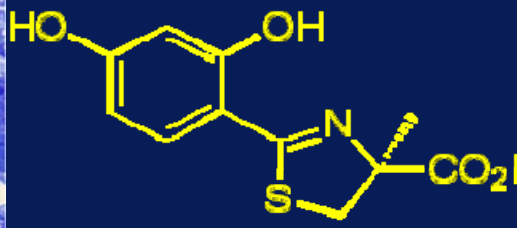
(*S*)-4'-(HO)-DADFT
237µmol BID x 7 days

400

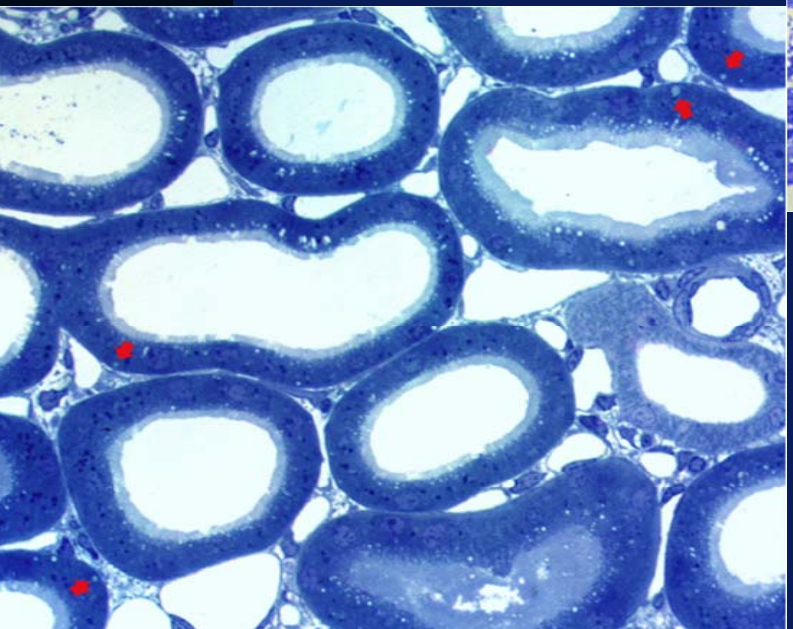
CONTROL

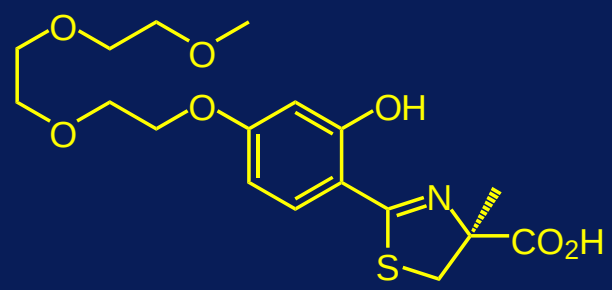






(*S*)-4'-(HO)-DADFT
237µmol BID x 7 days

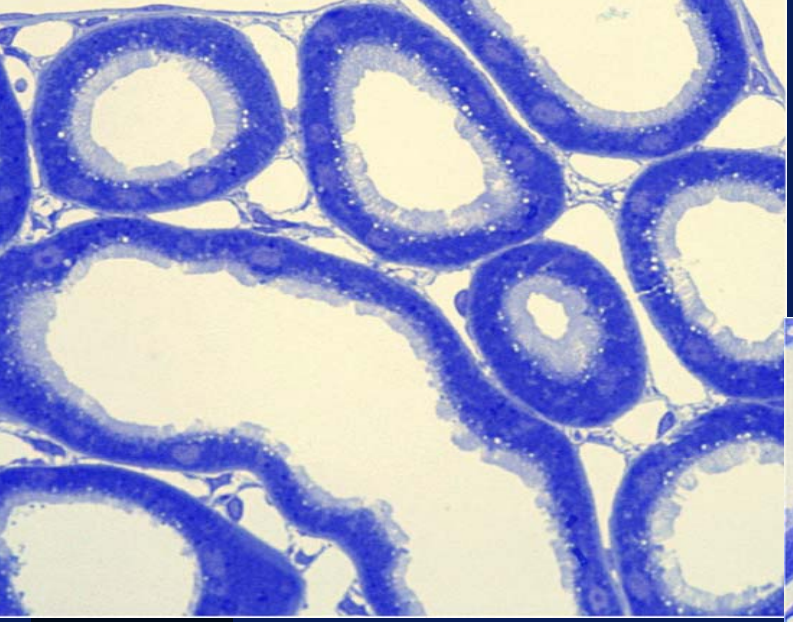


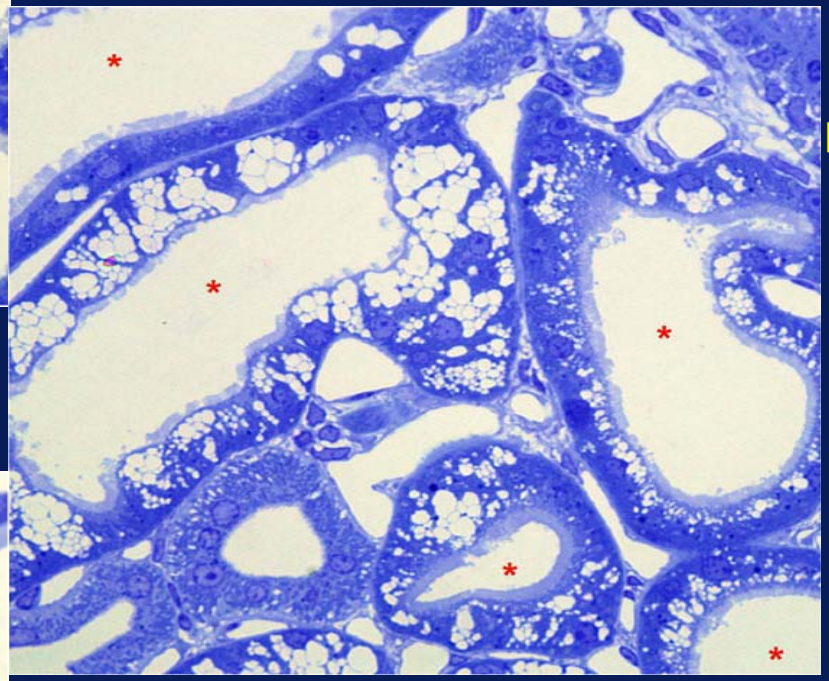


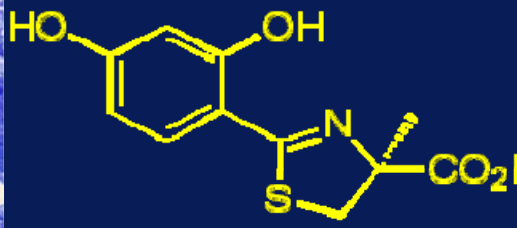
(*S*)-4'-(HO)-DADFT-PE
237µmol BID x 7 days

400x

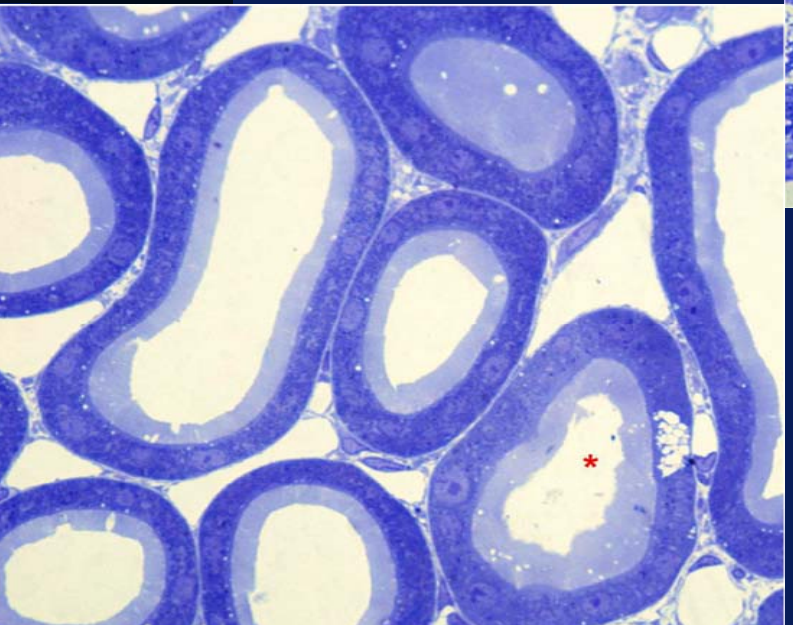
CONTROL

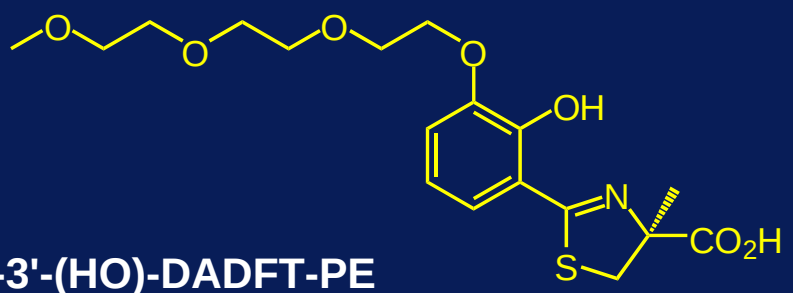






(*S*)-4'-(HO)-DADFT
237µmol BID x 7 days

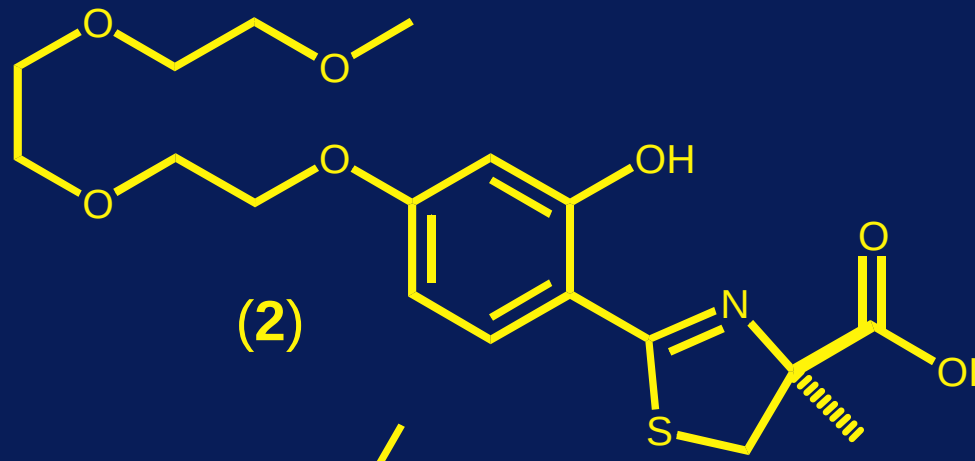




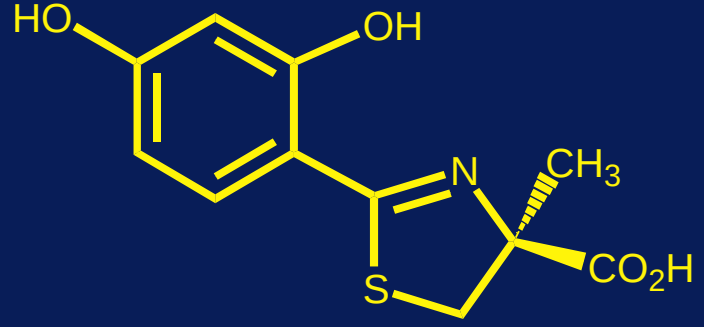
(*S*)-3'-(HO)-DADFT-PE
237µmol BID x 7 days

400x

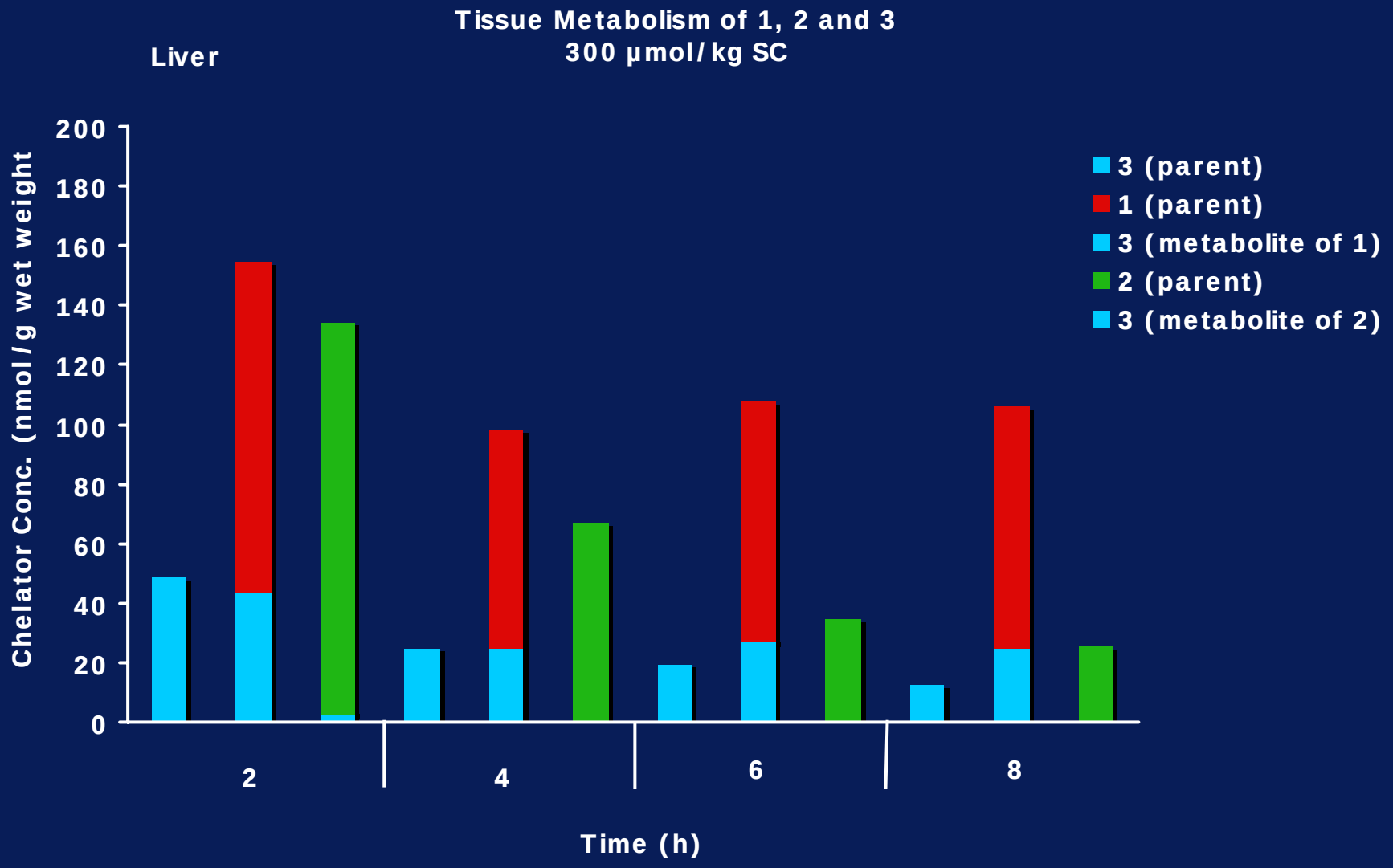
(1)

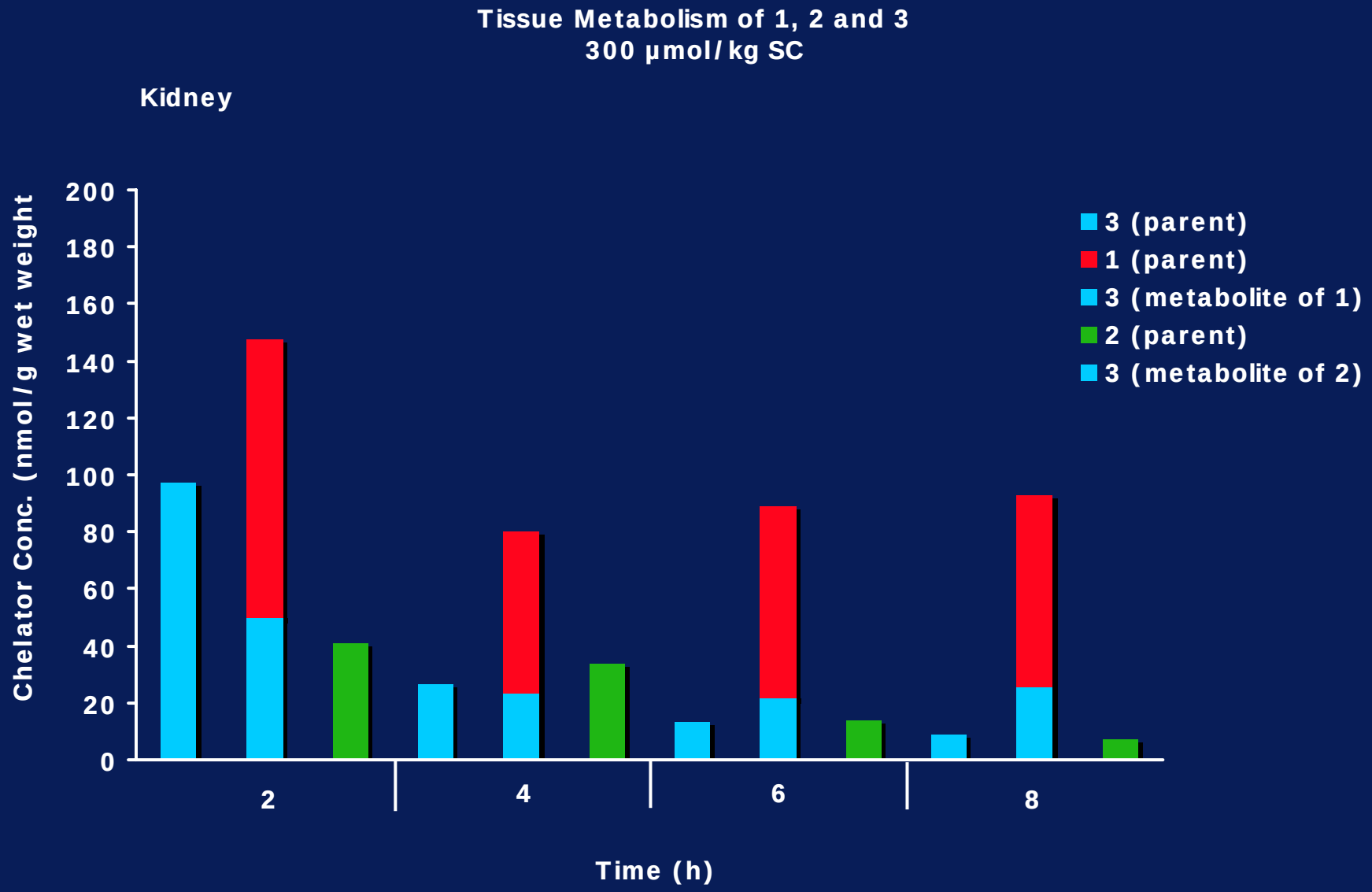


(2)

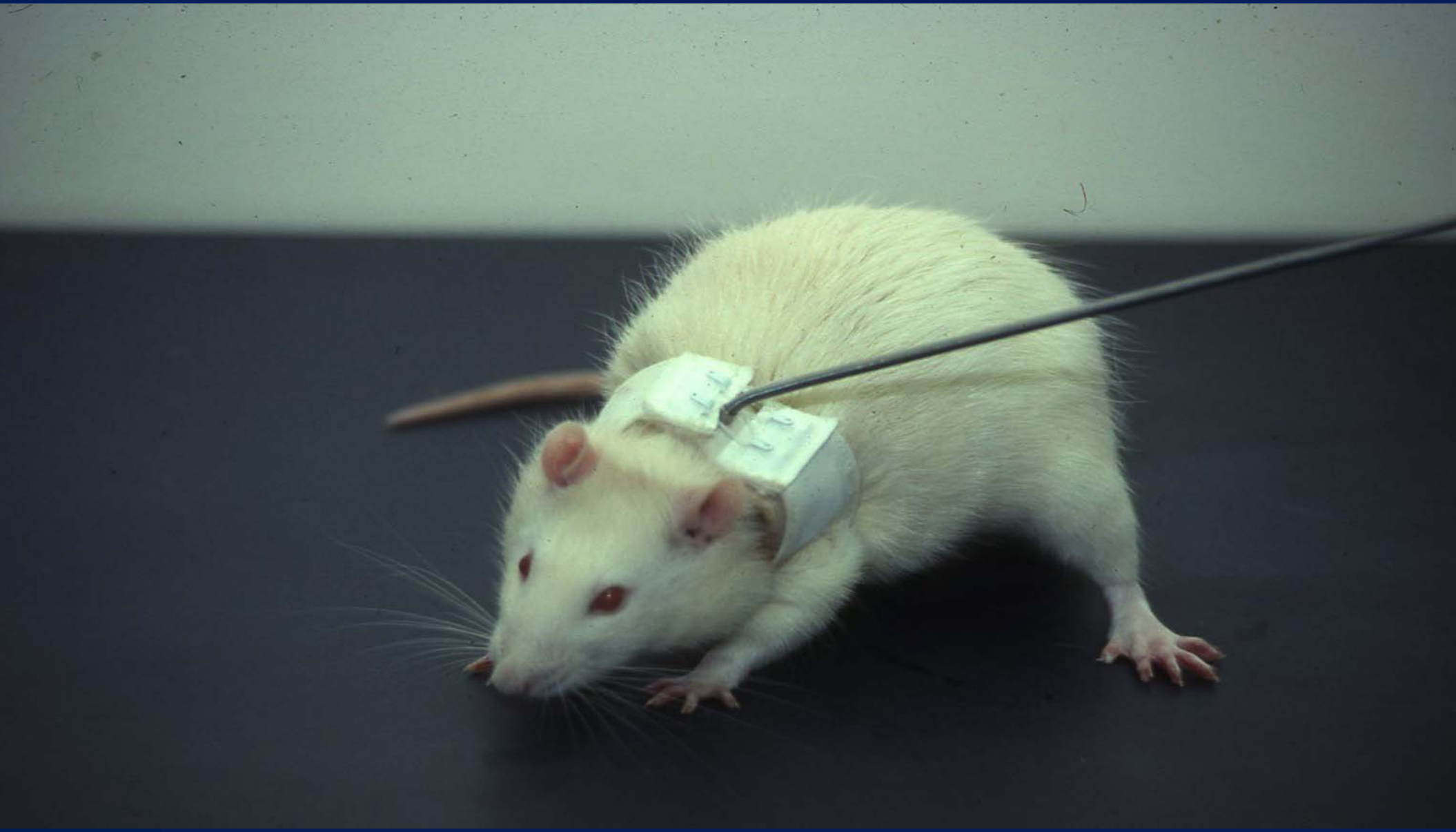


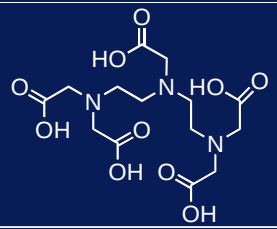
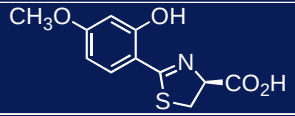
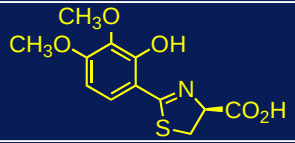
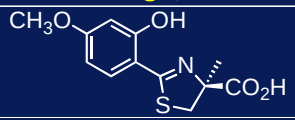
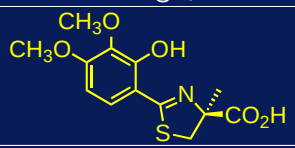
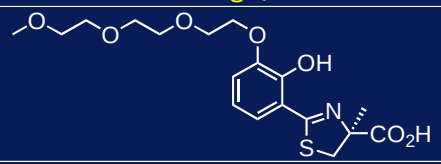
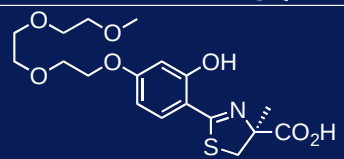
(3)

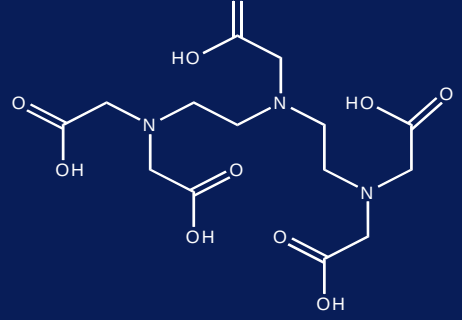

Tissue Metabolism of 1, 2 and 3
300 µmol/kg SC
Liver
Chelator Conc. (nmol/g wet weight
200
180
160
140
120
100
80
60
40
20
0
2
4
6
8
Time (h)
3 (parent)
1 (parent)
3 (metabolite of 1)
2 (parent)
3 (metabolite of 2)


Tissue Metabolism of 1, 2 and 3
300 µmol/kg SC
Kidney
Chelator Conc. (nmol/g wet weight
200
180
160
140
120
100
80
60
40
20
0
2
4
6
8
Time (h)
3 (parent)
1 (parent)
3 (metabolite of 1)
2 (parent)
3 (metabolite of 2)

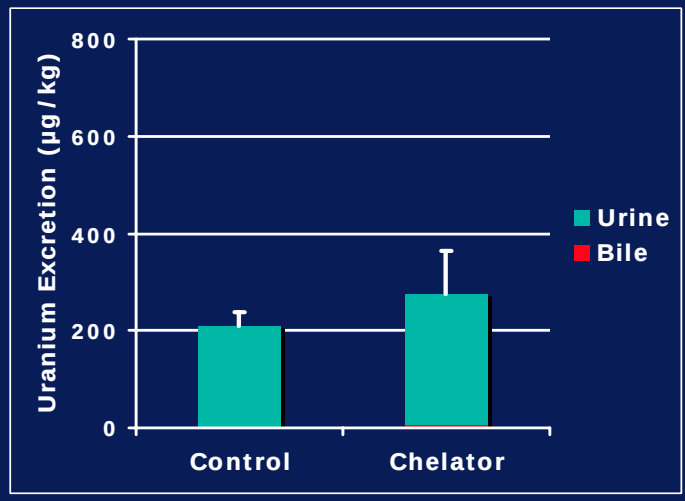
Uranium Decorporation



Compound	Structure
DTPA	
(*S*)-4'-(HO)-DADMDFT	
(*S*)-4'-(CH_3O)-DADMDFT	
(*S*)-3,4'-(CH_3O)$_2$-DADMDFT	
(*S*)-5'-(HO)-DADMDFT	
(*S*)-4'-(HO)-DADFT	
(*S*)-4'-(CH_3O)-DADFT	
(*S*)-3,4'-(CH_3O)$_2$-DADFT	
(*S*)-3'-(HO)-DADFT-PE	
(*S*)-4'-(HO)-DADFT-PE	



DTPA
150 µmol/kg SC



Tissue Uranium Conc. (PPM)

100
90
80
70
60
50
40
30
20
10
0

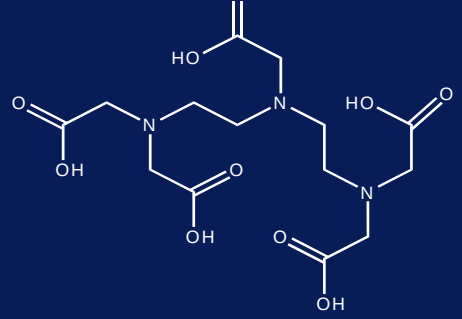
decrease,
p < 0.002

decrease,
p < 0.05

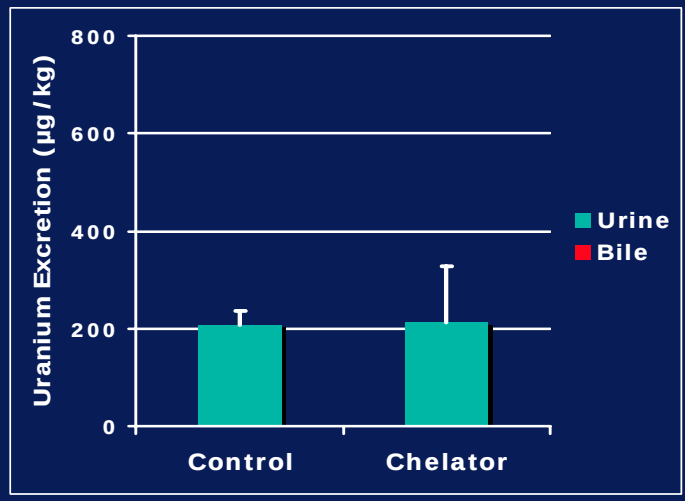
decrease,
p < 0.001

decrease,
p < 0.03

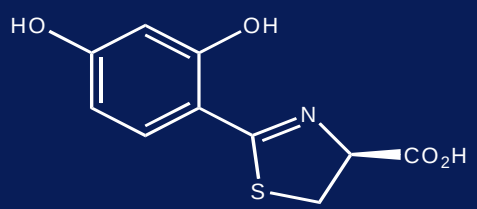
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	47.15	0.148	0.069	3.13	0.12



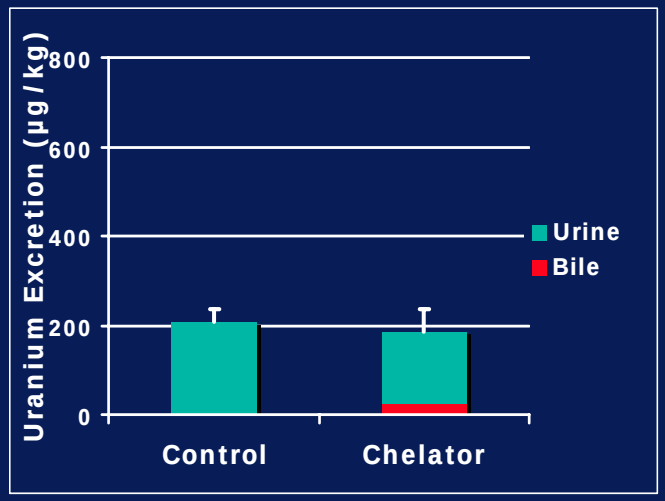
DTPA
300 µmol/kg PO



	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	53.61	0.131	0.100	4.29	0.16



(S)-4'-(HO)-DADMDFT
150 µmol/kg SC



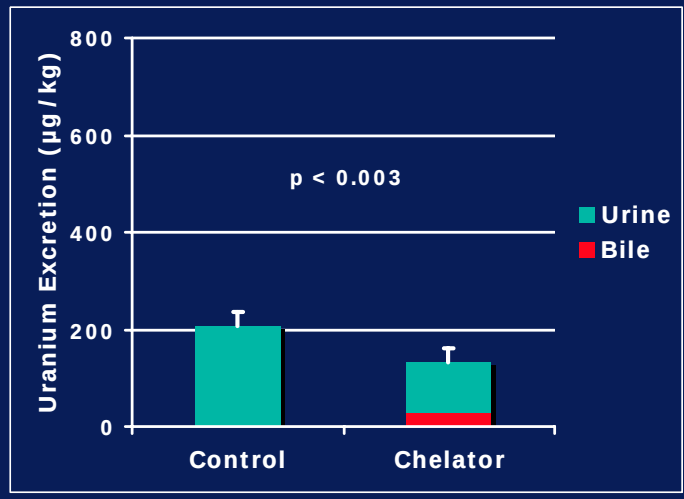
Tissue Uranium Conc. (PPM)

100
90
80
70
60
50
40
30
20
10
0

increase,
p < 0.003

	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	75.53	0.182	0.113	3.37	1.25

(S)-4'-(HO)-DADMDFT
300 µmol/kg PO

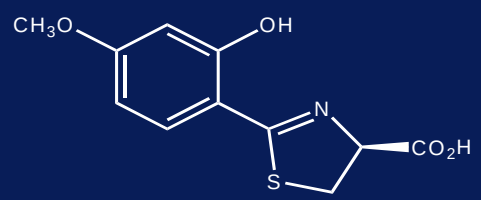


Tissue Uranium Conc. (PPM)

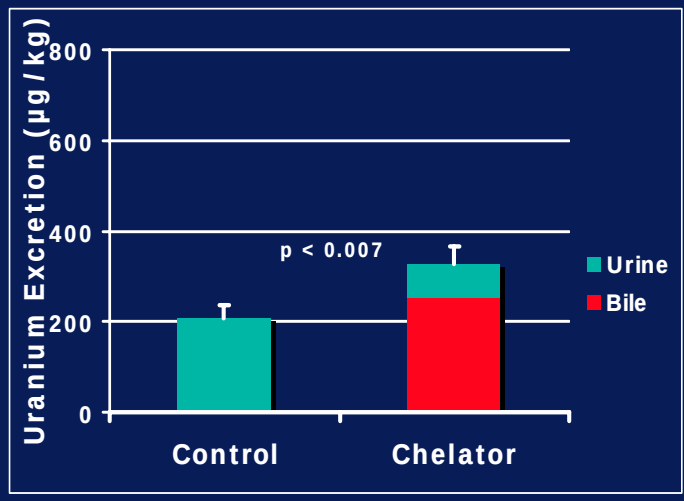
100
90
80
70
60
50
40
30
20
10
0

increase,
p < 0.001

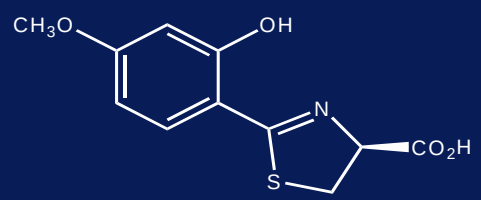
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	59.48	0.200	0.178	4.72	0.79



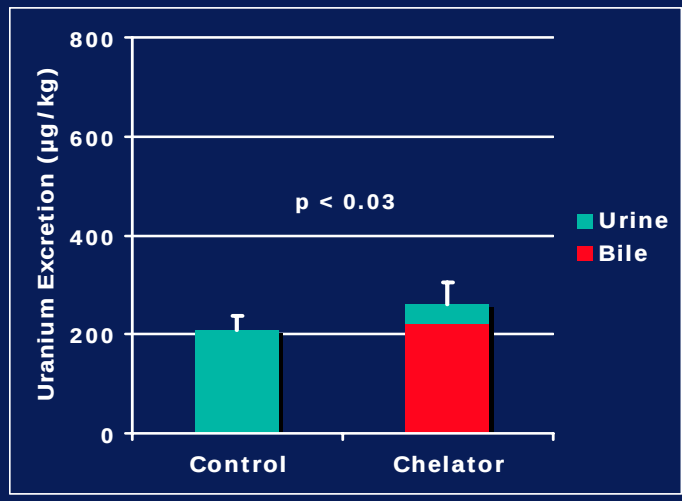
(S)-4'-(CH_3O)-DADMDFT
300 µmol/kg SC



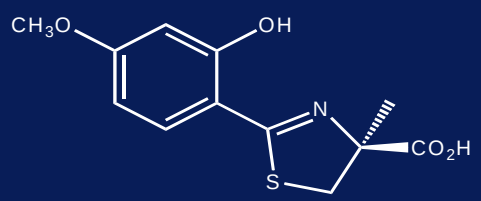
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	10.03	0.362	0.304	2.84	4.37



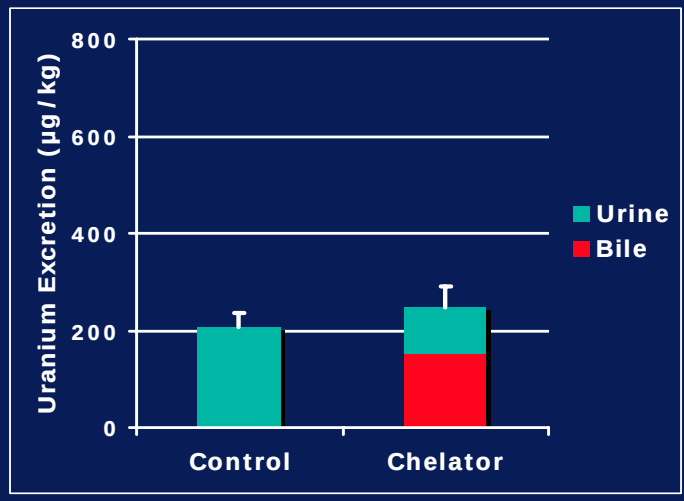
(S)-4'-(CH_3O)-DADMDFT
300 µmol/kg PO



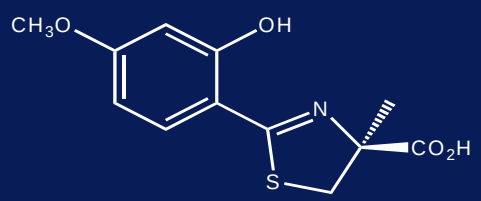
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	22.61	0.285	0.277	3.06	2.45



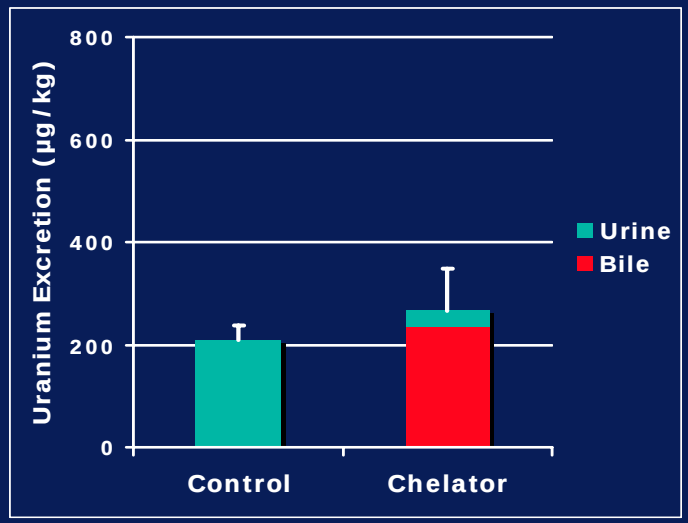
(S)-4'-(CH_3O)-DADFT
150 µmol/kg SC



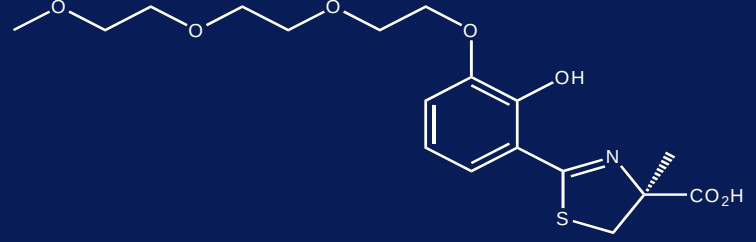
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	19.45	0.393	0.281	2.92	11.27



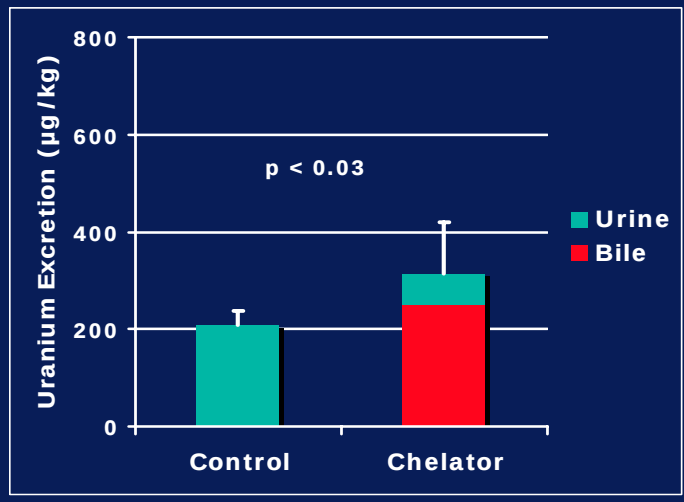
(S)-4'-(CH_3O)-DADFT
300 µmol/kg PO



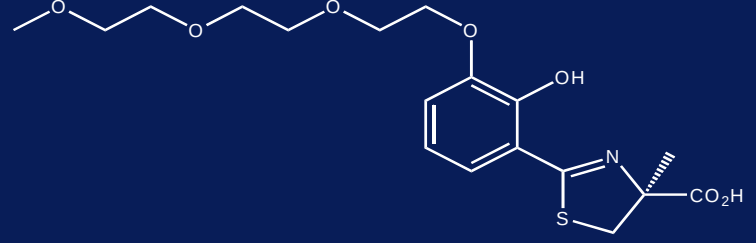
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	4.75	0.492	0.296	1.69	5.08



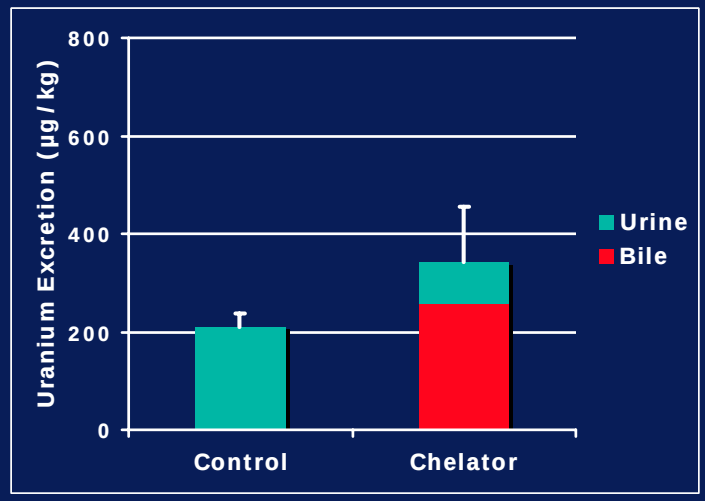
(S)-3'-(HO)-DADFT-PE
300 µmol/kg SC



	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	12.63	0.177	0.080	2.28	0.76



(S)-3'-(HO)-DADFT-PE
300 µmol/kg PO



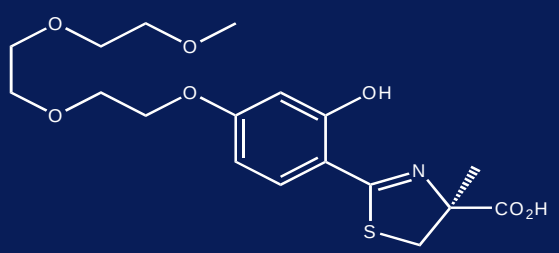
Tissue Uranium Conc. (PPM)

100
90
80
70
60
50
40
30
20
10
0

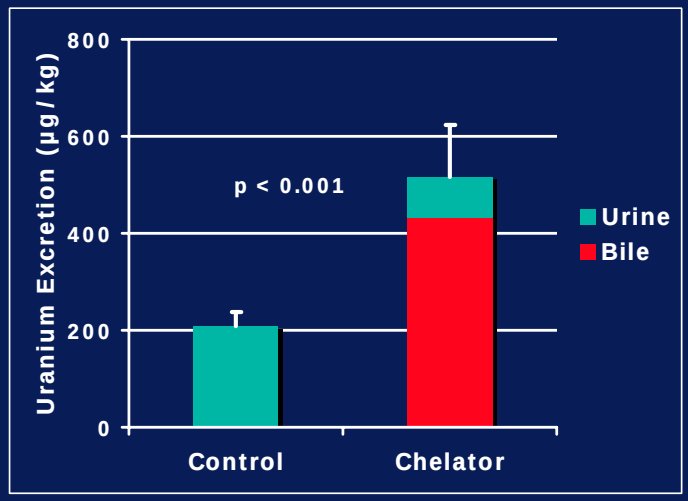
decrease,
p < 0.001

increase,
p < 0.02

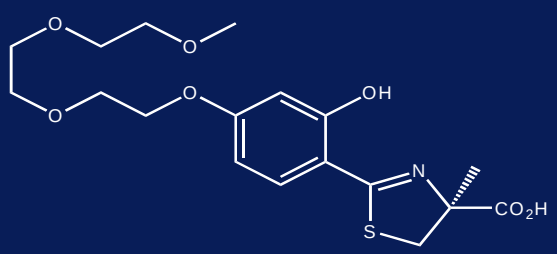
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	31.66	0.160	0.132	3.07	0.74



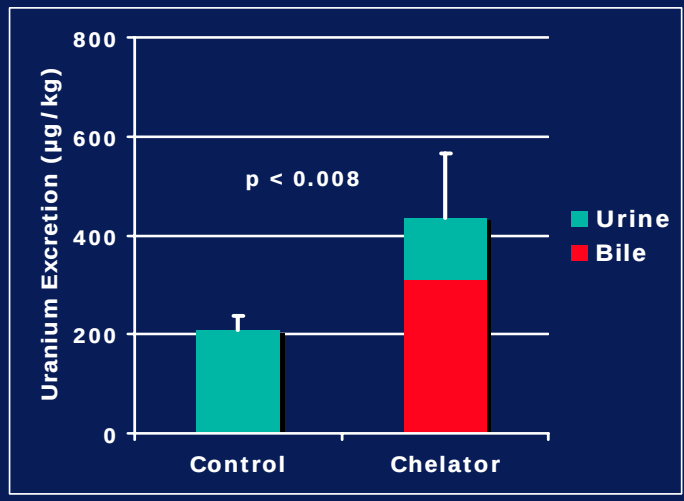
(S)-4'-(HO)-DADFT-PE
300 µmol/kg SC



	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	28.58	0.184	0.130	1.91	0.88



(S)-4'-(HO)-DADFT-PE
300 µmol/kg PO



Tissue Uranium Conc. (PPM)

100
90
80
70
60
50
40
30
20
10
0

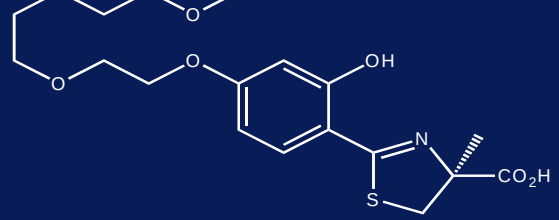
decrease,
p < 0.001

decrease,
p < 0.001

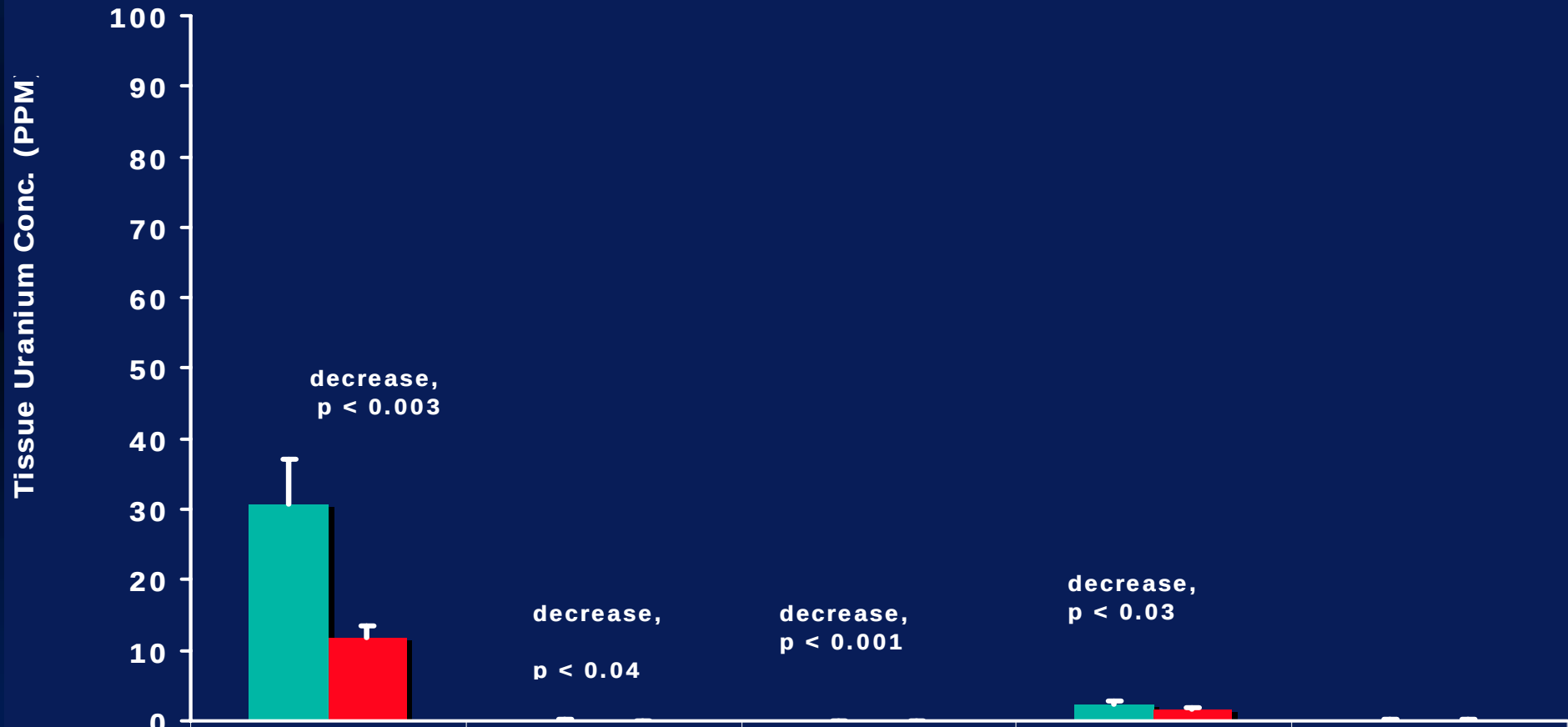
decrease,
p < 0.03

increase,
p < 0.003

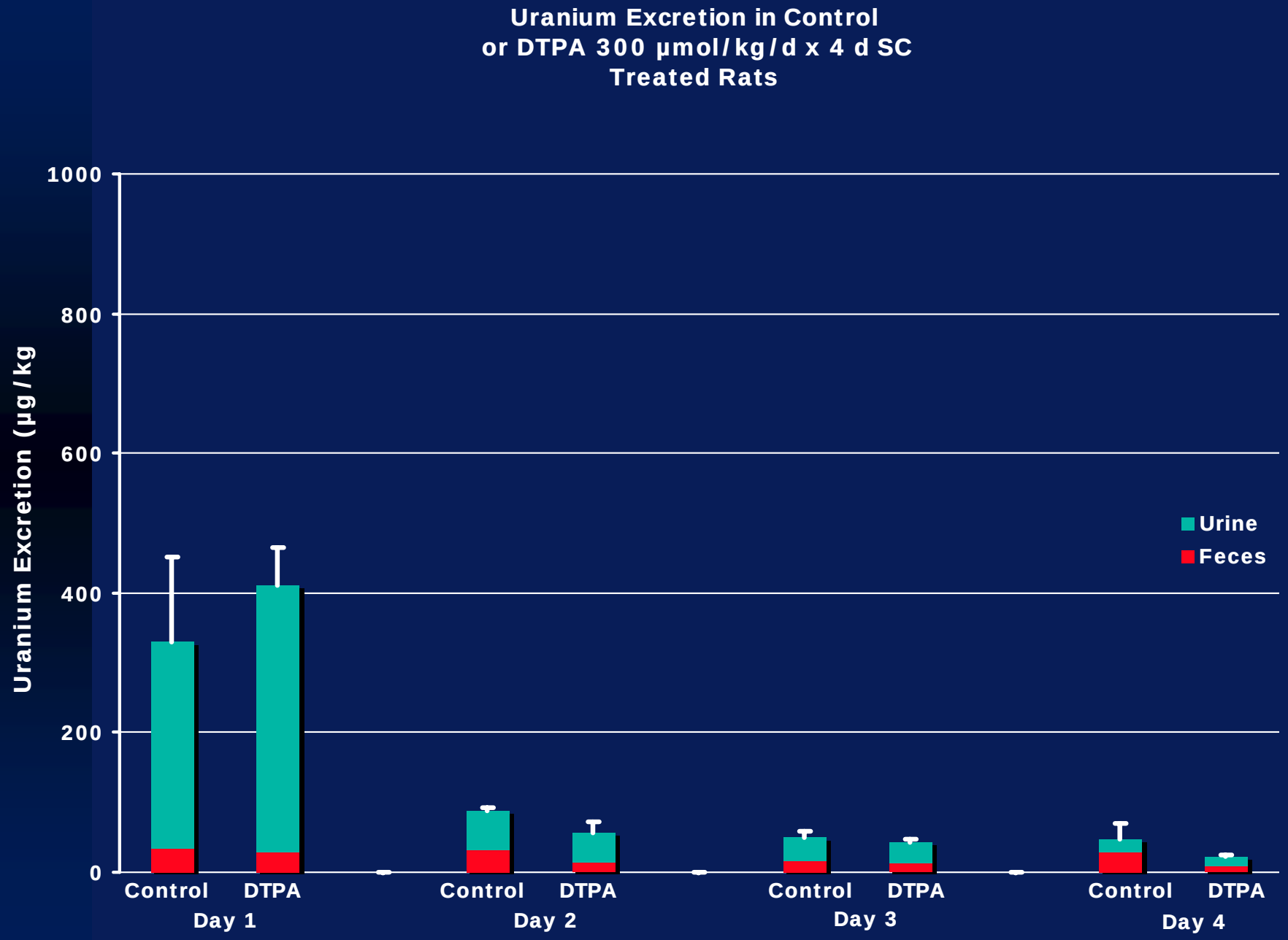
	Kidney	Spleen	Lung	Bone	Liver
Control	83.62	0.191	0.127	3.60	0.16
Chelator	35.83	0.132	0.100	2.74	0.56

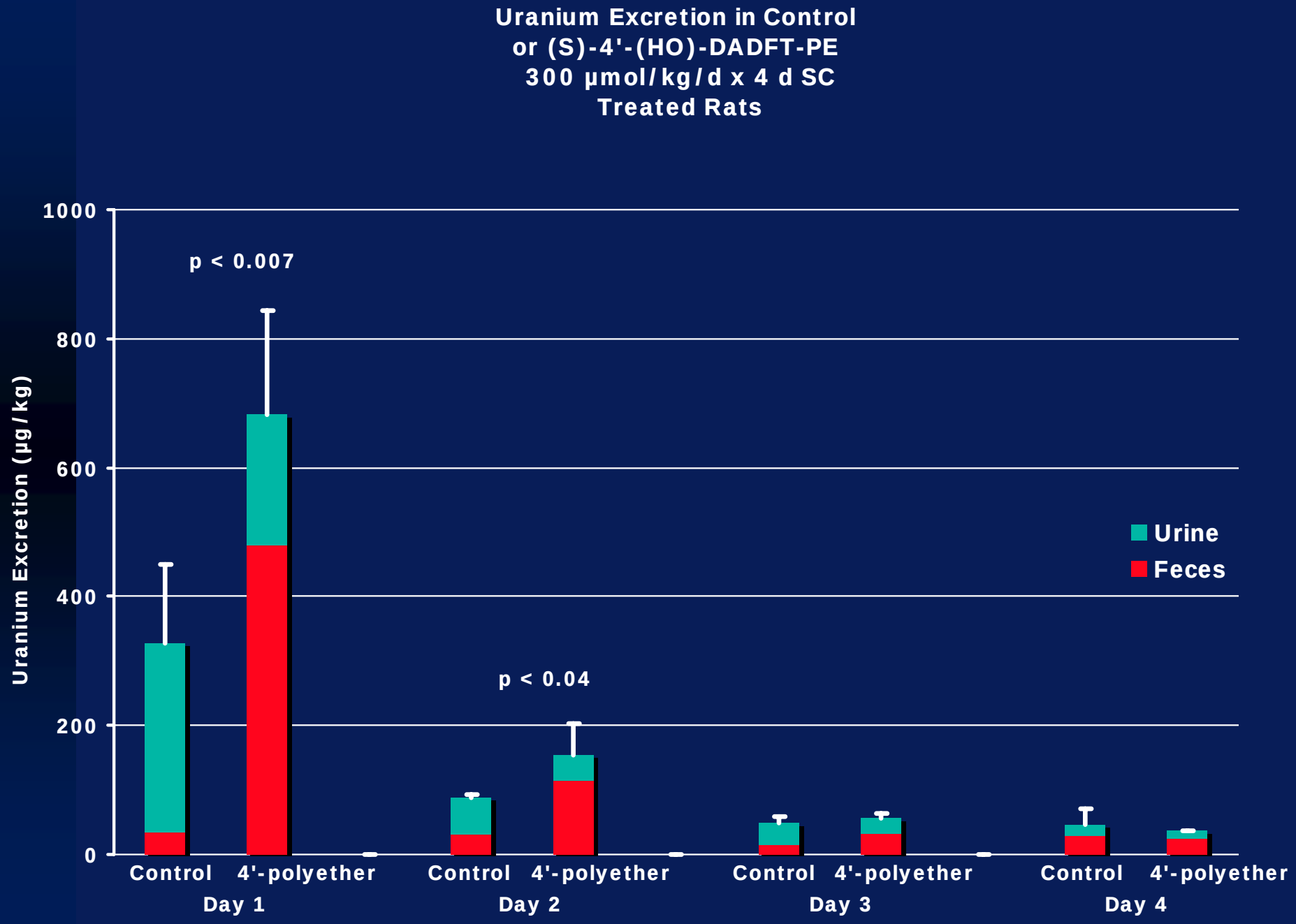


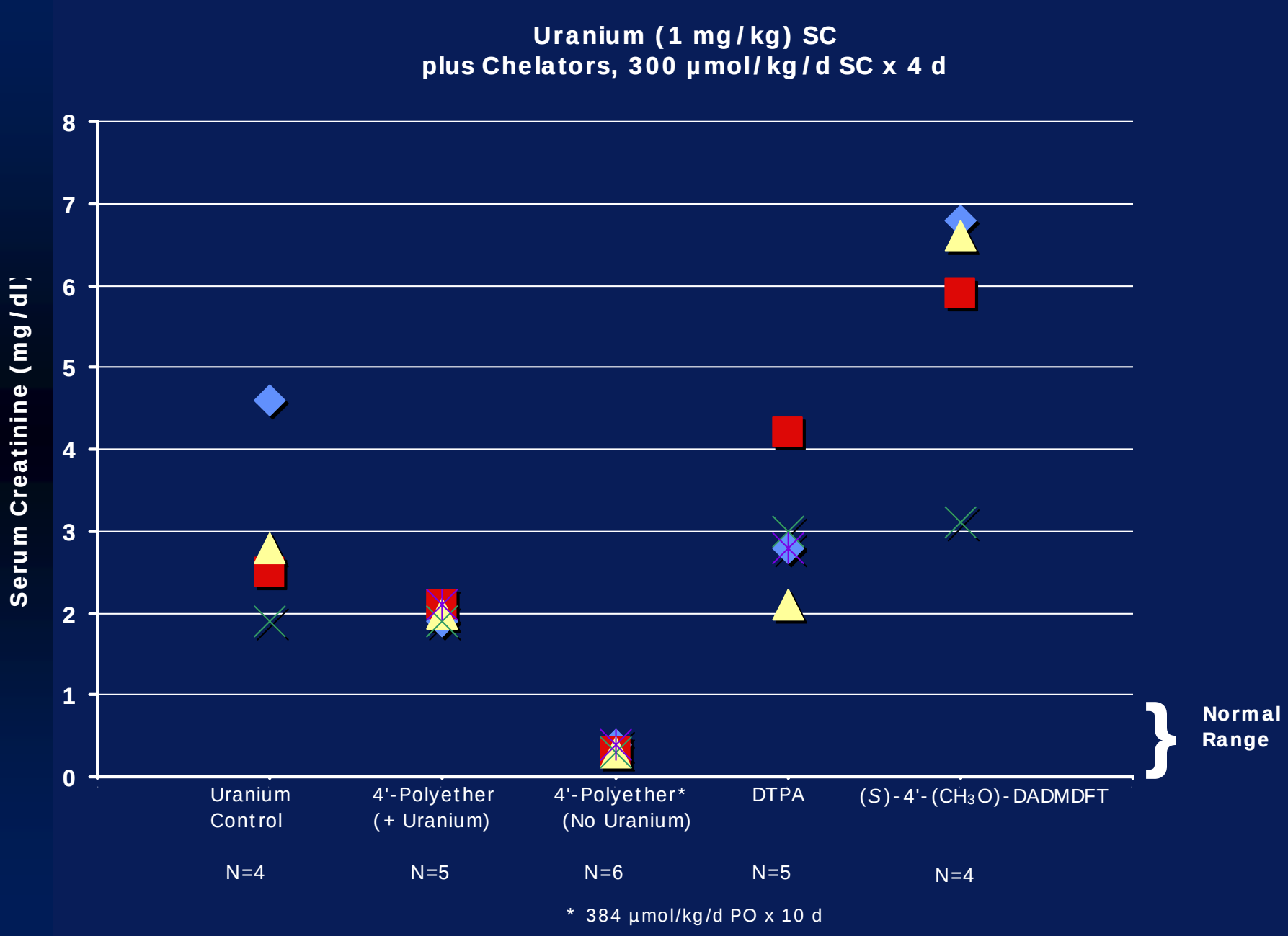
(S)-4'-(HO)-DADFT-PE
300 µmol/kg/d SC x 4 d

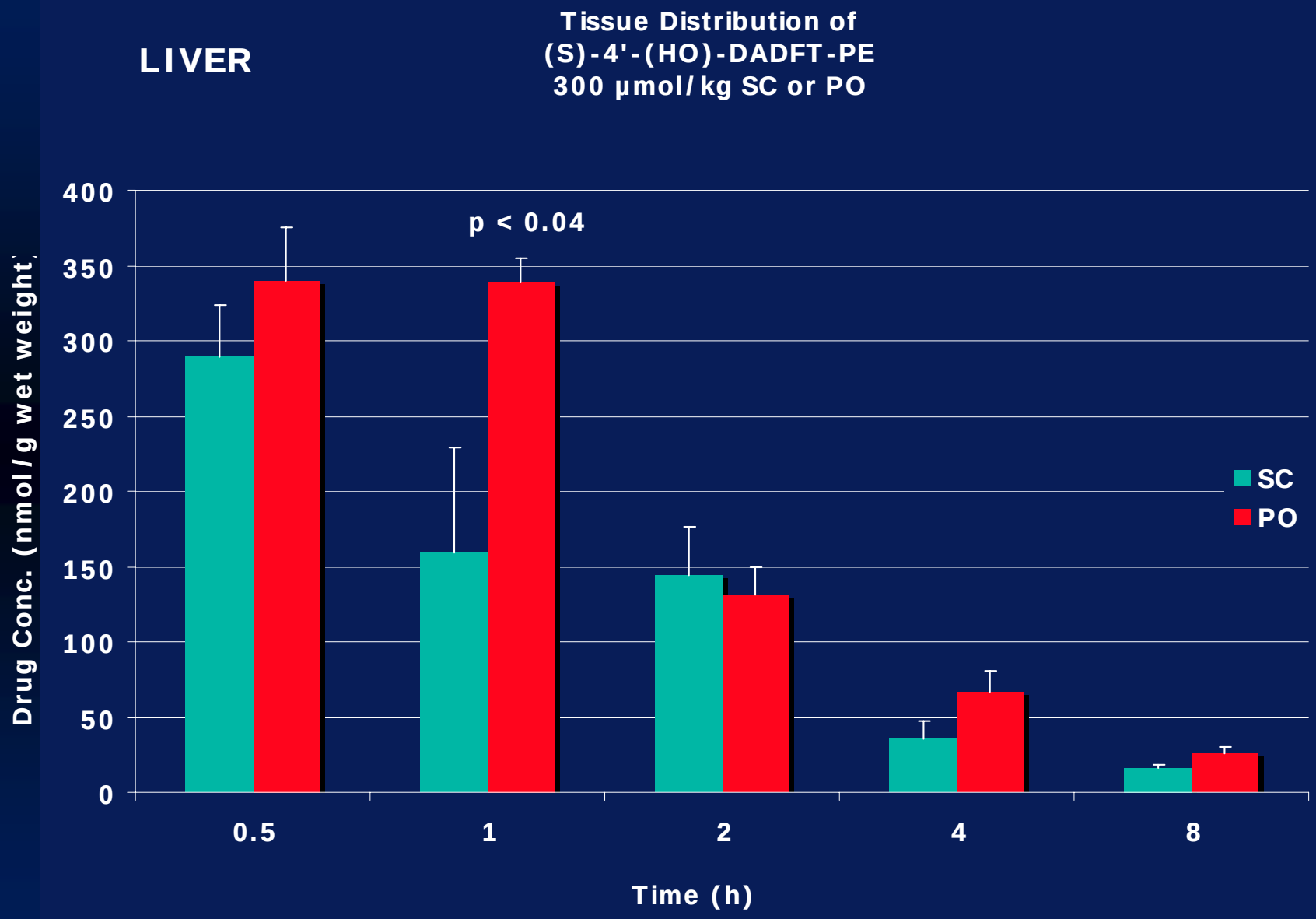


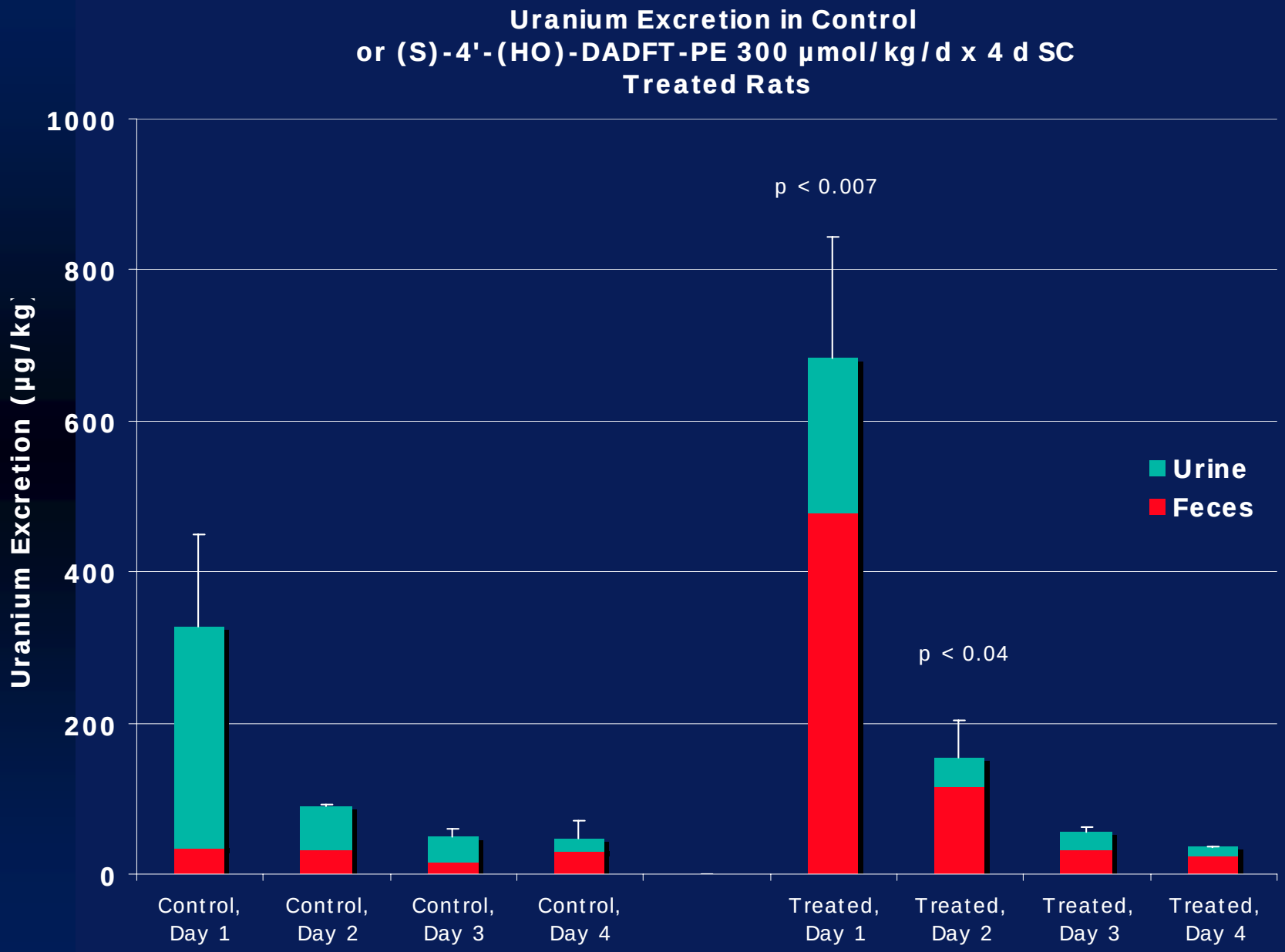
	Kidney	Spleen	Lung	Bone	Liver
Control	30.85	0.188	0.090	2.37	0.16
Chelator	11.77	0.079	0.032	1.58	0.13

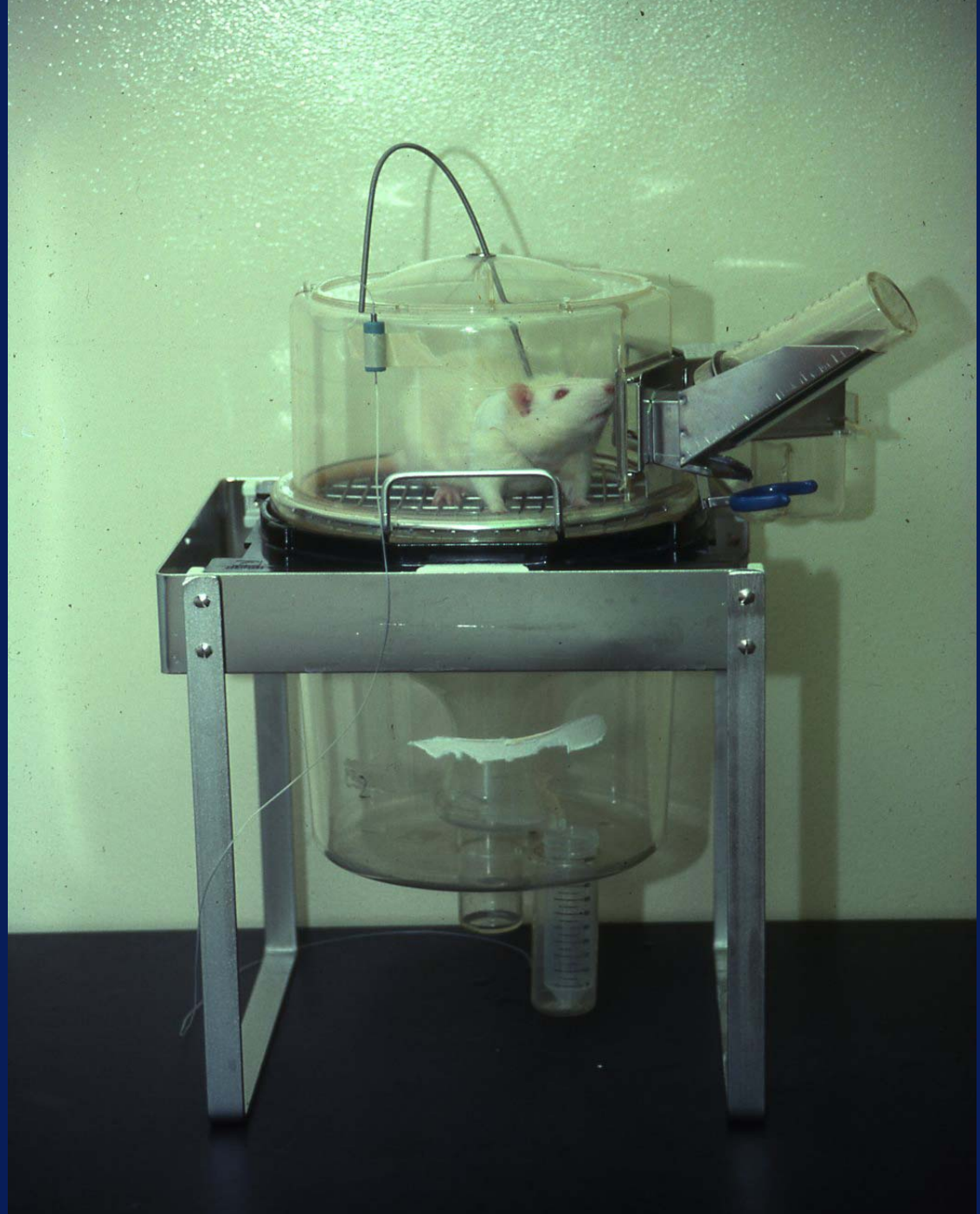

Uranium Excretion in Control
or DTPA 300 µmol/kg/d x 4 d SC
Treated Rats
Uranium Excretion (µg/kg
1000
800
600
400
200
0
Urine
Feces
Control
DTPA
Day 1
Control
DTPA
Day 2
Control
DTPA
Day 3
Control
DTPA
Day 4

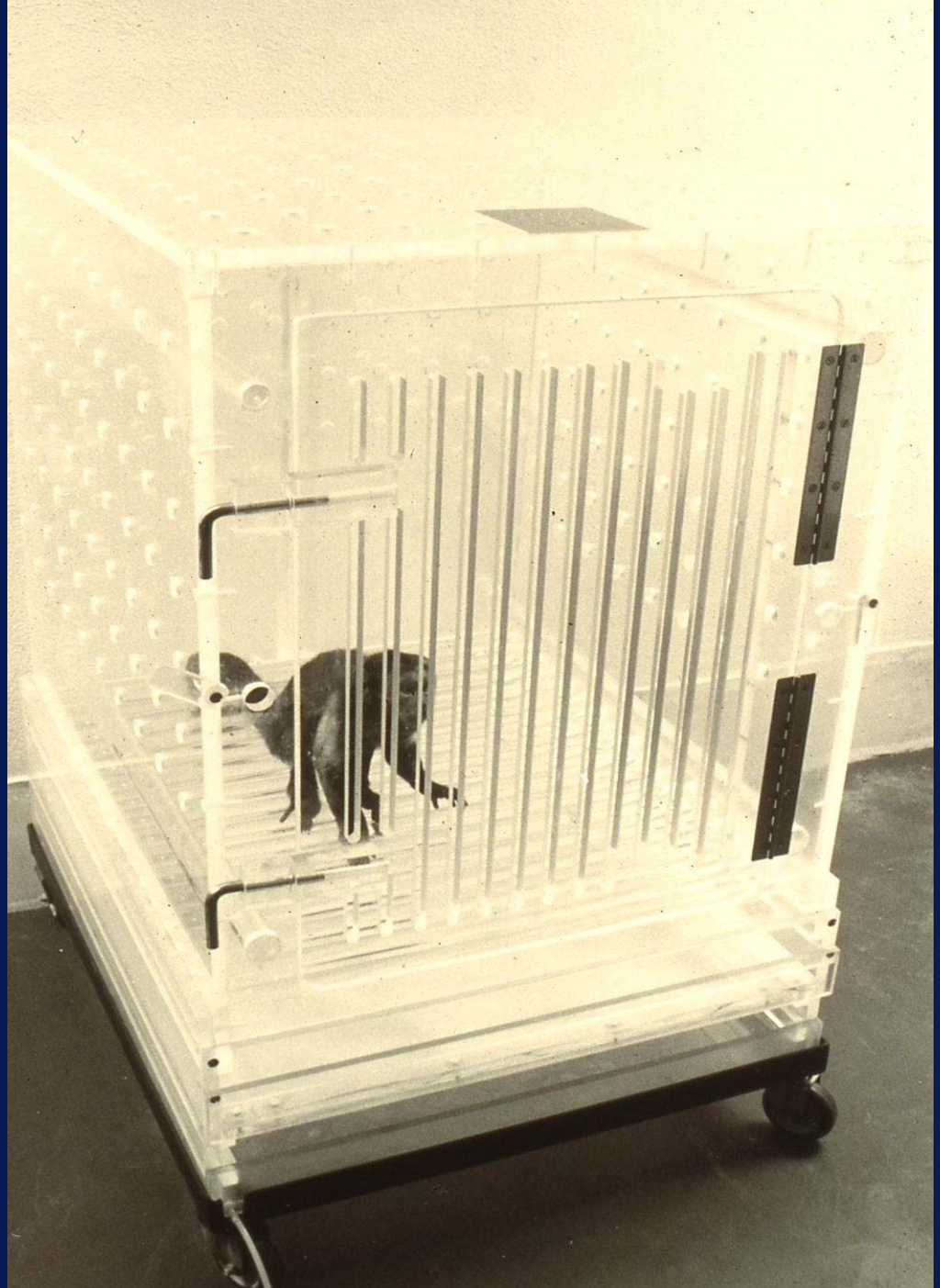

Uranium Excretion in Control
or (S)-4'-(HO)-DADFT-PE
300 µmol/kg/d x 4 d SC
Treated Rats
Uranium Excretion (µg/kg)
1000
800
600
400
200
0
p < 0.007
p < 0.04
Urine
Feces
Control
4'-polyether
Day 1
Day 2
Day 3
Day 4


Uranium (1 mg/kg) SC
plus Chelators, 300 µmol/kg/d SC x 4 d
Serum Creatinine (mg/dl)
8
7
6
5
4
3
2
1
0
Normal Range
Uranium Control
4'-Polyether (+ Uranium)
4'-Polyether* (No Uranium)
DTPA
(S)-4'-(CH3O)-DADMDFT
N=4
N=5
N=6
N=5
N=4
* 384 µmol/kg/d PO x 10 d

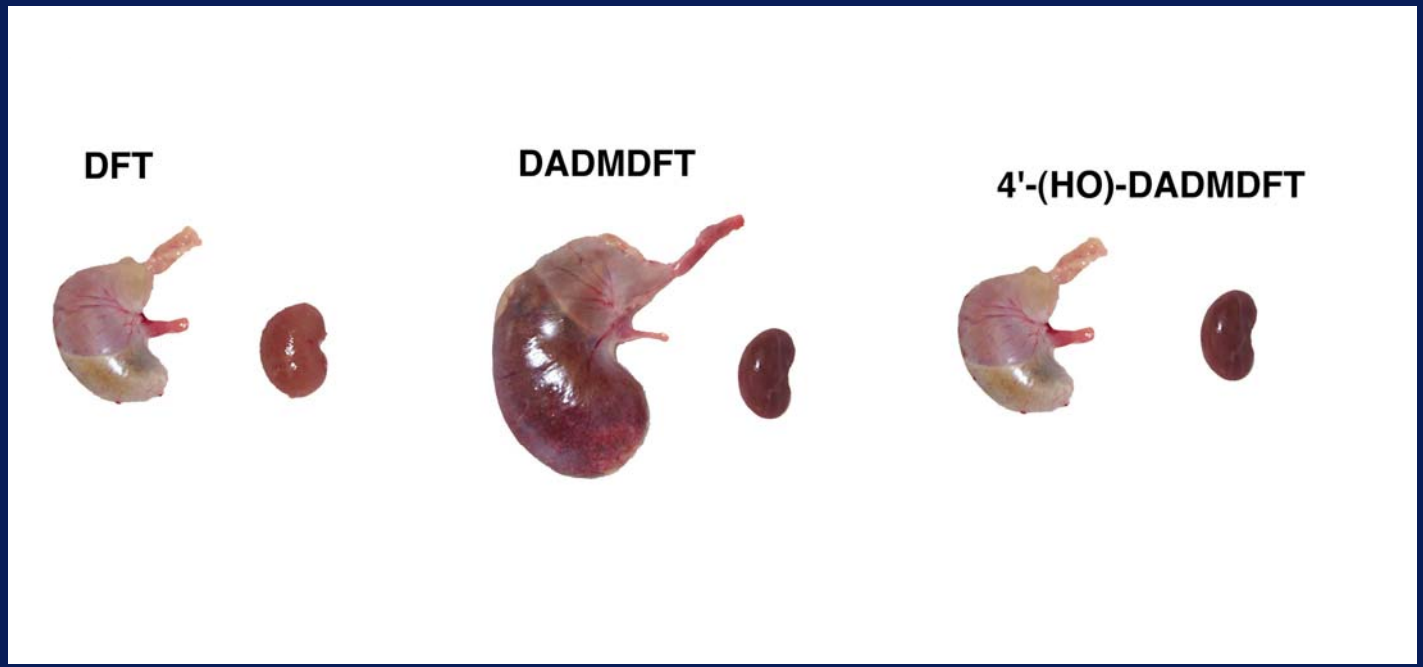

LIVER
Tissue Distribution of
(S)-4'-(HO)-DADFT-PE
300 µmol/kg SC or PO
p < 0.04
Drug Conc. (nmol/g wet weight)
400
350
300
250
200
150
100
50
0
0.5
1
2
4
8
Time (h)
SC
PO


Uranium Excretion in Control
or (S)-4'-(HO)-DADFT-PE 300 µmol/kg/d x 4 d SC
Treated Rats
Uranium Excretion (µg/kg)
1000
800
600
400
200
0
p < 0.007
p < 0.04
Urine
Feces
Control, Day 1
Control, Day 2
Control, Day 3
Control, Day 4
Treated, Day 1
Treated, Day 2
Treated, Day 3
Treated, Day 4



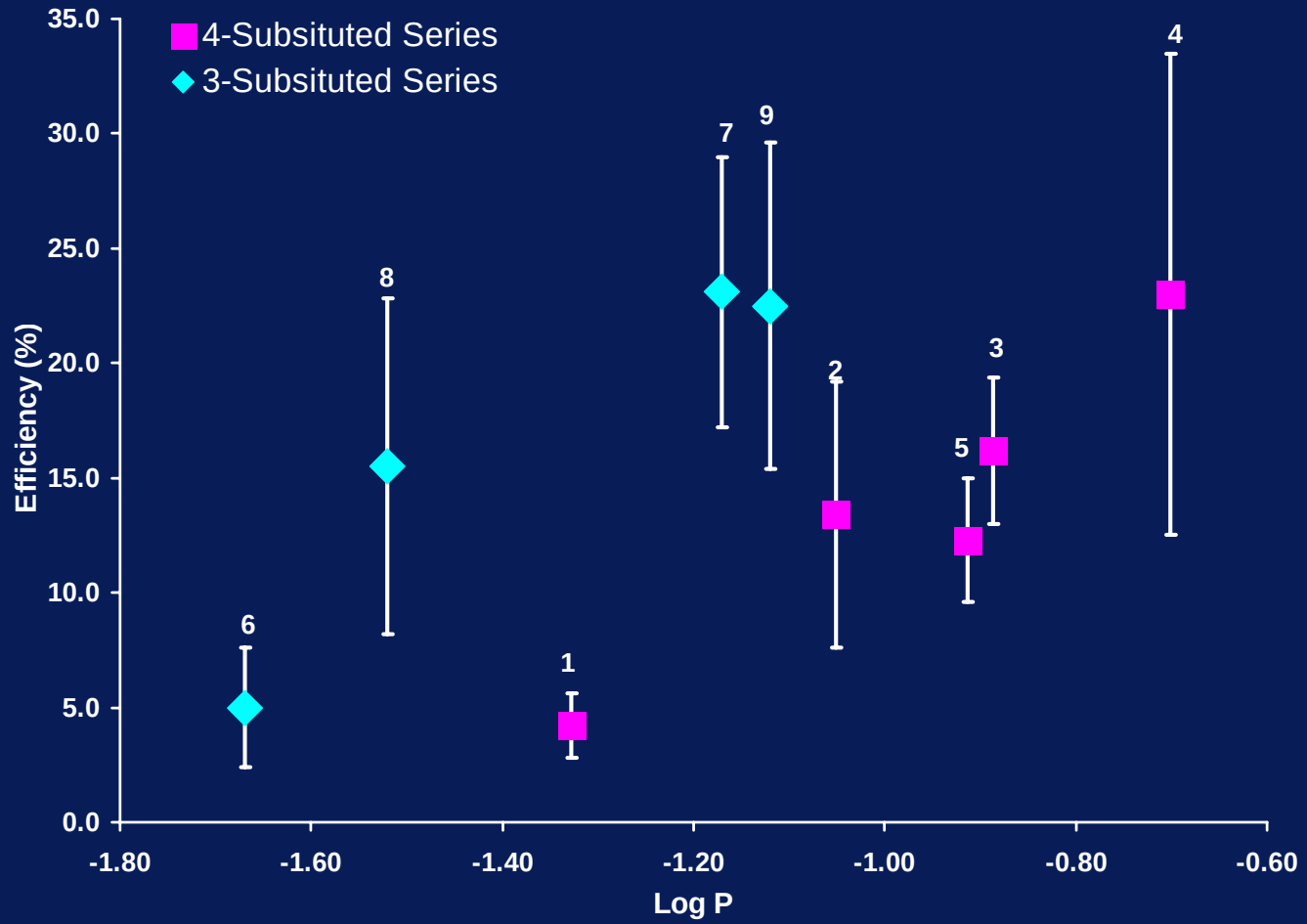


Addition of Electron-Donating Groups - Effect on Toxicity



Stomachs and kidneys of rats treated with **DFT** (left), **DADMDFT** (center), **4'-(HO)-DADMDFT** (right)

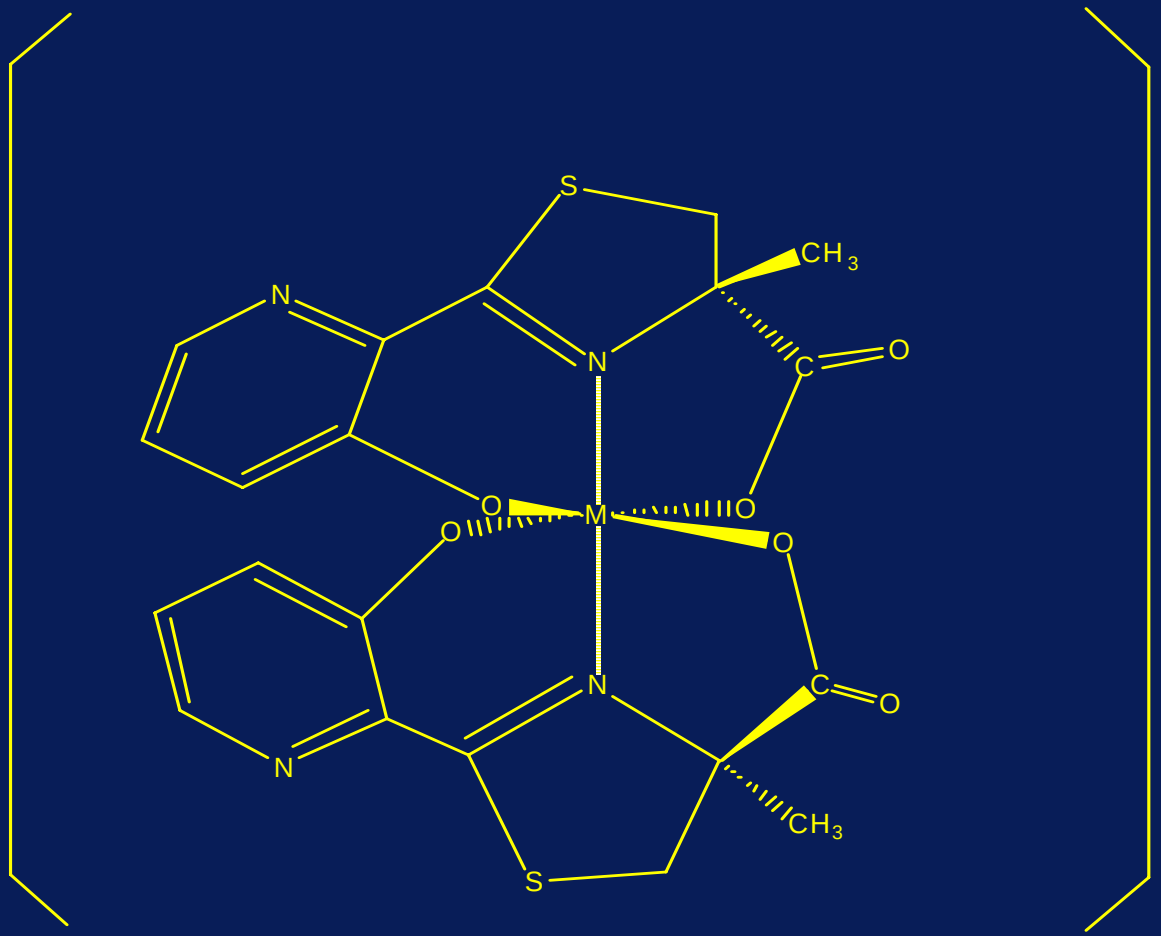
Fecal iron clearance vs the partition coefficients (log *P*) of the compounds



$$E_{C_{Fe}} = \frac{\left(\Sigma\, C_{Fe} L - \Sigma\, C_{Fe} \right)}{TCL} \times 100$$

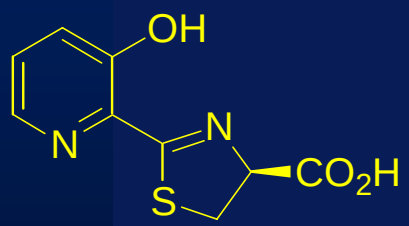
Ferrithiocin Complex

– Me_4N^+



(implied from Cr complex)

K. Raymond, et al J. Am.Chem. Soc. 1990, 112,1854



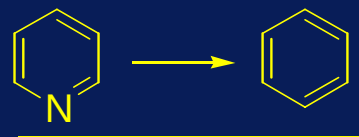
DMDFT

Rat: 2.4 ± 0.6 (po)
[82 bile, 18 urine]
Monkey (150 μmol/kg):
4.8 ± 2.7 (po)
[48 stool, 52 urine]
(300 μmol/kg):
8.0 ± 2.5 (po)
[42 stool, 58 urine]

-CH_3

DFT

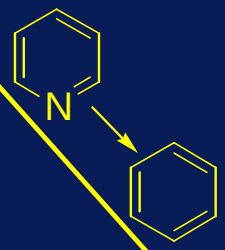
Rat: 5.5 ± 3.2 (po)
[93 bile, 7 urine]
Monkey (150 μmol/kg):
16.1 ± 8.5 (po)
[78 stool, 22 urine]



DADFT

Rat: 2.7 ± 0.5 (po)
[100 bile, 0 urine]
3.2 ± 1.8 (sc)
[98 bile, 2 urine]
Monkey (75 μmol/kg):
21.5 ± 12 (po)
[76 stool, 24 urine]
(300 μmol/kg)
13.1 ± 4.0 (po)
[86 stool, 14 urine]

-CH_3



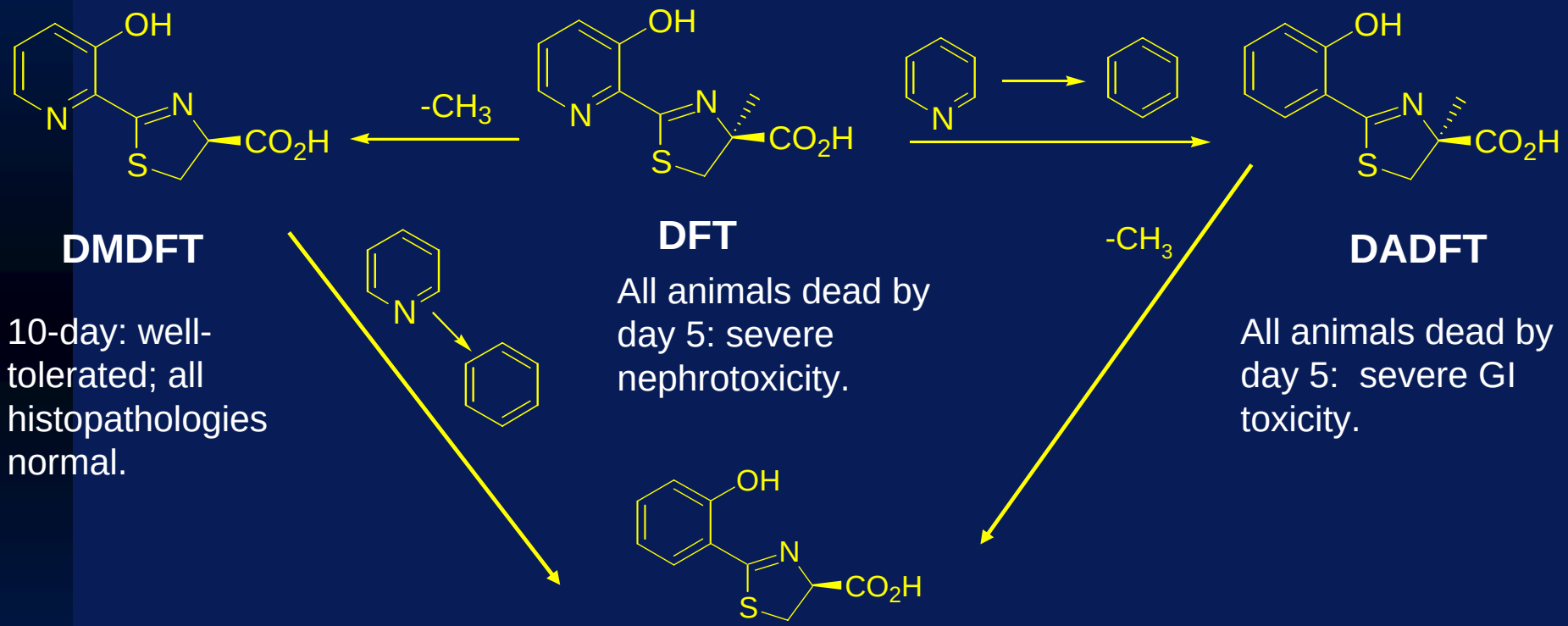
DADMDFT

Rat: 1.4 ± 0.6 (po)
[100 bile, 0 urine]
Monkey (300 μmol/kg):
12.4 ± 7.6 (po)
[90 stool, 10 urine]

Figure 35. SARs of the DFTs and Iron Clearing Efficiency.

The dose of DFT or analogue in the rats is 150 μmol/kg; the dose in the monkeys is as shown in parentheses for each ligand. The mode of administration is shown in parentheses next to the efficiency (%, ± standard deviation). The fraction of iron excreted in the bile or stool and urine is shown in brackets.

Figure 36. Structure–Activity Relationship of the DFTs and Toxicity



DMDFT

10-day: well-tolerated; all histopathologies normal.

DFT

All animals dead by day 5: severe nephrotoxicity.

DADFT

All animals dead by day 5: severe GI toxicity.

DADMDFT

All animals dead by day 6: severe GI toxicity.

The ligands were administered to rats at a dose of 384 μmol/kg/day, equivalent to 100 mg/kg/day of the sodium salt of DFT.

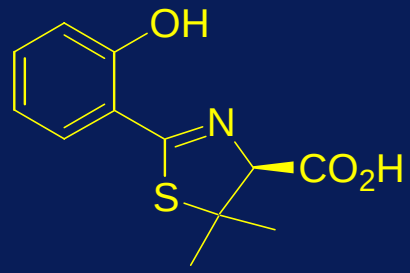
Addition of Electron-Donating Groups - Effect on Toxicity

DADMDFT

Rats: All animals dead by day 6: severe GI toxicity.

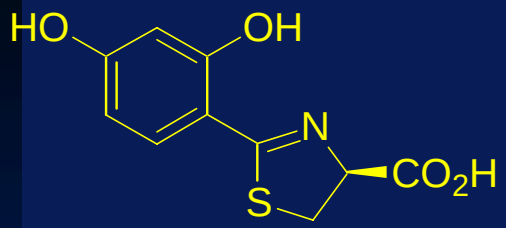
DADFT

Rats: All animals dead by day 5: severe GI toxicity.



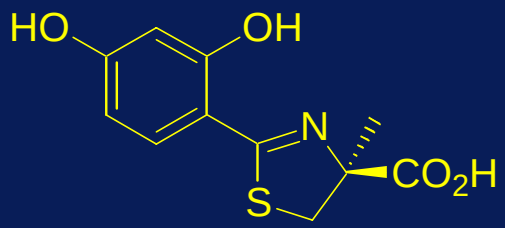
DM

Rats: All animals dead by day 6: severe GI toxicity.



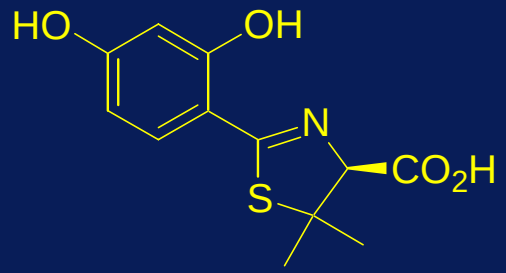
4'-(HO)-DADMDFT

Rats: 10-day: Well-tolerated; all histopathologies normal.
30-day: Well-tolerated; all histopathologies normal.



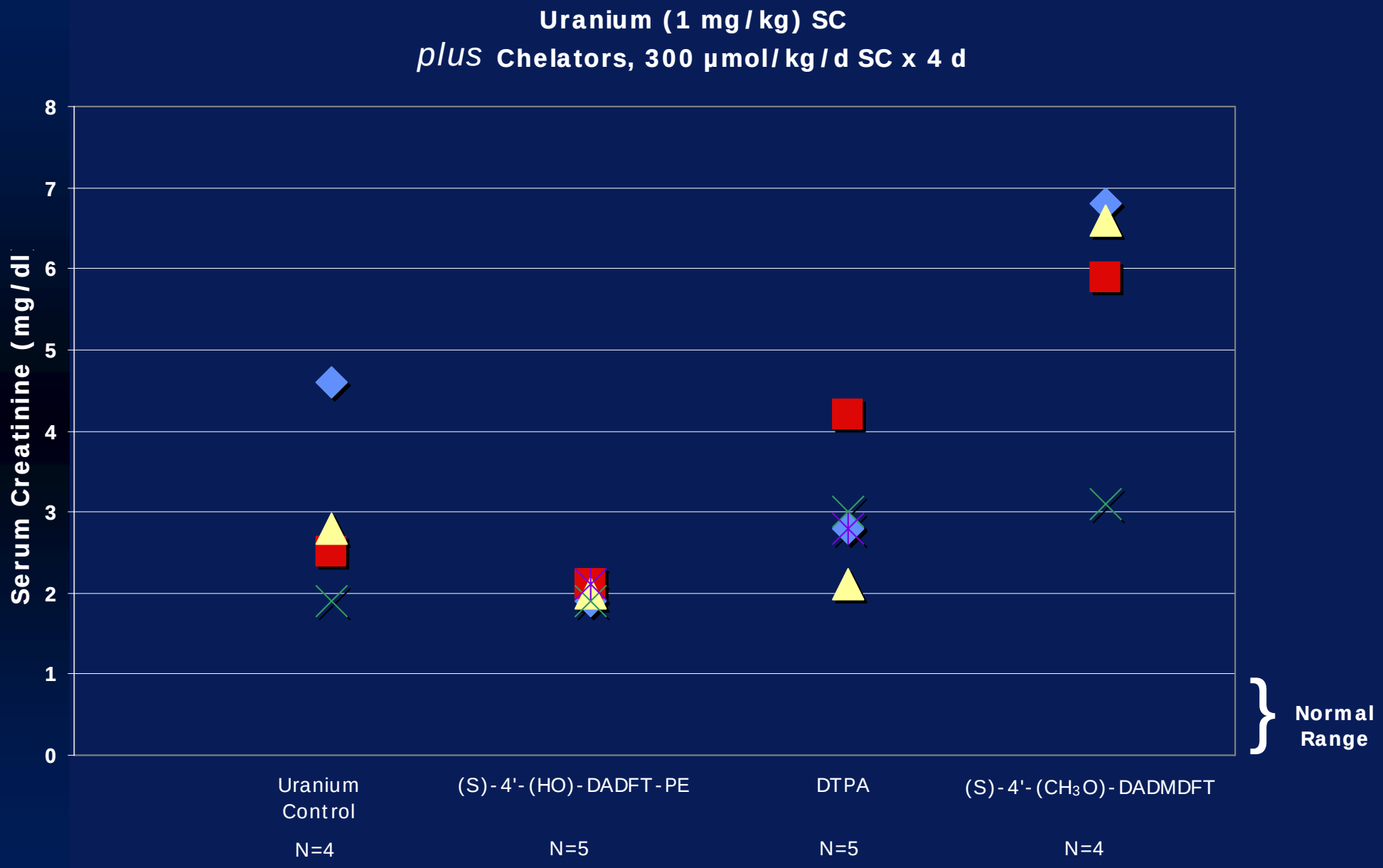
4'-(HO)-DADFT

Rats: 10-day: Well-tolerated. Histopathologies normal except for mild nephrotoxicity.
30-day: Well-tolerated; all histopathologies normal.

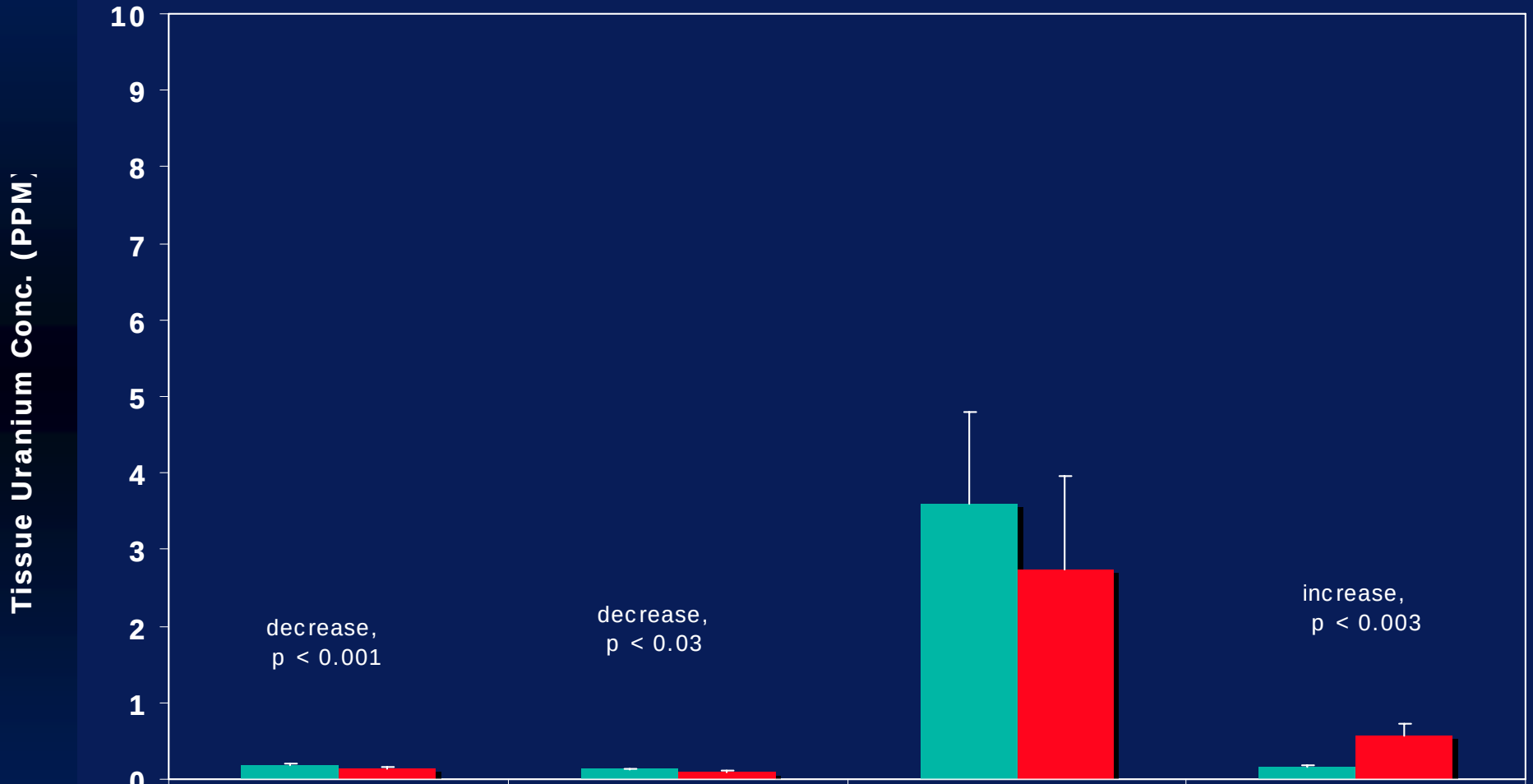


4'-(HO)-DM

Rats: 10-day: Well-tolerated. Histopathologies normal except for mild nephrotoxicity
30-day: Well-tolerated; all histopathologies normal.


Uranium (1 mg/kg) SC
plus Chelators, 300 µmol/kg/d SC x 4 d
Serum Creatinine (mg/dl)
8
7
6
5
4
3
2
1
0
Normal Range
Uranium Control
N=4
(S)-4'-(HO)-DADFT-PE
N=5
DTPA
N=5
(S)-4'-(CH3O)-DADMDFT
N=4

(S)-4'-(HO)-DADFT-PE
300 µmol/kg PO



	Spleen	Lung	Bone	Liver
Control	0.1908	0.1272	3.602	0.157
Treated	0.132	0.1	2.736	0.556


(S)-4'-(HO)-DADFT-PE
300 µmol/kg PO
Spleen Uranium Conc. (PPM)
0.25
0.20
0.15
0.10
0.05
0.00
p < 0.001
Control
N=5
4'-Polyether
N=5