
From: Travis Kim GBJH
Sent: Monday, May 23, 2011 8:47 PM
To: Sullivan Jonathan Dale CHBS
Subject: Slides for Wednesday morning
Attachments: Windsor kinetic slides Wed am May 2011.pptx

CONFIDENTIAL AND PRIVILEGED COMMUNICATION

Please can you review these slides for me,

Thanks,

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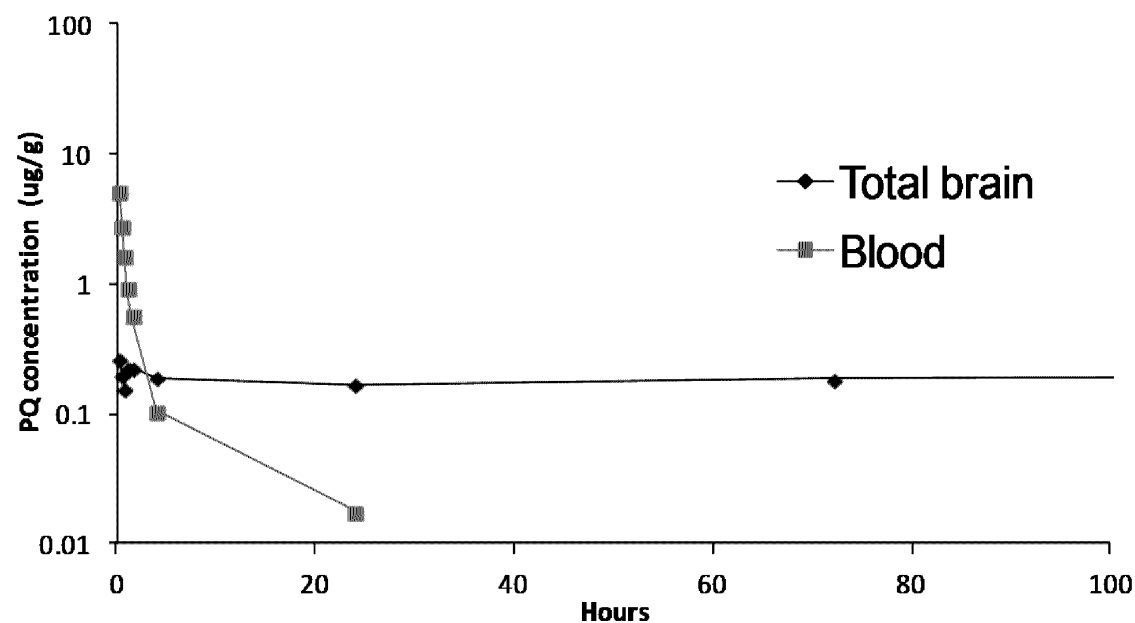
Predictive Modelling Network

Paraquat brain kinetics

(For Wednesday 25th morning)

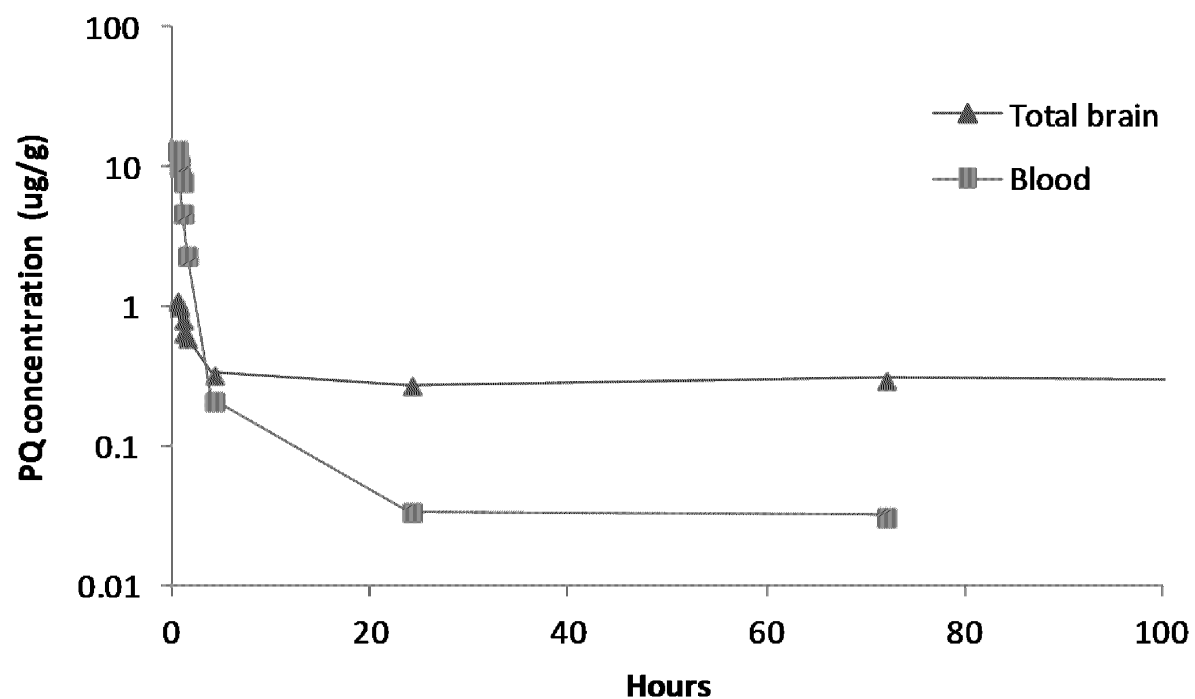
Brain and blood kinetics in the C₅₇Bl₆J mouse

- Single 10 mg/kg i.p. dose



Brain and blood kinetics in the rat

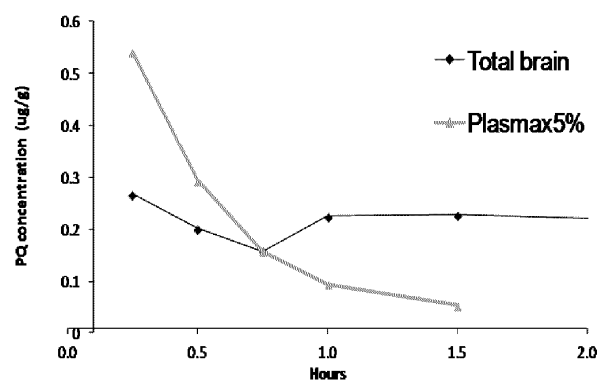
- Single 10 mg/kg i.p. dose



Kinetics in the first 90 minutes after dosing

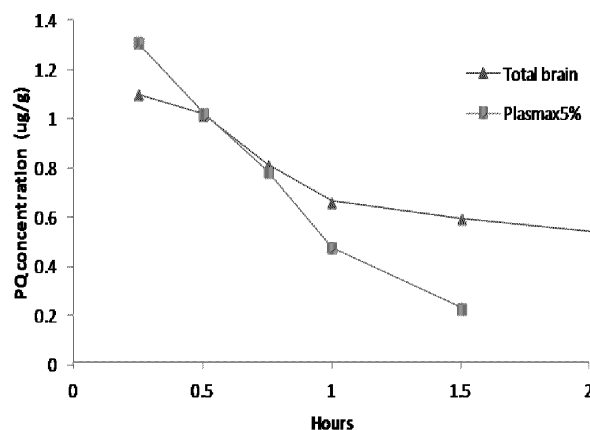
Mouse ip

(Syngenta data)



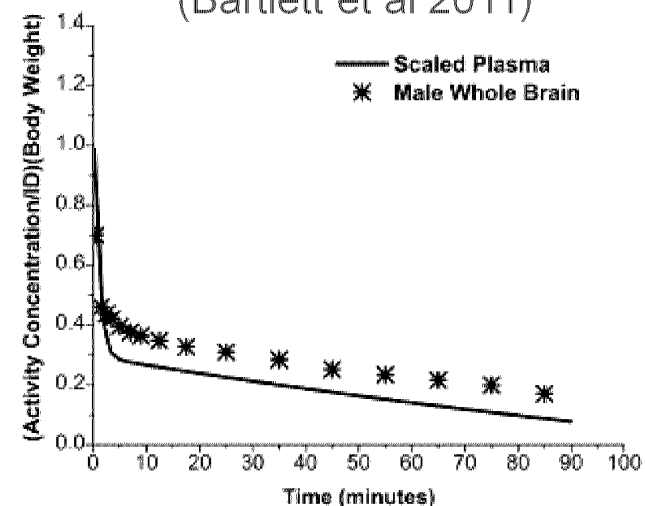
Rat ip

(Syngenta data)



NHP iv

(Bartlett et al 2011)



Species comparison summary

Animal	Mouse	Rat	Rhesus	Squirrel monkey
Route	ip	ip	iv	sc
Plasma PQ C _{max} (ug/ml at 15mins per mg/kg PQCl ₂ dosed)	1.1	2.8	data exist	-
Brain PQ C _{max} (ug/g at 15mins per mg/kg PQCl ₂ dosed)	0.02	0.11	data exist	-
Brain PQ t _{max}	5 mins	15 mins	1 min	-
Brain PQ C _{24hrs} (ug/g per mg/kg PQCl ₂ dosed)	0.02	0.03	-	0.02 (at +2 weeks)
Terminal t _{1/2}	21d	28d	-	>>6wks
Range of dose linearity (mg PQCl ₂ /kg)	1x1 to 3x15 mg/kg	1x1 to 3x10 mg/kg	1x0.0001-0.0004 mg/kg	6x2.5 mg/kg
Lowest lethal dose for this route	1x25 mg/kg	3x10 mg/kg	10 mg/kg	3x5 mg/kg

Kinetics long after dosing

Mouse ip

(Syngenta data)

$t_{1/2}$ = 21 days

Rat ip

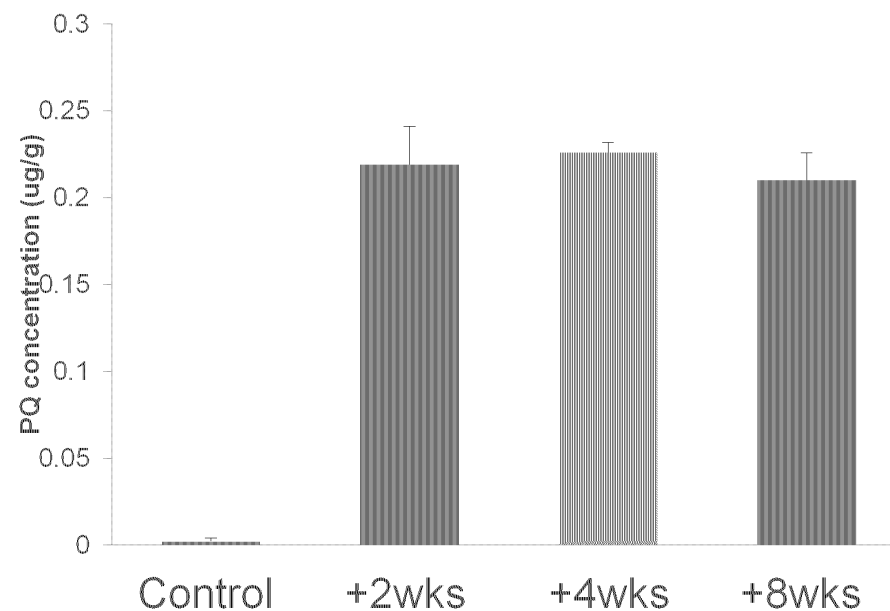
(Syngenta data)

$t_{1/2}$ = 28 days

NHP sc

(di Monte)

$t_{1/2}$ >>6 weeks



Where is the paraquat in the brain?

Mouse

Brain 2 - 3H-PQ, 24 hours
Slide 11 - brain sections 31,32



Slide 13 - brain sections 37,38



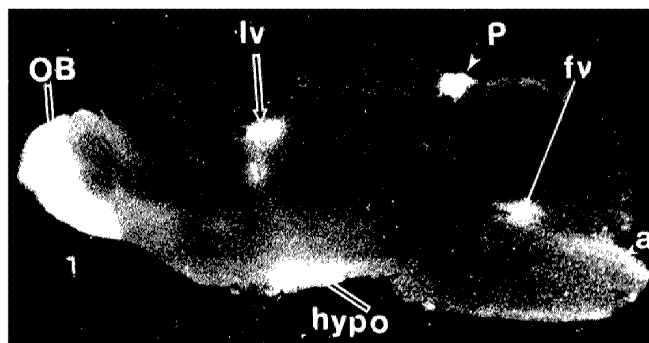
Slide 14 - brain sections 40,41



Slide 17 - brain sections 49,50



Rat



Lining of the lateral ventricles

Lining of the 4th ventricle

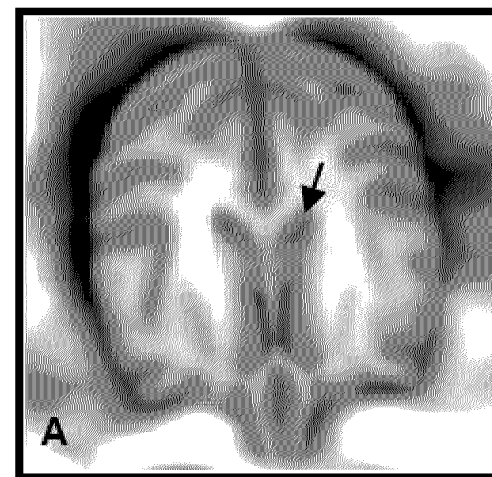
Pineal gland

Olfactory bulb

Hypothalamus

Area postrema

NHP



Posterior horns of the lateral ventricles

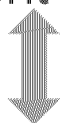
Pineal gland

Why is paraquat persistent in the brain?

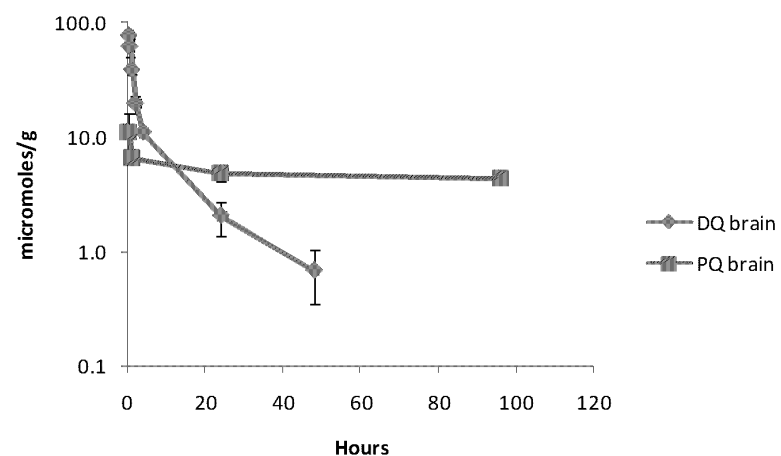
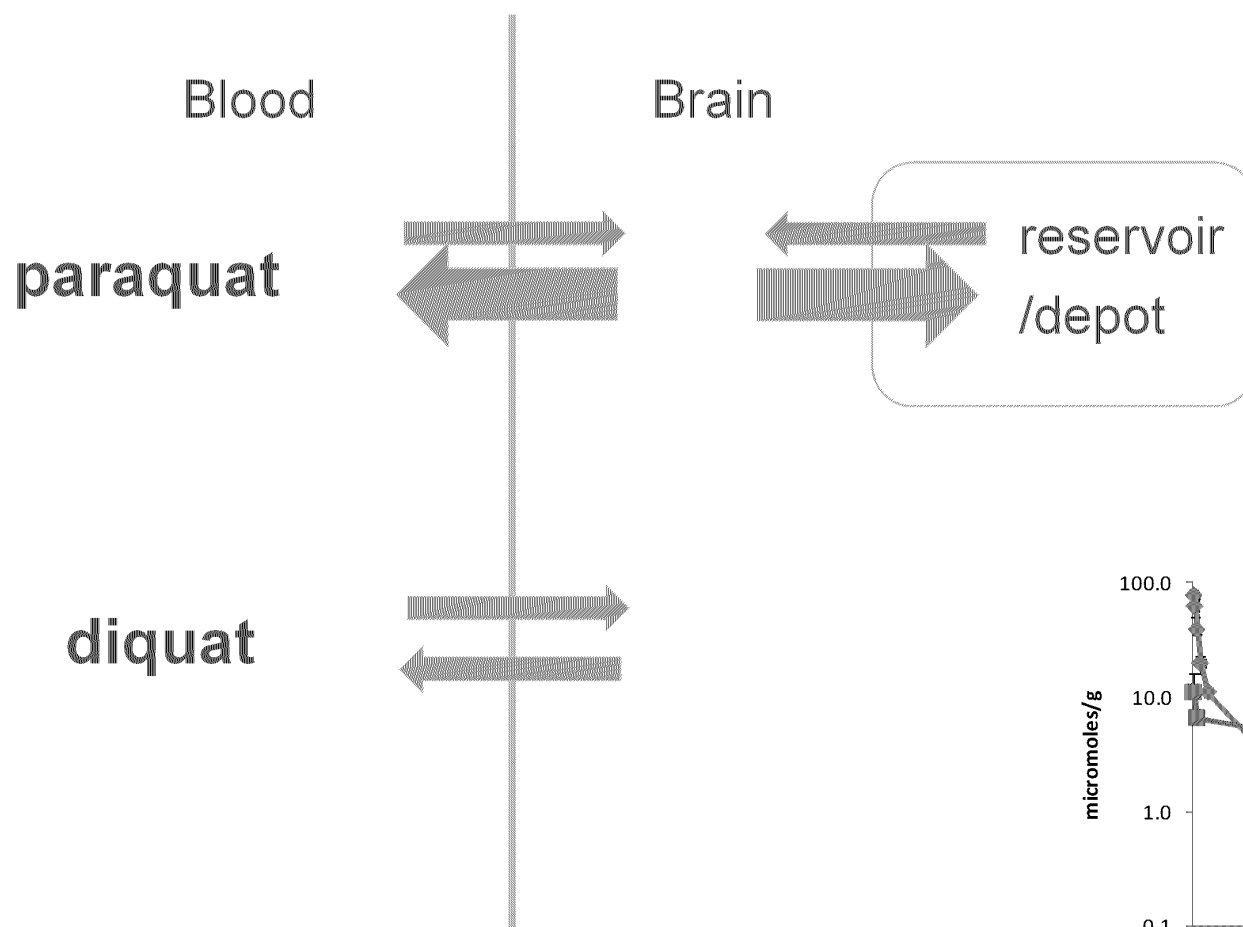
- Active transport

and/or

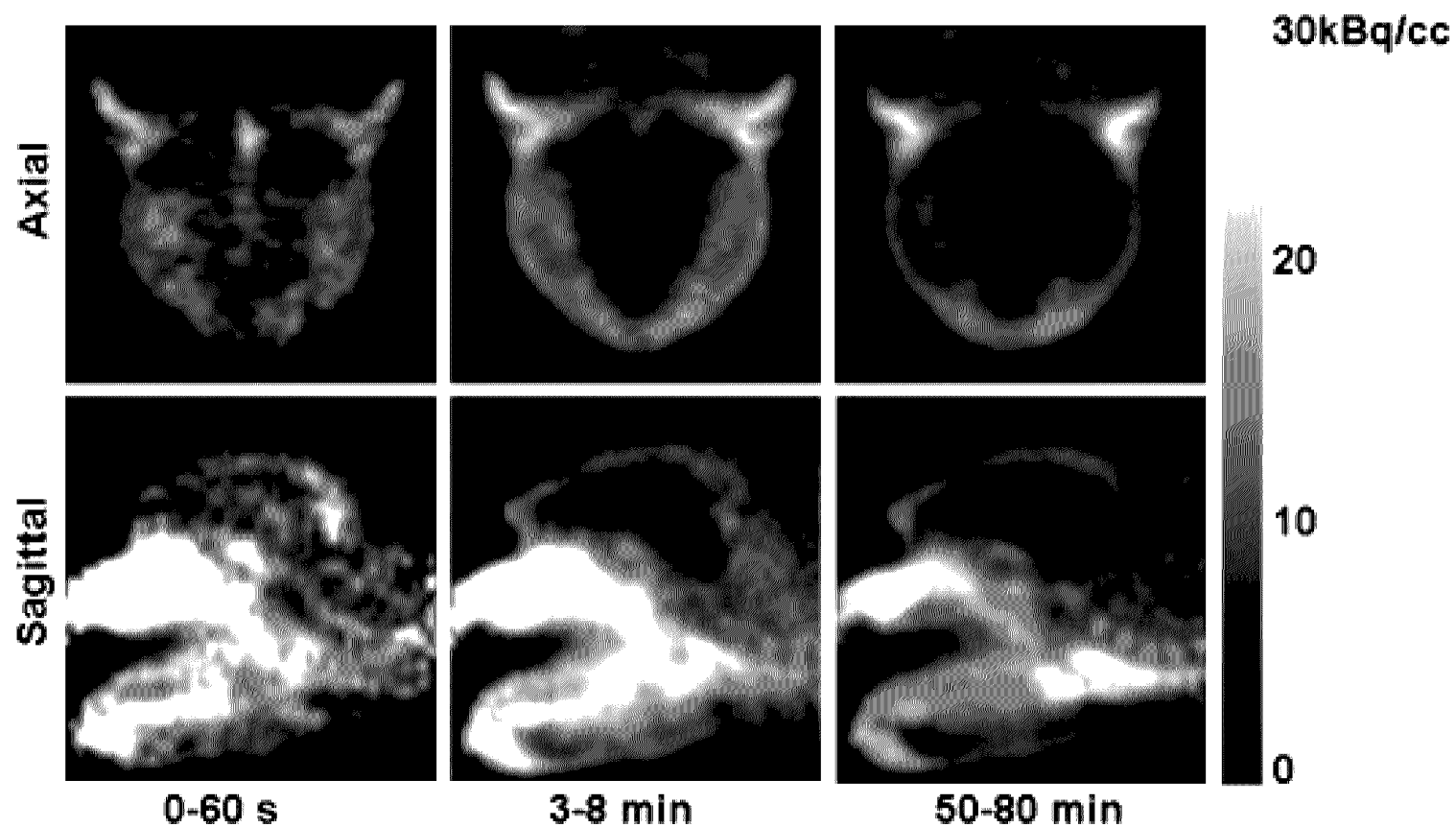
- Binding
 - Covalent binding
 - Weak ionic interaction



Potential role of active transport



Ionic binding of paraquat to cartilage



Bartlett et al. (2009)

Paraquat binding

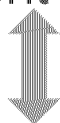
- Covalent
- Extremely strong: clay minerals and glass
- Strong: soil organic matter
- Moderate: cartilage, melanin
- Weak: DNA
- None: plasma protein

Why is paraquat persistent in the brain?

- Active transport

and/or

- Binding
 - Covalent binding
 - Weak ionic interaction



The challenges

- To understand species differences in PQ brain kinetics
- Why does paraquat persist in the brain and what state is it in?

to better understand the human situation