Scope

Differential CNS Health Effects from Exposure to Solvents and Metals

CNS Profiles of Adverse Effects Vary With:

* Short-term 8-hr acute exposures
* Sub-chronic 3-month exposures
* Chronic history of exposure
  and
* Biological Indices of exposure
* Individual genetic susceptibility

Contributions from:

Fatigue and Alcohol Team

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Toluene Research Team

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PCE Research Team

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Profiles of Occupationally Relevant Short-term Acute Exposures

- Fatigue and alcohol
- Toluene and alcohol
- Styrene
- PCE

The Lesson: how to detect a signal against large within and across subject variability in scores

Fatigue and alcohol: The Psychological Moment Hypothesis

The Score measures the width of Stroud's (1957) "psychological moment". One moment = (1/Hz) is normally a fraction of a second (15 msecs -125 msecs). The width of a moment is correlated with one's ability to perceive discrete events. The smaller the width the more events one perceives across moments.

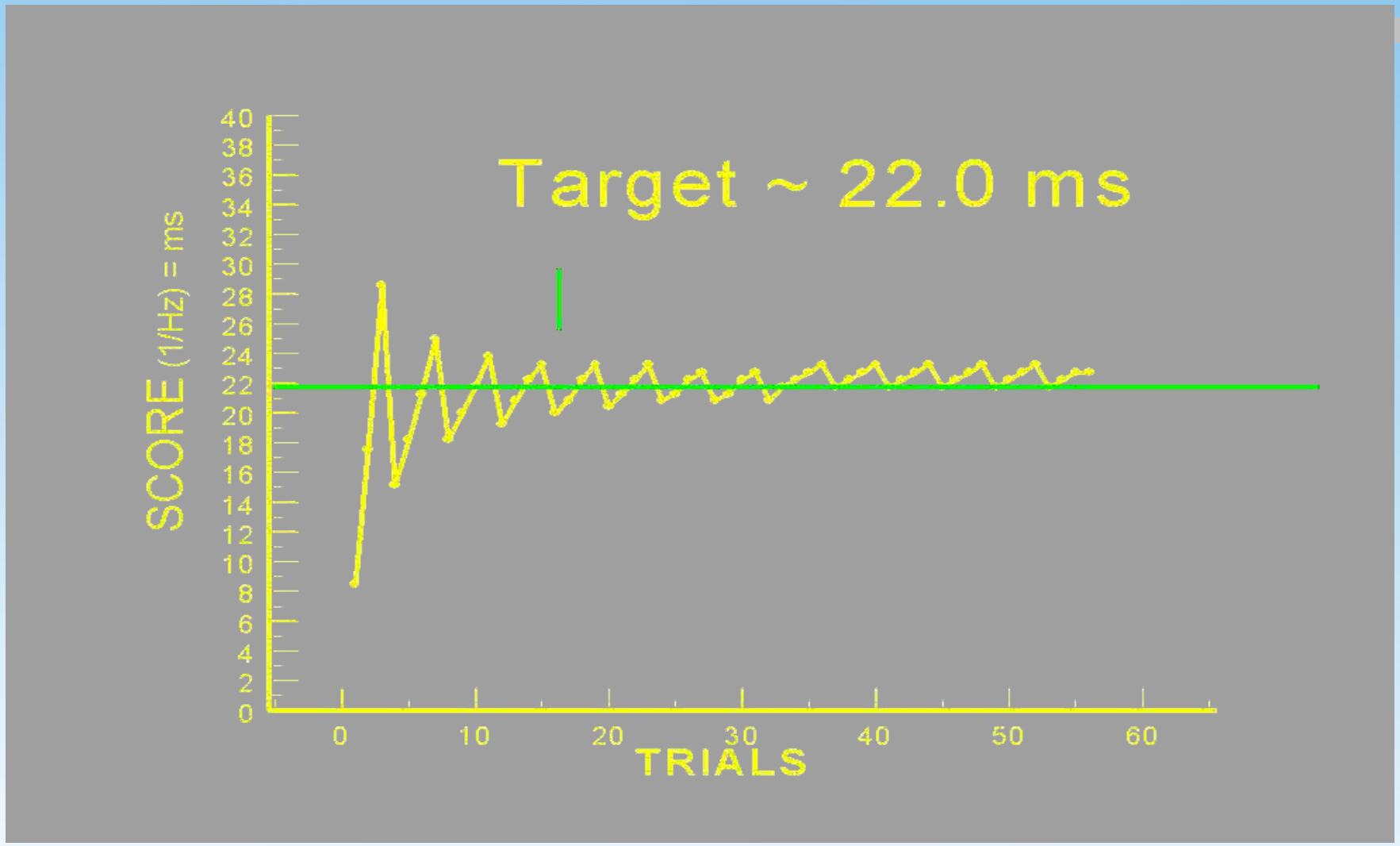
Stroud assumed one reference period corresponding to one central pacemaker to which other periods are harmonically related for a detection task -- behavioral resources are moment dependent.

We hypothesize that the **SCORE** will vary with

- ❑ Diurnal Variation
- ❑ Alcohol consumption
- ❑ Fatigue

--- Conditions that alter alertness/attention

Analytic Evaluation of SCORE



-- near-IR arrays (659 nm) which are sensitivity without by persistence.

-- a forced-choice Best-PEST paradigm (d‘) that avoids method of limits subjectivity e.g., *Beta* shifts

Demonstration Study

TASK	Day1	Day2	Day3

❑ Administered Score Intermittently ~ 3X /Hr

∧

Ascending

Descending

❑ Administered ETOH

End Day 2 BAC_{max}= 0.105+

Mean Width of the Moment

Width of the Moment (msecs)			
DAY	Mean	SD	N
1	19.81	1.28	26
2	21.12	2.90	128
3	20.62	0.51	5
Total	20.89	2.70	159

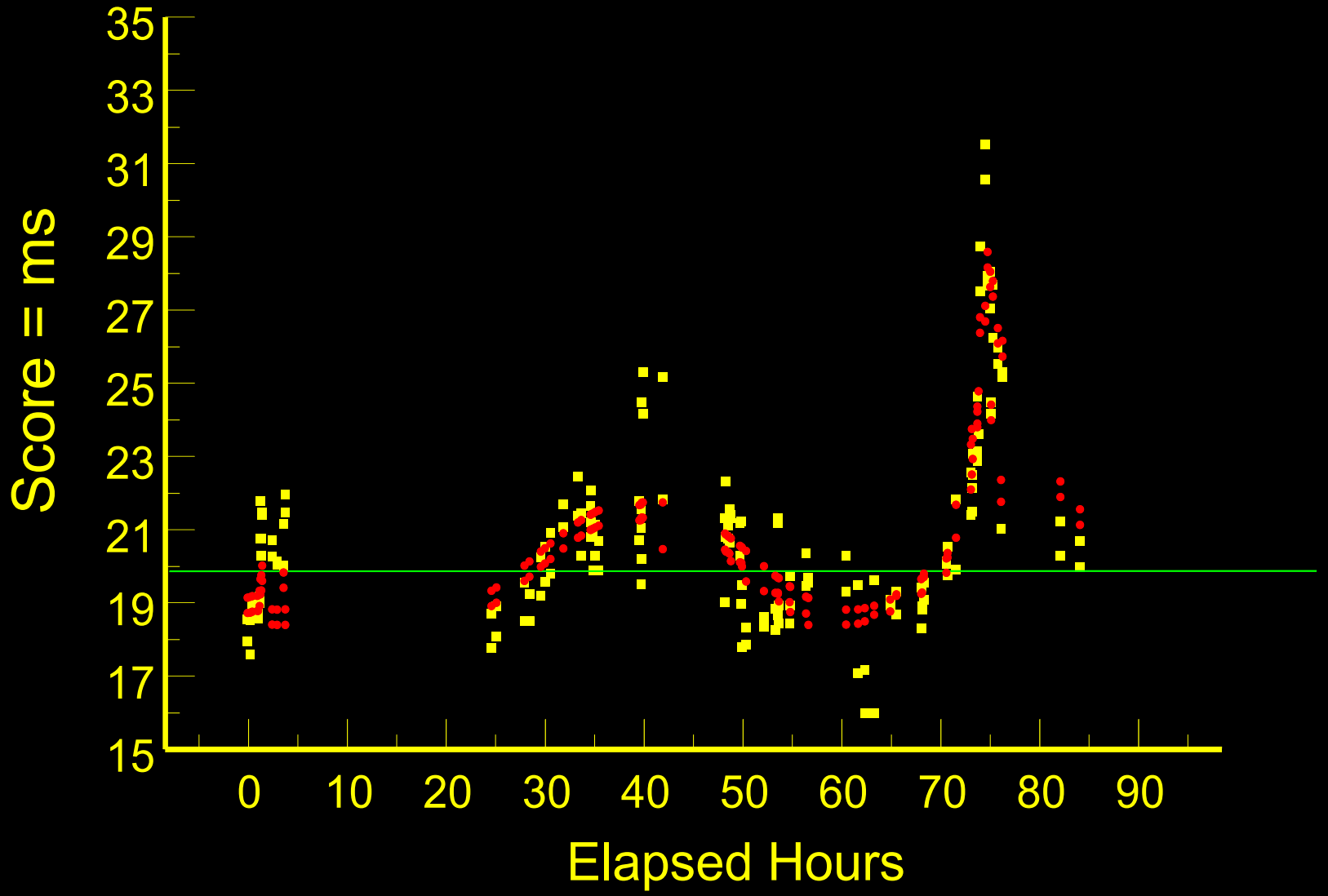
Regression Model with Interaction Between Ln BAC and Ascend/Desc. with Interaction Between Ascending and Descending Ln BAC

Model R =0.88 R Square =0.78

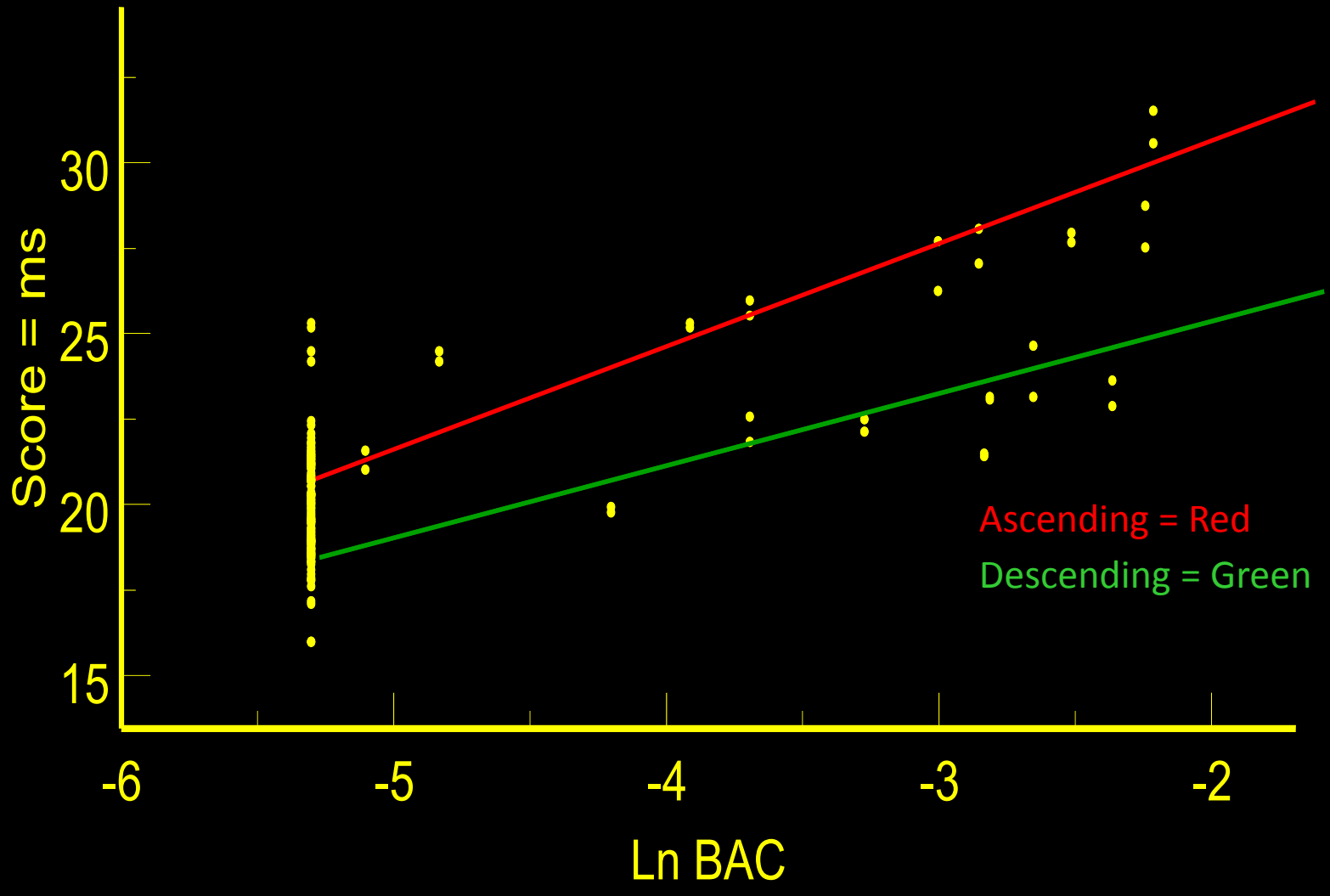
ANOVA	SS	df	Mean Sq	F	p
Regression	1318	6	220	137	4.59 E-73
Residual	372	231	1.61		
Total	1690	237			

	Beta	SE	Beta	t	P value
Ln Blood Alc	1.9	0.1	0.7	18	9.48 E-47
Ascend/Desc	3.6	0.8	0.6	4.8	3.01 E-06
Interaction	0.5	0.2	0.3	2.6	0.01
Cosine	1.4	0.1	0.4	9.9	1.68 E-19
Sin	0.3	0.1	0.1	2.7	7.74 E-03
Elapsed Hrs	-0.02	0.00	0.2	4.8	2.45 E-06
Right/Left Eye	0.1	0.1	0	1.2	0.2

Modeled Diurnal Variation Over Data Points



Correlation of LnBAC and SCORE



Results

- Predictable diurnal variation over 2.5 days
  - Partial correlation = 0.37
  - Moment diurnal range ~ 4.0 msecs (~20%)
- Profound reduction with ethanol
  - Sum of partial squared = 0.872 (Ln BAC + Ascending/Descending + Interaction)
  - Moment increased from 20.6 msecs to 32.0 msecs (~ 60%)
- Suggestion of fatigue over 2.5 days
  - Moment changed ~.02 msecs* hours in study

** If used for airport screeners one needs to obtain one daily personal baseline measure for occupational use

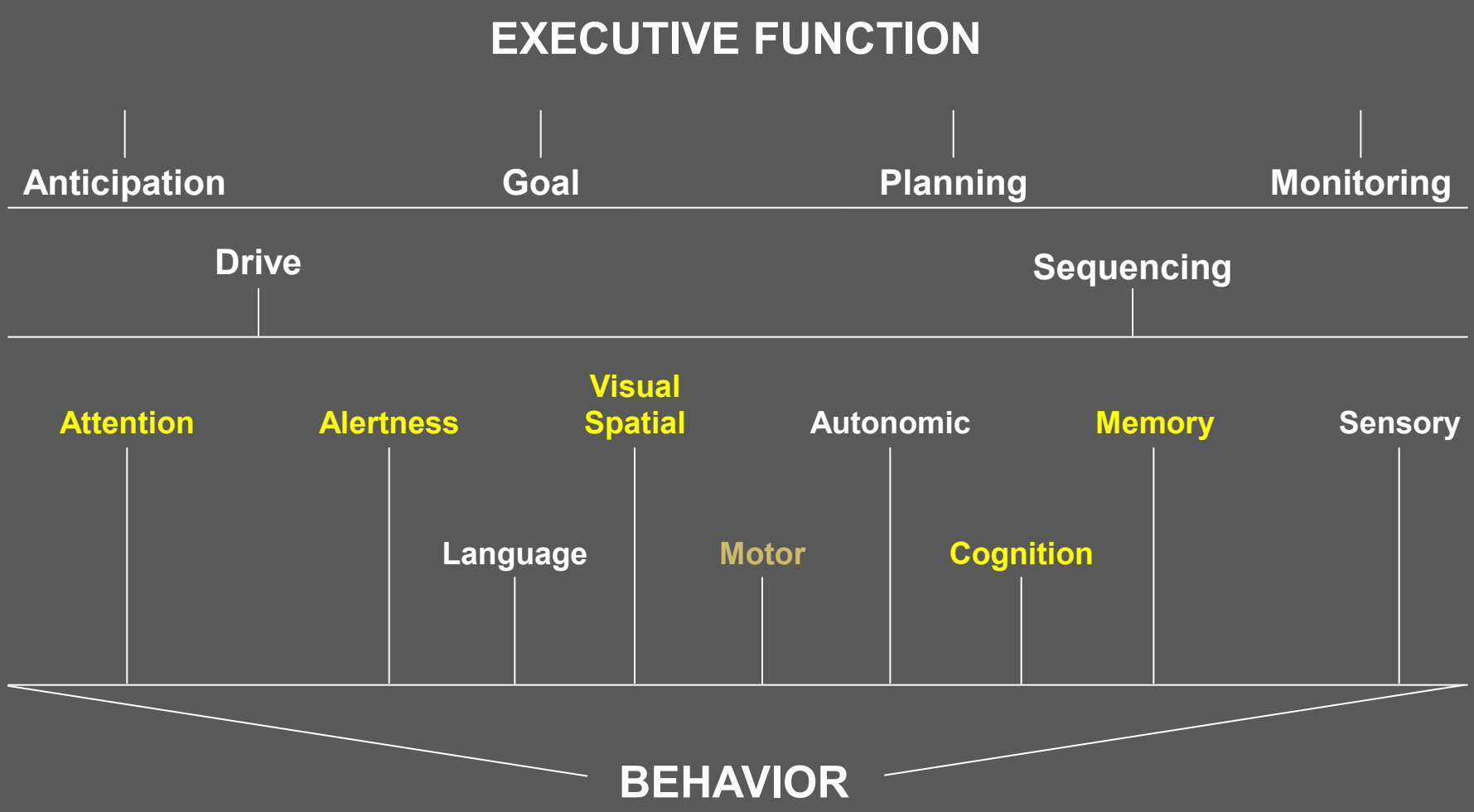
Toluene and Ethanol

Neurobehavioral hypothesis for solvents

- A frontal/limbic behavioral hypothesis is offered as the site of underlying pathology for occupationally related central nervous system effects

- We hypothesize that exposure to solvents affect the frontal system including attention, executive function, and visual spatial skills, as well as the limbic system including short term memory and mood, leaving motor and language skills such as long term memory in tact.

FRONTAL SYSTEM FUNCTIONS



Non-routine or novel situations provide conscious direction to process information.

– Benson & Stuss (1986)

Experimental design for am-pm behavioral scores
Toluene (ppm) or EToH dose (g/kg body weight)

	Toluene 8 Hr TWA ppm			Alcohol 20' dose		
Group	A	B	C	A	B	C
Day 1	150	75	0	0.00	0.33	0.66
Day 2	75	0	150	0.33	0.66	0.00
Day 3	0	150	75	0.66	0.00	0 33
No of subjects	14	14	14	14	14	14

The Test Order and Corresponding blood alcohol concentrations at 30, 60, 75, and 120 minutes after ingestion

Test Order	Mins	Blood Alcohol 0.33 g/ kg BW		Blood Alcohol 0.66 g/ kg BW
One Hole	0	0.00 %		0.00 %
Digit Span	12			
POMS	20			
Pattern Recognition	2	0.030 %	30'mins	0.063 %
Pattern Memory	2			
Hand-eye Coord.	2			
Symbol-digit	4			
Sternberg test	7			
Finger Tapping	4			
Reaction Time	5	0.022 %	60' mins	0.054 %
Continuous Performance	6			
Critical Tracking test	5			
		0.015 %	75' mins	0.049 %
		0.011 %	120' mins	0.039 %

Comparison of Study Populations

	Toluene		Ethanol	
	mn	sd	mn	sd
Age (mn sd)	22.6	-3.1	21.9	-3.5
Sex % males	54		50	
Education				
Graduate %	21.4		16.7	
Undergraduate %	78.6		83.3	
Vocabulary (n corr sd)	87.72	7.77	84.76	8.96
Mill Hill Synonym (N Corr)	87.72	7.77	84.76	8.96
% Correct guess of exposure or dose order:				
Exposure order	50			
Dose order by effect			78	
Dose order by taste			5	

Control data for the mean of 3 days and the mean % (am-pm) difference on the control day for 2 Tests Affected by Toluene

	Mean am	SD x	SD w/n	Mean am-pm	SDx	Mean(am-pm)	CV am	CV am-pm
Digit Span								
Toluene group	7.97	1.19	0.80	-0.45	0.76	5.66	0.15	1.69
ETOH group	8.04	1.3	0.77	-0.52	0.71	6.46	0.16	1.36
Pattern Recog (Lat) msecs								
Toluene group	2.31	0.6	0.58	0.432	0.54	18.7	0.26	1.26
ETOH group	2.07	0.51	0.57	0.386	0.47	18.69	0.25	1.21

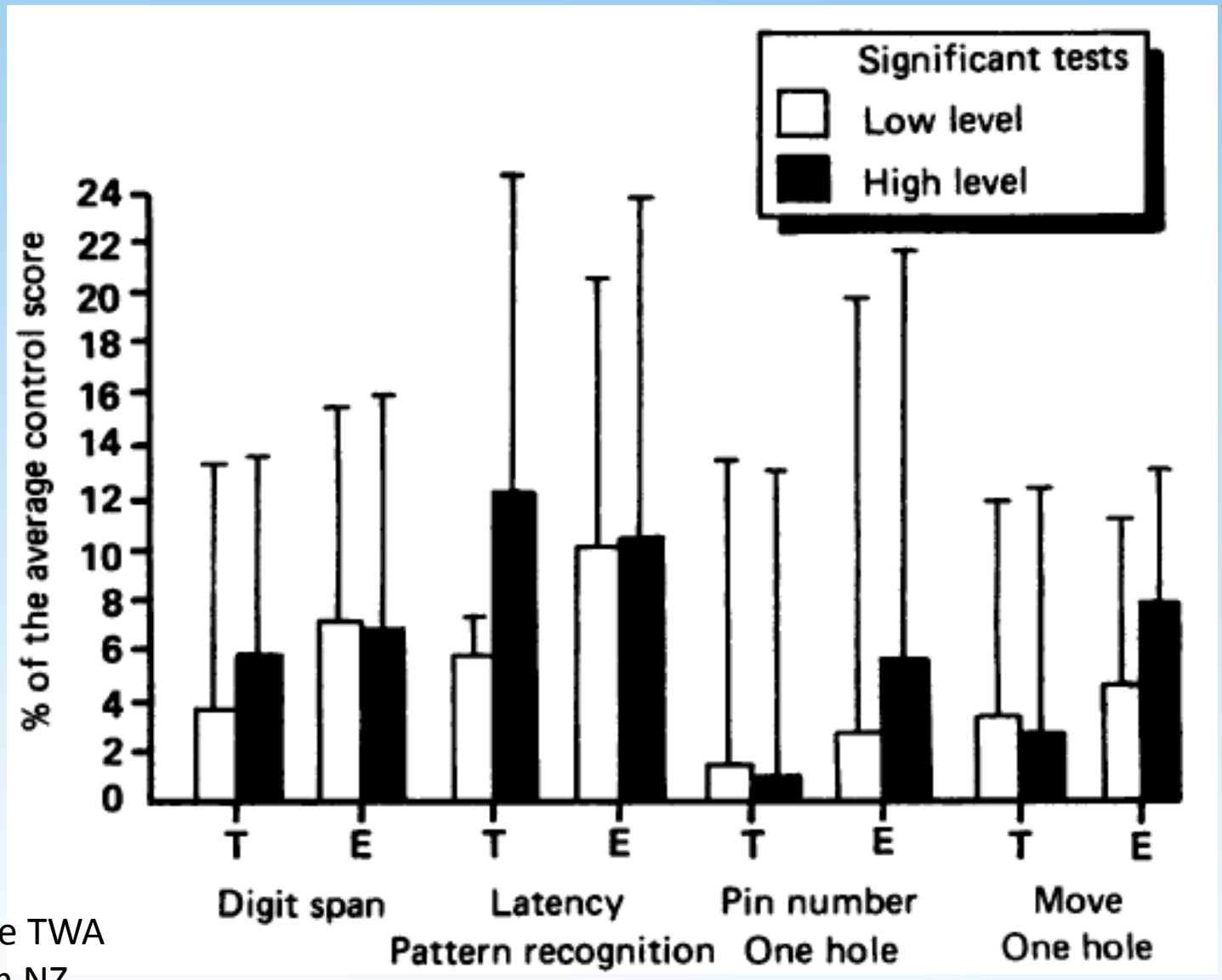
Summary of Behavioral Effects

EtoH \ Toluene	Significant	Non-significant
Significant	Digit Span One hole: pin, move Pattern Recognition: Latency ln	Pattern memory : Latency ln Continuous Performance Test Symbol Digit: Latency Finger tap: alternating Critical tracking^ Fatigue checklist
Non-significant	Pattern memory : N Corr Symbol Digit: N Incorr ^	Sternberg memory scan Benton visual memory Pattern recognition : N Corr Finger Tapping: R and L Hand-eye Coord One Hole Test: grasp, position, reach Mood^

* Significant when ANOVA and test for linear trend statistic had $p<0.05$

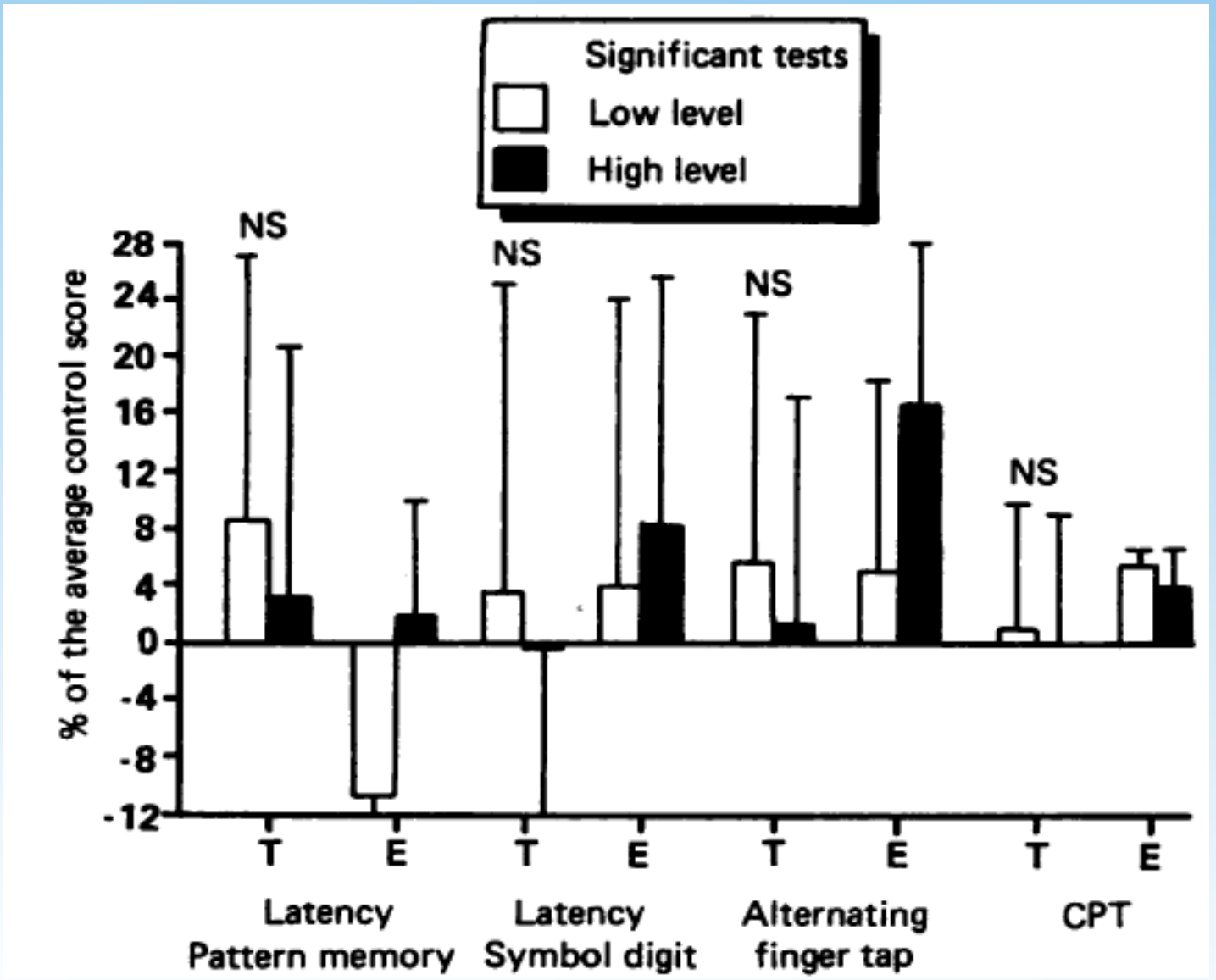
^ Sufficient stat power so solvent did not affect behavior

Statistically significant tests for toluene and ethanol

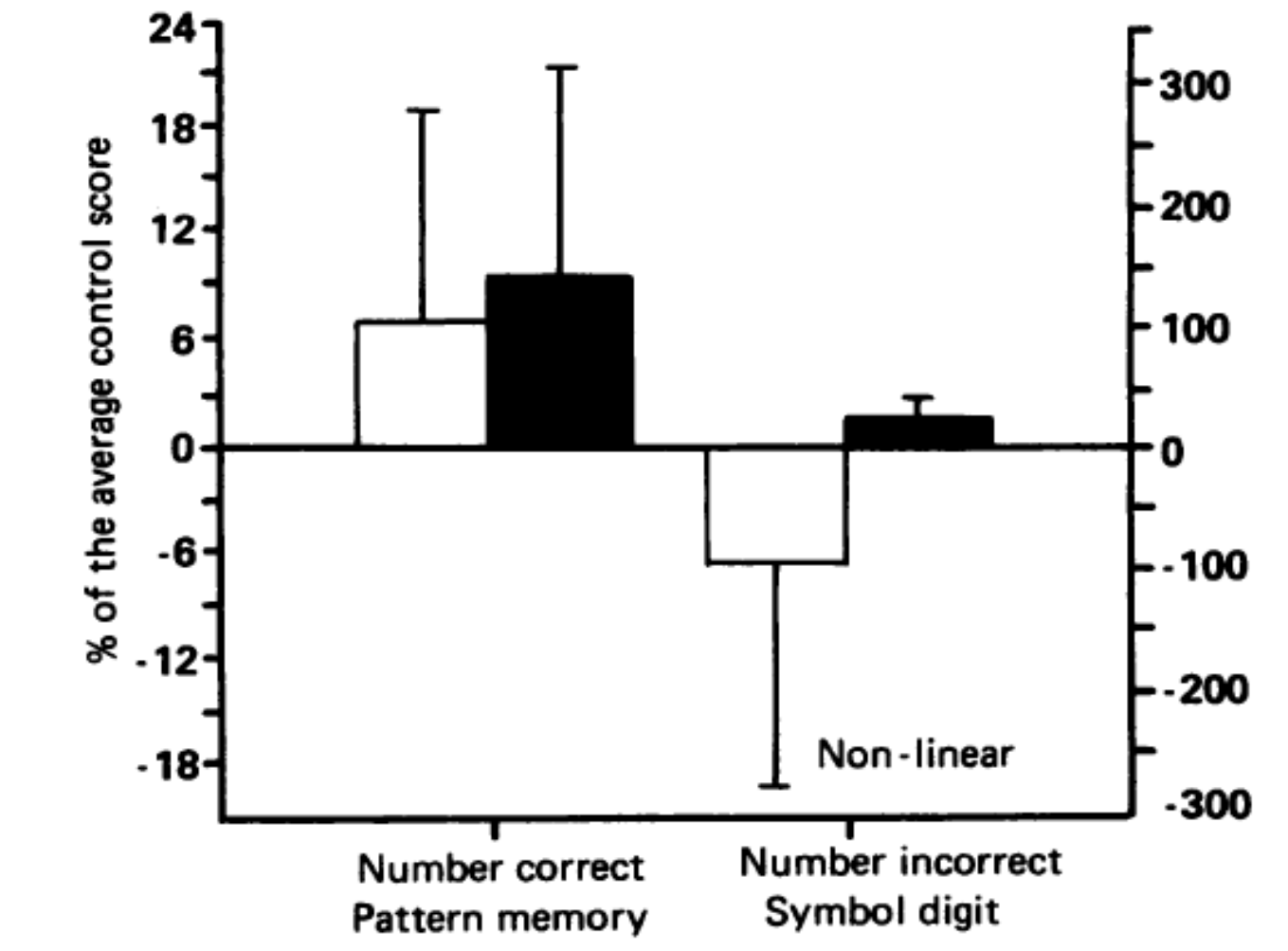


Toluene TWA
50 ppm NZ

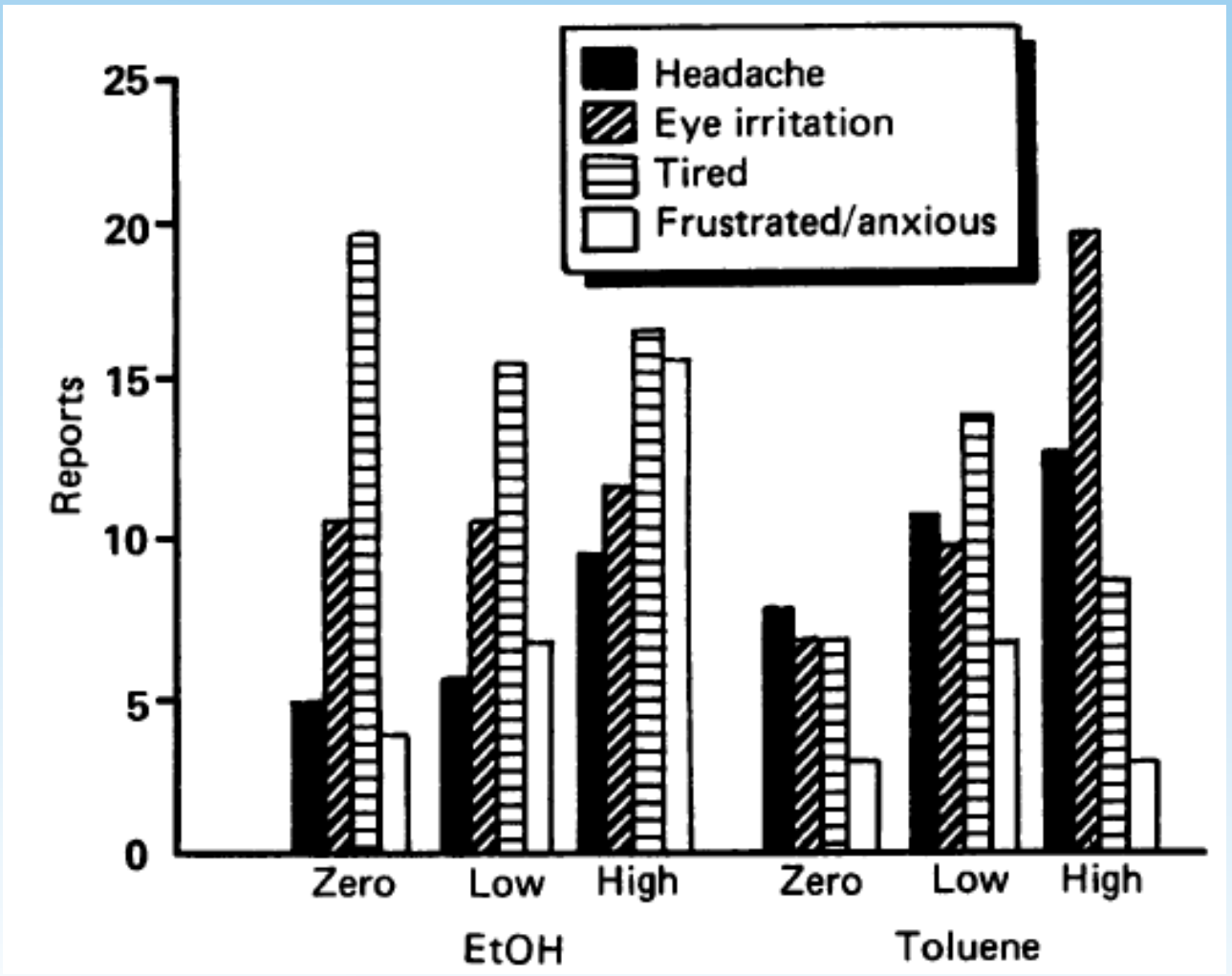
Comparison of tests only affected by EToH (T=Toluene; E= EToH)



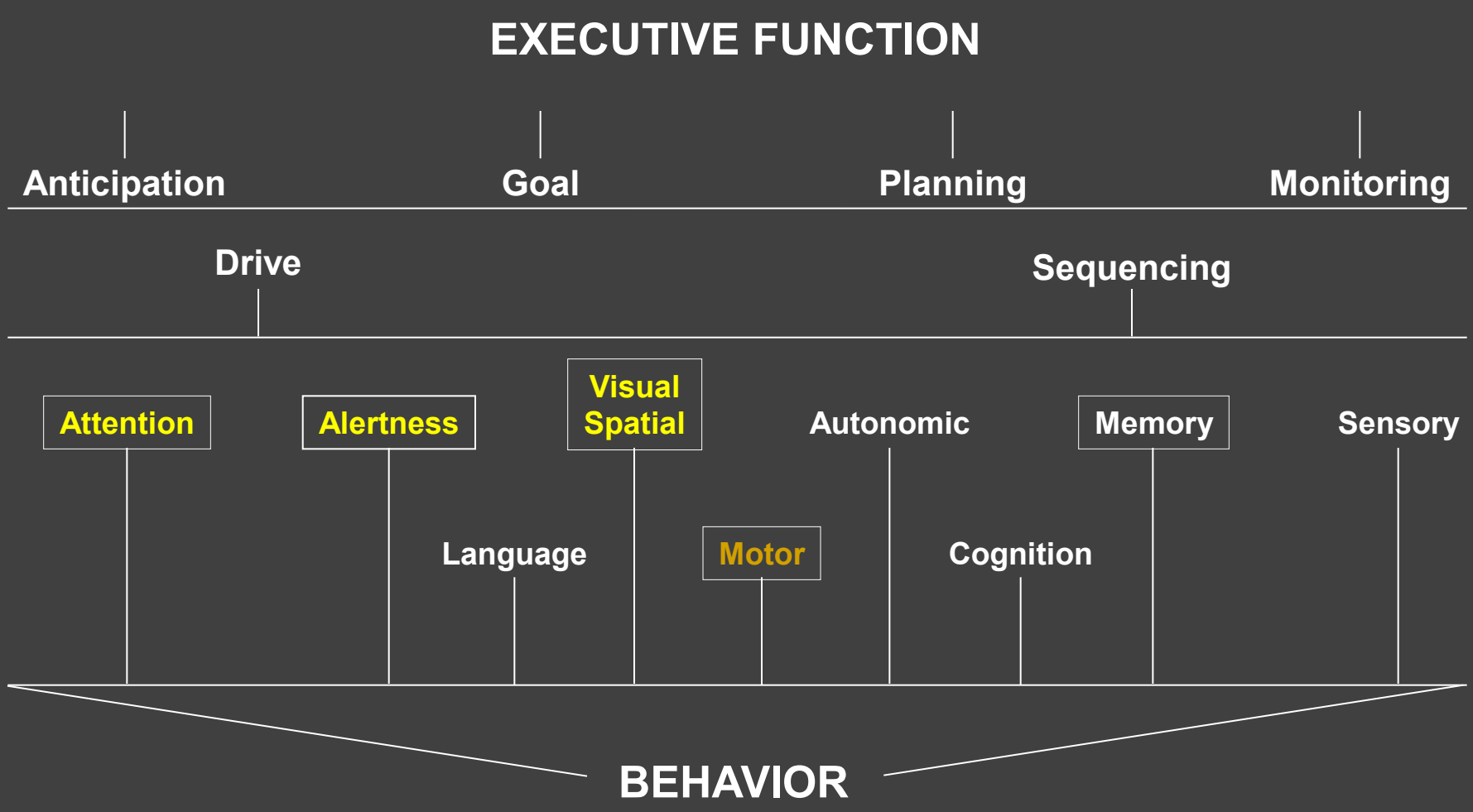
Statistically significant tests for toluene but not EToH



Comparison of Symptoms Between EtOH and Toluene



FRONTAL SYSTEM FUNCTIONS



Non-routine or novel situations provide conscious direction to process information.

– Benson & Stuss (1986)

Results

- Toluene affects attention, visual recognition, and hand coordination (to a lesser extent)
- Toluene effects can be expressed in equivalent ethanol units – increasing interpretation of work-related risk
- Symptoms and observed behaviors are more sensitive to toluene exposure than objective test scores
- Suggestion of fatigue at 75 and 150 ppm-
- NZ WES-TWA of 50 ppm prevents acute CNS deficits

Magnitude of variation for CNS scores suggests why alcohol impairment is measured by a BAC calibrated breath test

Short-term Acute Exposures (Continued)

Styrene and Perchloroethylene (PCE)

Styrene Study Design

Task	(1) 1997	(2) 1998	(2) 1999	(4) 2000	(5) 2001
Recruitment (n=350, 200 twice)					
•Behavioral Sessions (n=2/subject) Acute (AM and PM) n =68 SubChronic (AM and Day Off) Chronic (Day Off on Week-ends)		S W S W S W S W A1 A2 B2 B1			
•Industrial Hygiene Acute: Full-shift Air/Blood/Breath Sub Chronic: 3 full shift TWAs Chronic: Measurement and Wk Hx		Day of Testing: Am and PM Breath, FS TWAs, 6 Tubes Blood			

Study Population Characteristics

Characteristics	Styrene Exposed (n= 68)		PCE Exposed (n= 104)	
	mean	(sd)	mean	(sd)
Education	**12.3**	**(1.42)**	**12.1**	**(2.1)**
Age	**33.7**	**(9.22)**	**40.2**	**(12.9)**
% Male	**96**		**32**	
% Caucasian	**93**		**71**	
% Drink Alcohol	**76**		**51**	
Vocabulary (25 max.)	**17.5**	**(4.1)**	**19.5**	**(12.0)**

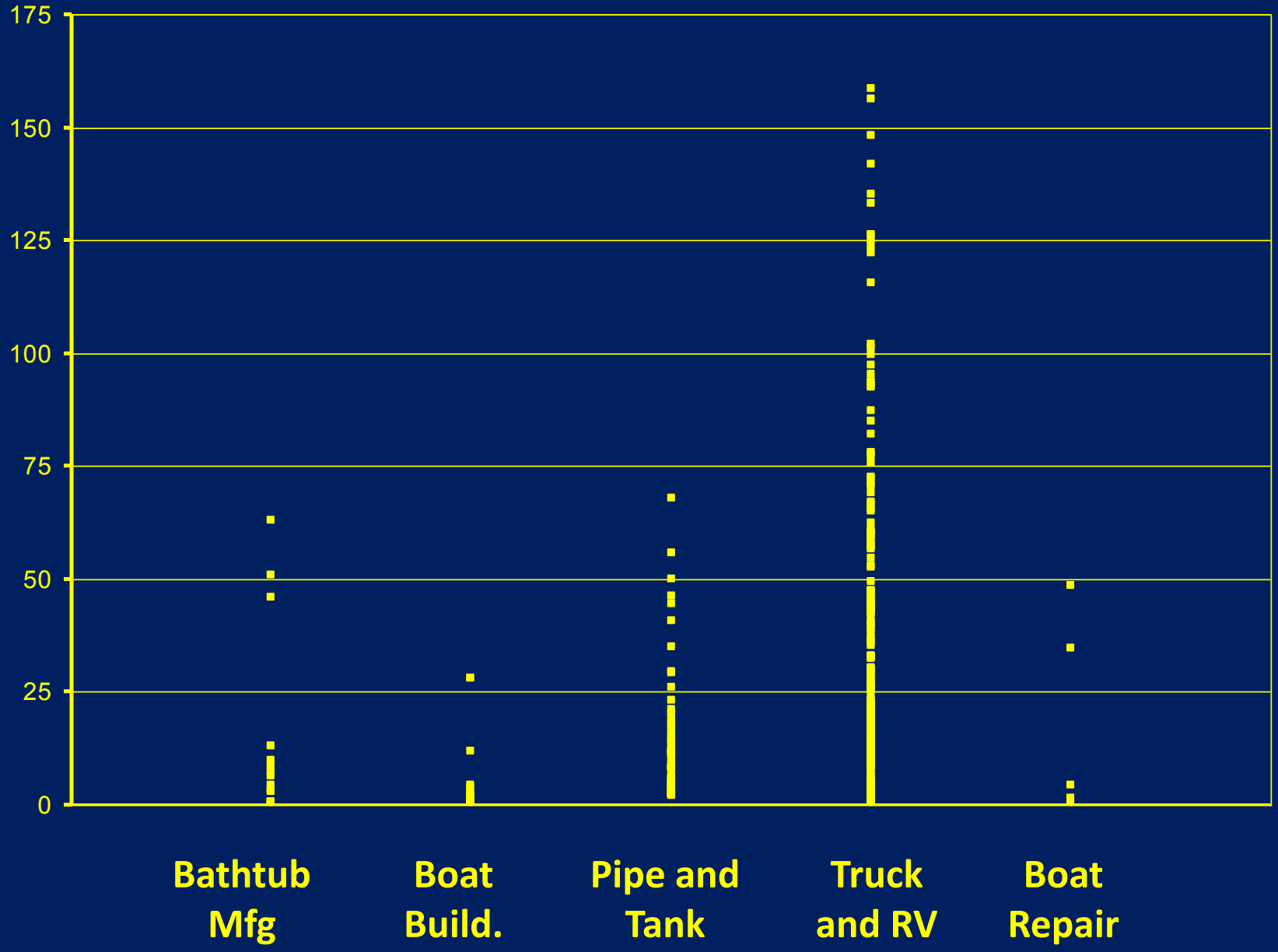
Work Stability, Exposure, and Alcohol Consumption by Industry

	N	Mean Years Current Job	Mean Years in Trade	Mean TWA	Mean # Drinks/Wk
STYRENE					
Boat Mfg.	28	4.6	9.9	58.1	11.5
Pipe & Tank	15	.8	3.8	34.2	5.8
Boat Repair	14	8.9	12.2	7.0	10.3
Resin Prod.	11	2.3	2.6	4.9	4.8
Total Pop.	68	4.2	7.8	33.7	8.9
PCE					
Dry Cleaning					
High	45	10.9	17.5	21.9	2.7
Low	59	2.6	4.9	3.7	2.4
Total Pop.	104	7.4	11.2	12.8	2.6

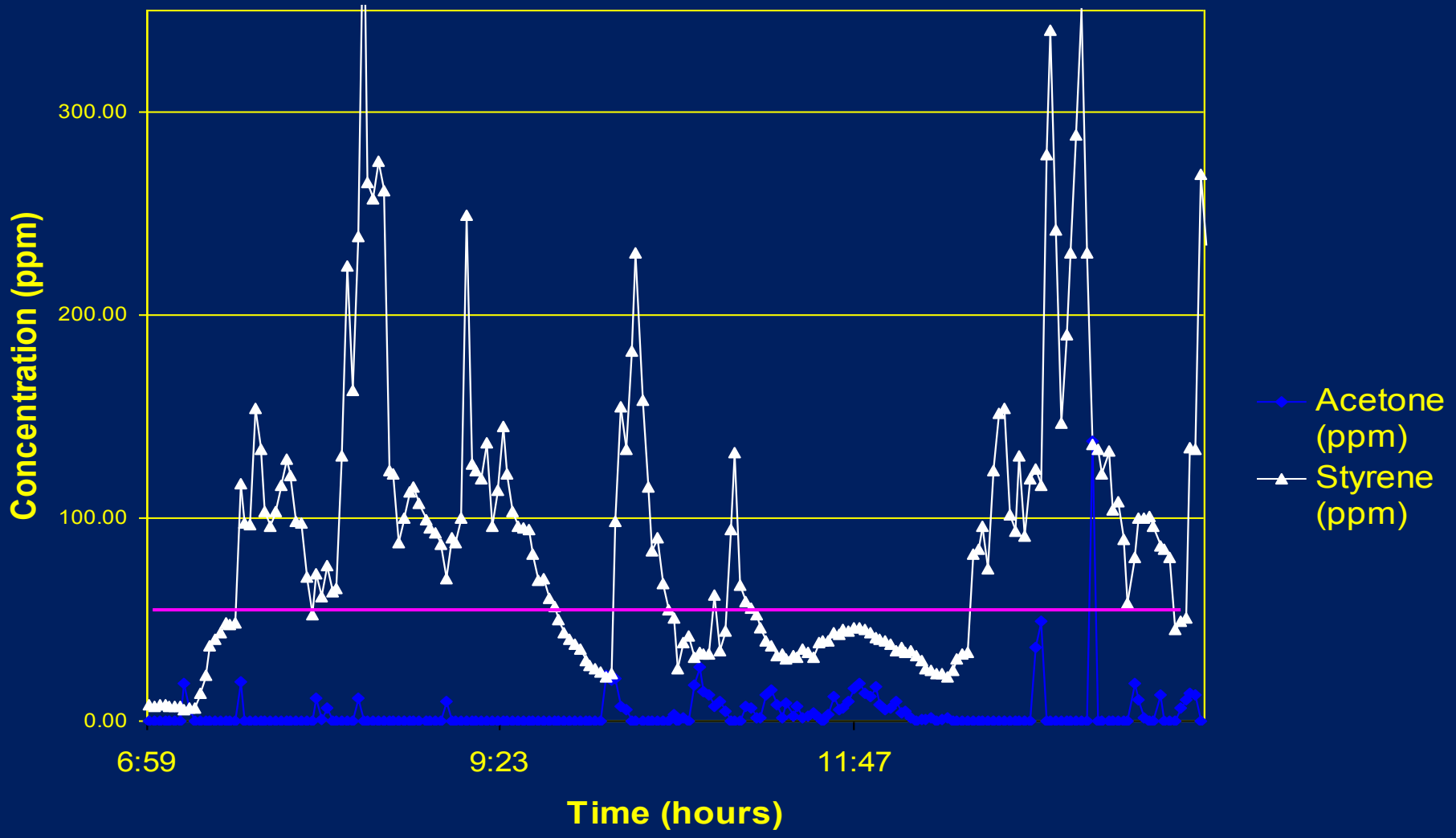
Styrene and Acetone In Air by Job Title (ppm)

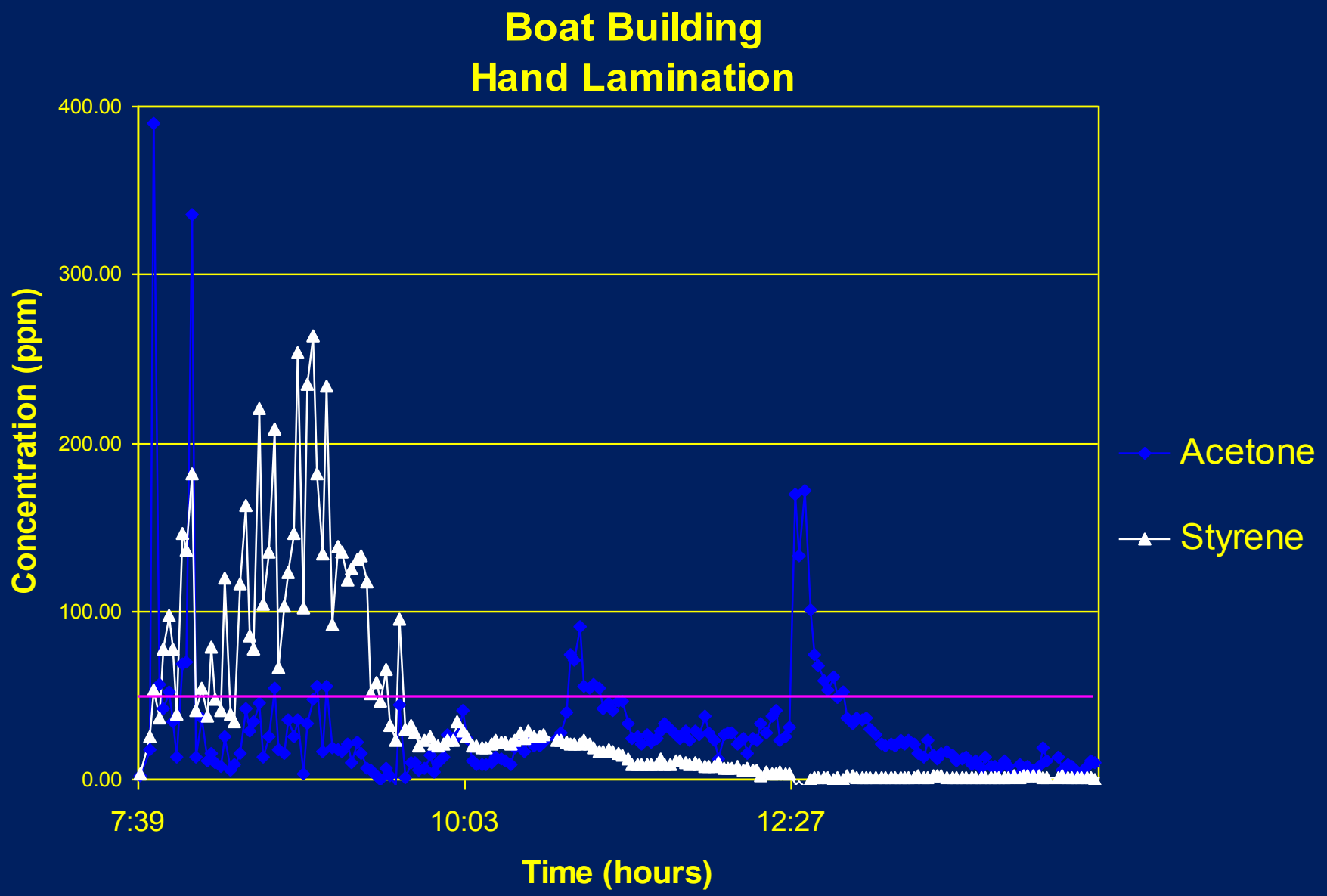
	Styrene		Acetone		Session1
	mean	sd	mean	sd	Samples
Laminator/Gelcoater	55.0	37.5	31.4	20.7	110
Developer	35.4	21.0	29.5	14.9	4
Supervisor/Foreman	21.0	22.5	21.9	29.8	17
Maintenance/Support	14.8	12.5	23.8	42.9	57
Assembly	12.2	2.6	14.0	19.2	12
Finishing/Repair	5.6	4.9	15.6	20.7	53
Trades	2.4	.2	9.4	2.5	3
Office	nd		1.3	1.3	10

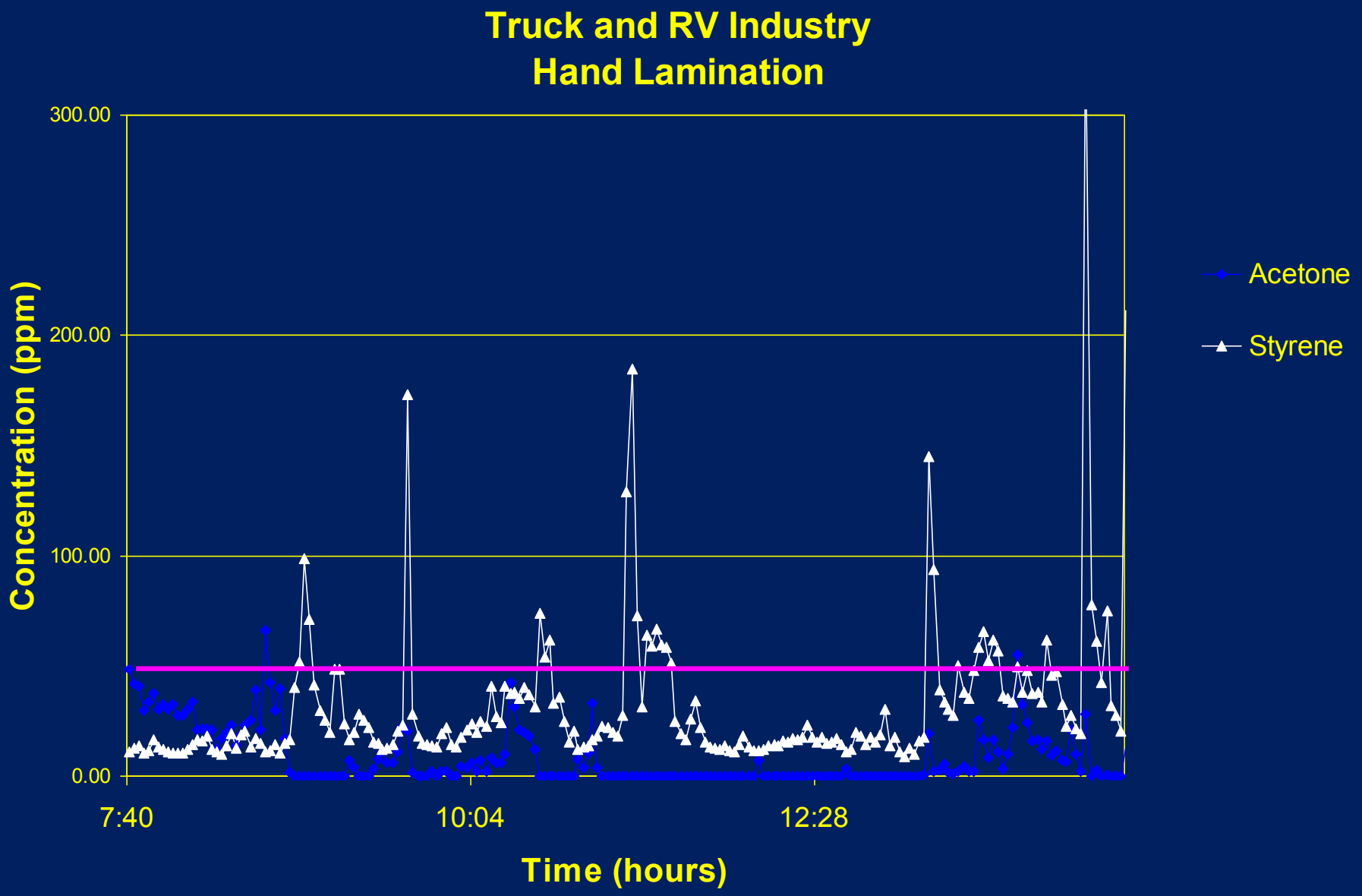
Range of Styrene Levels By Industry



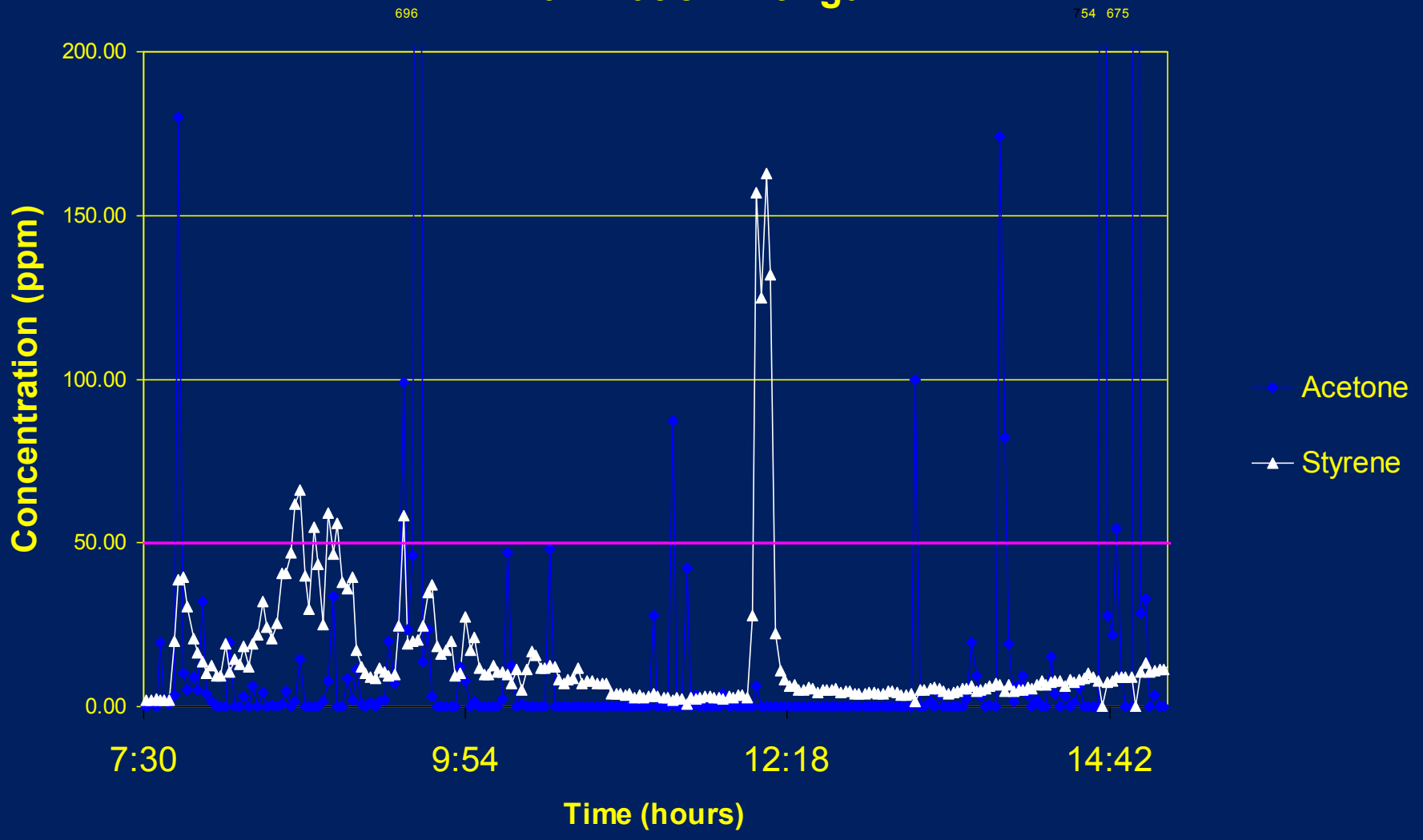
Truck and RV
Lay-up and Gelcoating with Gun.




Boat Building
Hand Lamination
400.00
300.00
200.00
100.00
0.00
Concentration (ppm)
7:39
10:03
12:27
Time (hours)
Acetone
Styrene


Truck and RV Industry
Hand Lamination
300.00
200.00
100.00
0.00
Concentration (ppm)
7:40
10:04
12:28
Time (hours)
Acetone
Styrene

Boat Building
Lamination with gun



Scheme for cross-sectional evaluation of effects

Name of Effect	Associated Exp Interval	Associated Test Time
Acute	Cross-shift (same day)	Pre- and Post-shift 1st d
Sub-chronic	Weeks to months (recent)	Pre-shift / Day Off
Chronic	Cumulative (lifetime)	Pre-shift / Day Off

Basic Data Collection Procedures for Day One

BEFORE WORK

- ❑ Consent form
- ❑ Breath sample

CNS tests:

Paper and Pencil Tests:	Visual Reproductions	Trail making A and B
	Hand Steadiness	
Computerized Tests:	Acute Symptoms	Switching Attention
	Manual Tracking	Digit Span
	Digit-symbol	Pattern Recognition
	Pattern Memory	Simple Reaction Time
	Finger Tap	Vocabulary

- ❑ put on a lapel air sampling badge and/or a small air sampling pump

AFTER WORK

- ❑ blood and breath sample, return pump and badge
- ❑ re-take the test battery

Behavioral Test Battery

CNS Domain	Function	Test (measure)
Subjective	symptoms	Q16 Modified (n reported)
	mood states	POMS (mood score)
Motor function	speed/coordination	One hole (pins/ml)
Objective		
Cognitive	visual memory	Visual reproductions (correct score)
		Pattern memory (secs)
	flexibility	Switching (secs)
		Trail making B (secs)
	attention	Trail making A (secs)
		Digit span — Verbal (n digits)
	perception	Pattern recognition (secs)
	reasoning	Similarities (n correct)
Control	verbal skill /intelligence /education	Vocabulary (n correct)

Coefficients for Acute Exposure to Solvents Potentially Associated with Behavior*

	STYRENE PERSONAL BADGE TWA			PCE PERSONAL BADGE TWA		
	Slope	**Partial R^2**	***P*-Value**	**Slope**	**Partial R^2**	***P*-Value**
Cognitive Flexibility						
Switching (sec)	-.031	(.007)	.	-.006	(.001)	.
Trail Making B (sec)	1.070	.01	.	-3.92	(.044)	.03
Attention						
Digit Span - Verbal (#)	-.060	.002	.	.145	(.020)	.
Digit Span - Computer (#)	-.205	.09	.01	-.204	.025	.08
Trail Making A (sec)	-.146	(.002)	.	.151	.000	.
Visual Memory						
Pattern Memory (sec)	.16	.04	.	-.001	(.000)	.
Visual Reproductions (score)	.009	(.002)	.	-.203	.011	.
Perception						
Pattern Recognition (sec)	.16	.09	.03	.045	.002	.
Motor Function						
One Hole (pins/min)	-.19	.002	.	.112	(.001)	.
One Hole Move Time (msec)	.004	.006	.	-.009	(.005)	.

*Adjusted for age, vocabulary score, alcoholic drinks per week, gender, shop owner race and missing glasses. ( ) indicates improvement with higher exposure.

Public Health Significance of Sparse Acute Exposure to Styrene

Just under < 34 ppm TWA

- Digit span (r^2 =0.09, p<0.02) and Pattern Recognition (r^2 = 0.09, p<0.02) were affected by exposure indicating reduced attention and potentially worse visual recognition of items, maps, etc

-Styrene 50 ppm NZ WES-TWA, 100 ppm NZ WES-STEL

NZ standard may not prevent work related mild deficits in performance

Sub-chronic
3-month exposure
to styrene and perchloroethylene (PCE)

Basic Data Collection Procedures for Day Off

- Consent form
- Breath sample quantified for styrene and ethanol
- Occ Hx and Mx Questionnaire

PNS tests:

Sural Nerve Conduction Velocity
Vibratron
Optec Vision Tests
Audiometry

R'R' intervals and Valsalva
Accusway Platform
Color Hue
Smell Identification

CNS tests:

Adaptive Vocabulary
Similarities
Wexler Memory Scale
(stories and figures)

Tremor
Brief Cognitive Profile
Object Memory

Behavioral Results Associated with Subchronic Exposure to Styrene and PCE*

	STYRENE PERSONAL BADGE TWA						PCE PERSONAL BADGE TWA					
	N	Grand Mean	MEAN RESIDUAL		REGRESSION		N	Grand Mean	MEAN RESIDUAL		REGRESSION	
			X < 25 ppm	X < 50 ppm	PARTIAL R^2	*P*-VALUE			x = 4 ppm	x = 22 ppm	PARTIAL R^2	*P*-VALUE
ALL TESTS	**68**				**.18**	**.00**	**94**				**.000**	.
SUBJECTIVE TESTS					**.002**	**.**					**.002**	**.**
Symptoms (#)		21.5	-0.5	+0.5	.006	.		19.0	.1	-.2	.000	.
Profile/ Mood States (Sc)		11.1	(.0)	(.0)	(.001)	.		11.1	.0	-.1	.007	.
OBJECTIVE TESTS					**.20**	**.00**					**.001**	**.**
Cognitive Flexibility					**.10**	**.01**					**.003**	**.**
Switching (sec)		1.62	-0.04	+0.05	.07	.04		1.52	.0	.1	.023	.08
Trail Making B (sec)		77.2	-3.8	+4.1	.05	.10		68.2	.0	.1	.002	.
Reasoning												
Similarities (# corr)		19.5	+0.4	-0.4	.07	.04		17.7	-.1	.2	.002	.
Paced Auditory Serial AdditionTest - PASAT								6.6	.1	-.3	.002	.
Attention					**.05**	**.09**					**.003**	**.**
Digit Span Verbal (#)		6.8	+0.1	-0.1	.04	.10		7.1	-.1	.3	.007	.
Digit Span Computer (#)		6.1	+0.1	-0.1	.003	.		6.3	-.1	.4	.011	.
Trail Making A (sec)		30.6	-0.3	+0.4	.05	.08		34.2	.0	.0	.002	.
Visual Memory					**.13**	**.00**					**.003**	**.**
Pattern Memory (sec)		7.1	-0.1	+0.1	.04	.		6.1	.0	-.1	.014	.
Visual Reprod(score)		11.0	+0.6	-0.7	.08	.03		9.8	.2	-.9	.007	.
Perception												
Pattern Recognition (sec)		3.9	-0.1	+0.1	.02	.		3.9	.1	-.4	.037	.04
Motor Function												
One Hole (pins/min)		33.0	(-1.1)	(+1.1)	(.002)	.		37.7	.4	-1.3	.001	.
One Hole Move (msec)								545	10	50	.048	.03

*Adjusted for age, vocabulary score, alcoholic drinks per week, gender, shop owner, race and missing glasses. ( ) indicate improvement with higher exposure). **Bold** = Summary Score results.

Associations Between Summary Scores and Exposure: r^2 and *p*-value

Clinical Domains	Rank Sum		Factor$_r$		F
	r^2	p	r^2	p	r^2
Subjective	0.001	0.80	0.004	0.60	
Dexterity	—	—	—	—	
Visual memory	0.126	0.003	0.116	0.004	
Flexibility	0.095	0.01	0.085	0.02	
Attention	0.040	0.11	0.063	0.04	
Perception	—	—	—	—	
Reasoning	—	—	—	—	

Public Health Significance

Subchronic repeated exposure to styrene over 3 month

Found consistent deficits < 35 ppm

- **Objective tests** $p < .001$
- Found no **subjective** responses
- **Cognitive flexibility and reasoning tasks** have a stronger contribution to the partial r^2 than simpler memory tasks.
- **Motor function** was not adversely affected.
- Effect do not support a 25 ppm occupational standard or a 50 ppm WES standard since we did not find a threshold of effect.

Behavioral Results Evaluating Chronic Exposure to Styrene and PCE*

	STYRENE						PCE					
	N	Grand Mean	MEAN RESIDUALS		REGRESSION		N	Grand Mean	MEAN RESIDUALS		REGRESSION	
			< 30 ppm	>30 ppm	PARTIAL R^2	*P*			LOW	HIGH	PARTIAL R^2	*p*
ALL TESTS	**61**				**(.11)**	**(.01)**	**78**				**.003**	**.**
SUBJECTIVE TESTS	68				**(.03)**	**.**	**94**				**.000**	**.**
Symptoms (#)		21.5	-.6	0.5	(.03)	.		19.0	0.0	0.0	.014	.
Profile/ Mood States (Sc)		11.1	0.2	-.2	(.04)	.		11.1	0.0	0.0	.003	.
OBJECTIVE TESTS					**(.11)**	**(.01)**					**.002**	**.**
Cognitive Flexibility					**(.05)**	**(.08)**					**.002**	**.**
Switching (sec)		1.62	-.01	0.01	(.07)	(.04)		1.52	-.0	0.0	.000	.
Trail Making B (sec)		77.2	-1.5	1.2	(.02)	.		68.2	-.0	0.0	.015	.
Reasoning												
Similarities (# corr)		19.5	-.9	0.7	(.07)	(.04)		17.7	0.4	-.4	.006	.
PASAT			0.3	-.2								
								6.6	0.6	-.9	.028	.08
Attention					**(.03)**	**.**					**.002**	**.**
Digit Span -Verbal (#)		6.8	0.0	0.0	(.03)	.		7.1	-.1	0.1	.004	.
Digit Span -Computer (#)		6.1	0.0	0.0	.000	.		6.3	0.0	0.0	.001	.
Trail Making A (sec)		30.6	-.7	0.5	(.02)	.		34.2	0.0	0.0	.002	.
Visual Memory					**(.02)**	**.**					**.040**	**.03**
Pattern Memory (sec)		7.1	-.2	0.2	(.005)	.		6.1	-.0	0.0	.041	.03
Visual Reprod(score)		11.0	0.0	0.0	(.01)	.		9.8	0.4	-.5	.046	.03
Perception												
Pattern Recognition (sec)		3.9	0.1	0.0	(.03)	.		3.9	-.1	.1	.026	.07
Motor Function												
One Hole (pins/min)		33.0	-1.2	1.0	(.08)	(.03)		37.7	0.3	-.4	.008	.
One Hole Move (msec)								545	-11	13	27	.08

*Adjusted for age, vocabulary score, alcoholic drinks per week, gender, shop owner, race and missing glasses. ( ) indicate improvement with higher exposure. **Bold** = Summary Score results

Potential Deficits Associated with C*hronic* Cumulative Exposure of Styrene and PCE

Styrene

- No associations with industry years or cumulative exposure
- Selection is a factor as performance improved with time

PCE

- Adverse effects associated with chronic exposure are restricted to 2 tests of visual memory

Evidence for Frontal Limbic System Hypothesis

Compelling evidence at 34-37 ppm

Frontal System: WAIS Similarities
Switching Attention
TRAILS B
Digit Span
TRAILS A
Visual Reproductions

Limbic System: Pattern Memory to a lesser extent

Motor function is spared, consistent with a focal effect

Study Strengths

- Can distinguish acute, subchronic, and chronic exposure
- Captures individual differences two ways:
  - vocabulary controls for pre-morbid verbal intelligence
  - PM scores are covaried for AM scores which partial out differences in learning age, education, vocabulary
- Summary measures improve sensitivity and reliability of the analysis – diverse methods yield similar results

❑ Differential Health Effects of Elemental Mercury at very low levels of exposure

CNS Profiles of Adverse Effects Vary With:

* Chronic history of exposure,
* Biological Indices of exposure
* Individual genetic susceptibility

STUDY HYPOTHESIS

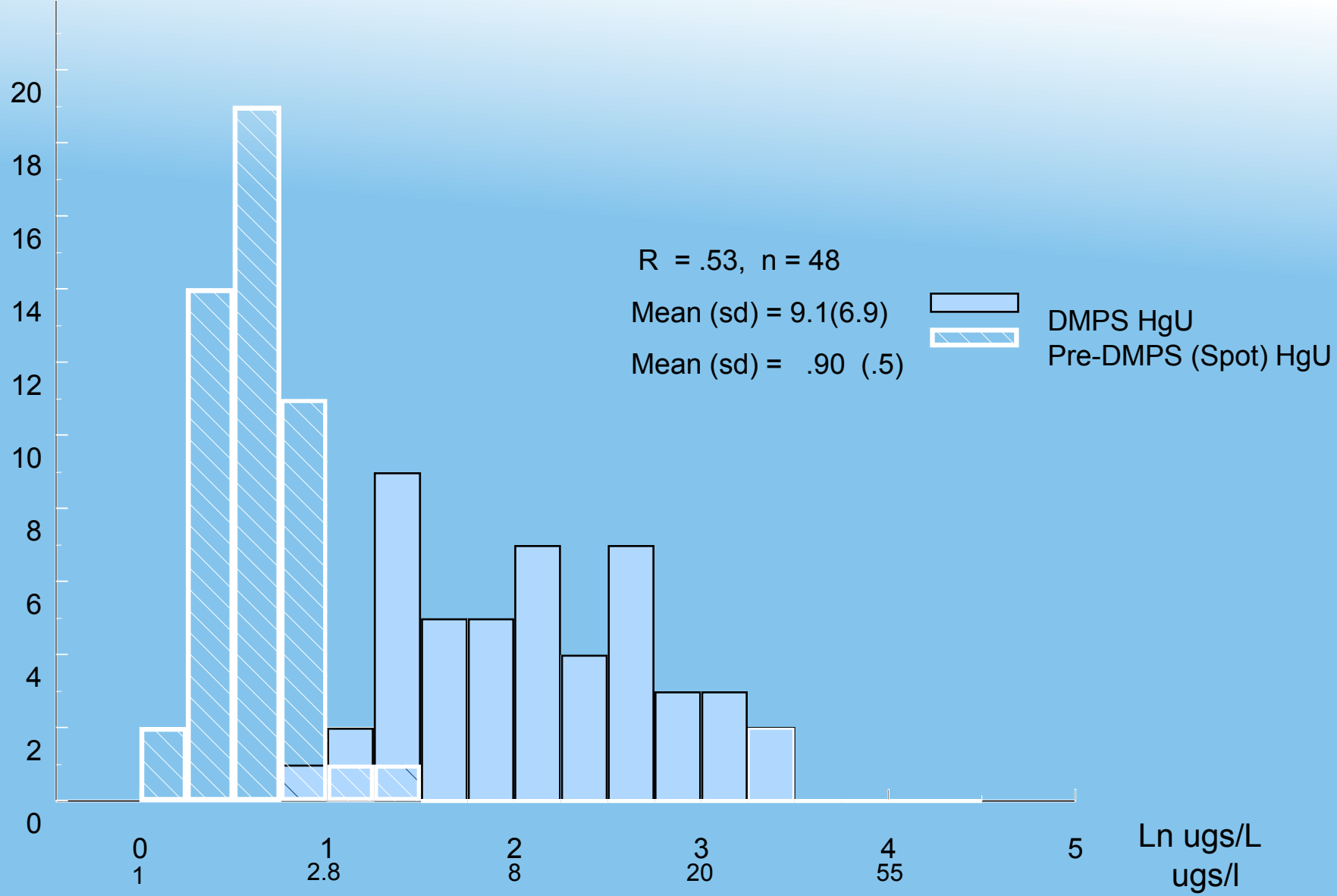
Diverse clinical effects indicate multiple mechanisms of action involving multiple systems.

Therefore we hypothesize,

Exposure-effect curves exist at very low levels of exposure to Hg^o that permit characterization of

- Symptoms
- Mood
- Motor Function
- Cognitive Skills

And that adverse effects are associated with chronic body burden as measured by DMPS-chelated HgU.



Distribution of Pre- and Post-DMPS Chelated Urinary Hg Levels (ln of µg/l)

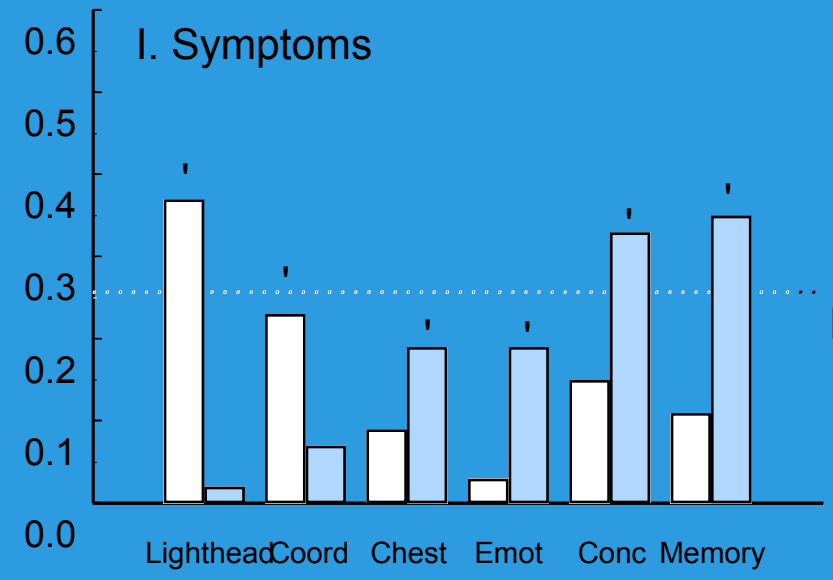
Echeverria, Woods, Heyer et al., 1999

PREDICTORS OF SPOT Hg⁰ LEVELS

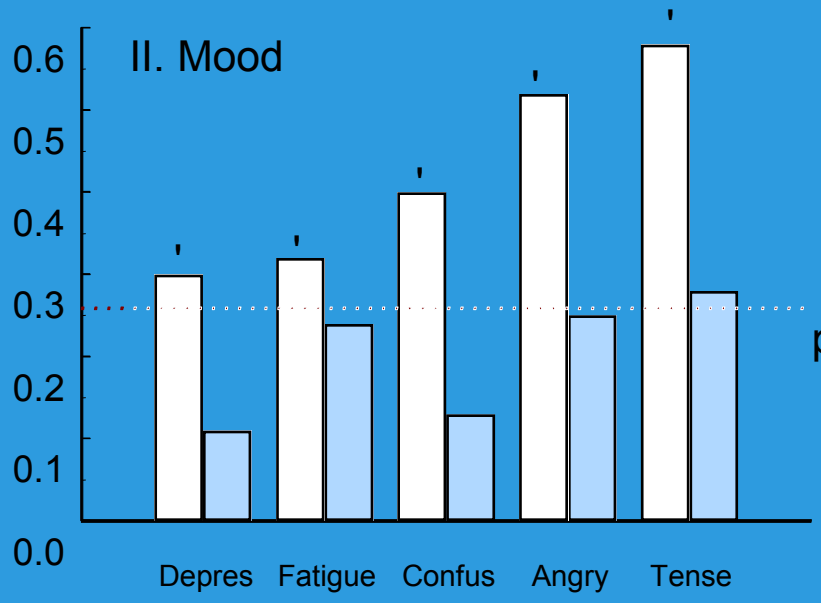
			Regression Model	
Significant predictors	**Mean**	**sd**	**b_{lnHg}**	**$_{partial}r$**
DMPS-chelated HgU	9.1	6.9	0.16	0.43***
No. restorations/wk	16.1	8.2	0.01	0.34***
No mask	15 %		0.38	0.32***
Personal amalgam	1.6	0.8	0.08	0.25**

Full Model R = .61

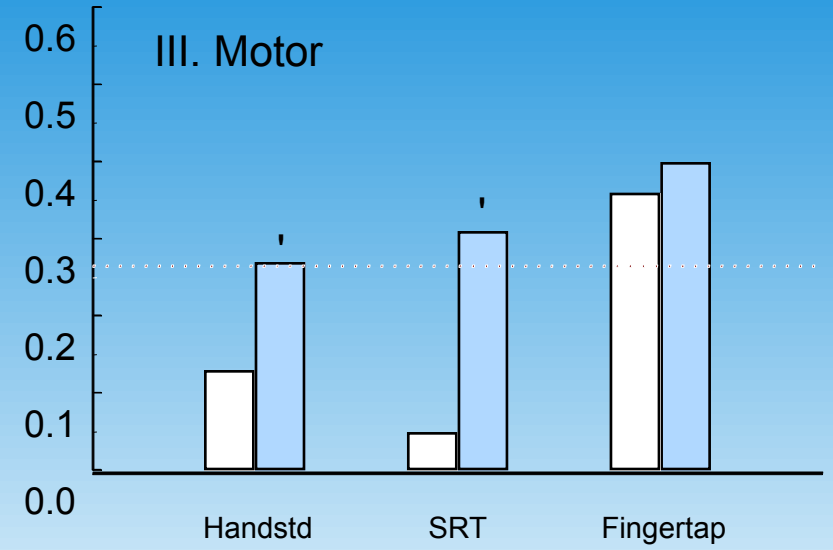
x = p <.10
xx = p < .05
xxx = p <.001



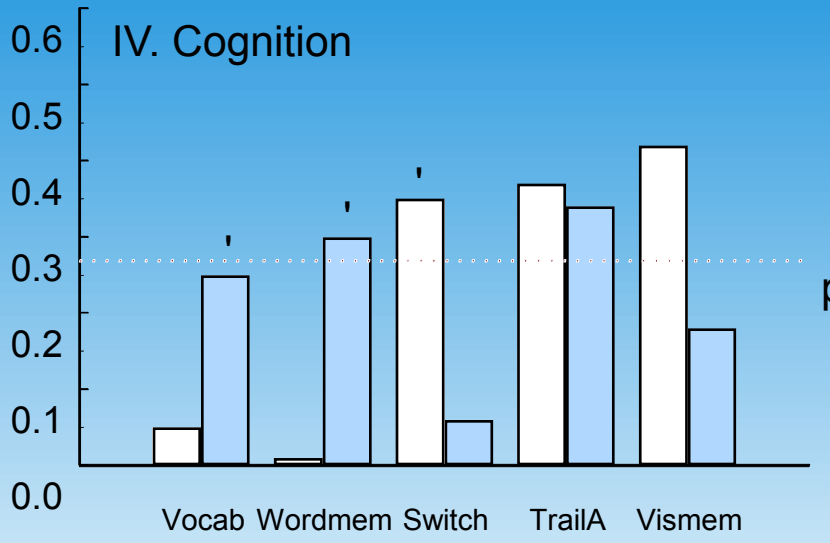
p<.05



p <.05



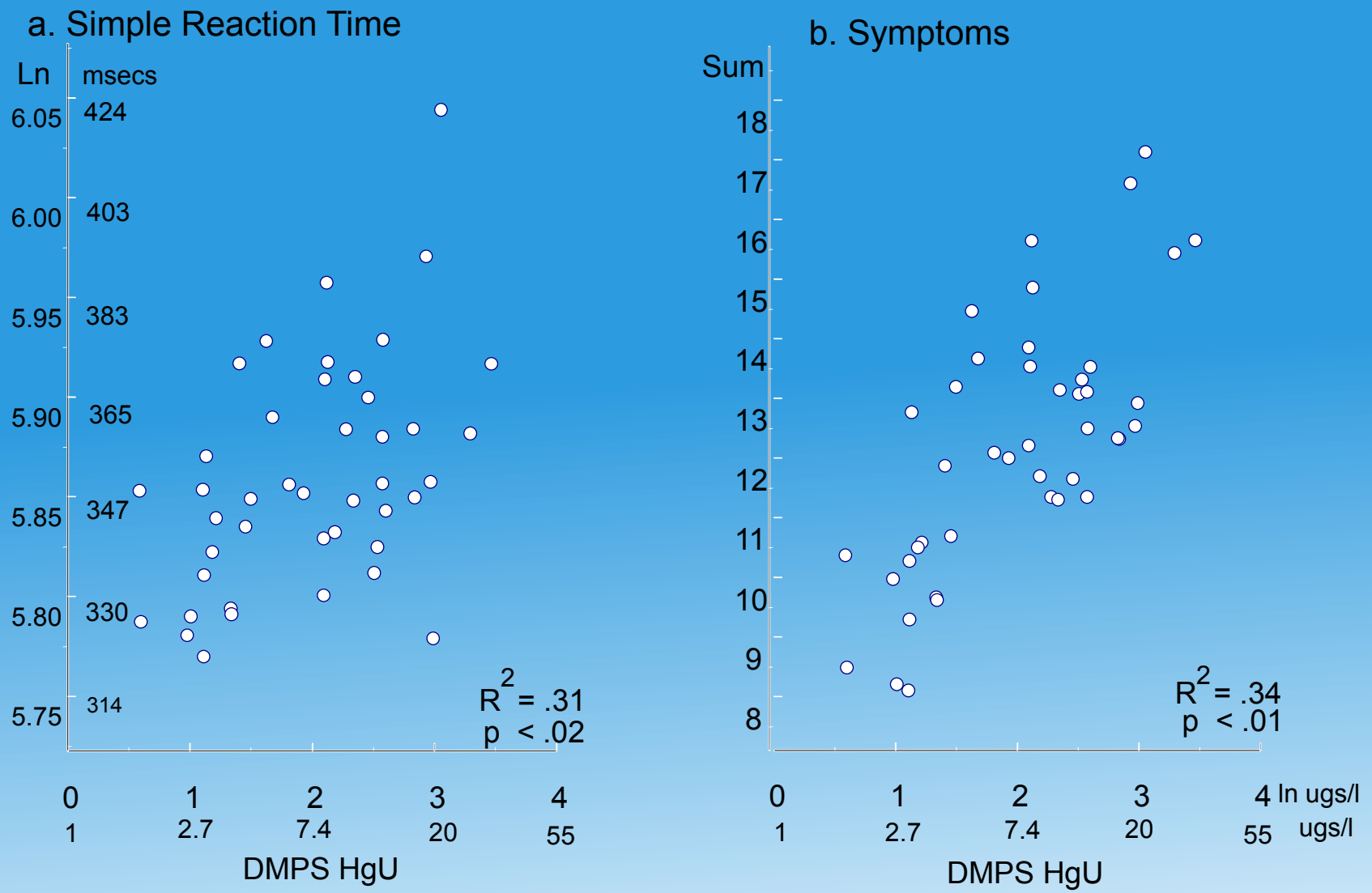
p< .05



p< .05

Comparison of standardized Beta coefficients

DMPS HgU
Spot H gU



Associations between Simple Reaction Time scores and Symptoms with DMPS-chelated HgU levels (ln ugs/l)

STUDY STRENGTHS

- Sufficient statistical power to detect deficits in behavior at very low levels of exposure ranging from (0-3 µg/s HgU)
- Distinguish subchronic exposure from chronic body burden based on spot HgU and DMPS-chelated HgU levels - the correlation is R = 0.53
- New Zealand Biologic Exposure Indices 0.25mol/litre (50g/litre) is not necessarily protective
- Occupational practices reduce exposure

NEW STUDY DESIGN

Task		1997	1998	1999
Recruitment		———		
Test Sessions (n=400) Speciation in Urine and Blood Kidney function tests		S A1	W A2 B1	S B2
Industrial Hygiene Assessments (n=200 offices)		———	———	
DMPS-Chelation Study (n= 20 Low, 20 Mod, 20 High) 20 zero				———

NEW BEHAVIORAL TEST SESSION

- Consent form
- Occ Hx

Ethanol in breath

Mx and Symptom Questionnaire

PNS tests: (2 hours)

R'R' intervals and Valsalva
Accusway Platform
Color Hue
Smell Identification

Vibratron
Optec Vision Tests
Audiometry
Nerve Conduction Velocity

CNS tests: (1 hour)

Word Memory
Visual Reproductions
Pattern Memory
Digit Span
Switching Attention
Manual Tracking
Digit-symbol
Trails A and B
Pattern Recognition

Adapted Vocabulary
Hand Steadiness Battery
Simple Reaction Time
Forced Choice Reaction Time
Intentional Tremor
Finger Tap
Vigilance test

Observed Associations between CNS scores and exposure to elemental Hg and the presence of genetic mutations in dental populations

Table 2. Associations Between Neurobehavioral Scores, Exposure to Hg, and Genetic Variants Among Adults

BEES Neurobehavioral Domains[#]	HgU	CPOX4[15]	HgU	5-HTTLPR[20,21]	HgU	BDNF[17,18]	HgU	COMT[+,30]
Attention Digit Span Fwd (digits)	-0.13**	-0.13**	-0.13**	-0.18**	-0.13**	-0.11**	-0.13**	
Visual Memory Pat Mem (secs);Vis Reprod (n corr)	-0.13**	-0.15**		-0.24	-0.14**	-0.11*		-0.11*
Working Memory Digit Span Bkwd (digits)	-0.16**	-0.13*	-0.13**	-0.20**	-0.16**	-0.13*	-0.11**	
Visuomotor Processing Symbol Digit (rate)	-0.17**	-0.13**				-0.17**		-0.22**
Sustained Attention Vigilance (hits)	-0.11**		-0.22**	-0.31***		-0.11*	-0.11**	
Perception Patt Disrim (secs)	-0.13*		-0.11**	-0.26**		-0.13*	-0.11**	-0.13*
Cognitive Flexibility Switching (Rate); Trailmaking B (secs)		-0.12*	-0.14***	-0.12**	-0.16**	-0.13*	-0.14**	-0.16**
Reaction Time Simple RT (msecs)		-0.10**		-0.28***			-0.13*	-0.12**
Finger Speed Finger Tapping Dom/NDom (Taps)	-0.18**		-0.13**	-0.20**	-0.18**	-0.12*	-0.11**	-0.12*
Hand Steadiness (Factor)	-0.17**		-0.19**	-0.18**	-0.70**	-0.42*	-0.15**	
Mood								
Beck Depression Index	0.14*	0.21**	0.21**	0.35***				
Profile on Mood States - Depress	0.24**		0.12**	0.20**	0.11**	0.13**	1.22**	2.45**
Profile on Mood States - Confusion				0.28**			0.69**	1.39**
Profile on Mood States - Overall	0.22**	0.12*	0.21**	0.25**	0.12**	0.12*	6.05***	12.57***
Symptoms								
Anxiety	0.13*	-0.12*		0.26**	0.14**	0.18**		
Confusion	0.14**	0.12**	0.26**				0.22**	1.59**
Depression				0.43***				

[#] Regression models control for age, education, alcohol use, and premorbid intelligence(vocab);+ manuscript in preparation

*p <0.06 ; ** p<0.05; ***p<.005

Children may be more susceptible population to mercury exposure

Study population characteristics for participants at Entry (baseline) and in Year 2 and Year 7

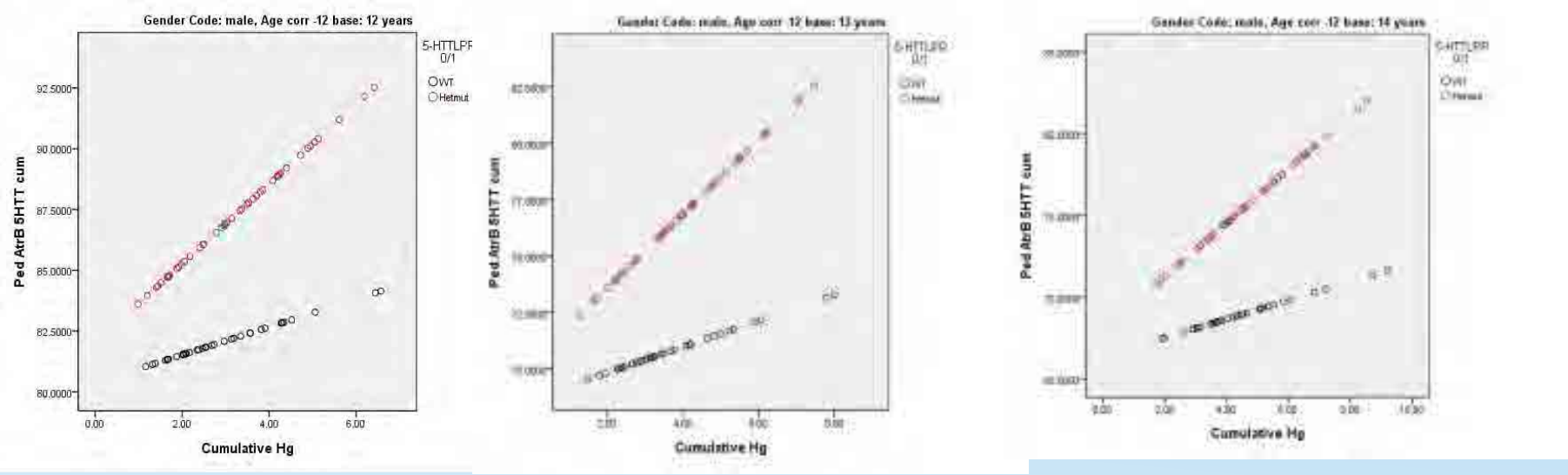
Characteristic	BOYS			GIRLS		
	ENTRY	YEAR 2	YEAR 7	ENTRY	YEAR 2	YEAR 7
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	10.15 (.84)	12.20 (.84)	17.14 (.86)	10.10 (.92)	12.16 (.95))	17.08 (1.02)
School Year	4.04 (1.05)	5.78 (1.2)	9.40 (2.04)	4.15 (1.07)	5.92 (1.16)	9.86 (1.52))
Non-Verbal IQ (at entry only)	86.26 (10.37)	---	---	86.26 (10.37)	---	---
Urinary Mercury Concentrations						
Raw HgU[a]	1.65 (1.25)	2.17 (2.02)	1.25 (3.00)	1.98 (2.40)	2.86 (2.63)	1.77 (2.27)
Calculated HgU[b]	0.89 (0.41)	1.02 (0.49)	0.62 (0.48)	0.94 (0.48)	1.18 (0.57)	0.83 (0.56)
Calculated Maximum[b]	---	---	1.46 (0.52)	---	---	1.68 (0.54)
Calculated Cumulative[c]	---	---	2.47 (0.50)	---	---	2.74 (0.55)
Distribution	**% (N)**	**% (N)**	**% (N)**	**% (N)**	**% (N)**	**% (N)**
Total Subjects (N)	164	160	121	166	151	118
Caucasian - % (N)	74.4% (122)	74.4% (119)	71.9% (87)	71.1% (118)	68.9% (104)	69.5% (82)
CPOX4						
Wildtype (A/A)	71.3% (117)	71.3% (114)	67.8% (82)	65.1% (108)	64.2% (97)	61.9% (73)
Heterozygous (A/C)	28.0% (46)	28.1% (45)	31.4% (38)	27.7% (46)	27.8% (42)	28.8% (34)
Homozygous Mutant (C/C)	0.6% (1)	0.6% (1)	0.8% (1)	7.2% (12)	7.9% (12)	9.3% (11)

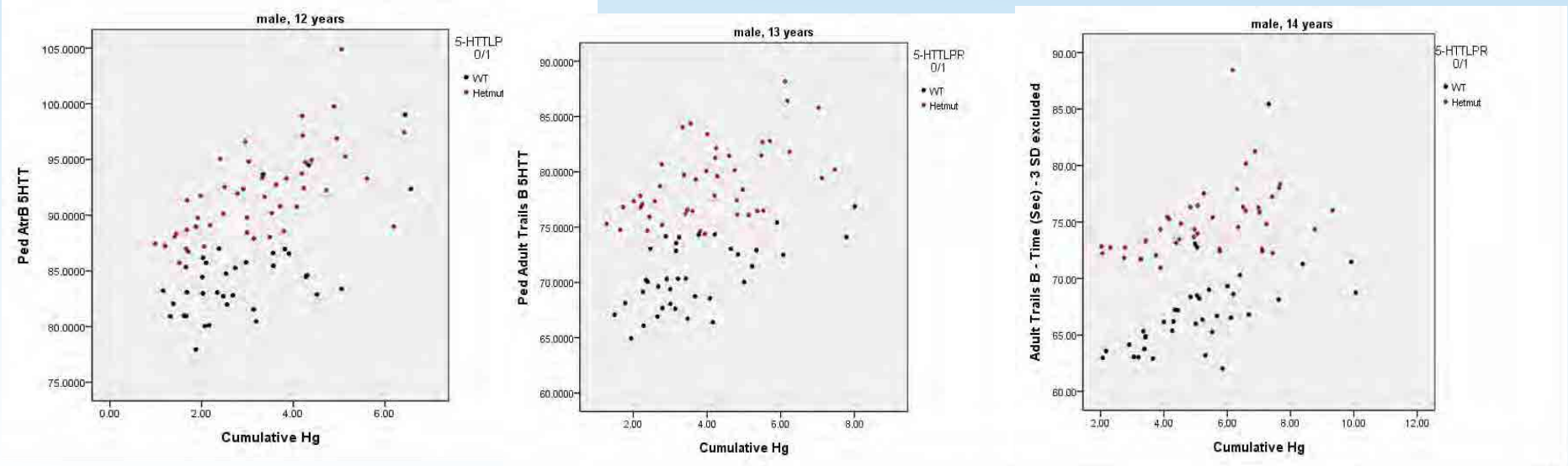
Woods James S, Heyer N, Echeverria D, et al., under review 2012

Executive Function- Adult Trailmaking B secs

Top – predicted values corrected for age and learning or repetition

Bottom – predicted values corrected for age

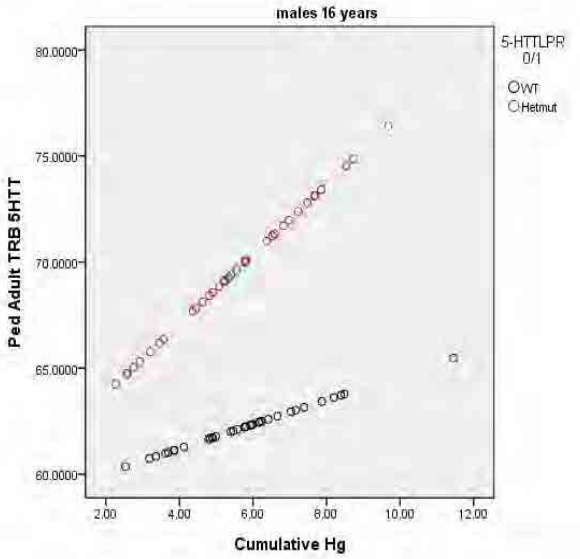


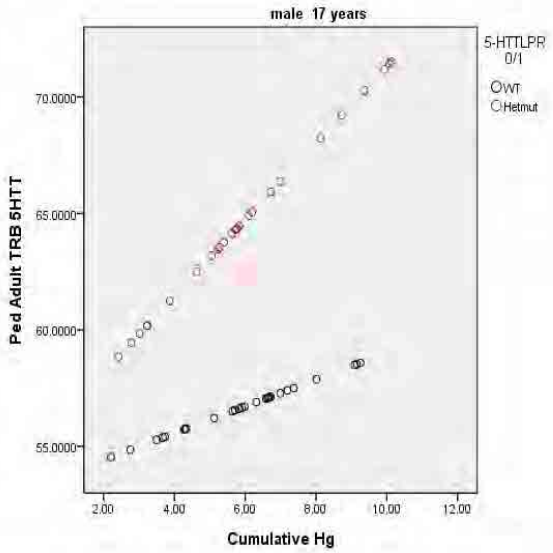


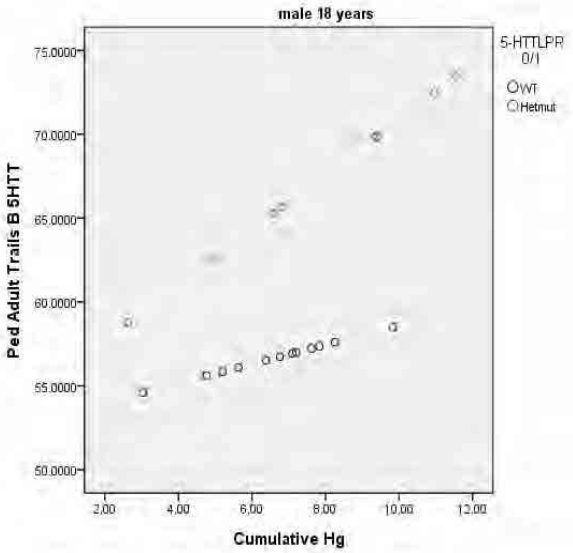
Executive Function- Adult Trailmaking B secs

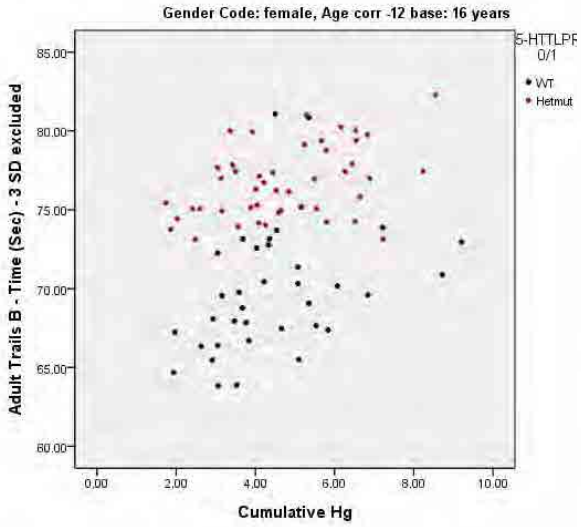
Top – predicted values corrected for age and learning or repetition

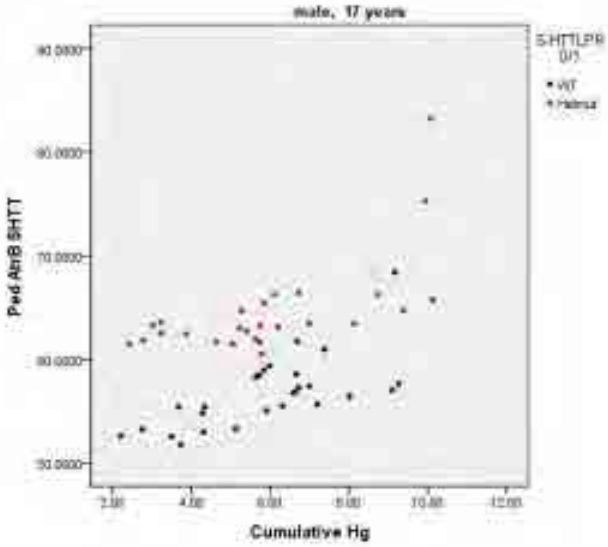
Bottom – predicted values corrected for age

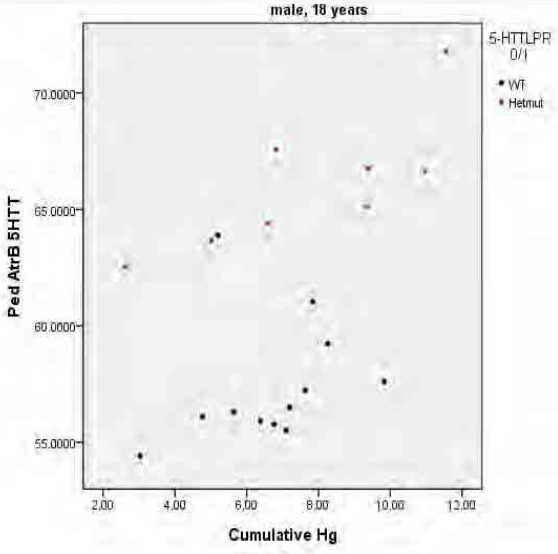






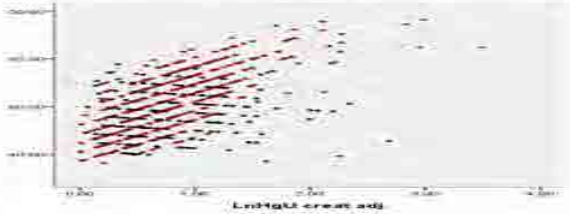




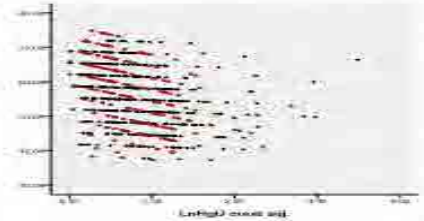


Interactions for CPOX4-HgU (Black=WT; Red=Het/Mut)

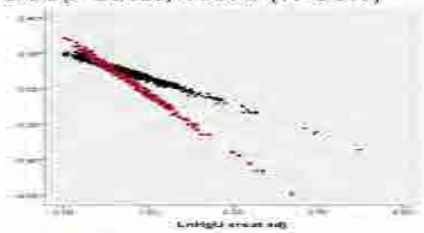
Exec Function: Trails B (secs)



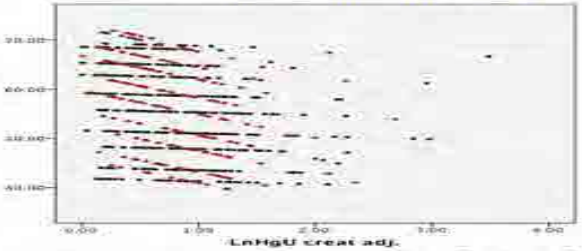
Visual Reproductions (N Corr)



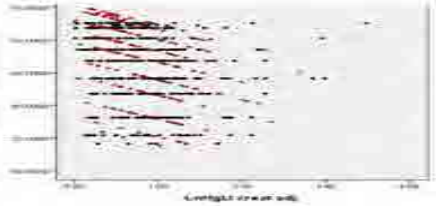
Stroop Color/Word (N Corr)



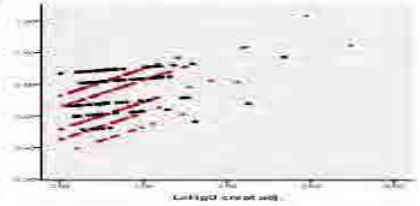
The Continuous Visual Memory Test (d-prime)



Finger Tap

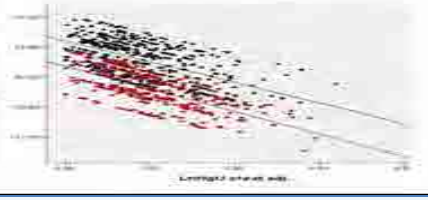


Hand Steadiness Touch



VAMS Tired

VAMS Tense



Acute Hg^0 dose-response effects among boys and girls with CPOX WT or CPOX4 variant in Year 2

Measure	WT		Het or Mut	
	Beta (SE)	r_{part} (p)	Beta (SE)	r_{part} (p)
BOYS				
Attention Domain				
Stroop Test – Color	-.19 (1.80)	-01 (.92)	**-8.40 (2.80)**	**-.42 (.005)**
Stroop Test – Word/Color	1.09 (1.51)	.07 (.47)	**-3.50 (1.68)**	**-.31 (.04)**
Motor Domain				
Finger Tapping – Dominant	1.21 (.91)	.13 (.19)	**-3.25 (1.53)**	**-.32 (.04)**
GIRLS				
Learning and Memory Domain				
RAVALT TR 5	.28 (.43)	.07 (.51)	**-1.34 (.47)**	**-.38 (.006)**
RAVALT TR 8 - List A 20'	.34 (.45)	.08 (.46)	**-1.69 (.55)**	**-.40 (.003)**

Values in **bold** signify $p \leq 0.05$.

Woods James S, Heyer N, Echeverria D, et al., under review 2012

Behavioral Test	N 121	Cumulative Hg^0				Maximum Hg^0			
		WT		HET OR MUT		WT		HET OR MUT	
		Beta (SE)	r_{part} (p)	Beta (SE)	r_{part} (p)	Beta (SE)	r_{part} (p)	Beta (SE)	r_{part} (p)
ATTENTION									
Stroop Test - Color		-1.14 (2.32)	-.06 (.63)	-12.55 (4.05)	**-.47 (.004)**	.73 (2.24)	.04 (.74)	**-11.17 (3.80)**	**-.45 (.006)**
Word		-2.90 (3.20)	-.10 (.37)	-18.06 (4.89)	**-.54 (.001)**	-.77 (3.10)	-.03 (.80)	**-17.10 (4.51)**	**-.54 (.001)**
WAIS-III - Digit Span		.11 (.77)	.02 (.88)	-3.57 (1.12)	**-.48 (.003)**	.87 (.74)	.13 (.24)	**-3.90 (.98)**	**-.57 (.0001)**
WMS-III - Spatial Span		.17 (.62)	.03 (.79)	-2.45 (.97)	**-.40 (.02)**	.57 (.60)	.11 (.35)	**-2.89 (.85)**	**-.50 (.002)**
Adult Trails A - Time (Sec)		-.80 (2.07)	-.04 (.70)	11.25 (3.83)	**.45 (.006)**	-2.37 (1.98)	-.14 (.24)	**13.04 (3.30)**	**.56 (.0001)**
VISUAL SPATIAL									
SRT Mean		.00 (.03)	.01 (.96)	.15 (.05)	**.44 (.007)**	.01 (.03)	.02 (.86)	**.14 (.05)**	**.46 (.005)**
WAIS-III - Digit Symbol		-2.46 (3.33)	-.08 (.46)	-20.70 (6.08)	**-.50 (.002)**	-.32 (3.32)	-.01 (.92)	**-18.17 (5.75)**	**-.48 (.003)**
EXECUTIVE FUNCTION									
Adult Trails B		---	---	---	---	1.98 (6.08)	.04 (.75)	**22.26 (7.03)**	**.48 (.003)**
LEARNING & MEMORY									
RAVALT TR5 - List A		---	---	---	---	.51 (.43)	.13 (.24)	**-1.78 (.80)**	**-.36 (.03)**
TR7 - A/ post B		---	---	---	---	.52 (.52)	.11 (.33)	**-2.24 (.82)**	**-.42 (.01)**
TR8 - List A 20'		.32 (.60)	.06 (.60)	-2.01 (.92)	**- .35 (.04)**	.84 (.58)	.16 (.15)	**-2.14 (.83)**	**-.40 (.01)**
MOTOR									
WRAVMA – Pegs Dominant		---	---	---	---	-.55 (1.58)	-.04 (.73)	**-7.16 (2.90)**	**-.39 (.02)**
Non Dom		.41 (1.49)	.03 (.27)	-5.87 (2.92)	**-.33 (.05)**	.79 (1.44)	.06 (.58)	-5.34 (2.72)	-.32 (.06)
Finger Tapping - Dominant		1.59 (1.22)	.15 (.20)	-4.03 (1.76)	**-.37 (.03)**	**2.59 (1.15)**	**.25 (.03)**	**-3.46 (1.65)**	**-.34 (.04)**
Non-Dom		1.07 (1.27)	.10 (.40)	-7.24 (1.67)	**-.60(.0001)**	2.14 (1.21)	.20 (.08)	-5.83 (1.66)	**-.52 (.001)**

Woods James S, Heyer N, Echeverria D, et al., under review 2012

Summary of Hg^0 Observations

In children, repeated measures mixed Model (III) analyses (controlling for gender, age, race, and pre-exposure IQ) support significant associations between HgU and CPOX4, and their interaction.

Examples of potential gene-HgU interactions for test scores suggest the severity of the slopes differ between the WT (Black) and the pooled Heterogenous /Mutant (Red) groups. Interaction terms were not found in occupationally exposed adults, demonstrating *the possibility of identifying children who may be susceptible to the effects of Hg exposure*.

Future Direction:

This possibility remains to be confirmed through additional genotyping for TDO2, TPH2, GRIN2A variants. The analyses will be extended to at least 360 children in newly proposed research.