Latent Effects of Gestational Exposure to Heptachlor Epoxide

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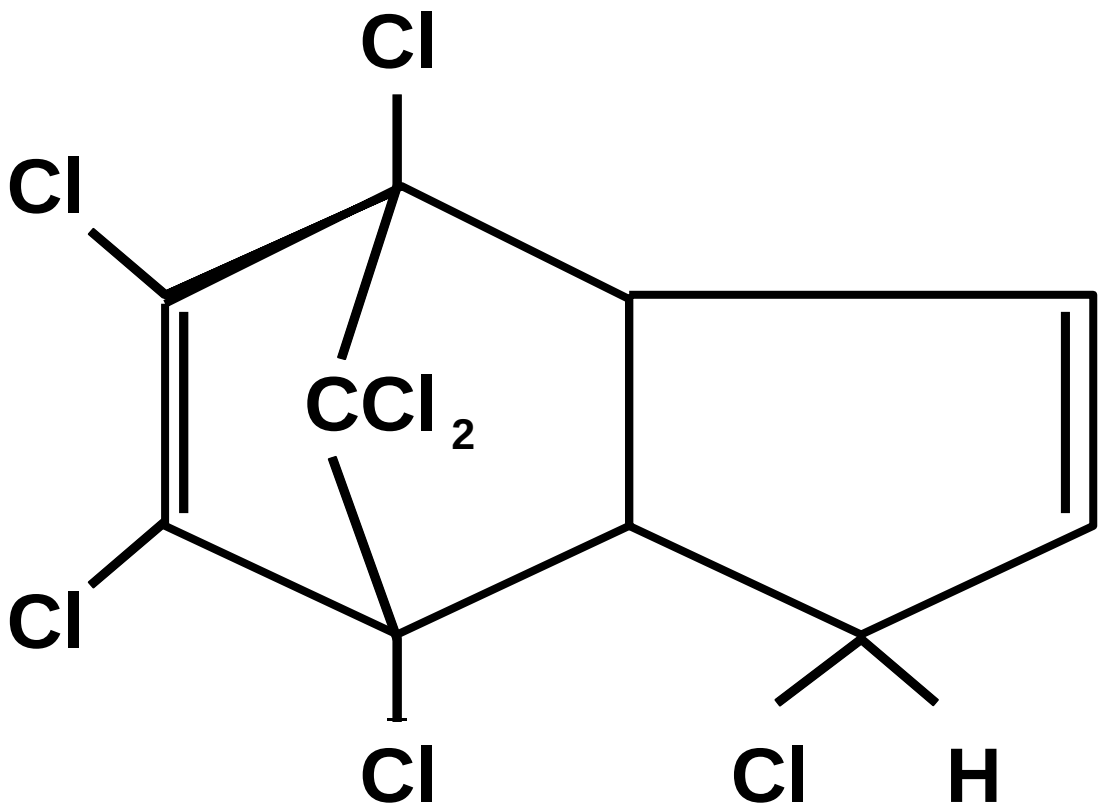
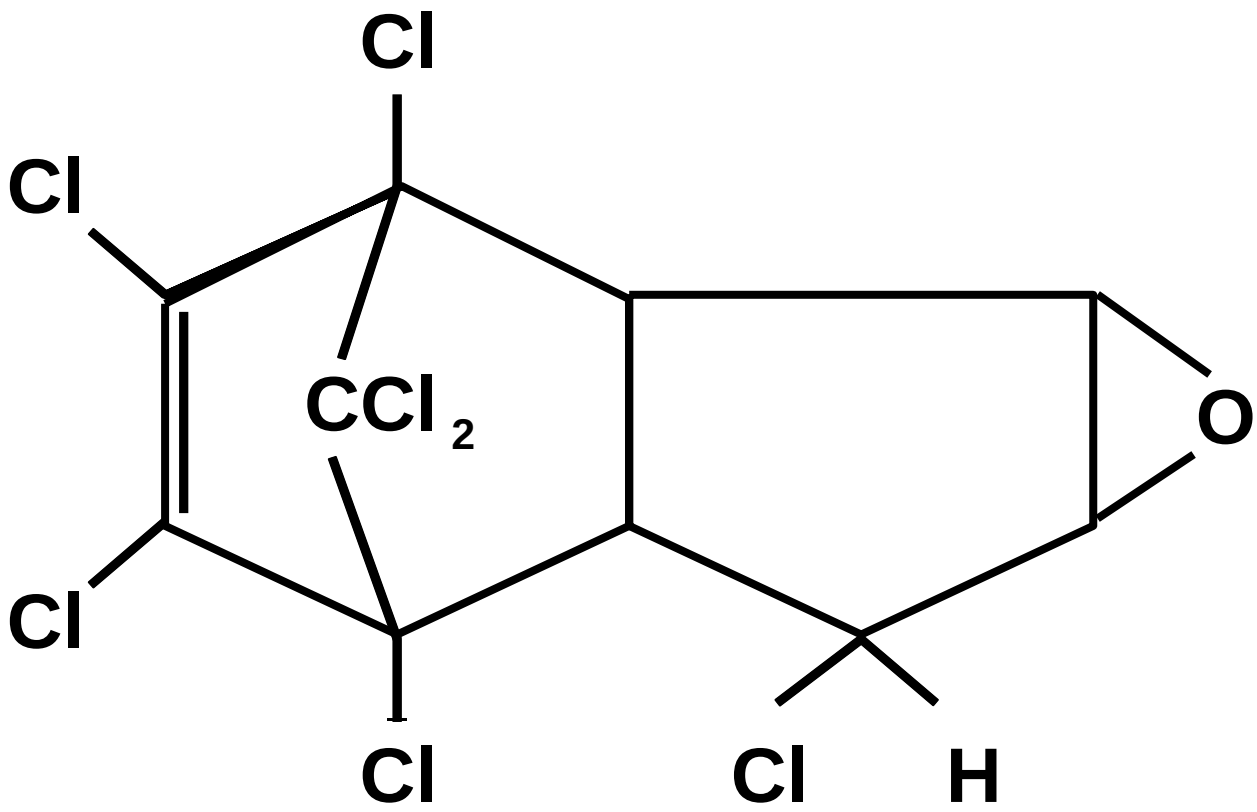
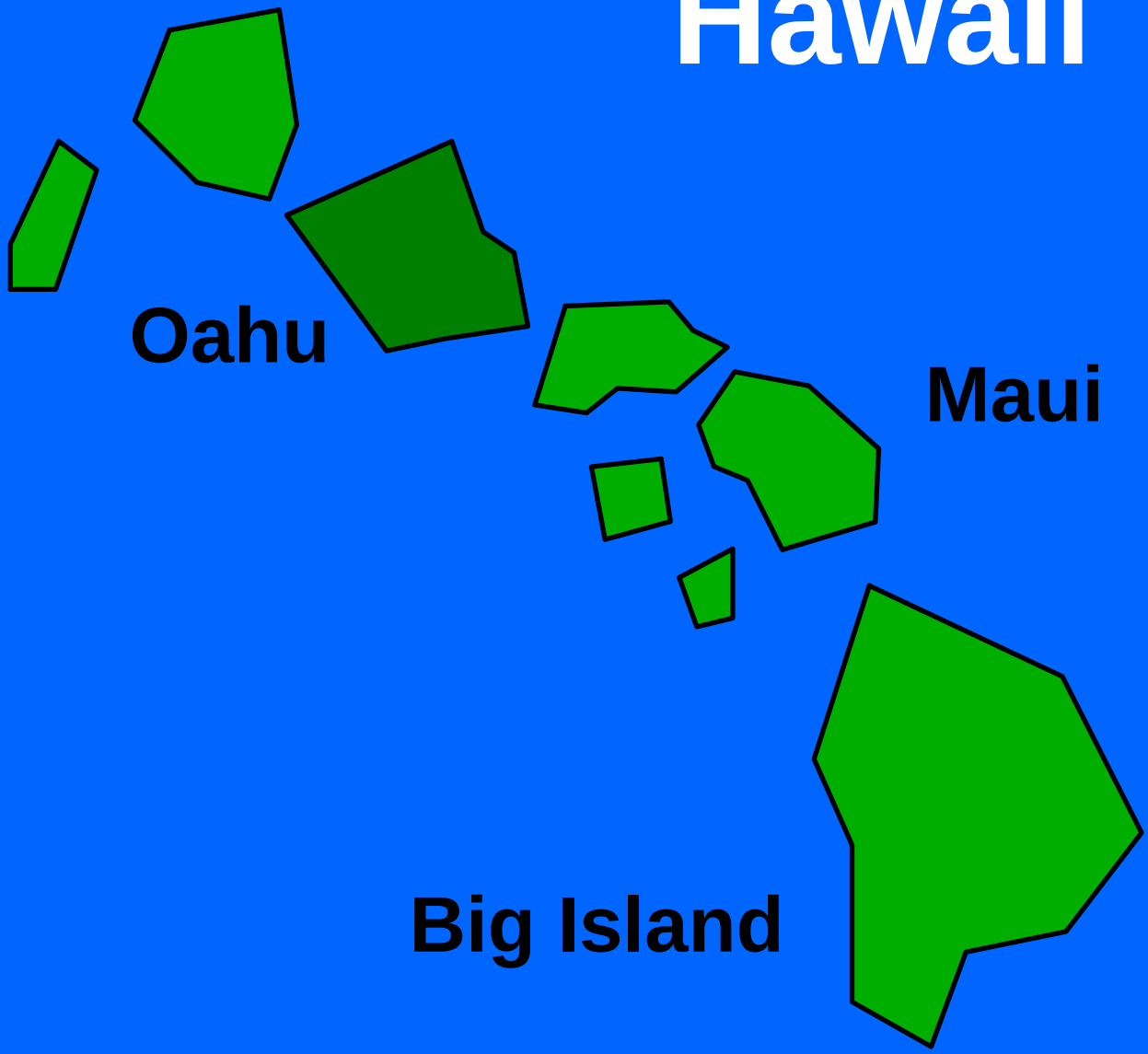
Heptachlor



Heptachlor Epoxide

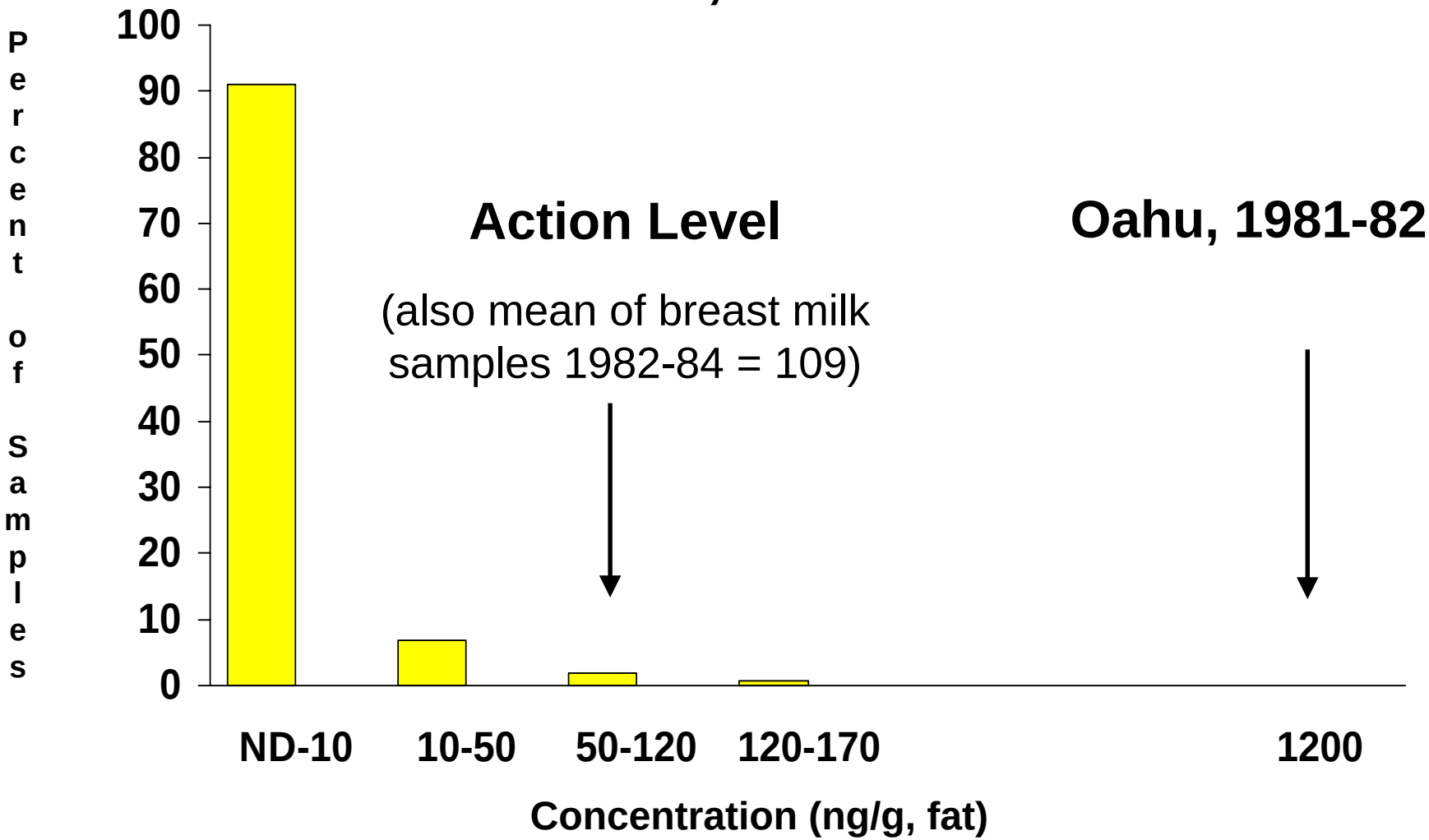


Hawaii



Heptachlor Epoxide in Milk Supply

Total United States, 1979-1982 and Oahu, 1981-1982



Effects of Juvenile Heptachlor Exposure on Nervous Function in Adult Rats

Robert Chapin, et al.

- NIEHS/EPA Juvenile Pesticide Study
- **Design**
  - Dams: gd 12 to pnd 7; pups: until pnd 42
  - Doses = 0.03, 0.3, & 3.0 mg/kg/d
    - Low dose was 95% of human milk levels in Hawaii
- **Results**
  - Righting reflex was slower in high dose female pups
  - Levels of activity and reactivity were altered in Functional Observational Battery; but no clear pattern
  - Tests of chloride flux and GABA binding were negative
  - Impairment in spatial learning in water maze (m>f)

Timeline

- **Milk contamination on Oahu :** 1980-1982
- **Exposure – biological indicator study :** 1989-1991
  - Human breast milk and serum study
- **Neurobehavioral effects study :** 1998-2002
  - Island-wide eligibility survey of 20,000 high school students
  - Neurobehavioral testing and academic achievement of stratified random sample (n = 445)
  - Mail back survey of parents (n = 1,455)
- **Immune and reproductive function study :** 2003-2006
  - Follow-up of participants in neurobehavioral study
  - Immune and reproductive function tests

Heptachlor Epoxide Exposure Study

Dean Baker, Sherry Loo,
Mary Wolff, John Tessari

1989 – 1991

Funding: Hawaii Heptachlor Research and Education Foundation

Exposure Study Conclusions

- Heptachlor epoxide concentrations in human milk and serum were significantly greater on Oahu than on the Neighbor Islands

- Reported cows milk consumption was significantly associated with heptachlor epoxide concentrations in both human milk and serum of adults

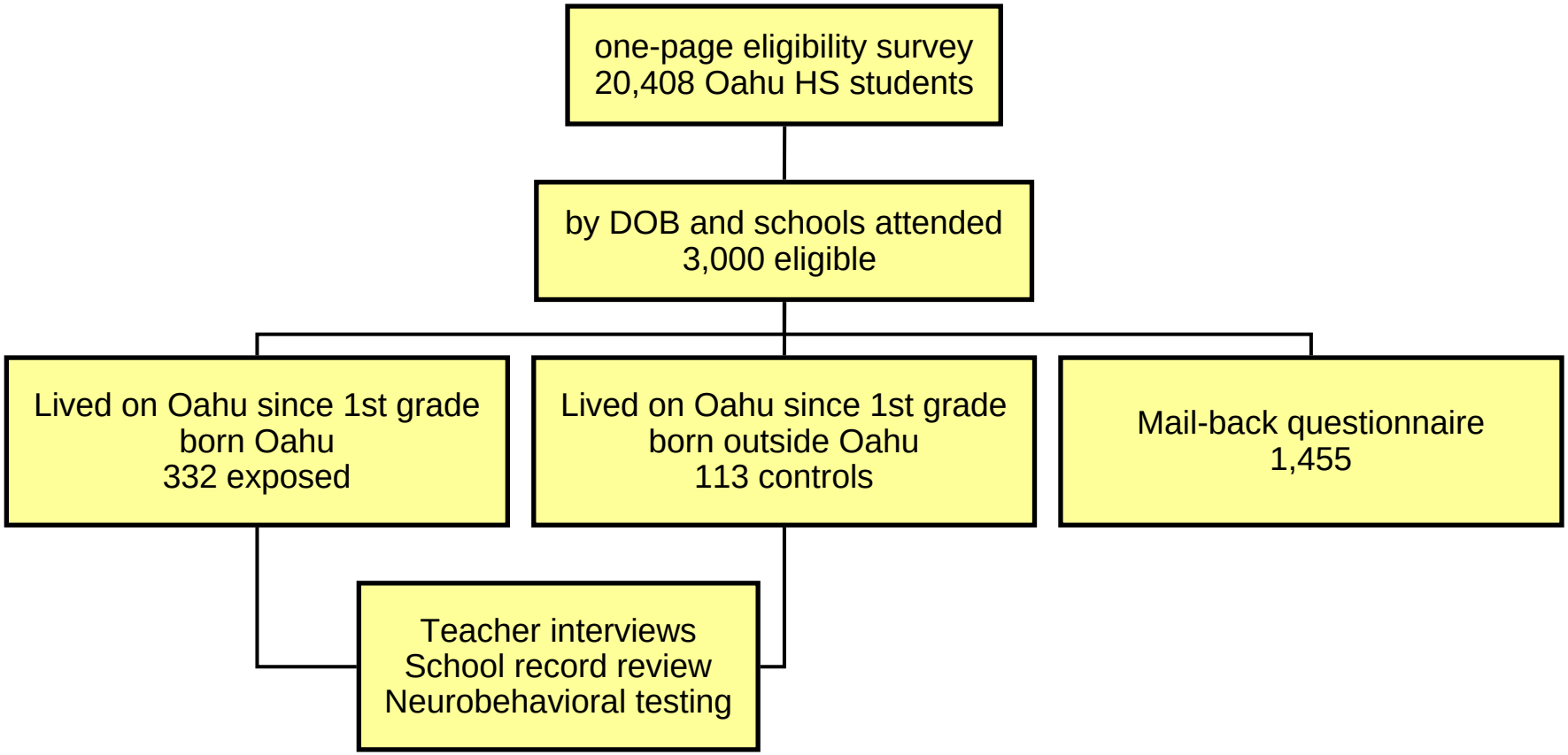
Neurobehavioral Effects Study Among High School Students

Dean Baker, Haiou Yang, Frank Crinella

1998 – 2002

Funding: Hawaii Heptachlor Research and Education Foundation

Neurobehavioral Study Population



- Born July 1981 – June 1982
- Reside on Oahu and have gone to school on Oahu since first grade
- Frequency-matched by school district and ethnicity

Data Sources

- **Student**
  - Questionnaire
  - Neurobehavioral testing
  - CBCL (Youth Self-Report)
- **Parent**
  - Questionnaire & CBCL
  - Raven
- **Teacher**
  - Questionnaire & CBCL (TRF)
- **School**
  - School records for student

Surrogate Exposure Variables

- **Birth Location**
  - Oahu versus born elsewhere
- **Mothers cows milk consumption at time of pregnancy**
  - Glasses per day

Potential Confounders

- **Demographic characteristics** - ethnicity, language
- **Socio-economic status**
  - Household members and living arrangements
  - Parents' birthplace, education, occupation
  - Household income and assistance
- **Health status and health history**
- **Sources of other toxicant exposures**
  - Residential history (farms, homes treated for termites)
  - Mother's occupation when pregnant
  - Alcohol and drug use by mother and student
- **Family, neighborhood, and school environment**
  - Principal component and factor analysis to obtain factor-derived variables
  - Home (8), neighborhood (2), school (2) factors

Results of Neurobehavioral Main Study

- Neurobehavioral test results
- CBCL internalizing and externalizing
- School performance

Neurobehavioral Tests Results by Mothers Cows Milk Consumption in Pregnancy –

Change in Variable Score per 1 Glass Milk/Day

Test	Oahu Born		Born Elsewhere	
	coef	(95% CL)	coef	(95% CL)
Raven	–0.7	(-1.4, 0.0)	0.4	(-0.9, 1.7)
WRAML VL	0.3	(-0.5, 1.0)	1.0	(-0.7, 2.7)
Trailmaking	–0.6	(-1.3, 0.1)	1.0	(-0.7, 2.6)
Color-Word Test Factor	–0.9	(-1.6, -0.1)	–0.4	(-2.0, 1.2)
CPT Factor 1: (↓ commis., ↑ HRT)	0.4	(-0.4, 1.1)	0.4	(-1.3, 2.1)
CPT Factor 2: (↓ omissions)	–0.3	(-1.1, 0.4)	0.0	(-1.8, 1.8)
WCST Factor 1: (↓ errors, ↓ perseverative responses)	–0.1	(-0.9, 0.6)	–0.2	(-1.8, 1.4)
WCST Factor 2: (↓ failure to maintain set)	0.8	(0.1, 1.6)	2.3	(0.6, 3.9)

Summary Scales of Behavior Problems by Mothers Cows Milk Consumption in Pregnancy –

Change in Outcome per 1 Glass Milk/Day

Item Summary Scale	Oahu Born		Born Elsewhere	
	coef	(95% CL)	coef	(95% CL)
YSR – Internalizing	0.1	(-0.5, 0.7)	-0.6	(-2.0, 0.9)
YSR – Externalizing	0.0	(-0.5, 0.6)	-0.3	(-1.3, 0.7)
TRF – Internalizing	0.4	(0.1, 0.7)	-0.5	(-1.1, 0.1)
TRF – Externalizing	0.6	(0.1, 1.1)	0.0	(-1.1, 1.1)

* Normative outcome is for a lower score on scale.

School Performance by Mothers Cows Milk Consumption in Pregnancy –

Change in Outcome per 1 Glass Milk/Day

Performance Measure	Oahu Born		Born Elsewhere	
	coef	(95% CL)	coef	(95% CL)
Cumulative GPA	0.0	(-0.1, 0.0)	0.0	(-0.1, 0.1)
Standardized reading	–0.9	(-2.3, 0.6)	3.5	(0.6, 6.4)
Standardized math	–0.2	(-1.2, 0.8)	1.7	(-0.4, 3.8)

Conclusions

- Moderate effect of mothers cows milk consumption during pregnancy:
  - Worse neurobehavioral performance, especially abstract concept formation, visual perception, and motor planning
  - More behavior problems, especially in internalizing domain
- No effect on academic achievement

Effects of Gestational Heptachlor Epoxide Exposure on Reproductive and Immune Function

Dean Baker, Ulrike Luderer, Haiou Yang, Sastry Gollapudi – UC Irvine

James Kesner – NIOSH

Sponsor: US Environmental Protection Agency

Study Population

- Target of 600 young adults from Oahu recruited from sampling frame of participants in the neurobehavioral effects study

Exclusion Criteria for women:

- More than 6 months since being pregnant
- More than 3 months since last breast feeding or use of IUD, hormonal contraception, or other hormonal replacement/medication
- Had no surgery on the reproductive system
- No current endocrine disorder or reproductive disease

Surrogate Exposure Variables

- **Birth Location**
  - Oahu versus born elsewhere
- **Mothers cows milk consumption at time of pregnancy**
  - Glasses per day
  - Reported by biological parent in parent questionnaire

Indicators of Reproductive Function

- **Serum**: LH and FSH in both sexes;
  - Estradiol and progesterone (women)
  - Testosterone and free testosterone (men)
- **Urine** (women): daily first morning urine and menstrual histories for six weeks
  - LH, FSH, estrone 3-glucuronide, pregnanediol 3-alpha-glucuronide
- **Semen** (men): count, motility, morphology

Indicators of Immune Function

- **Cell mediated (Th1) immunity:** cutaneous delayed hypersensitivity (DTH) reaction to standard recall antigens: candida, tetanus toxoid, saline control
- **Antibody mediated (Th2) immunity** by antibody titer response to immunization with tetanus and multivalent pneumococcal vaccine
- **Proportion of Th1 and Th2** type CD4+ cell subsets in peripheral blood assessed using *in vitro* analysis of cytokine expression following activation (IFNγ and IL-4)

Logistics of Specimen Collection and Analysis

- **Collection of biological specimens**:
  - Skin testing, vaccinations, phlebotomy – project office
  - Semen – licensed medical laboratory
  - Urine – participants' homes; picked-up by project staff
- **Processing and analysis of specimens:**
  - Antibody titers – medical laboratory in Hawaii
  - Semen analysis – medical laboratory in Hawaii
  - Reproductive hormone assays – NIOSH, Cincinnati, OH
  - Immunological function assays – UC Irvine

Analytical Strategy

- **Compare outcomes between Oahu born and non-Oahu born**
- **Compare outcomes within Oahu-born group**
  - By reported cows milk consumption by mother while she was pregnant with the participant
- **Multivariable analysis - GLM and regression**
  - Co-variates in regression models: ethnicity, mother's age at child's birth, mother's cigarette smoking during pregnancy, and reported substance use: cigarettes, alcohol, and marijuana
  - Gender as covariate or stratified by gender for analysis of endocrine-related variables

Initial Results

- Field work began in 2003 with follow-up tracing of participants from earlier study
- Field work completed in April 2006 when reached end of sampling frame
- 456 participants completed most of the protocol
- Batch analysis of some endocrine specimens is pending
- Final analysis of some immune function assays is pending (Fas, FasL, apotosis)

Place of Birth and Gender

	Number	%
Place of Birth		
Oahu	399	87.5
Neighbor Island	5	1.1
Mainland State	37	8.1
Other County	15	3.3
Gender		
Males	249	54.6
Females	207	45.4

Ethnicity

	Number	%
White	26	5.7
Asian	114	25.0
Filipino	33	7.2
Hawaiian—Non-White mix	82	18.0
Hawaiian-White mix	61	14.4
White—Non-Hawaiian mix	70	15.4
Other	70	15.4

Mothers Cows Milk Consumption During Pregnancy

	Number	%
0-5 glasses/wk	166	37.6
6-11 glasses/wk	118	26.8
12-19 glasses/wk	96	21.8
20-26 glasses/wk	42	9.5
27-56 glasses/wk	19	4.3
Missing (no Parent Qr)	15	

Univariate Analysis – Outcome Measures of Low Prevalence

- Diabetes, thyroid disease, Dx immune disorder, cancer

Males

- Hypospadia, cryptorchidism, orchitis, varicocele, trouble getting erection

Females

- PMS, absence of periods, anovulatory cycles, uterine fibroids, genital tract polyps, ovarian cysts

Age of Developmental Milestones – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Male			
Hair – armpits	0.32	(-0.3, 0.9)	0.29
Hair – legs	0.07	(-0.7, 0.9)	0.86
Hair – pubic area	0.30	(-0.3, 0.9)	0.31
Voice changed	0.12	(-0.5, 0.8)	0.72
Started shaving	0.61	(0.2, 1.4)	0.14
First ejaculation	-0.78	(-1.8, 0.2)	0.12

Age of Developmental Milestones – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Female			
Hair – armpits	0.36	(-0.5, 1.3)	0.44
Hair – legs	0.21	(-0.7, 1.1)	0.65
Hair – pubic area	0.30	(-0.5, 1.1)	0.46
Breast development	0.41	(-0.6, 1.4)	0.41
First menstrual cycle	0.19	(-0.6, 1.0	0.64

Serum Reproductive Endocrine – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Male			
LH (mIU/mL)	-0.02	(-1.1, 1.1)	0.97
FSH (mIU/mL)	-1.01	(-2.0, 0.0)	0.04
Testosterone (ng/mL)	-0.41	(-1.2, 0.4)	0.30
Free Testosterone	-0.05	(-12 , 12)	0.99
SHBG (nmol/L)	-3.28	(-17 , 11)	0.64
Inhibin-B (pg/mL)	4.69	(-47 , 56)	0.86

Serum Reproductive Endocrine – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Female *			
LH (mIU/mL)	3.18	(-12 , 18)	0.67
FSH (mIU/mL)	-0.65	(-2.6, 1.3)	0.51
Estradiol (pg/mL)	6.82	(-39 , 52)	0.77
Progesterone (ng/mL)	-3.84	(-3.8, 5.4)	0.74

* Does not include 9 females with anovulatory cycles

Female Urinary Reproductive Endocrine – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Follicular phase length (days)	1.10	(-3.8, 5.9)	0.66
Early follicular FSH	0.88	(-1.1, 2.8)	0.37
Early follicular $E_1$3G	-1.02	(-3.4, 1.4)	0.40
Periovulatory $E_1$3G	-0.10	(-11 , 11)	0.99
Follicular Pd3G	0.35	(-0.2, 0.9)	0.23
Preovulatory LH	5.30	(-10 , 21)	0.49

$E_1$3G = estrone 3-glucuronide / creatinine (ug/mg)

Pd3G = pregnanediol 3-glucuronide / creatinine (ng/mg)

Female Urinary Reproductive Endocrine – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Luteal phase length	-0.57	(-2.6, 1.5)	0.58
Mid-luteal $E_1$3G	-2.40	(-10 , 5.3)	0.53
Mid-luteal Pd3G	1.25	(-4.6, 7.3)	0.68

$E_1$3G = estrone 3-glucuronide / creatinine (ug/mg)

Pd3G = pregnanediol 3-glucuronide / creatinine (ng/mg)

Male Semen Analysis – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Sperm count (million)	7.53	(-105, 120)	0.90
Sperm concentration (million/ml)	-4.30	(-39 , 31)	0.82
Sperm % total motility	8.61	(-0.7, 18)	0.07
Sperm morphology (% normal)	1.58	(-7.4, 11)	0.73

Logistic Regression of Reproductive Function Variables – Born on Oahu versus Elsewhere

	OR	(95% CL)	p-value
Male			
Trouble erection	1.26	(0.3, 6.3)	0.78
Sperm conc < 20 mil/ml	0.86	(0.3, 2.4)	0.77
Sperm motility < 50%	2.42	(0.4, 13)	0.10
Sperm morph < 50%	1.27	(0.5, 3.1)	0.60
Female			
Irregular cycles	2.21	(0.5, 10)	0.31
Absent periods	3.00	(0.4, 24)	0.30
Anovulatory cycles*	-		

* 9 females with anovulatory cycles – all lived on Oahu

Blood Counts – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
WBC	0.39	(-0.2, 1.0)	0.18
Platelet Count	-2.31	(-21 , 16)	0.81
Neutrophils	1.47	(-1.6, 4.5)	0.34
Lymphocytes	-0.69	(-3.2, 1.9)	0.59
Eosinophils	-0.92	(-1.7, -0.1)	0.02

Immune Function Assays – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Vaccination Antibody			
Tetanus – max titer (IU/mL)	0.26	(-0.4, 0.9)	0.42
Pneumo. – max titer (ug/mL)	-1.66	(-10 , 6.9)	0.70
Pneumo. titer response	-0.59	(-8.7, 7.5)	0.89
DTH (skin test) area			
Candida net area (mm^2)	26.6	(-79, 132)	0.62
Tetanus net area (mm^2)	30.8	(-45, 107)	0.43

Lymphocyte Cytokine Expression – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Act-Unact IFNγ (TH1) (% expressed cf. CD4)	-0.18	(-2.9, 2.5)	0.90
Act-Unact IL-4 (Th2) (% expressed cf. CD4)	0.43	(-1.3, 2.2)	0.63
Unact Th1/Th2 (IFNγ / IL-4 expression)	-1.02	(-2.2, 0.2)	0.11
Act. Th1/Th2 (IFNγ / IL-4 expression)	-17.3	(-40, 5.0)	0.13

Lymphocyte Apotosis Assays – Born on Oahu versus Elsewhere

	delta	(95% CL)	p-value
Baseline Fas	-1.37	(-5.8, 3.0)	0.54
Baseline Fas Ligand	0.47	(-0.6, 1.5)	0.39
Act. Fas Ligand	2.10	(-1.7, 5.9)	0.28
Baseline Apotosis	3.15	(-0.5, 6.8)	0.09

(% cells)

Age of Developmental Milestones – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Male			
Hair – armpits	0.11	(-0.05, 0.3)	0.17
Hair – legs	0.05	(-0.2, 0.3)	0.62
Hair – pubic area	0.09	(-0.1, 0.2)	0.26
Voice changed	0.14	(-0.03, 0.3)	0.12
Started shaving	0.06	(-0.2, 0.3)	0.61
First ejaculation	-0.09	(-0.3, 0.2)	0.49

Age of Developmental Milestones – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Female			
Hair – armpits	-0.23	(-0.4, -0.02)	0.03
Hair – legs	-0.17	(-0.4, 0.04)	0.11
Hair – pubic area	-0.15	(-0.3, 0.04)	0.13
Breast development	-0.14	(-0.4, 0.1)	0.23
First menstrual cycle	-0.02	(-0.2, 0.2)	0.88

Serum Reproductive Endocrine – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Male			
LH (mIU/mL)	-0.03	(-0.3, 0.3)	0.84
FSH (mIU/mL)	0.04	(-0.2, 0.3)	0.74
Testosterone (ng/mL)	-0.07	(-0.3, 0.1)	0.47
Free Testosterone	-1.12	(-4.4, 2.1)	0.50
SHBG (nmol/L)	0.00	(-3.7, 3.7)	0.99
Inhibin-B (pg/mL)	3.05	(-10 , 16)	0.64

Serum Reproductive Endocrine – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Female *			
LH (mIU/mL)	-1.76	(-5.4, 1.9)	0.34
FSH (mIU/mL)	-0.23	(-0.7, 0.2)	0.33
Estradiol (pg/mL)	2.28	(-8.7, 13)	0.68
Progesterone (ng/mL)	0.16	(-1.0, 1.3)	0.78

* Does not include 9 females with anovulatory cycles

Female Urinary Reproductive Endocrine – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Follicular phase length	-0.16	(-1.2, 0.9)	0.76
Early follicular FSH	0.09	(-0.3, 0.5)	0.65
Early Follicular $E_1$3G	0.10	(-0.4, 0.6)	0.67
Periovulatory $E_1$3G	0.04	(-2.5, 2.6)	0.97
Follicular Pd3G	0.01	(-0.1, 0.1)	0.84
Preovulatory LH	-2.21	(-5.6, 1.2)	0.20

$E_1$3G = estrone 3-glucuronide / creatinine (ug/mg)

Pd3G = pregnanediol 3-glucuronide / creatinine (ng/mg)

Female Urinary Reproductive Endocrine – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Luteal phase length	-0.04	(-0.5, 0.4)	0.85
Mid-luteal $E_1$3G	-0.47	(-2.3, 1.4)	0.61
Mid-luteal Pd3G	-0.37	(-1.9, 1.2)	0.63

$E_1$3G = estrone 3-glucuronide / creatinine (ug/mg)

Pd3G = pregnanediol 3-glucuronide / creatinine (ng/mg)

Male Semen Analysis – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Sperm count (millions)	0.18	(-29 , 29)	0.99
Sperm concentration (million/ml)	-2.82	(-12, 6.0)	0.53
Sperm % Total Motility	1.82	(-0.3, 4.0)	0.10
Sperm Morphology (% normal)	0.22	(-2.0, 2.4)	0.84

Logistic Regression of Reproductive Function Variables – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	OR	(95% CL)	p-value
Males			
Trouble erection	0.79	(0.4, 1.4)	0.41
Sperm conc < 20 mil/ml	0.99	(0.7, 1.3)	0.96
Sperm motility < 50%	0.76	(0.5, 1.3)	0.29
Sperm morph < 50%	1.00	(0.8, 1.3)	0.99
Females			
Irregular cycles	0.79	(0.5, 1.2)	0.28
Absent periods	0.93	(0.6, 1.4)	0.73
Anovulatory cycles	0.63	(0.3, 1.4)	0.25

Blood Count – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
WBC	0.06	(-0.1, 0.2)	0.40
Platelet Count	-1.35	(-6.1, 3.4)	0.57
Neutrophils	-0.15	(-0.9, 0.6)	0.70
Lymphocytes	0.07	(-0.6, 0.7)	0.84
Eosinophils	0.21	(0.01, 0.4)	0.04

Immune Function Assays – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Vaccination Antibody			
Tetanus – max titer (IU/mL)	0.04	(-0.1, 0.2)	0.60
Pneumo. – max titer (ug/mL)	-3.10	(-5.2, -1.0)	0.003
Pneumo. titer response	-2.17	(-4.0, -0.3)	0.02
DTH (skin test) area			
Candida net area (mm^2)	6.43	(-20 , 33)	0.64
Tetanus net area (mm^2)	-4.47	(-25 , 16)	0.66

Lymphocyte Cytokine Expression – Mothers Cows Milk Consumption in Pregnancy (gl/day)

	coef	(95% CL)	p-value
Act-Unact IFNγ (Th1) (% expressed cf. CD4)	-0.22	(-0.9, 0.4)	0.49
Act-Unact IL-4 (Th2) (% expressed cf. CD4)	0.24	(-0.2, 0.7)	0.26
Unact Th1/Th2 (IFNγ / IL-4 expression)	0.03	(-0.2, 0.2)	0.78
Act. Th1/Th2 – (IFNγ / IL-4 expression)	-1.26	(-6.5, 4.0)	0.64

Lymphocyte Apotosis Assays – Mothers Cows Milk Consumption in Pregnancy
(gl/day)

	coef	(95% CL)	p-value
Baseline Fas	0.29	(-0.8, 1.3)	0.59
Baseline Fas Ligand	0.15	(-0.4, 0.1)	0.28
Act. Fas Ligand	-0.31	(-1.3, 0.6)	0.52
Baseline Apotosis	-0.23	(-1.1, 0.6)	0.59

(% cells)

Impressions of Initial Findings

- **Developmental Milestones**
  - Minimally later development in males
  - Suggestion of earlier development in females by mothers cows milk consumption during pregnancy
- **Semen**
  - No apparent associations
- **Serum Reproductive Hormones**
  - No apparent associations
- **Urinary Reproductive Hormones - Females**
  - No apparent associations in follicular phase
  - Suggestion of decreased luteal phase $E_1$3G & Pd3G by mothers cows milk consumption during pregnancy

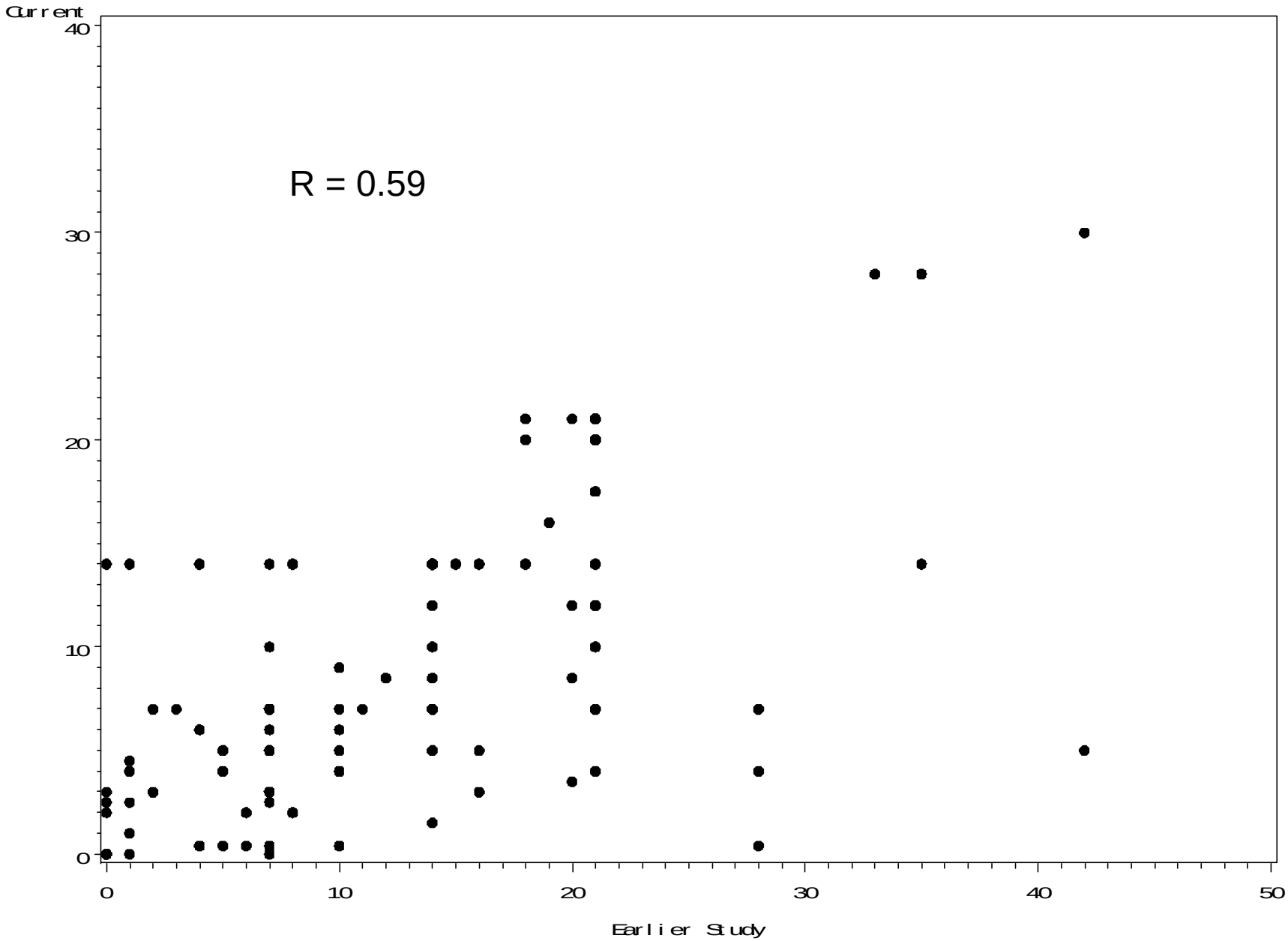
Impressions of Initial Findings

- **Antibody titer response to vaccination**
  - No apparent associations for tetanus
  - Decreased titers and response to pneumococcal vaccination among Oahu born and by mothers cows milk consumption during pregnancy
- **Cell-mediated immunity (DTH)**
  - No apparent associations
- **Lymphocyte cytokine expression**
  - No significant associations
  - Suggestive pattern of lower IFN-γ (Th1) and higher IL-4 (Th2) among Oahu born and by mothers cows milk consumption during pregnancy

Challenges & Limitations

- Logistics
  - Follow-up of mobile, young population
  - Specimen collection and analysis
- Small study population with few “controls”
  - Oahu born (88%), elsewhere (12%)
- Exposure measures
  - Lack of biological indicator of relevant gestational exposure
  - Recall of mothers cows milk consumption as surrogate exposure variable

Correlation of Mother's Reported Cows Milk Consumption - Mother report in 1998-99 and 2004-06



Overall Impressions

- No substantial effects of gestational heptachlor epoxide exposure on reproductive or immune function in young adults
  - Suggestive gender-specific effect on onset of puberty
  - Decreased antibody response to pneumococcal vaccination
  - Suggestive pattern of Th1–Th2 shift
- However, analysis is limited by small study population and exposure misclassification due to non-differential recall bias of mothers cows milk consumption at time of pregnancy

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