George Lambert, MD Director

Center of Oxidative Stress and Intervention

UMDNJ
UNIVERSITY OF MEDICINE & DENTISTRY OF NEW JERSEY

"Translational & Therapeutic Intervention Research Group"

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William Johnson	Dept. of Neurology	UMDNJ-Piscataway
Bernd Spur	Dept. of Cell Biology	UMDNJ-SOM
Peter Stein	Dept. of Surgery	UMDNJ-SOM
Xue Ming	Dept. Neurology & Neuroscience	UMDNJ-Newark
Edward Scot Stenroos	Dept. of Neurology	UMDNJ-Piscataway
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Jim Zhang	Occupational and Environmental Health	UMDNJ-School of Public Health
Larry Needham	Human Health Effects Laboratory-NHANES	CDC-Atlanta
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Sandra Harris	Douglass Center	Rutgers University
Dana Barr	School of Public Health	Emory University
Leon Guo	Envir and Occupational AHealth	National Taiwan U
Ping Chi	Environmental Sciences	National Kaioshung U
Xiao Huang	Environmental Sciences	Peking University

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Thank you for the Invitation

- NATIONAL CHILDREN ‘ S STUDY
- NICHD

NEURODEVELOPMENTAL SUSCEPTIBILITY TO ENVIRONMENTAL EXPOSURE

MAY 13, 2011
NICHD/NIH- BETHESDA

George Lambert, MD
Division of Pediatric Pharmacology and Toxicology
RWJMS- UMDNJ

What we Know

- Environmental Chemicals (Ecs) are Developmental Toxicants to the Human and the impact can be severe
- Developing human is more sensitive to Neurotoxicant Effects – as fetus and child
- Developing Human Frequently Has Higher Levels of Exposure and Unique Exposures to ECs
- Subpopulations have increased susceptibility to environmental toxins-genetic or disease specific or time specific ?CNS and critical subpopulations have been ignored,
- Environmental chemical exposure can be reduced by simple means by knowledgeable parents and their pediatricians-

SUSCEPTIBILITY OF THE OFFSPRING VS MOTHER

- RUBELLA
- THALIDOMIDE
- ALCOHOL / FAS
- METHYL MERCURY
- POLYCHLORIN-ATED BIPHENYLS

WINDOWS OF SUSCEPTIBILITY- TERATOGENIC WINDOWS

- THALIDOMIDE- PHOCOMELIA / AUTISM
- ORGANOPHOSPHATES- PRENATAL but not POSTNATAL EXPOSURES AND IQ
- LEAD- CHILDHOOD & PRENATAL EXPOSUE AND IQ AND CRIMINALITY – ZEBRAFISH AND STAGES OF DEVELOPMENT HOURS AFTER FERTILIZATION- alteration of neurodevelopmental gene expression

The developing human is a canary of the species

- Susceptibility
- Sensitivity
- Most susceptible are compromised children ie children with autism, asthma, etc
- Reliability
- ***Diversity of adverse effects***

Overview – Introduction

- What are some of the known diverse clinical effects of environmental chemicals on neurobehavioral function of the developing human
- Why children are at greatest risk from neurotoxic environmental chemicals
- Overview of some of the issues of studying the effects of environmental toxins on neurodevelopment using Pb, PCBs, OPs

Diversity of neurotoxicants' effects

- Environmental Chemicals are Developmental Neurotoxicants To The Human
  - Alters growth (HC*) – PCBs*, Ethanol*, Organophosphate pesticides*, DDT, smoking
  - Alters function
    - Cognitive Function - PCBs, Hg, Pb, Ops, Mn
    - Behavior – PCBs in gender specific function
      - Also impulsivity, stress response, violent behavior, etc etc
    - Neuroendocrine Function – Pb, Cocaine, corticosteroids

CORTICOSTERIODS

- PRENATAL ALCOHOL AND CIGARETTE EXPOSURE REDUCED THE CORTISOL RESPONSE TO STRESS (IMMUNIZATIONS) IN THE 2 MONTH OLD BUT NOT 6 MONTH OLD INFANT.(Ramsay et al, J Pediatr Psychol 1996. 21: 833)

Overview – Introduction

- What are the known diverse clinical effects of environmental chemicals on neurobehavioral function of the developing human
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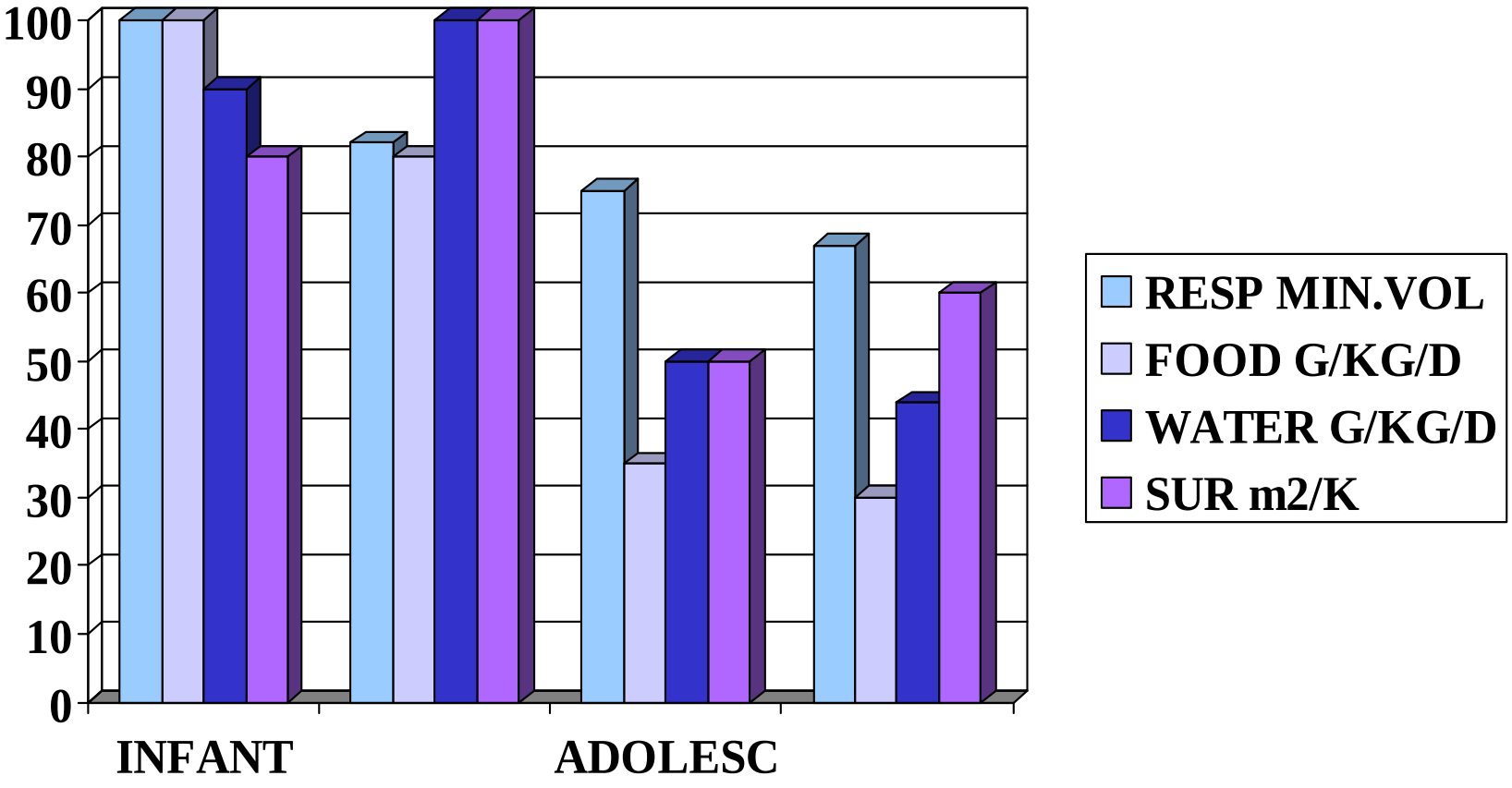
PEDIATRIC TOXICOKINETICS & DYNAMICS OF NEUROTOXINS

- EXPOSURE
- ABSORPTION
- DISTRIBUTION
- METABOLISM
- CLEARANCE
- END ORGAN SUSCEPTIBILITY

NORMALIZED EXPOSURE**



Unique Exposure

- ***EXPOSURE***
  - ***BEGIN AT MATERNAL CONCEPTION & BEFORE***
    - ***EPIGENETICS-PERINATAL IMPRINTING***
    - ***DIET/FISH***
  - ***UNIQUE EXPSOURES***
    - ***STUFF ANIMALS****
    - ***TRANSPLACENTAL & TRANSMAMILARY***
    - ***PICA- increased with autism***
    - ***Toys***
    - ***Environments-air/soil***

Breast milk and environmental chemical exposure

	Typical levels*	FDA [action]	ADI ug/kg	BM Intake
Dieldrin	1-6	7.5	0.1	0.8
Hepato-chlor Ep	8-30	7.5	0.5	4
PCBs	40-100	62.5	1	14
DDTs	50-200	50	5	28

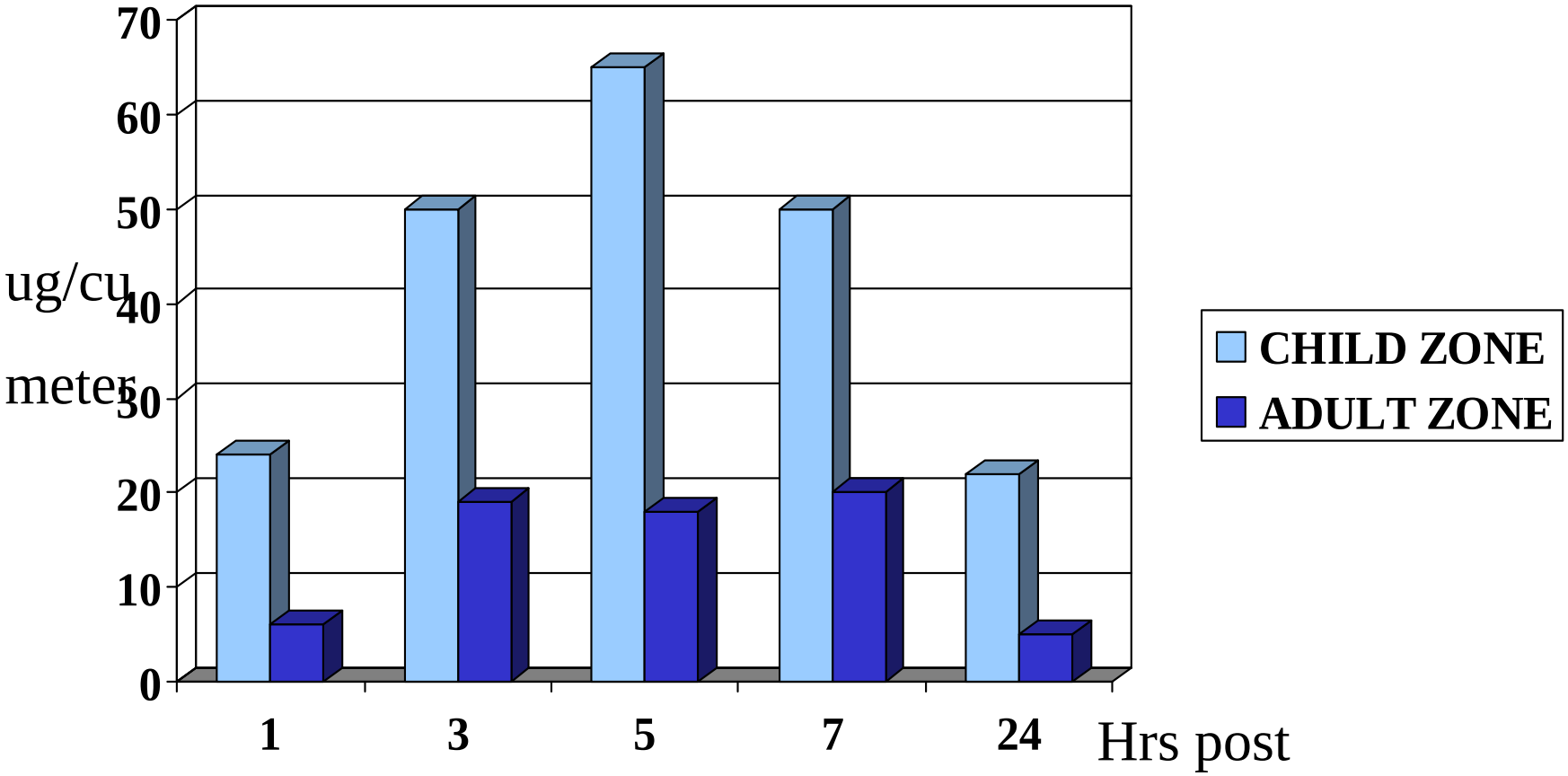
•parts/billion [BREAST MILK IS BEST] Rogan, NEJM ’80

•PEDIATRICIANS AND EXPOSURE OF KIDS

Center for Child & Reproductive Environmental Health & Neurotox Center

- ***EXPOSURE***
  - ***BEGIN AT MATERNAL CONCEPTION***
    - ***DIET/FISH***
  - ***UNIQUE EXPSOURES***
    - ***STUFF ANIMALS****
    - ***TRANSPLACENTAL & TRANSMAMILARY***
    - ***PICA- increased with autism***
    - **Play spaces – floor/direct lower levels of air quality**

Breathing zones in room post chlorpyrifos treatment



Fenske '93

Comparative estimated resp dose for chlorpyrifos

Hrs/dy	Resp rate M3/hr	[Air] ug/m3	Est. Dose ug/kg/day
child			
16	.126 rest	66.8	37.4
8	.378active	66.8	
adult			
8	.487 rest	66.8	9.8
12	.600 active	45.7	

Usepa ‘89

ABSORPTION

- SKIN - MORE SURFACE AREA AND LESS CORNIFICATION
- LUNGS - MORE SURFACE AREA FOR ABSORPTION
- GI - CAN BE SIGNIFICANTLY GREATER IN CHILDREN

PER CENT OF LEAD GI ABSORPTION

AGE (YRS)	GI ABSORPTION %
0-1	42 - 53
1-2	42 - 53
2-6	30 - 40
6-7	18 - 24
ADULT	7 - 15

- USEPA-89

COMPARATIVE TOXICOKINETICS of LEAD

INTAKE	CHILD	ADULT	MAX C/A
INHAL*	0.05	0.01- .02	5
GI DIET*	2.5	0.65	4
DUST	2.1	0.06-.09	35
ABSORB	42%	15-30	3
LUNG			
GI	42%	7-17%	8
RETAIN	0.33	0.01-.04	30

*ug/kg/day

USEPA ‘86 ‘90

TOXICODYNAMICS

- EXPOSURE
- ABSORPTION
- DISTRIBUTION*
- METABOLISM*
- CLEARANCE
- END ORGAN SUSCEPTIBILITY

SUSCEPTIBILITY OF THE OFFSPRING VS MOTHER

- RUBELLA
- THALIDOMIDE
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- METHYL MERCURY
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LEAD LOAELS ug/dl

	ADULTS	CHILDREN
ENCEPHALO PATHY	100 -200	80 - 100
DEC. CNS FX	40	< 10 ?,<1?
DEC. NERVE CONDUC-TION	30	15
ANEMIA	80	70
USEPA 1992		
Dec IQ		1-5
Altered puberty		1vs 3

Children’s unique relationship to Environmental chemicals (NT)

- Surroundings – child’s work area (dirt, floor), breathing zone areas, stuffed animals
- Food, air, water intake GREATER THAN adults
- Activities and Behavior – mouthing their environment, eating dust and dirt
- Increase end organ susceptibility especially the brain

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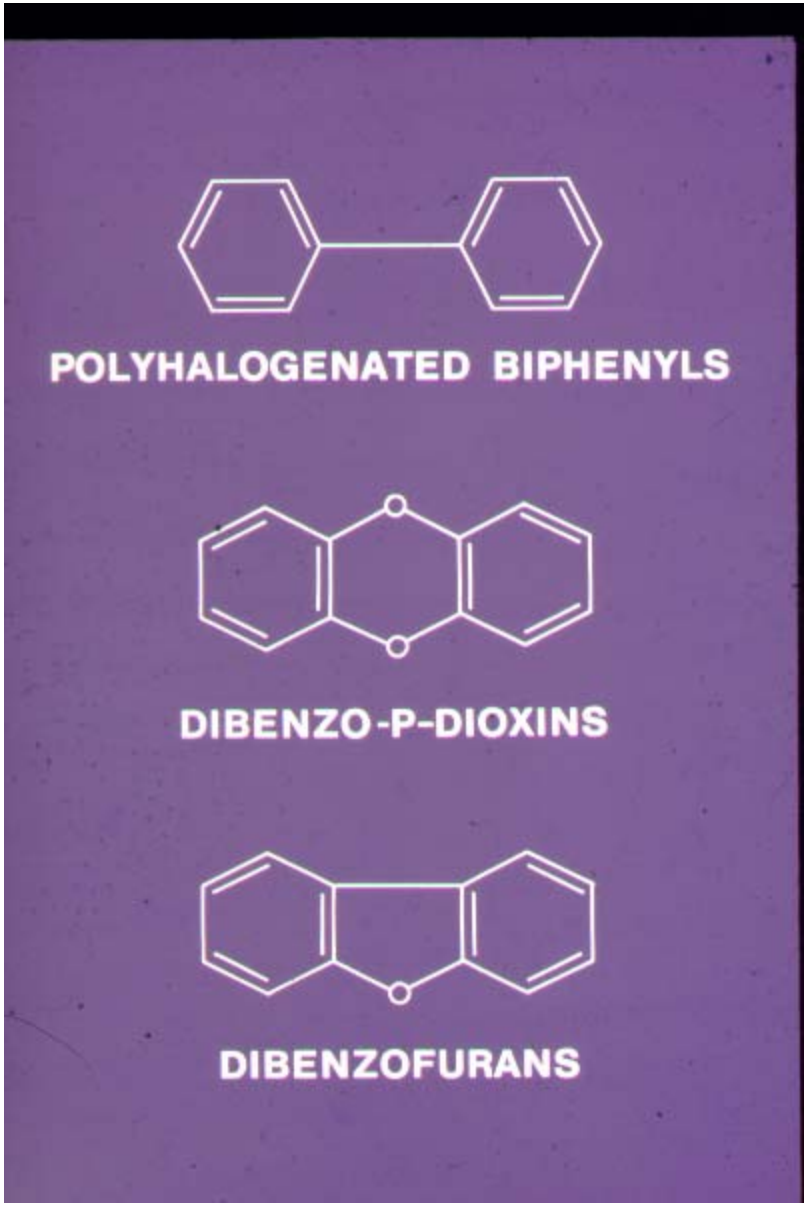


World wide/ half life in environment and body/diverse human health effects

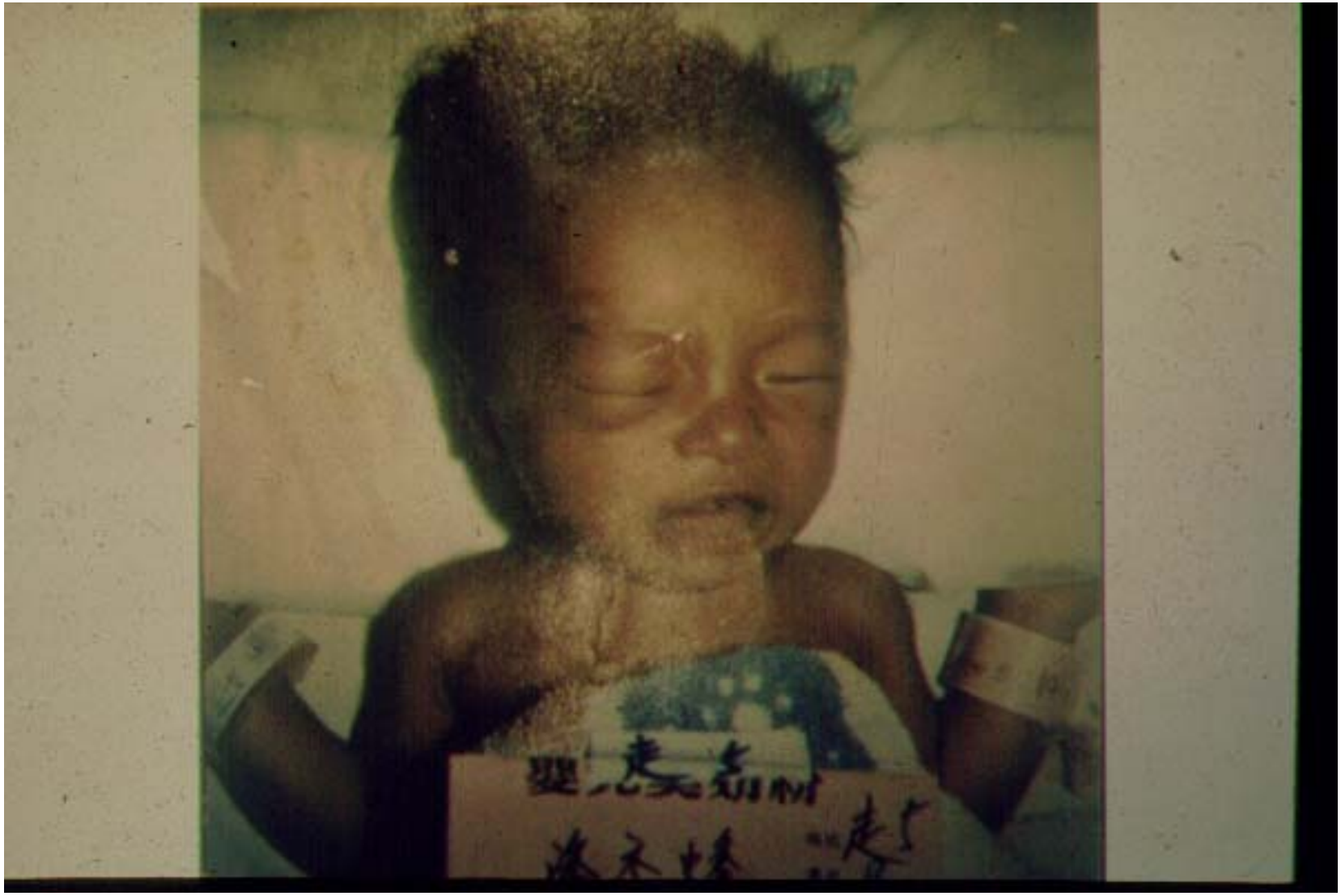
Exposed Cohorts

- PCB/PCDF YuCheng Cohort rice oil Taiwan
- PCB G.L. Fisheaters & Silo farmers Michigan
- Dioxin Seveso Cohort Industrial Italy explosion

'YU CHENG

(YU SHO JI)

LIQUID FIELD DISEASE CHILDREN



YuCheng IUGR

	% Control	95% con. limits
HEIGHT	97	95.8-98.6
WEIGHT	93	90.3-96
HEAD CIRC.	99	98.3-99.9

Rogan et al Science 1990

POLYCHLORINATED BIPHENYLS & PCDFs

- MOTHERS
- chloracne
- transient peripheral neuropathy
- transient elevated LFTs

- OFFSPRING
- abnormal growth & development
- ectodermal dysplasia
- permanent (?) neuro-logical dysfunction
- recurrent infections
- death

Cognitive Development of Yu-Cheng ('Oil Disease') Children Prenatally Exposed to Heat-Degraded PCBs

Yung-Cheng Joseph Chen, MD, MPH; Yue-Liang Guo, MD, PhD; Chen-Chin Hsu, MD, PhD; Walter J. Rogan, MD

Objective.—To compare the cognitive development in Taiwanese children who had been exposed prenatally to high levels of heat-degraded polychlorinated biphenyls (PCBs) with control children who were exposed to background levels. The disorder was called Yu-Cheng, "oil disease," in Taiwan.

Design.—Matched-pair cohort study.

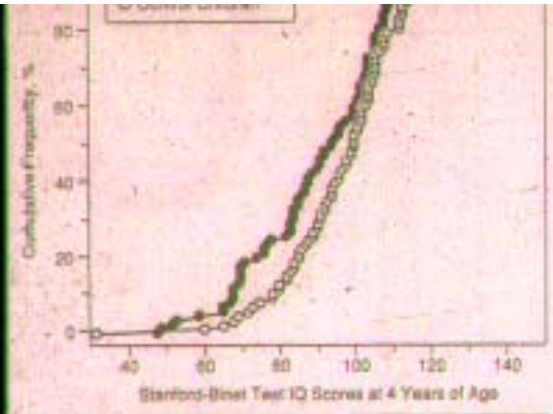


Fig 1.—Cumulative frequency distribution of Stanford-Binet test IQ scores in Yu-Cheng children (mean, 91.6) and control children (mean, 97.3) at the age of 4 years ($P = .02$ by Wilcoxon's signed rank test).

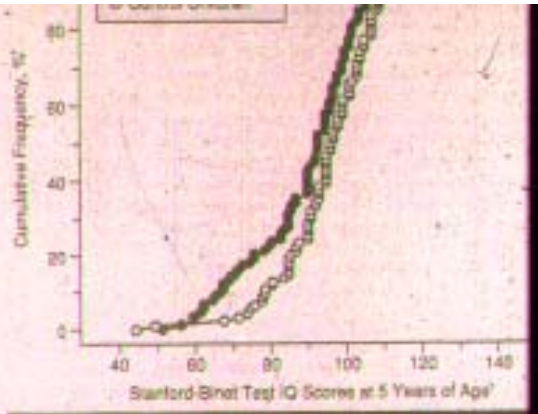


Fig 2.—Cumulative frequency distribution of Stanford-Binet test IQ scores in Yu-Cheng children (mean, 90.9) and control children (mean, 95.9) at the age of 5 years ($P = .005$ by Wilcoxon's signed rank test).

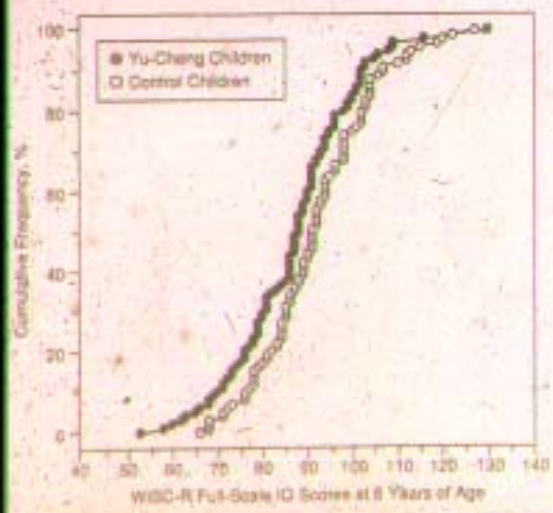


Fig 3.—Cumulative frequency distribution of full-scale IQ scores on the Wechsler Intelligence Scales for Children, Revised (WISC-R), in Yu-Cheng children.

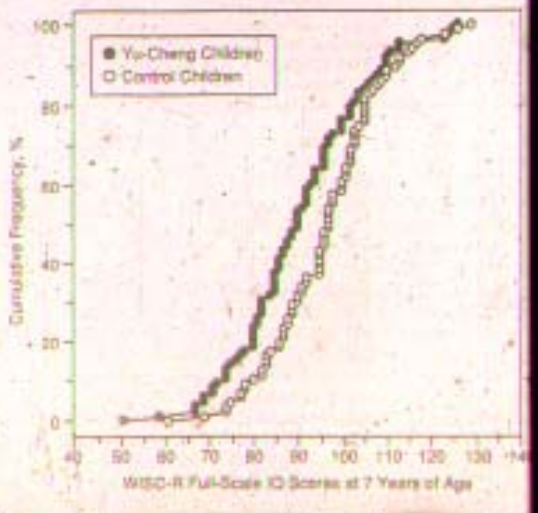
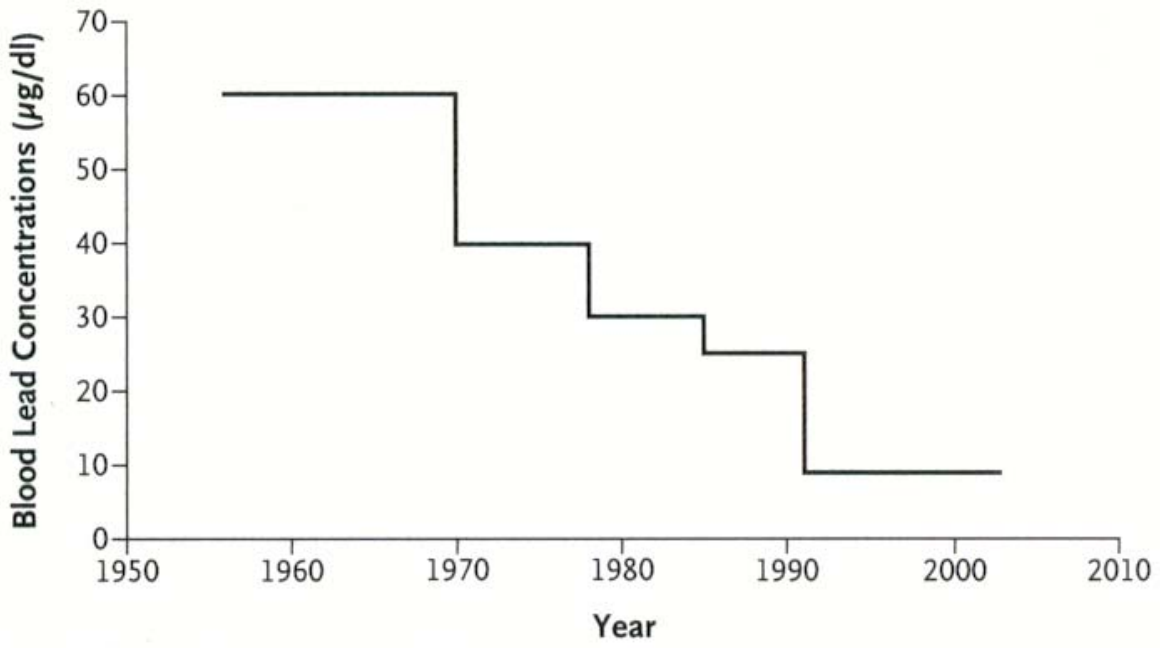


Fig 4.—Cumulative frequency distribution of full-scale IQ scores on the Wechsler Intelligence Scales for Children, Revised (WISC-R), in Yu-Cheng children.

RAVENS PROGRESSIVE MATRIXES IN YUCHENG

	MEAN (STD DEV)
FEMALES	
– EXPOSED	26 (2)
– CONTROL	27 (2)
MALES	
– CONTROL	34 (4)
– EXPOSED	24 (3) $P<0.05$

- Guo et al



Blood Lead Concentrations Considered to Be Elevated by the Centers for Disease Control and Prevention.

To convert the values for blood lead concentrations to micromoles per liter, multiply by 0.0483. Data are from the Centers for Disease Control and Prevention, 1991.[1]

LEAD LOAELS ug/dl

	ADULTS	CHILDREN
ENCEPHALO PATHY	100 -200	80 - 100
DEC. CNS FX	40	< 10 ?,<1?
DEC. NERVE CONDUC-TION	30	15
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Altered puberty		1vs 3

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 17, 2003 VOL. 348 NO. 16

Intellectual Impairment in Children with Blood Lead Concentrations below 10 μg per Deciliter

Richard L. Canfield, Ph.D., Charles R. Henderson, Jr., M.A.,
Deborah A. Cory-Slechta, Ph.D., Christopher Cox, Ph.D., Todd A. Jusko, B.S.,
and Bruce P. Lanphear, M.D., M.P.H.

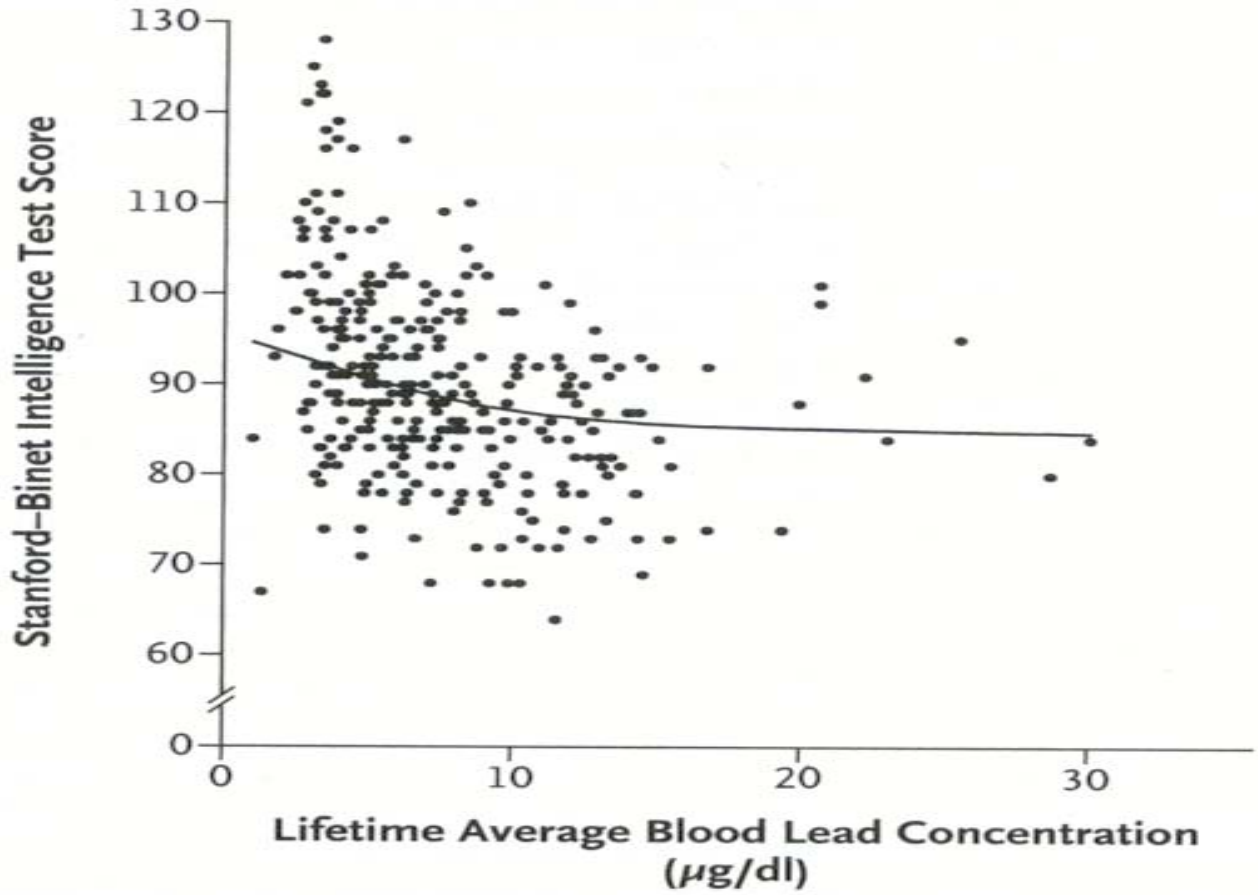

Figure 2. IQ as a Function of Lifetime Average Blood Lead Concentration.

IQ was assessed with use of the Stanford–Binet Intelligence Scale, fourth edition. The line represents the relation between IQ and lifetime average blood lead concentration estimated by the covariate-adjusted penalized-spline mixed model. Individual points are the unadjusted lifetime average blood lead and IQ values. To convert values for lead to micromoles per liter, multiply by 0.0483.

Lead and Windows of Susceptibility

- Lead levels were monitored during pregnancy and throughout childhood until the age of 6 ½ yrs old.
- Rates of arrest and violence were determined for these individuals up to 30yrs old
- Prenatal and postnatal BLL were associated with arrests and violence. RR- 0.5for every increase of BLL by 5 mcg/dl

» Wright et al PloS medicine 2008: 5:e101-

Lead and Susceptible Windows

Exposure of Zebrafish to 10microgram/dl

After 72 hr postfertilization (hpf)- 90 redundant genes with well established neurodevelopmental function to human genes expression was altered

However

The gene set at 120hpf did not share association with neurodevelopment or disease states

Peterson et al EHP 2010. 119:615-622

Organophosphates- Windows of Susceptibility Bouchard et al EHP 2011.

Organophosphate exposure was assessed by dialkyl phosphate (DAP) metabolites in urine, levels were monitored during pregnancy and then in the offspring for 5 yr

Cognitive function (Wechsler Intelligence Scale for Children) was measured at 7 yrs- > earlier age

Maternal DAP was associated with poorer working memory, processing speed, verbal comprehension, perceptual reasoning & FS IQ-7from highest to lowest quintrile- {children levels-No effect on outcome}

Environmental Chemicals Whose Background/Rfd Levels Cause Adverse Neurobehavioral Effects

- Lead – below 10 micrograms/dl, but also levels below which can be detected appear to cause loss of IQ
- Manganese in Drinking water (not food) demonstrates loss of cognitive function- below the Rfd
- Organophosphates- Levels that appear to be below the Rfd results in loss of IQ

Biomarkers

- EXPOSURE- LEVELS
- EFFECTS – NEUROBEHAVIORAL TESTING
- SUSCEPTIBILITY – PATHWAYS OF TOXICITY INCLUDING GENE DEPENDANT PATHWAYS (op & ROS)

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"Lipid mediators: Translational & Therapeutic Intervention Research Group"

Oxidative stress: lipid metabolism

Substrates
Endogenous
Exogenous

Enzymatic
Non Enzymatic

Reactive substrates

Biochemical Detoxification of substrates (GSH, etc.) → Excreted, No effects

Reactive species
effect Organs, Lipids
Proteins

→ **Cellular / Organ Adverse effects**
Disease states
Autism
Asthma
Alzheimer's
Stroke
etc.

→ **Biomarkers**-
urine, etc

AA
DHA

Metabolize → **Lipoxins**, **Resolvins**

Can Down Regulate Oxidative Stress

Oxidatation → Isoprostanes, Neuroprostanes

Oxidative stress biomarkers in autism

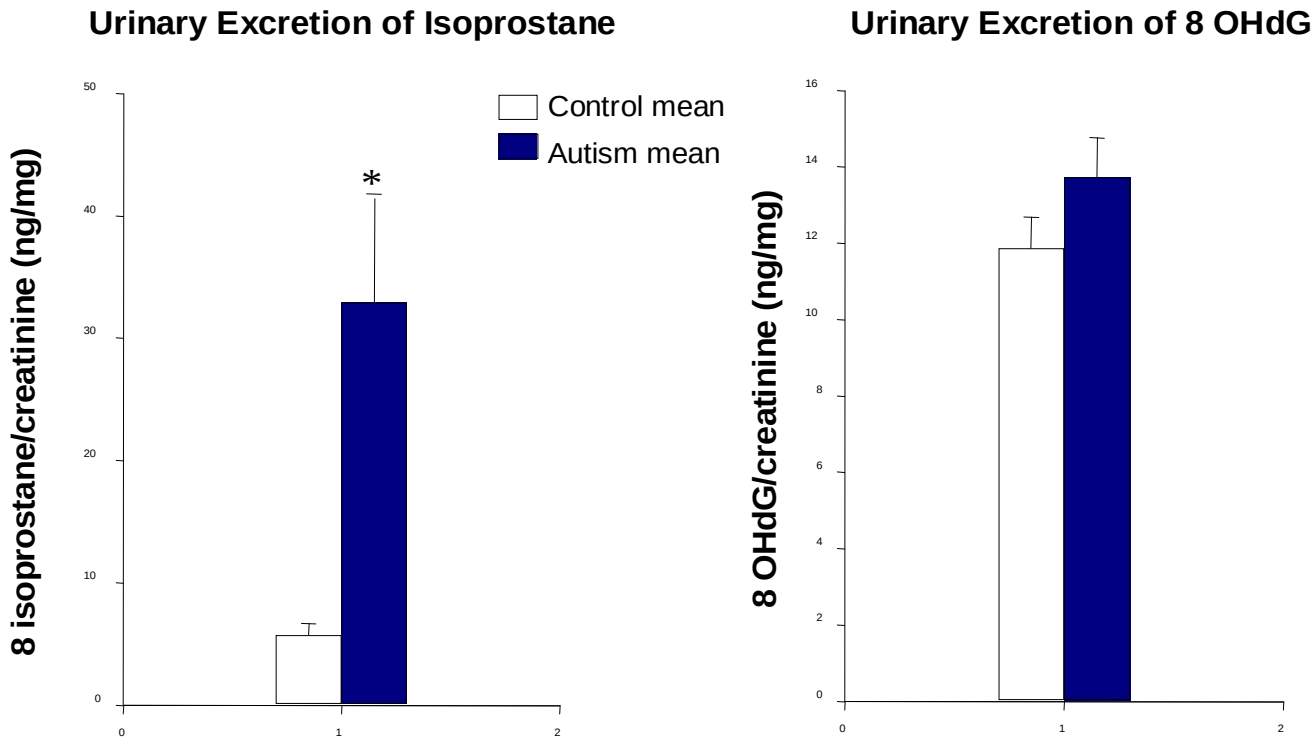


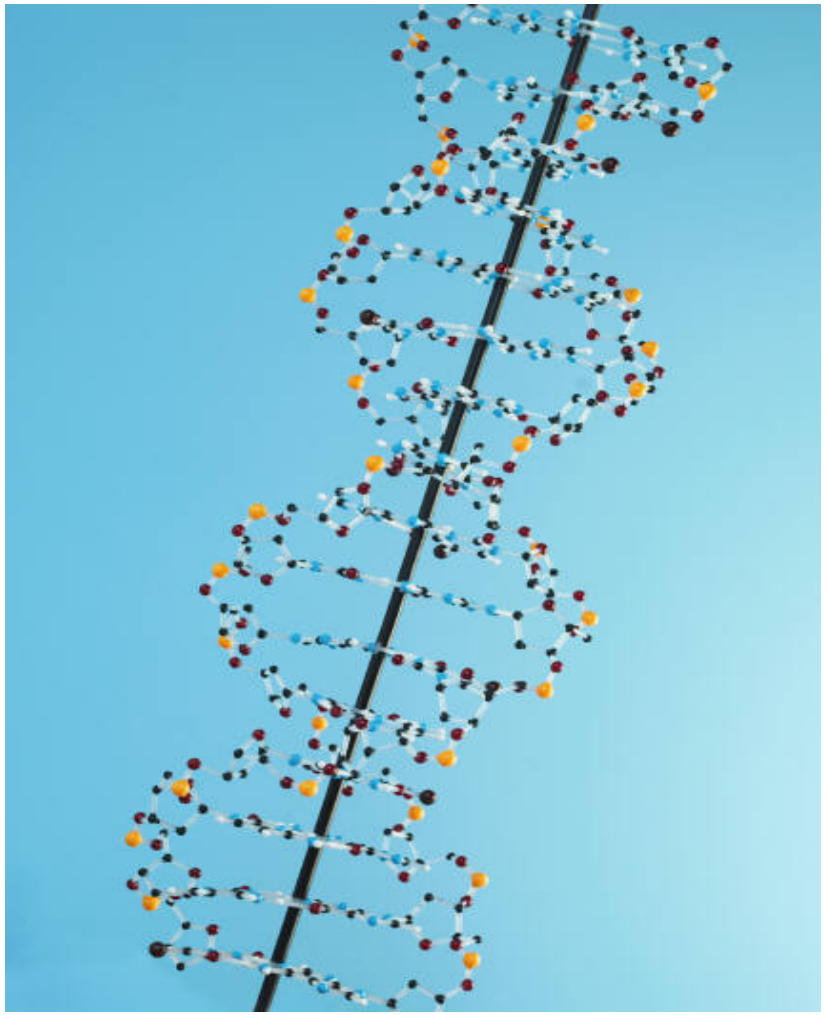
Figure 1: Preliminary data showing no significant difference in urinary excretion of 8 OHdG in subjects with autism vs control subjects.

Transmission Disequilibrium Testing (TDT)of subject's triad; gene effects on disease prevalence (Buyske, Williams, Johnson, Lambert et al BMC Genetics 2006)

- Blood is obtained from the index case and the TRIAD (Mother and Father) and if possible the grandparents.
- **Single** Gene Hypothesis is examined after initial gene study in other patients- Glutathione transferase
- Then TDT statistics are applied as developed by Steve Buyske PhD Neurostatistician
- Greatly improves the power and specificity of the study as described in our study above.

Glutathione Transferase (GST) Polymorphisms & Autism:

T. Williams, W. Johnson et al



- Gene deletions/null of Specific Genes related to the handling of glutathione detoxification (GST-M1) are increased in the child with autism and the father (general pop. 42%, autism 72% in child and autism)asthma
- Mother has different gene profile that has specific polymorphism of the glutathione transferase p1 gene

GSTM1 & Isoprostanes

- In children with autism:

Children with the deletion of GSTM1 gene has of elevated oxidative stress (elevated levels of isoprostane) as compared to children with autism who have the active GSTM1 gene.

Lambert, Stein, Ming, Spur, and remainder of the lipid mediator translational research group unpublished

Glutathione Peroxidase and Autism; Ming, Johnson, Lambert et al in press

- Glutathione Peroxidase polymorphism – TDT studies demonstrate that the expression of the polymorphism with defective protein is markedly increased incidence in children with autism

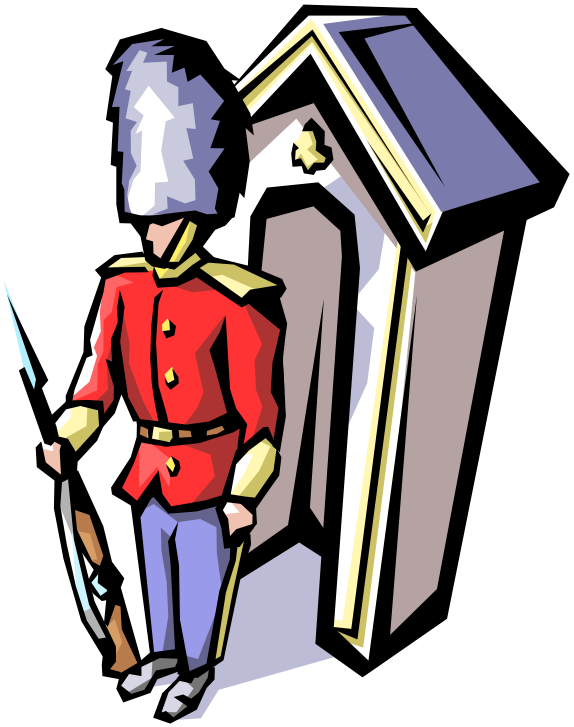
Genetic susceptibility for autism

- 55+ genes associated autism and ***currently*** 10 associated with inflammatory/oxidative stress pathways

- James et al report markedly decreased levels of glutathione in children with autism.

ISOPROSTANE BIOMARKERS

- ENVIRONMENTAL CHEMICALS
  - Population exposure, effect, and susceptibility
    - Park et al in Korea (2009, EHP) showed that in large numbers of people elevated isoprostane levels correlated with exposure of the population to environmental chemicals.
    - Zhang et al demonstrated that in people with asthma there was a direct correlation with increased exposure to air pollutants and increased urinary levels of isoprostane (2010, NEJM)
    - Isoprostanes/neuroprostanes/lipoxins/resolvins can be used to monitor altered susceptibility to neurological and environmental chemical associated disease states.



The developing human is a canary of the human species

Susceptibility

- Sensitivity
- Reliability
- ***Diversity of effects***
- ***Children with HEALTH concerns may be the most sensitive***
- ***Protect the children and protect everyone***

SUMMARY

- Environmental Chemicals can cause diverse neurobehavioral adverse effects, probably limited by the sensitivity of our methods- Neuro and biochemical monitoring
- Children are at greatly increased Neurodevelop-mental risk from many ECs- due to EC and child-dependent PKPD factors
- There are specific windows of susceptibility which are increased prenatally but are also present at older ages of childhood- also dependent on PKPD factors

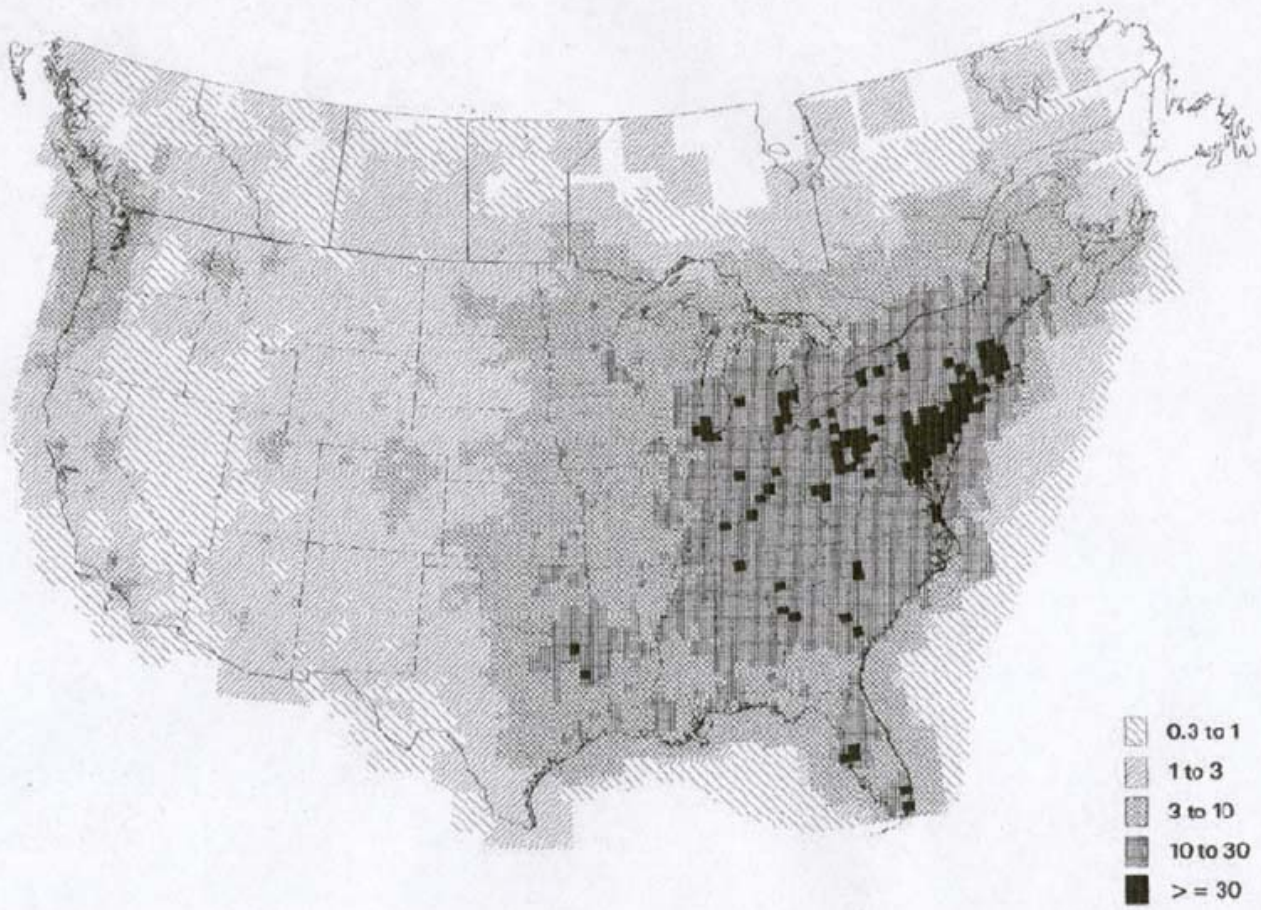
SUMMARY

- Several Rfds for certain ECs appear to be set too low and are above the LOAEL
- Genes in the offspring, mother and father can alter neurodevelopmental disease state susceptibility
- Biomarkers of altered susceptibility can be used in populations to monitor environmental and disease based organ dysfunction (brain/lung/etc)
- Clearly additional data needs to be generated if we are to protect our most precious asset- our children. We are only scratching the surface

“Thank You, Thank You”

Many sentinel contributions to Developmental Environmental Health Sciences and Overall Health of Children ….

Figure 3-3
Total Simulated Wet + Dry Deposition of Mercury in All Forms
Units: $\mu g/m^2$



Source: EPA 1997 Mercury Report to Congress

MERCURY

- INORGANIC
  - environment
- ORGANIC
  - METHYL Hg
    - fish
  - ETHYL Hg
    - Immunizations

What is safe????

10% - 15% of women of childbearing Age above known safe levels

in who, what age, what other Ecs, unhealthy?

ROS IN ASD IN EYGPT

MOSTAFA ET AL , J NEUROIMMUNOLOGY, 219: 2010

- KIDS WITH ASD AS COMPARED TO AGE MATCHED CONTROL KIDS HAD
  - MARKED INCREASED ISOPROSTANES >95%til OF 81% OF THE KIDS WITH ASD
  - MARKED DECREASE OF GSH-PX 12%
  - EITHER INCREASED ISOP. OR GSH-PX DECREASED ACTIVITY IN 89% OF TOTAL
  - DECREASED CAPACITYCORRELATED WITH SEVERITY OF ASD
  - INCREASED ANTINEURONAL ANTIBODY IN 55% VS 5% AND OR OF 12
  - INCREASED FAMIY HISTORY OF AUTOIMMUNE DISEASE .*KNOWN ASSOCIATION WITH ALTERED ROS ETC

Associated with autism in at least one dataset:

Symbol	Name	Function	representative ref
Antiox/oxidative stress:			
GSTM1	Glutathione S-transferase, MU-1	Detoxification/oxidative stress/regulation of MAPK cascade	[1]
GSTP1	Glutathione S-transferase, PI	Detoxification/oxidative stress/regulation of MAPK cascade	[2]
PON1	Paraoxonase	Detoxification/oxidative stress	[3]
Immune related genes:			
HLA-A	Major histocompatibility complex, class I, A	MHC class I	[4*]
HLA-DRB1	Major histocompatibility complex, class II, DR beta-1	MHC class II	[5*]
C4B	Complement component 4B	Complement system	[6]
PTGS2 (COX2)	Prostaglandin-endoperoxide synthase 2	Prostaglandin/leukotriene/lipoxin metabolism	[7*]
Folate related genes:			
MTHFR	5,10-methylenetetrahydrofolate reductase	Folate metabolism	[8]
TCN2	Transcobalamin II	Transcobalamin metabolism	[8]
RFC-1	Reduced folate carrier 1	Folate metabolism	[8]
Stress signaling genes:			
PRKCB1	Protein kinase C, beta-1	Several signaling pathways	[9]
PIK3CG	Phosphatidylinositol 3-kinase, catalytic, gamma	Phosphatidylinositol signaling	[10]

*CENTER DATA CONFIRMS AND EXTENDS-UNPUBLISHED

1. Buyske, S., et al., BMC Genet, 2006. **7**(1): p. 8.
2. Williams, T.A., et al.,. Arch Pediatr Adolesc Med, 2007. **161**(4): p. 356-61.
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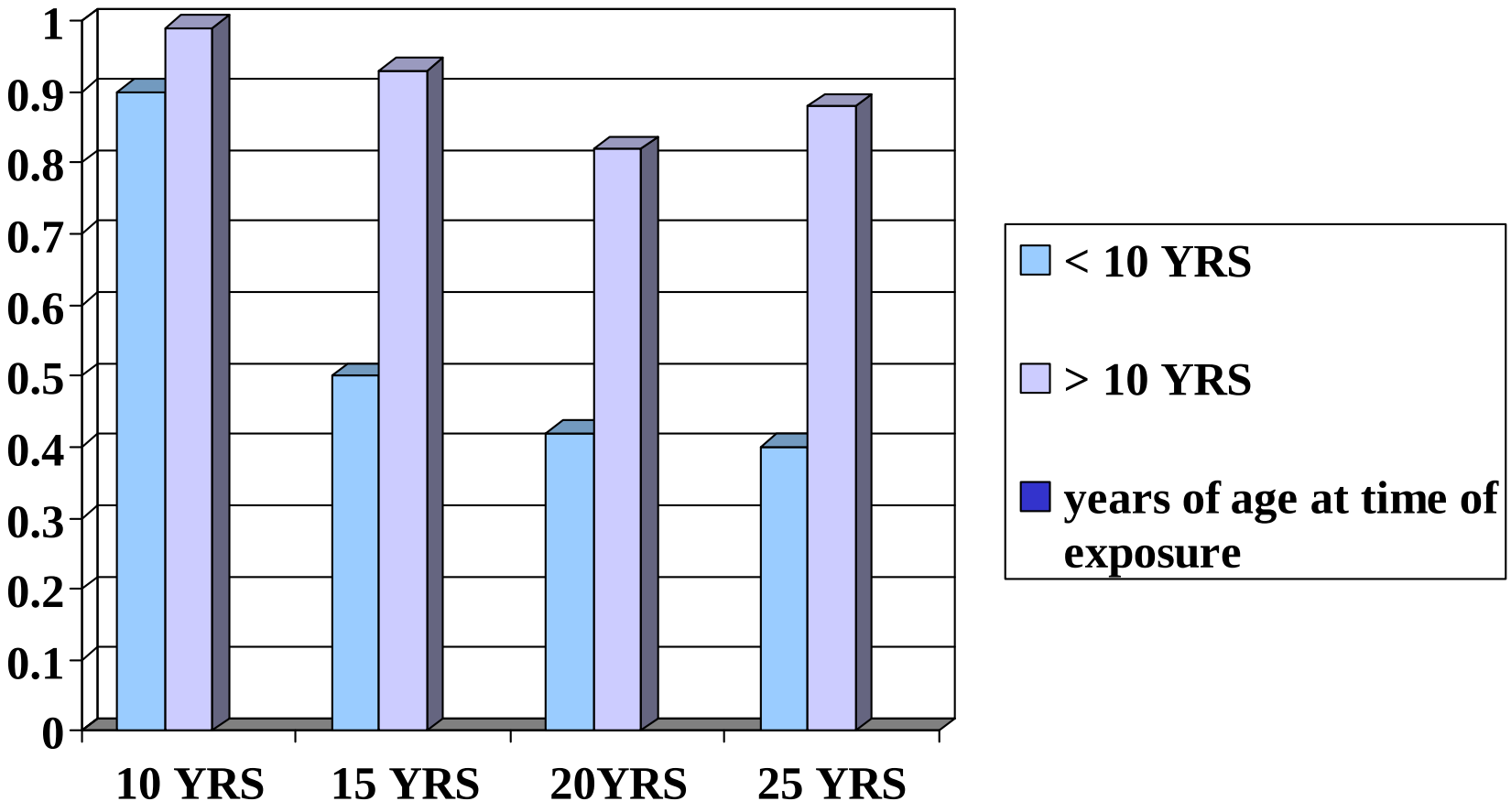
10. Serajee, F.J., et al., J Med Genet, 2003. **40**(11): p. e119.

REDUCE MERCURY EXPOSURE

- Do not play with quick silver
- Check gas switches in basement to see if broken, if so call gas company
- Examine ethnic associated sources
- Be careful of rituals that have mercury in the rituals
- **Fish, know what you are eating and the advisories – Pediatricians should hand out or make available to fish eating families local and national fish eating advisories**
- **Teach how to cook fish**

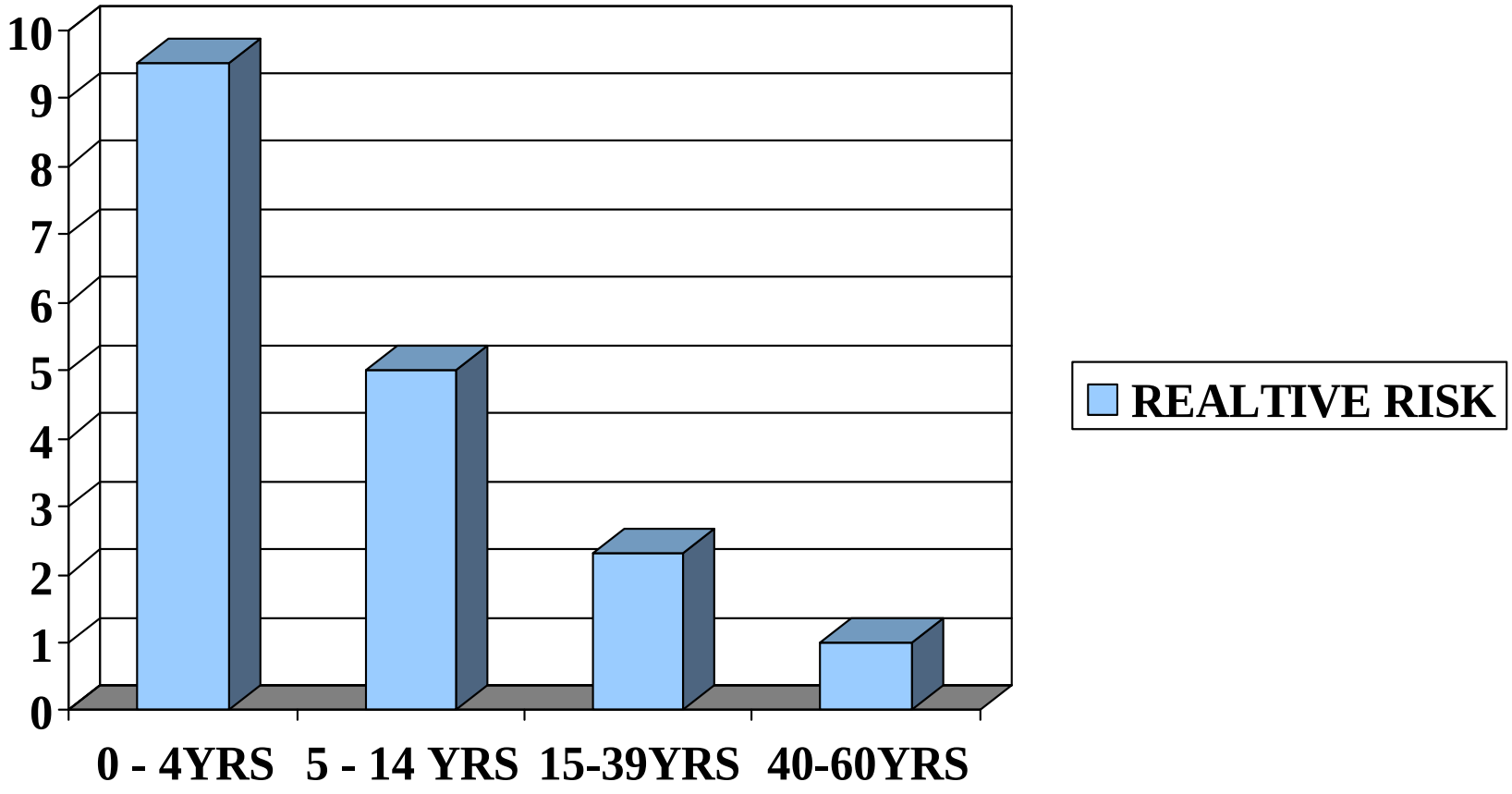
% DISEASE FREE FROM THYROID NODULES OR CA IN MARSHALLESE



Good sources 2-3 /wk

- Farm catfish, or trout
- Anchovies, clams, blue crab, fish sticks, flounder, wild salmon or canned Alaskan
- Know what not to eat, brown fat
- Farm raised salmon has 4X ECs
- A Great Lakes salmon has ECs of 1 million gallons of Lake Michigan water

BREAST CANCER BY AGE OF EXPOSURE IN JAPAN



1 meal per week

- Bluegill, perch, smelt, whitefish
- Cod, crab (dungeness, blue, stone)
- Haddock, herring, mahi mahi, mussels, oysters, scallops, canned chunk tuna

Canned tuna ???

- Women of child bearing years 7 oz/wk
- Children ½ can per week
- Do not eat canned albacore tuna (4x higher)

Do not eat

- Fresh water bass, catfish, muskie/northern over 30 inches, lake trout or steel head trout or walleye over 20inches
- Salt water mackeral, orange roughy, shark, red snapper, swordfish, tilefish, albacore tuna
- LOCAL ADVISORIES IN THE STATE'S ADVISORIES AS TO RIVERS AND LAKES, ETC.
- PEDIATRICIANS SHOULD HAND OUT THESE MATERIALS

Reduce lead

- Wet mopping – 34% decrease in children lead levels
- Mats and taking shoes off (arsenic decking)
- Control Paint Dust in homes 1978 and older
- Window sills high in mercury and lead and arsenic

Ways to decrease exposure:

CHECK HOME FOR LEAD (1978)

Damp mop floors and house (34% reduction in Pb)

Frequent hand washing

Ways to decrease exposure:

CHECK WATER AND IF IN PIPES RUN WATER 1 MINUTE WITH FIRST USE

CHELATON IS CONTRAINDICATED AT HIGHER LEVELS 10-25

THE CENTER FOR Childhood Neurotoxicology and Exposure Assessment

a healthy environment for children

What we Know

- Environmental Chemicals are Developmental Neurotoxicants To The Human
  - Alters growth (HC*) – PCBs*, Ethanol*, Organophosphate pesticides*, DDT
  - Alters function
    - Cognitive Function - PCBs, Hg, Pb, OPs
    - Behavior – PCBs in gender specific function
    - Neuroendocrine Function – Cocaine

THE SENTINEL CANARY SUSCEPTIBILITY

- AS THE CANARY WAS A SENSITIVE SENTINEL FOR THE MINERS
- THE DEVELOPING HUMAN MAY BE THE SENTINEL FOR THE GENERAL PUBLIC – especially children with autism

CHILDREN'S ENVIRONMENTAL HEALTH CAUCUS

108TH - 111TH US CONGRESS

LEADERSHIP

REPRESENTATIVE RUSH HOLT (D)

REPRESENTATIVE JIM SAXTON- FRANK LO BIONDO (R)

MEMBERSHIP FROM

BOTH SIDES OF HOUSE

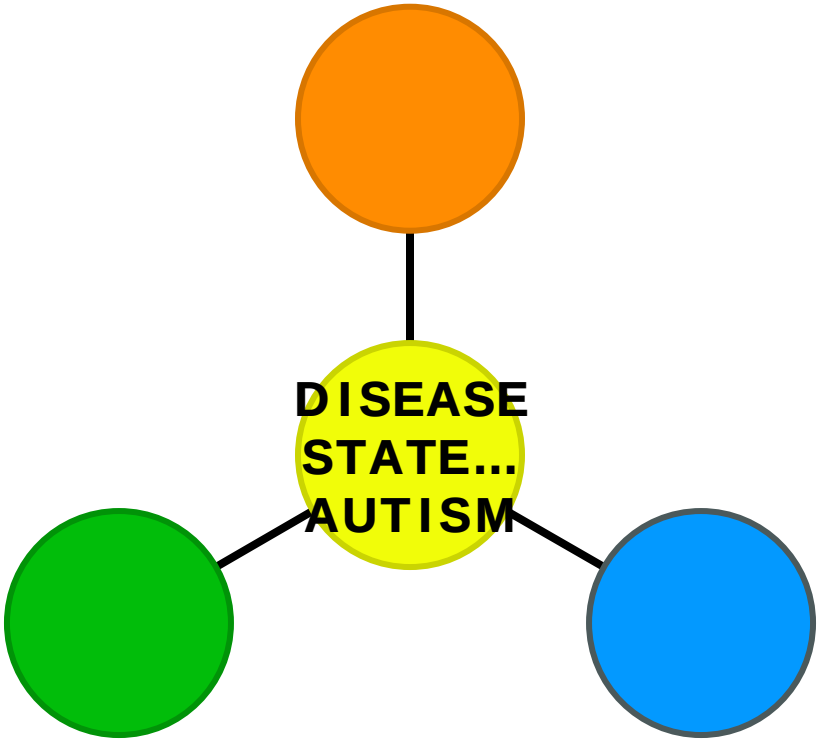
BOTH HOUSES

10 STATES- 50 attendees

PLEASE have your Congressmen JOIN THE CAUCUS

Goal is to provide unbiased information – Healthy schools, TSCA, Air quality around schools, Susceptible Populations, NCS

AUTISM ….



Autism

- Neurological or brain disorder that *profoundly* effects a person's ability to
  - Communicate
  - Form relationships
  - Respond appropriately to their surroundings
- Cognitive function is involved in many with IQ<70 in the majority
- Regression in 1/3rd of children
- Detected in infancy or early childhood
- Genetic linkage – Identical twins & sibs, gender, +++
- REPORTED INCREASE INCIDENCE -1% NJ (CDC)