Are the kids alright? Strengthening regulatory decision-making in the uncertain world of children's health research

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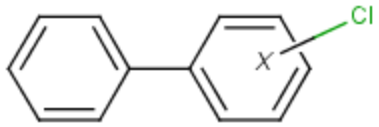
The findings and conclusions in the manuscripts and presentations are those of the authors and do not necessarily represent the views of Cefic-LRI, the National Institutes of Health or the US Environmental Protection Agency.

What did the RFP ask for?

Part 1. Critical review of currently available testing methods for neurodevelopmental disorders in children and their potential for application in epidemiological studies.

Part 2. Critical review of the available evidence on neurodevelopmental disorders in children and association with chemical exposure.



Part 3. Guidelines and quality criteria for epidemiological research in the area of neurodevelopmental disorders and exposure to chemicals.

Part 1. Critical review of available testing methods for neurodevelopmental disorders in children and their potential for application in epidemiological studies

- Literature review
  - identified important methodological considerations

- Workshop with international experts in:
  - Experimental neurodevelopmental biology
  - Neurology
  - Neuropsychology
  - Psychology
  - Pediatrics
  - Epidemiology
  - Statistics/methodology
  - Chemical risk assessment

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Article

Advancing the Selection of Neurodevelopmental Measures in Epidemiological Studies of Environmental Chemical Exposure and Health Effects

Eric Youngstrom [1], Judy S. LaKind [2,3,4,*], Lauren Kenworthy [5], Paul H. Lipkin [6], Michael Goodman [7], Katherine Squibb [8], Donald R. Mattison [9], Bruno J. Anthony [10] and Laura Gutermuth Anthony [5]

Lost in Translation

- Uncertainties in the degree of measurement equivalence when tests are transported into different languages and cultures

Q: American child, what are they doing?

Q: British child, what are they doing?

A: Playing baseball!

A: Playing cricket!

Table 1. *Cont.*

Executive Function—Omnibus			
Wisconsin Card Sorting Test (WCST)	E	Multiple scores	NA
Behavior Rating Inventory of Executive Functioning (BRIEF)	R	Global Executive Composite	1
Executive Function—Flexibility			
Wisconsin Card Sorting Test (WCST)	E	Perseverative Errors	NA
BRIEF	R	Flexibility Index	1
Executive Function—Organization/Planning			
Rey Complex Figure Test	E	Copy Strategy	NA
Tower of London-DX	R	Total Move Score	1
Executive Function—Response Inhibition			
CPT II	E	Commissions	NA
BRIEF	R	Inhibit Scale	1
Executive Functioning—Working Memory			
Wechsler Intelligence Scale for Children-Revised (WISC-R)	E	Arithmetic	NA
Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV)	R	Working Memory Index	3
General Cognitive Measures: Infants and Toddlers			
Mullen Scales of Early Learning	E	Early Learning Composite	NA
Bayley Scales of Infant Development	E/R (3rd Edition)	Adaptive behavior Cognitive Language Composite Motor Composite	3

Youngstrom et al. 2010. Advancing the selection of neurodevelopmental measures in epidemiological studies of environmental chemical exposure and health effects. *International Journal of Environmental Research and Public Health* 7:229-268.

Table 2. Description (including advantages and disadvantages) of widely used neurodevelopmental measures and alternate recommended measures (see Table 1). Norm quality was rated on a four point scale: ****=Exemplary, with nationally representative demographics and good sample size across relevant age spans, *** = Good, with some shortcomings (such as dated norms, coarsely clustered sampling, or omission of important group), ** = Suboptimal (e.g., badly out of date, or convenience sample that was not nationally representative), * = Flawed.

Measure	Scale Name	Age Range (yrs unless otherwise indicated)	Admin. Time	Norm (N)/Norm Quality Standard Score M (SD)	Reliability (Type)	Standard Error of Measurement	Stability (*r*)	Construct Validity	Predictive Validity	Advantages	Disadvantages	References
Academic Achievement												
Wide Range Achievement Test 4	Word Reading	5- 94 yr 11 mo	15-25 minutes for ages 5 to 7 for whole test; 30-45 minutes for over age 7 for whole test	3021/**** 100 (15)	0.96 (median alpha); 0.90 immediate retest alt. form	3.0	0.85 *r* for alternate form delayed test retest (*Mean*=1 month; range 8 to 86 days) 0.74 *r* for alternate form delayed test retest (*M*=1 month; range 8 to 86 days)	Good: Moderate to high correlations with other achievement measures	Some evidence of predictive validity in terms of educational classification	Short, alternative forms allows re-testing, part can be administered in group format	Captures basic learning difficulties with reading decoding, and math computation, but is not sensitive to learning disabilities associated with executive function, processing speed, motor output, reading comprehension, or written expression.	[10]
	Sentence Comprehension				0.96 (median alpha); 0.86 immediate retest alt. form	3.0	0.88 *r* for alternate form delayed test retest (*M*=1 month; range 8 to 86 days)					
	Reading Composite				0.98 (median alpha)	2.3	0.83 *r* for alternate form delayed test retest (*M*=1 month; range 8 to 86 days)					
	Spelling				0.95 (median alpha); 0.89 immediate retest alt. form	3.4	0.83 *r* for alternate form delayed test retest (*M*=1 month; range 8 to 86 days)					
	Math Computation				0.94 (median alpha); 0.88 immediate retest alt. form	3.7						
Woodcock-Johnson-III	Academic Fluency Subtests	2 to 90+	Variable, ~5 min. per test	8818/**** 100 (15)						Relatively easy to administer; sensitive to the effects of processing speed and motor output deficits on academics.	Moderately old norms	[11]
Adaptive Behavior												
Adaptive Behavior Assessment System-II	Parent Form Global Assessment of Competence	Birth to adult	15-20 min	1350/**** 100 (15)	0.97 (alpha)	2.12	0.88 (2 days to 5 weeks, *M*=12 days)	Extensive	Used in identification of mental retardation	Multiple versions for different ages and parents and day care providers; extensive construct validity	Like any parent checklist, ABAS is susceptible to misinterpretation and bias.	[12]
Vineland Adaptive Behavior Scale-II (a brief research edition is also available)	Parent Interview Edition	0-18	20-60 minutes and 15-30 minutes to score	1670/****					Used in identification of mental retardation	Well validated in multiple clinical groups	Time and expertise intensive measure for the interview version; can take more than 1 hour to complete. Administration of interview version requires expertise gained through graduate level training programs in psychology or social work.	[13]
	Parent Form Global Assessment of Competence (GAC)	5-21	15-20 min	1670/**** 100(15)	0.98 (alpha)	1.57	0.93 (5 days to 6 weeks; avg of 11 days)	Extensive		Self-report version; multiple versions for different ages and parents and day care providers; extensive construct validity		

Youngstrom et al. 2010. Advancing the selection of neurodevelopmental measures in epidemiological studies of environmental chemical exposure and health effects. *International Journal of Environmental Research and Public Health* 7:229-268.

Conclusion: Part 1

Field of environmental epidemiology needs to develop a formal set of methodological and reporting guidelines to guide the design of future studies

Part 2. Critical review of available evidence on neurodevelopmental disorders in children and association with chemical exposure

1. To examine consistency of study methods with respect to:

   exposure assessment

   outcome ascertainment

   data analysis

2. To assess the feasibility of conducting a quantitative WOE assessment of existing epidemiologic data (i.e., a meta-analysis)

Overview of PCB Cohort Studies

- 12 cohort studies of children for whom pre- or neonatal PCB exposures were measured or estimated

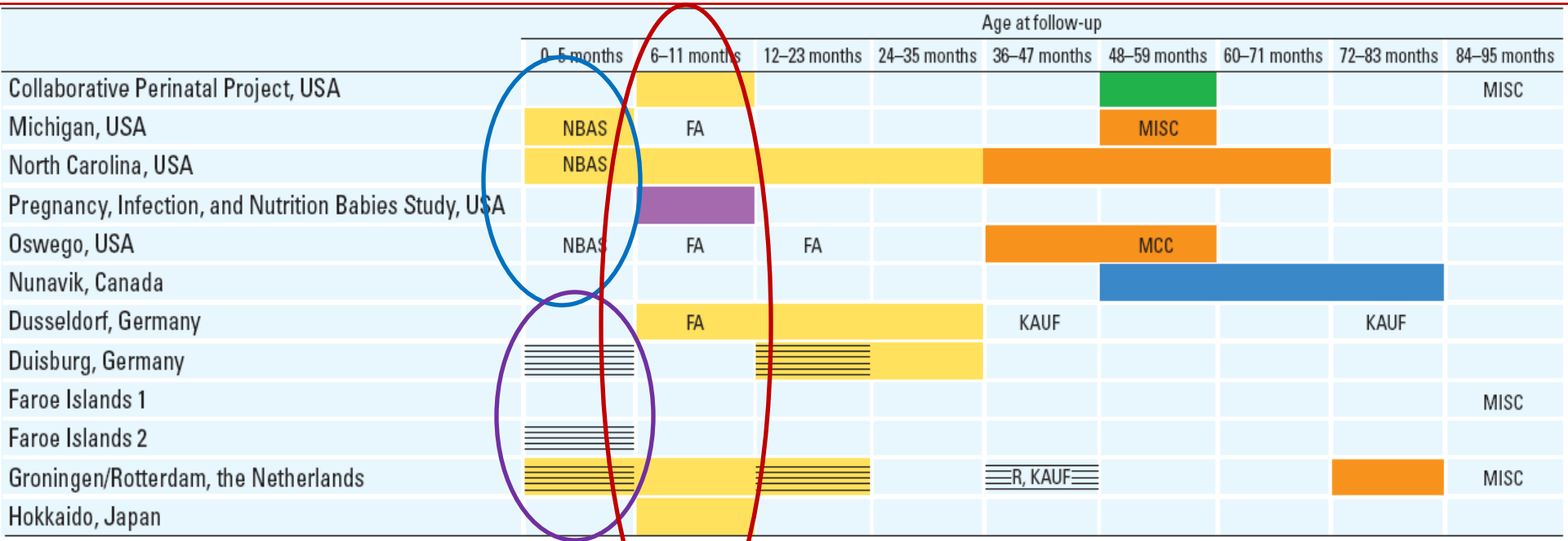
- 6: United States and Canada

  5: Europe

  1: Japan

- Neurodevelopmental outcomes at various ages were described in 40 articles with publication dates spanning a 26-year interval from 1984 through 2009

Summary of tests used in the PCB cohorts by age



	Bayley Scales of Infant Development
	Stanford–Binet IQ test
NBAS	Brazelton Neonatal Behavioral Assessment Scale (NBAS)
FA	Fagan Test of Infant Intelligence
	McCarthy Scales of Children's Abilities
	Neurologic Optimality Score (Prechtl, Hempel)
R	Reynell Developmental Language Scales
MCC	Michigan Catch the Cat
KAUF	Kaufman Assessment Battery for Children
	Multiple neuromotor tests
	Mullen Scales of Early Learning; MacArthur–Bates Communicative Development Indices
MISC	Miscellaneous tests including Peabody, Beery, Kagan, Sternberg, Wide Range Achievement Test, individual subsets of Wechsler Intelligence Scale for Children (WISC), Bender Visual Motor Gestault Test, Boston Naming Test, etc.

Goodman et al. 2010. Using systematic reviews and meta-analyses to support regulatory decision-making for neurotoxicants: Lessons learned from a case study of PCBs. *Environmental Health Perspectives* 118:727-734.

Conclusions: Part 2

- Even for age intervals examined by several research groups, presumably testing the same hypothesis, a meaningful meta-analysis of PCB studies is not possible at this time

- Studies lack consistency in terms of both research methods and reporting of results

REVIEW OPEN ACCESS

Using Systematic Reviews and Meta-Analyses to Support Regulatory Decision Making for Neurotoxicants: Lessons Learned from a Case Study of PCBs

Article

Michael Goodman[1], Katherine Squibb[2], Eric Youngstrom[3,4], Laura Gutermuth Anthony[5,6,7], Lauren Kenworthy[5,6,7,8], Paul H. Lipkin[9,10], Donald R. Mattison[11], Judy S. LaKind[12,13,14]

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Abstract Top

Part 3. Guidelines and quality criteria for epidemiological research in neurodevelopmental disorders and exposure to chemicals

Pediatric neurodevelopmental disorders: High visibility

Study: A Link Between Pesticides and ADHD
17 May 2010

Do Toxins Cause Autism?
February 24, 2010

Common Chemicals May Have Autism Link
May 15 2008

Chemicals known to be neurotoxic to humans

- Most based on acute exposure

-Only 5 are known human neurodevelopmental toxicants

List from: Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet. 2006 368(9553):2167-78.

Why aren't more chemical regulations based on neurodevelopmental outcomes?

- Factors related to study conduct:
  - Adequacy of sample size
  - Inconsistent testing methodologies
  - Questions about the selection or implementation of testing procedures
  - Inadequate consideration of confounding factors
  - Uncertainties regarding the exposures
  - Reproducibility of the study findings
  - Inconsistencies due to timing or life stage of assessment

- Factors related to the overall database:
  - Strength of the findings within the comprehensive weight-of-evidence of the hazard and dose-response database
  - Placement of observed exposure-related findings in context of the range of responses observed at the lower end of the dose-response array
  - Few chemicals in the data base had human neurodevelopmental data.

Part 3. Guidelines and quality criteria for epidemiological research of neurodevelopmental disorders and exposure to chemicals

✓ Tools for evaluation of research (CONSORT, QUADAS):

✓ 1st shot at guidelines for inter-study consistency to enhance regulatory weight-of-evidence

Proposed Checklist for Assessment Selection, Administration, and Reporting in Neurodevelopmental Studies of Environmental Chemical Toxicity

Item	Yes	No	Unclear
Sampling & Participants			
1. Were participant selection criteria clearly described?			
2. Were there clearly defined groups of participants, similar in all important ways other than exposure to the chemical?			
3. Were the participants representative of the population to whom results would be generalized in practice?			
4. Were withdrawals from the study explained? (e.g., flow diagram, or other accounting)			

Part 3: Conclusions and next steps

You can't always get what you want…
But if you try sometimes you might find
You get what you need – *Mick Jagger*

Multi-stakeholder, international process for developing a tool for:

Harmonizing environmental epidemiology research to facilitate public health protection

Step 1: Planning committee meeting – early 2011

Step 2: Workshop – interested parties – mid-late 2011

Step 3: Development of “checklist”

Step 4: Begin outreach