(30)

Nordenberg, Tamar

From: Carson, Louis J
Sent: Tuesday, November 07, 2000 9:36 AM
To: Buchanan, Robert L; Bolger, Philip M; Spiller, Philip C; Levitt, Joseph A; Nordenberg, Tamar; Davidson, Marjorie L; Levy, Alan S; Williams Jr, Richard A
Cc: Lake, Lloyd R
Subject: FW: Overheads


Table 8-3-revised.wpd


Mac Word 3.0


Microsoft PowerPoint 97


Microsoft PowerPoint 97


Table 1-1-revised.wpd


Table 7-1.wpd


Table 7-2-revised.wpd


Table 7-3-revised.wpd


Table 7-5-revised.wpd


Table 8-2-revised.wpd


Mac Word 3.0

The NAS presentation is attached.

Lou
-----Original Message-----
From: Michelle Catlin [mailto:mcatlin@nas.edu]
Sent: Monday, November 06, 2000 2:39 PM
To: Carson, Louis J
Subject: Overheads

Here are the overheads that were presented on Friday (along with some that we did not get to). The table numbers correspond to the tables in the report. The "Calculation Table" and the "Calculation of Annual Newborns" are two different ways of presenting the "60,000 kids calculation". The "differences" is the slide that Joe Jacobson showed outlining the differences between the Faroe and Seychelles studies. Let me know if you need anything else or have any more questions.

Michelle

(See attached file: Table 8-3-revised.wpd)(See attached file: Calculation Table.doc)(See attached file: differences.ppt)(See attached file: Main Presentation.ppt)(See attached file: Table 1-1-revised.wpd)(See attached file: Table 7-1.wpd)(See attached file: Table 7-2-revised.wpd)(See attached file: Table 7-3-revised.wpd)(See attached file: Table 7-5-revised.wpd)(See attached file: Table 8-2-revised.wpd)(See attached file: Calculation of Annual Newborns.doc)

Population Margins of Exposure (MOE)[a] for Selected BMDLs and Exposure Estimates (ppm of Hg in maternal hair or estimated equivalent to maternal hair)

		MOE					
		Estimated MeHg Exposure in Selected Populations					
		New Jersey Pregnant Women [b]		EPA Region V Population [c]		U.S. Women of Childbearing Age [d]	
Study	Selected BMDL (value, ppm)	Mean (0.53)	95th Percentile (2.0)	Mean (0.29)	95th Percentile (1)	Mean (0.36)	95th Percentile (2.4)
New Zealand	Most sensitive (4)	7.5	2.0	13.8	4	11.1	1.7
Faroe Islands	Most sensitive (10)	18.9	5.0	34.5	10	27.8	4.2
Faroe Islands	Most-sensitive-reliable, cord-blood derived (12)	22.6	6.0	41.4	12	33.3	5.0
Seychelles Islands	Median (22)	41.5	11	77.3	22	61.1	9.2
Integrative analysis	Lower 5% (7)	13.2	3.5	24.1	7	19.4	2.9
Iraq	(11)[e]	20.8	5.5	37.9	11	30.6	4.6

[a]MOE, BMDL/exposure estimate.
[b]Data from Stern et al. (2000); [c]Data from Pellizzari et al. (1999); [d]Data from Smith et al. (1997); [e]Current RfD basis.

Abbreviations: BMDL, lower 95% confidence limit on the benchmark dose; RfD, reference dose.

Annual Number of Newborns at High Exposure Risk

U.S. population of women aged 15 to 44 years[1]	60,208,000
Percent reporting fish consumption[2]	30.5 Percent
Female fish consumers aged 15 to 44 years	18,363,440
Population of concern (highest 5% exposed, consume 100g fish/day)	918,172
Birth rate for women 15-44[3]	65.6 per 1000
Annual number of newborns at high exposure risk	60,232

[1] Population Estimates Program, U.S. Census Bureau, POP@CENSUS.GOV December 23, 1999
[2] Continuing Surveys of Food Intake by Individuals, 1989/1990
[3] National Center for Health Statistics, National Vital Statistics Report, Vol. 48, No. 3, March 2000

Differences in Research Design between the Faoroes and Seychelles Studies

- Biomarker of exposure (maternal hair vs. cord blood)
- Type of neuropsychological test (domain specific vs. global)
- Age at testing (7 vs. 5.5 years)
- Sources and pattern of exposure (whale meat vs. fish)
- Exposure to other contaminants (PCBs)

- Differences in vulnerability (including diet)
- Power

TOXICOLOGICAL EFFECTS OF METHYLMERCURY

Committee on Toxicological Effects of MeHg

Robert A. Goyer (Chair), University of Western Ontario

H. Vasken Aposhian, University of Arizona

Lenore Arab, University of North Carolina

David C. Bellinger, Harvard Medical School

Thomas M. Burbacher, University of Washington

Thomas A. Burke, The Johns Hopkins University

Joseph L. Jacobson, Wayne State University

Lynda M. Knobeloch, State of Wisconsin Bureau of Environmental Health

Louise M. Ryan, Harvard School of Public Health and Dana-Farber Cancer Institute

Alan H. Stern, New Jersey Department of Environmental Protection

Sponsor of Study

U.S. Environmental Protection Agency (EPA)
(requested by U.S. Congress)

Background to Study

- Hg is widespread and persistent in the environment
- EPA identified fossil-fuel power plants (coal-fired utility boilers) greatest source of Hg emissions
- MeHg can accumulate up food chain in aquatic systems
- Consumption of contaminated fish major source of MeHg exposure in U.S.
- Well-documented population poisonings, high-level occupational exposures, and world wide chronic low-level environmental exposures
- Because of data gaps, Congress directed EPA to request NAS to perform an independent study

Committee's Charge

1. Evaluate evidence that led to EPA's RfD for MeHg
   - determine if critical study, end point of toxicity and uncertainty factors (UFs) are appropriate
2. Evaluate new data not considered in 1997 *Mercury Study Report to Congress*
3. Consider exposures in environment that support evaluation of likely human exposures (especially subpopulations and consumption of fish)
4. Identify data gaps and make recommendations for future research

Committee's Approach To Its Charge

- Evaluated body of scientific basis for risk assessments conducted by EPA and other agencies
- Evaluated new findings since EPA developed RfD
- Met with investigators of major ongoing epidemiological studies
- NOT charged to calculate RfD, but provided scientific guidance to EPA

Committee's Approach To Its Charge

- Reviewed effects of MeHg to determine target organ, critical study, end point of toxicity, and dose for RfD
- Evaluated appropriateness of biomarkers for estimating dose
- Evaluated sources of uncertainty for RfD
- Statistically analyzed available dose-response data
- Performed margin of exposure analysis to assess public-health implications of MeHg

Current RfD

- Based on neurodevelopmental effects seen following poisoning in Iraq (Marsh et al. 1987)
- Calculated a benchmark dose of 11 ppm Hg in hair (corresponds to intake dose of 1 µg/kg-d)
- Composite UF of 10:
  - 3 for variability in human population (half-life and hair-to-blood ratio)
  - 3 for lack of two-generation reproductive study and data on effect of exposure duration on sequelae of developmental neurotoxicity and adult paresthesia
- RfD of 0.1 µg/kg-d

Health Effects

- Extensive data on effects of MeHg on development of brain
- Most severe effects in humans following high-dose poisoning episodes (Japan and Iraq)
  - -mental retardation, cerebral palsy, deafness, and blindness in individuals exposed in utero
- Chronic, low-dose prenatal MeHg (maternal consumption of fish) associated with subtle end points of neurotoxicity in children (tests of attention, fine-motor function, language, visual-spatial abilities, and verbal memory)
- Two studies found associations between MeHg exposure
  - -New Zealand (Kjellstrom et al.)
  - -Faroe Islands (Grandjean et al.)
- One study did not find associations
  - -Seychelles Islands (Clarkson et al.)
- All 3 studies well designed and carefully conducted, examining exposures within range of general U.S. population exposures

Health Effects

- Neurodevelopmental effects in animals similar to those seen in humans

- Also evidence in humans and animals for:
  - -adverse effects on developing and adult cardiovascular system (some evidence demonstrates effects at or below MeHg levels where neurodevelopment effects seen)
  - -immunotoxicity

- Committee concludes neurodevelopmental deficits most sensitive well-documented effects, and currently most appropriate for derivation of RfD

Choice of Critical Study

- Large body of evidence showing adverse neurodevelopmental effects, RfD should not be derived from a study that did not observe associations (i.e., Seychelles Islands study)
- Advantages of Faroe Islands study over New Zealand study include larger study population, the use of two measures of exposure, and more extensive peer review in epidemiological literature, in 1998 NIEHS workshop, and in response to committee's questions
- Given strengths of Faroe Islands study, it is most appropriate study for deriving RfD

Dose-Response Assessment

- Because data from Faroe Islands study is measured on continuous scale, no widely accepted procedure for determining a dose with no adverse effect. Therefore, statistical approach should be used to determine point of departure - i.e., calculation of benchmark dose

- Benchmark dose is the lowest dose, estimated from the modeled data, that is expected to be associated with a small (5%) increase in the incidence of adverse outcome

- Dose response data based on Hg concentrations in cord blood should be modeled using K-power model ($K \approx 1$)

- Most, sensitive reliable endpoint from that study is the Boston Naming Test

- Based on single endpoint, Faroe Island study
  BMDL = 58 ppb Hg in cord blood (12 ppm in hair)

- Integrative analysis using data from all 3 studies is consistent (but not recommended as sole basis of RfD because of exploratory nature)

Dose Estimation

- Exposure to MeHg can be estimated from dietary records or by measuring concentration of Hg in blood or hair
- Use of two or more measurement methods increases likelihood of uncovering true dose-response relationships
- Use of umbilical-cord-blood or maternal-hair Hg concentrations as biomarkers of exposure is adequate for estimating dose
- Differences between toxicokinetics in individuals creates uncertainty
  - an uncertainty of 2-3 would account for individual differences in the estimation of dose in 95% to 99% of the general population

Committee's Recommendations

- Value of EPA's current RfD (0.1 µg/kg-d) is a scientifically appropriate level that adequately protects public health
- Iraqi study should no longer be used as scientific basis of RfD
- RfD should be based on neurodevelopmental effects
- Faroe Island study should be used as critical study for derivation of RfD
- Most, sensitive reliable endpoint from that study is the Boston Naming Test
- Dose response data based on Hg concentrations in cord blood should be modeled using K-power model ($K \approx 1$)

- Yields a BMDL of 58 ppb Hg in cord blood
  -corresponds to a BMDL of 12 ppm of Hg in hair as a point of departure for derivation of RfD

Committee's Recommendations

- BMDL should be divided by uncertainty factors to account for:
  - -toxicokinetic variability:
    - factor of 2-3 would account for toxicokinetic variability in 95% to 99% of the general population
  - -data-base insufficiencies:
    - include possible sequelae and latent effects, immunotoxicity, and cardiovascular effects
- Considering the toxicokinetic variability and what is known about data-base insufficiencies, the committee supports an overall composite uncertainty factor of at least 10

Research Needs

- Health end points, BP, Immunological effects, Delayed Neurological Effects
- Mechanisms
- Nutritional Interactions
- Exposure to all forms of mercury and potential synergistic effects

Agency	Key Studies	End Points	Biomarker and Exposure Level	Critical Dose	Uncertainty Factors	Acceptable Level
EPA [a]	Iraqi study (Marsh et al. 1987)	Combined instance of neurological effects following in utero exposure [b]	Maternal hair, 11 ppm; equivalent to intake of 1.1 μg/kg/d	Benchmark dose, 1.1 μg/kg/d [c]	UF, 10 [d]	RfD, 0.1 μg/kg/d (based on fetal effects)
ATSDR	Seychelles study (Davidson et al. 1998)	Developmental neurotoxicity measured by neurologic evaluation, behavioral, psychological tests	Maternal hair, 15.3 ppm; equivalent to intake of 1.3 μg/kg/d	NOAEL, 1.3 μg/kg/d	UF, 4.5 [e]	MRL, 0.3 μg/kg/d
FDA	Japanese data (Friberg et al. 1971)	Overt neurological symptoms in adults	Adult blood, 0.2 ppm; equivalent to intake of 300 μg/d	LOAEL, 4.3 μg/kg/d	SF, 10 [f]	Action level in fish, 1 ppm in edible portion [g] (equivalent to 0.5 μg/kg/d)

[a] The agency is awaiting the results of this NRC report before updating its RfD based on more recent data.

[b] Data for delayed onset of walking and talking, neurological scores of less than 3, mental symptoms, and seizures grouped together for analysis.

[c] EPA carried out the analysis using the polynomial model and the Weibull model. The results of the two models were within 3% of each other. EPA based its analysis on the Weibull model due to goodness of fit and history of use.

[d] The following uncertainty factors were applied: 3 for the variability in human population (variability in the half-life of methylmercury and in hair-to-blood ratio) and 3 for the lack of a two-generation reproductive study and data on the effect of exposure duration on sequelae of the developmental neurotoxicity effects and on adult paresthesia.

[e] The following uncertainty factors were applied: 1.5 for human pharmacokinetic variability, 1.5 for human pharmacodynamic variability and 1.5 to account for domain-specific findings in the Faroe study.

[f] Arbitrary value; the *Federal Register* states that, in cases in which human data are available, the safety factor used is 10.

Estimates of Standardized Regression Coefficients Based on Reported Study Results

Study	Exposure SD	Outcome	Outcome SD	Raw Regression Coefficient	Standardized Regression Coefficient
Faroe Islands [a]	0.375	Finger Tapping	6.15	-1.1	-0.07
		CPT-Errors [b]	0.54	0.12	0.08
		CPT-Reaction Time	80	40.3	0.18
		Digit Span	1.5	-.27	-0.06
		Boston Naming Test–no cues	5.3	-1.77	-0.12
		Boston Naming Test–cues	5.3	-1.91	-0.13
		CVLT-Short-term	3.1	-0.57	-0.06
		CVLT-Long-term	3.8	-0.55	-0.05
New Zealand [c]	3.31	TOLD-Language Development	16	-0.6	-0.12
		WISC-R:PIQ	16	-0.54	-0.11
		WISC-R:FSIQ	16	-0.55	-0.11
		McCarthy Perceptual Performance	10	-0.53	-0.17
		McCarthy Motor Test [b]	0.15	-0.007	-0.15

[a] Exposures measured on the log-scale. Exposure SD and regression coefficients provided by study investigators (Grandjean et al. 1997). Outcome SDs estimated by dividing the interquartile range by 1.3.

[b] Log transformed.

[c] Data from Crump et al. 1998.

Abbreviations: CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; TOLD, Test of Language Development; WISC-R:PIQ, Wechsler Intelligence Scale for Children-Revised Performance IQ; WISC-R:FSIQ, Wechsler Intelligence Scale for Children-Revised Full-Scale IQ.

Benchmark Dose Calculations (ppm MeHg in maternal hair) from Various Studies and For Various End Points

Study	End point	BMD[a]	BMDL
Seychelles Islands [b]	Bender Copying Errors	*** [e]	25
	Child Behavior Checklist	21	17
	McCarthy General Cognitive	***	23
	Preschool Language Scale	***	23
	WJ Applied Problems	***	22
	WJ letter/word Recognition	***	22
Faroes Islands [c]	Finger Tapping	20	12
	CPT Reaction Time	17	10
	Bender Copying Errors	28	15
	Boston Naming Test	15	10
	CLVT: Delayed Recall	27	14
New Zealand [d]	TOLD Language Development	12	6
	WISC-R:PIQ	12	6
	WISC-R:FSIQ	13	6
	McCarthy Perceptual Performance	8	4
	McCarthy Motor Test	13	6

[a] BMDs are calculated from the K-power model under the assumption that 5% of the responses will be abnormal in unexposed subjects ($P_0 = 0.05$), assuming a 5% excess risk (BMR = 0.05).
[b] Data from Crump et al. (1998, 2000). "Extended" covariates.
[c] Data from Budtz-Jørgensen et al. (1999)
[d] Data from Crump et al. (1999, 2000)
[e] *** Indicates value exceeds 100.

Abbreviations: WJ, Woodcock-Johnson Tests of Achievement; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; TOLD, Test of Language Development; WISC-R:PIQ, Wechsler Intelligence Scale for Children-Revised performance IQ; WISC-R:FSIQ, Wechsler Intelligence Scale for Children-Revised Full-Scale IQ.

Benchmark Dose Calculations (ppb MeHg in cord blood) from the Faroe Islands Study For Various End points

End point	BMD[a]	BMDL
Finger Tapping	140	79
CPT Reaction Time	72	46
Bender Copying Errors	242	104
Boston Naming	85	58
CVLT: Delayed Recall	246	103

[a] BMDs are calculated from the K-power model under the assumption that 5% of the responses will be abnormal in unexposed subjects ($P_0 = 0.05$), assuming a 5% excess risk (BMR = 0.05).

Abbreviations: CPT, Continuous Performance Test; CVLT, California Verbal Learning Test.

Source: Budtz-Jørgensen et al. (1999)

Approaches to Benchmark Dose Calculation (ppm MeHg in hair)

Approach	BMD	BMDL
Most sensitive endpoint from New Zealand	8	4
Median end point from New Zealand	12	6
Most sensitive end point from Faroe study	15	10
Median end point from Faroe study	20	12
Integrative analysis	21 [a]	8 [b]

[a] Logically equivalent to a BMD.
[b] Logically equivalent to a BMDL.

Lower 5th percentile from meta-analysis median from the estimate distribution of BMDs.

Sources of Uncertainty in Key Epidemiological Studies

Susceptible subpopulations

- Interindividual toxicokinetic variability in dose reconstruction
- Toxicodynamic variability
- Nutritional deficits

Measures of exposure

- Lack of dietary-intake data
- Extrapolation from biomarker Hg content to MeHg intake
- Nutritional and dietary confounders and effect modifiers
- Co-exposure to other neurotoxins (e.g., PCBs)
- Co-exposure to other forms of Hg
- Inability to measure peak exposures
- Temporal matching of exposure to critical periods of susceptibility for the developing fetal brain

Lack of consideration of other key or most-sensitive health end points

- Potential cardiovascular or immune-system effects
- Neurological sequelae (i.e., late emerging effects)