ICMGP 2024

CAPE TOWN • SOUTH AFRICA • 21 - 26 JULY

Leonid Kopylev

Scientific Challenges in Analysis of Methylmercury Neurotoxicity

WWW.MERCURYCAPETOWN.COM

Leonid Kopylev, Deborah Segal, Michael Dzierlenga, Yu-Sheng Lin, Rebecca Nachman, Elizabeth Radke

Center for Public Health and Environmental Assessment

Office of Research and Development

US Environmental Protection Agency

Outline of the Presentation

- Background
- Choice of MeHg biomarker for dose-response: history
- Choice of MeHg biomarker for dose-response: analysis
- Conclusions

Background: Existing RfD

- Developmental neurotoxicity (DNT) hazard of Methylmercury (MeHg) is widely accepted.
  - Multiple health agencies (Health Canada, 2007; UNEP, 2002; US EPA, 2001, 1997; ATSDR, 1999) and the US National Academy of Sciences (NAS, 2000) have established that prenatal oral exposure to methylmercury in humans causes developmental neurotoxicity (DNT).

- Existing EPA Reference Dose (RfD) for MeHg published in 2001 was based on NAS (2000) report (that report considered 3 cohorts: Faroe Islands, Seychelles, New Zealand)
  - Quantitative analysis preferred cord blood to maternal hair.

- Multiple DNT outcomes supported the 2001 RfD of 0.1 µg/kg-day.

- RfD is specifically based on neuropsychological impairment in Faroe Islands cohort of children prenatally exposed to MeHg.

Background: Existing RfD

- Since 2001, when the RfD was published, the number of epidemiological studies greatly increased from 3 cohorts in 2000 to about 60 cohorts in 2022!
  - Studies in Africa, Asia, Europe, North and South America
  - More than 250 new studies with dose-response information on DNT outcomes

- Almost all of these studies used either maternal blood or cord blood or maternal hair as biomarkers of MeHg prenatal exposure. A few used children's biomarkers – blood or hair.

- Are any of these biomarkers preferable for dose-response analysis of DNT effects of MeHg?
  - We looked at cord blood and maternal hair

Biomarkers of MeHg: history

Which biomarker is best has been debated for many years:

- Cernichiari et al. (1995) advocated for use of maternal hair for dose-response analyses.
- NRC (National Research Council, 2000); Grandjean and Budtz- Jørgensen (2007) suggested using cord blood was more reliable for dose-response.
- The recent NASEM (National Academy of Sciences, Engineering, and Medicine, 2024) report on fish consumption and development indicated that “cord blood mercury may be a better biomarker of fetal exposure than mercury in maternal hair”

Biomarkers of MeHg: Methods

Literature search (1998-2022):
PubMed, Web of Science, Toxline, Science Direct, and SCOPUS.

↓

SWIFT Review:
Filtered by applying epidemiology and dose-response search strings.

↓

Title/abstract and full-text screening:
- *Two independent reviewers.*
- *Goal: identify studies with quantitative dose-response data for DNT effects.*

↓

Included studies:
Moved forward to sensitivity and risk of bias evaluation

Biomarkers of MeHg: Methods

- For this analysis we only considered studies that passed Systematic Review and evaluated dose-response using more than one biomarker of MeHg.
- All the studies used different log-transformations of exposure. We used recently developed methods (Dzierlenga et al. 2020) to transform everything to the un-transformed scale.
- We transformed all results to the common biomarker of maternal blood, by using well-established conversion factors, 1.7 for cord blood and maternal blood and 250 for maternal hair and maternal blood (Stern and Smith 2003; Grandjean and Budtz-Jørgensen 2007).
- We compared results for each domain of neurodevelopment separately. The subdivisions covered 8 domains of neurodevelopment and 4 omnibus test categories (e.g. attention, executive function, motor function, etc) (White et al. 2022)

Biomarkers of MeHg: Results

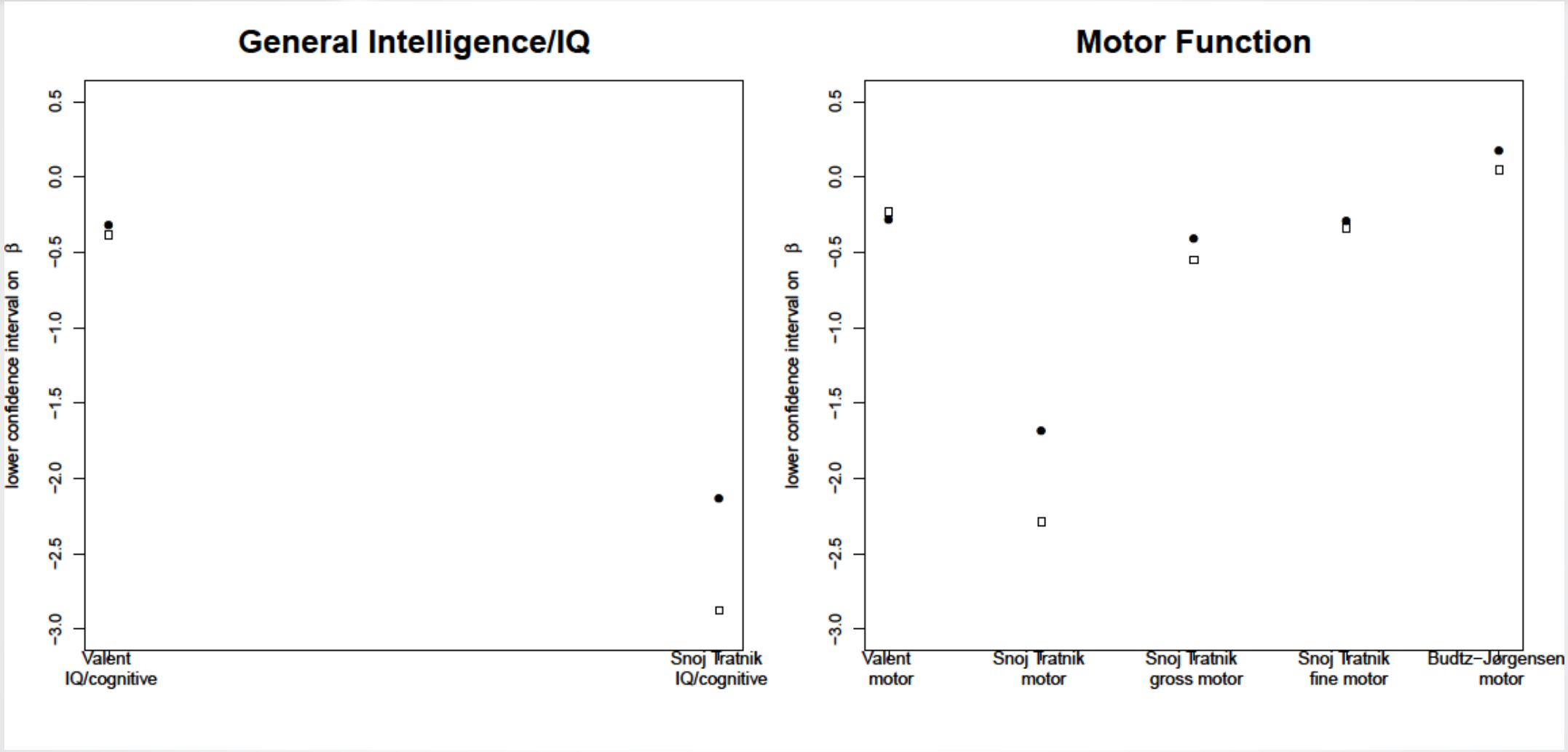
The literature search identified 17,661 studies. Following all of the systematic review steps, 5 papers were found, with 2 more papers (Barbone et al., 2019 and Murata et al., 1999) investigating the same populations.

Author, Year	Location	N	Child age (y)	Cord blood concentration (µg/L)*	Maternal hair concentration (µg/g)*	Maternal hair timing	Maternal Hair length/ location	DNT Tests
Budtz-Jørgensen et al. 1999	Faroe Islands Cohort I	917	7	GM 22.9 IQR (13.4–41.3)	GM 4.27 IQR (2.6–7.7)	Birth	at least 100 mg, most were > 5 cm in length, close to the root	NES2, BNT, Bender, CVLT
Murata et al. 2004	Faroe Islands Cohort I	859	14	GM 22.6 IQR (13.2-40.8)	GM 4.2 IQR (2.55-7.68)	Birth	at least 100 mg, most were >5 cm in length, close to the root	BAEP
Snoj Tratnik et al. 2015	Croatia, Slovenia	361	1.5	GM 2.05 95% CI 2.05 (1.87–2.25)	GM 0.36 95% CI (0.33–0.40)	34 week or birth	1-3 cm closest to scalp	BSID III
Valent et al. 2013	Italy	606	1.5	Mean (SD) 5.54 (4.83) IQR (2.40-7.02)	Mean (SD) 1.06 (1.03) IQR (1.03-1.28)	20-22 week	1 gram	BSID III
Yorifunji et al. 2013	Faroe Islands Cohort II	139	7	GM 22.8 IQR (13.7 – 41.2)	GM 4.6 IQR (2.7 – 8.2)	Birth	at least 100 mg, most were > 5 cm in length, close to the root	VEP

Biomarkers of MeHg: Results

Study	Number of subtests with cord blood more adverse than maternal hair/total number of subtests	Overall range (mean; median) of relative difference when cord blood is more adverse	Overall range (mean; median) of relative difference when maternal hair is more adverse
Budtz-Jørgensen et al. 1999	5/5		
Murata et al. 2004	8/8		
Snoj Tratnik et al. 2015	5/5		
Valent et al. 2013	4/5		
Yorifunji et al. 2013	10/12		
Overall	32 (35)	4 – 583% (75%; 44%)	7-29% (18%; 18%)

Biomarkers of MeHg: Results



Empty squares denote cord blood biomarker and filled circles denote maternal hair biomarker.
X axes show study name and domain of neurodevelopment in the study. Lower results are more adverse.

Biomarkers of MeHg: Results

There was less data for comparison of maternal blood with maternal hair or cord blood—only 2 studies each.

- For maternal blood vs maternal hair: two studies (Barbone et al., 2019, Rothenberg et al., 2016)
  - Stronger adverse results for Maternal blood Hg: mean 320%; range (43%-855%) based on 7 comparisons.
- For maternal blood vs cord blood: two studies (Barbone et al., 2019, Kim et al., 2020)
  - Stronger adverse results for Maternal blood Hg : mean 36%, range (15%-71%) based on 10 comparisons and in 2 comparisons cord blood Hg was more adverse (3% and 13%).

- There are no conversion factors for converting children's biomarkers into maternal biomarkers, so we couldn't investigate children's biomarkers.

Biomarkers of MeHg: Discussion

There could be several reasons why we found such a difference between cord blood and maternal hair biomarkers

- Analytical chemistry. Even when done well, it is difficult to achieve the same precision for hair that is achieved for blood, which may lead to greater measurement error with maternal hair biomarker.

- Cord blood may better describe fetal exposure. Populations in studies used in this analysis are regular fish consumer, so their mercury is likely in a steady state condition and in such situation, cord blood may be as good a predictor of longer exposure as traditionally considered for hair.

Biomarkers of MeHg: Discussion

There were some limitations:

- It would be great if there were more data both for cord blood and maternal hair, but also for other comparisons.
- Although other biomarkers (e.g., cord tissue, placenta tissue, dry blood spots, toenails) can be considered, these biomarkers are much less frequently examined in modeling of DNT effects in epidemiological studies and, therefore, comparisons could not be made.
- We only looked at DNT effects. Situation may be different for other effects of MeHg.
- All the studies in this analysis used THg, not MeHg. At the level of exposures in the considered studies THg is a good predictor of MeHg (Wells et al., 2022).

Biomarkers of MeHg: Conclusion

Hair Hg biomarkers have many potential benefits for surveillance and research purposes.

- Hair is both less expensive and less invasive than blood to collect and store.

THg or MeHg in hair remains an appropriate biomarker for population-level MeHg exposure analyses, such as identifying populations of concern and characterizing long-term temporal trends in MeHg exposures.

However, cord blood biomarkers are preferable for dose-response modeling of DNT effects of MeHg.