Methylmercury and the developing brain

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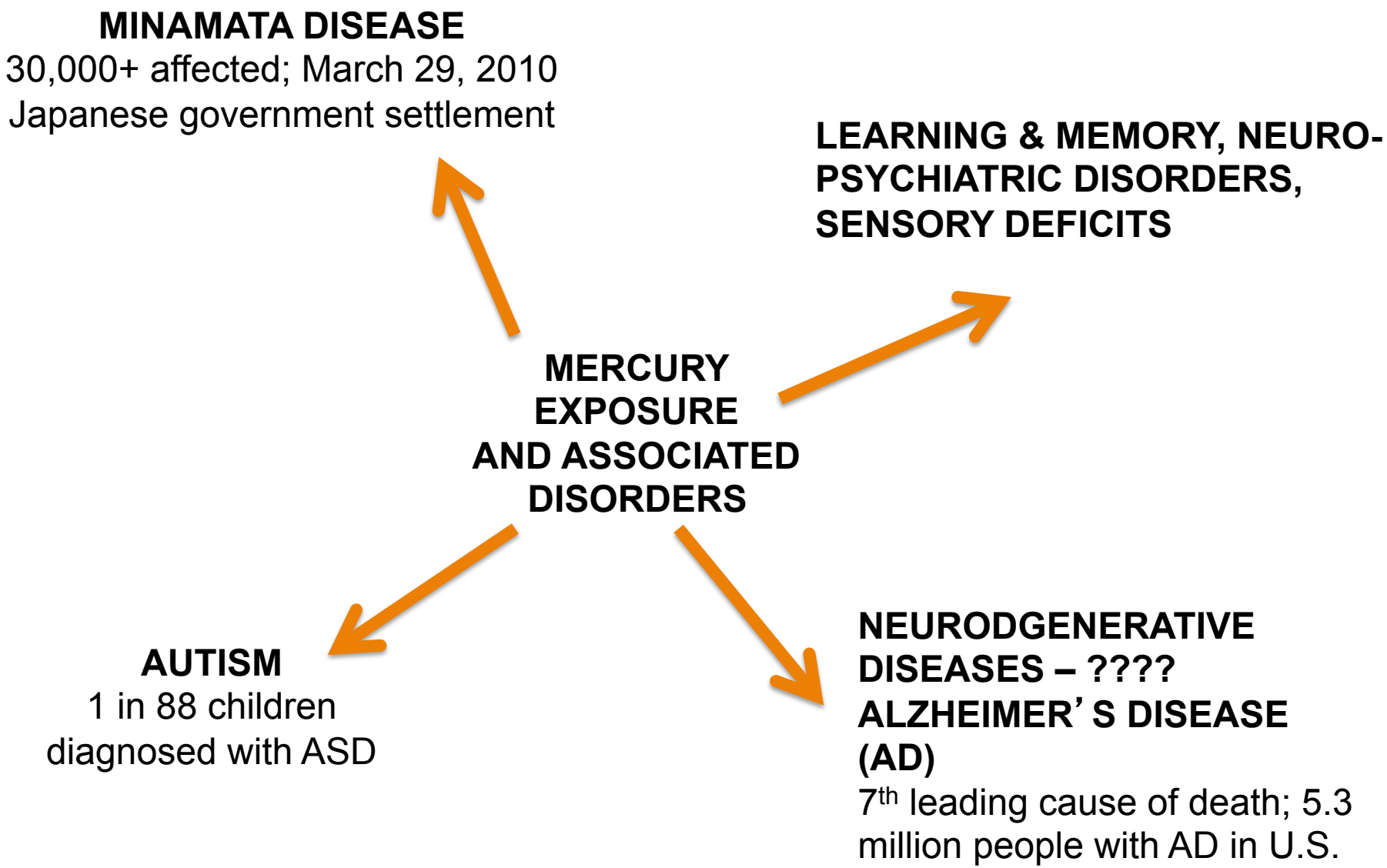
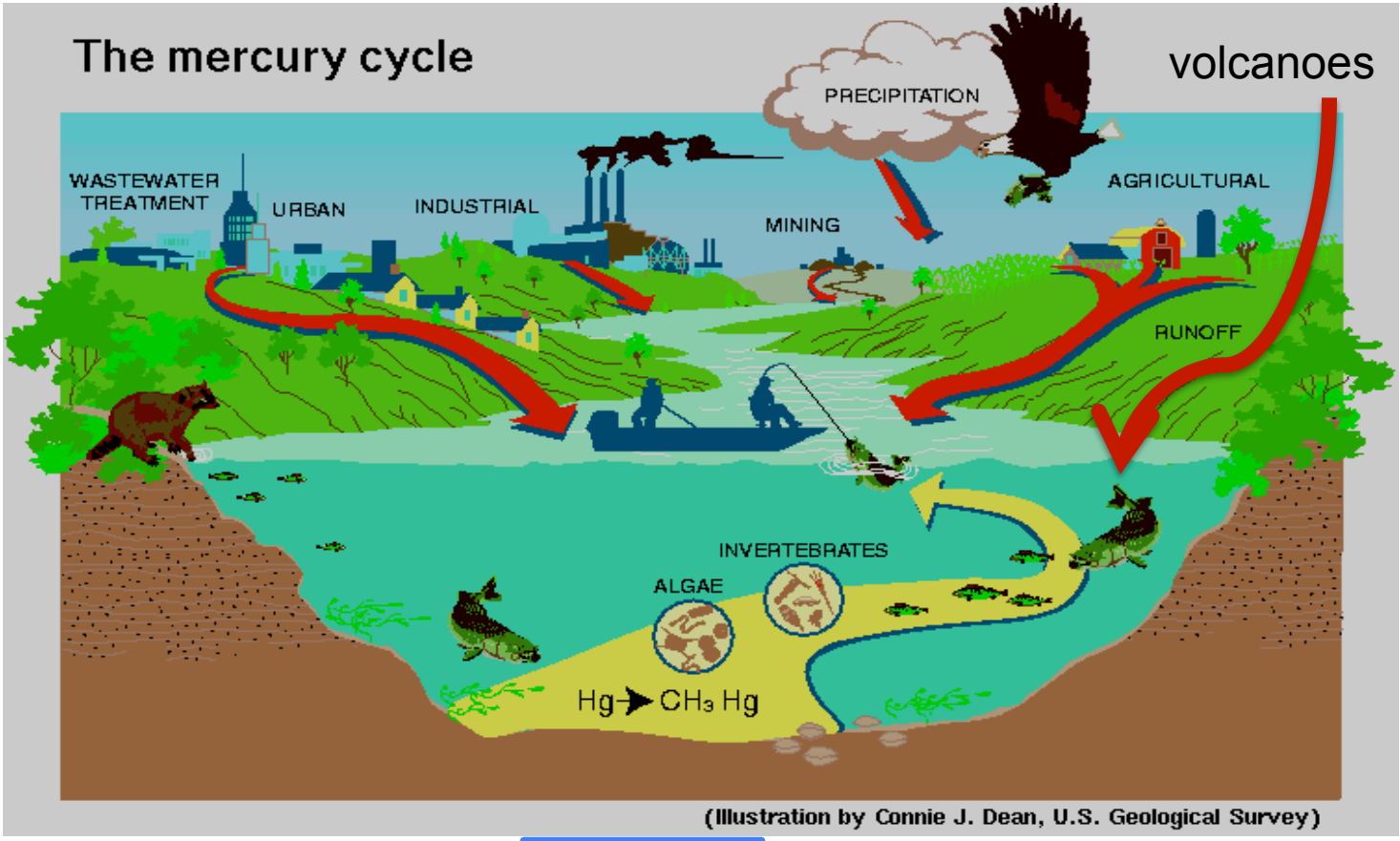

MINAMATA DISEASE
30,000+ affected; March 29, 2010
Japanese government settlement
LEARNING & MEMORY, NEURO-PSYCHIATRIC DISORDERS, SENSORY DEFICITS
MERCURY EXPOSURE AND ASSOCIATED DISORDERS
AUTISM
1 in 88 children diagnosed with ASD
NEURODGENERATIVE DISEASES – ????
ALZHEIMER'S DISEASE (AD)
7th leading cause of death; 5.3 million people with AD in U.S.

Follow-up studies of methylmercury exposures in Iraq revealed a significant dose-response relationship for prenatal methylmercury exposure:

Increased mercury exposure leads to increased or more severe adverse neurological problems.

Conclusion:

Prenatal exposures as low as 10 ppm measured in maternal hair samples might affect brain development of children exposed prenatally.



discharge

Inorganic mercury (Hg) → water sediments

biomethylation

methylmercury ($Hg\text{-}CH_3$)

bioaccumulation

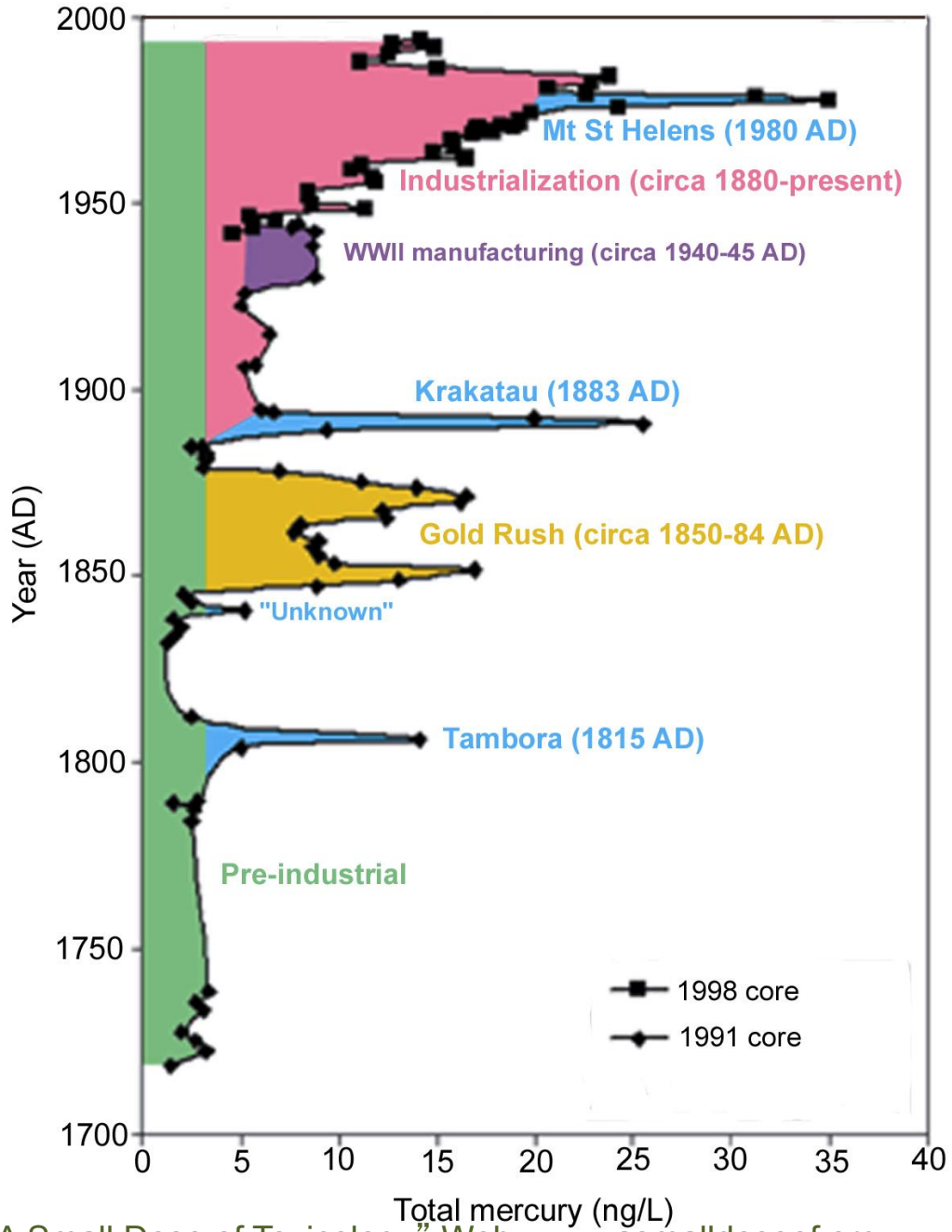
Edible fish

exposure

methylmercury in humans

"A Small Dose of Toxicology" Web: www.asmalldoseof.org

Figure 2



"A Small Dose of Toxicology" Web: www.asmalldoseof.org

270-year record

Major atmospheric releases

- **Natural**
  - **Background (42%)**
  - **Volcanic (6%)**
- **Anthropogenic (52%)**
  - **Gold rush**
  - **WWII**
  - **Industrialization**

The last 100 years

- **Anthropogenic (70%)**

Species	Mercury content (mg/kg or PPM ± SD)			
	Atlantic ocean	Number of fish measured	Pacific ocean	Number of fish measured
Herring	0.14 ± 0.06	15	0.04 ± 0.02	131
Flounder	0.08 ± 0.04	60	0.07 ± 0.07	58
Halibut	0.25 ±0.23	46	0.28 ± 0.09	11
Mackerel	0.22 ± 0.16	877	0.09 ± 0.06	30
Salmon (fresh)	0.13 ± 0.17	11	0.04 ± 0.01	289
Salmon (canned)	ND		0.04± 0.01	289
Snapper	0.28 ± 0.43	363	0.25 ± 0.09	17
Shark	0.75 ± 0.70	585	0.80 ± 0.37	35
Swordfish	0.98 ± 0.51	618	0.98 ± 0.51	618
Tuna (fresh)	0.28 ± 0.12	496	0.24 ± 0.10	555
Tuna (canned, light)	0.11 ± 0.10	199	0.11 ± 0.10	199
Tuna (canned, albacore)	0.37 ± 0.12	318	0.37 ± 0.12	328

Sutherland, EM. Environmental Health Perspectives 115(2):235-242, 2007.

What You Need to Know About Mercury in Fish and Shellfish

EPA-823-R-04-005

2004

EPA and FDA Advice For:

Women Who Might Become Pregnant
Women Who are Pregnant
Nursing Mothers
Young Children

- Do not eat Shark, Swordfish, King Mackerel, or Tilefish.
- Eat up to 12 ounces (2 average meals) a week of a variety of fish and shellfish that are lower in mercury, such as shrimp, canned light tuna, salmon, pollock, and catfish.
- Albacore ("white") tuna has more mercury than canned light tuna. It is recommended that one can consume up to 6 ounces (one average meal) of albacore tuna per week.

Toxicological Effects of Methylmercury

Committee on the Toxicological Effects of Methylmercury
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council
NATIONAL ACADEMY PRESS (2000)
Washington, DC

BDML = **benchmark dose level** = lowest dose expected to be associated with a small increase in the incidence of an adverse outcome (typically 1% to 10%).
BMDL for methylmercury is 58 parts per billion (PPB) of mercury in cord blood; based on adverse outcomes on standardized learning and memory tests.

EPA's current Reference Dose (RfD) for methylmercury = **0.1 µg/kg per day (0.1 PPB)**
0.0001 mg/kg per day

(Established in 1995)

Canned light tuna = 0.11 mg/kg methylmercury (110 PPB)

Two prospective **Faroe Islands** cohort studies

based on 182 newborns at 2 weeks of age, or 917 children at 7 years of age, respectively.

Both methylmercury in maternal hair during pregnancy and in cord serum served as the exposure markers.

The 7-year-old children were tested for their performance on tasks associated with neuropathologic abnormalities seen in methylmercury poisoning in Japan and Iraq.

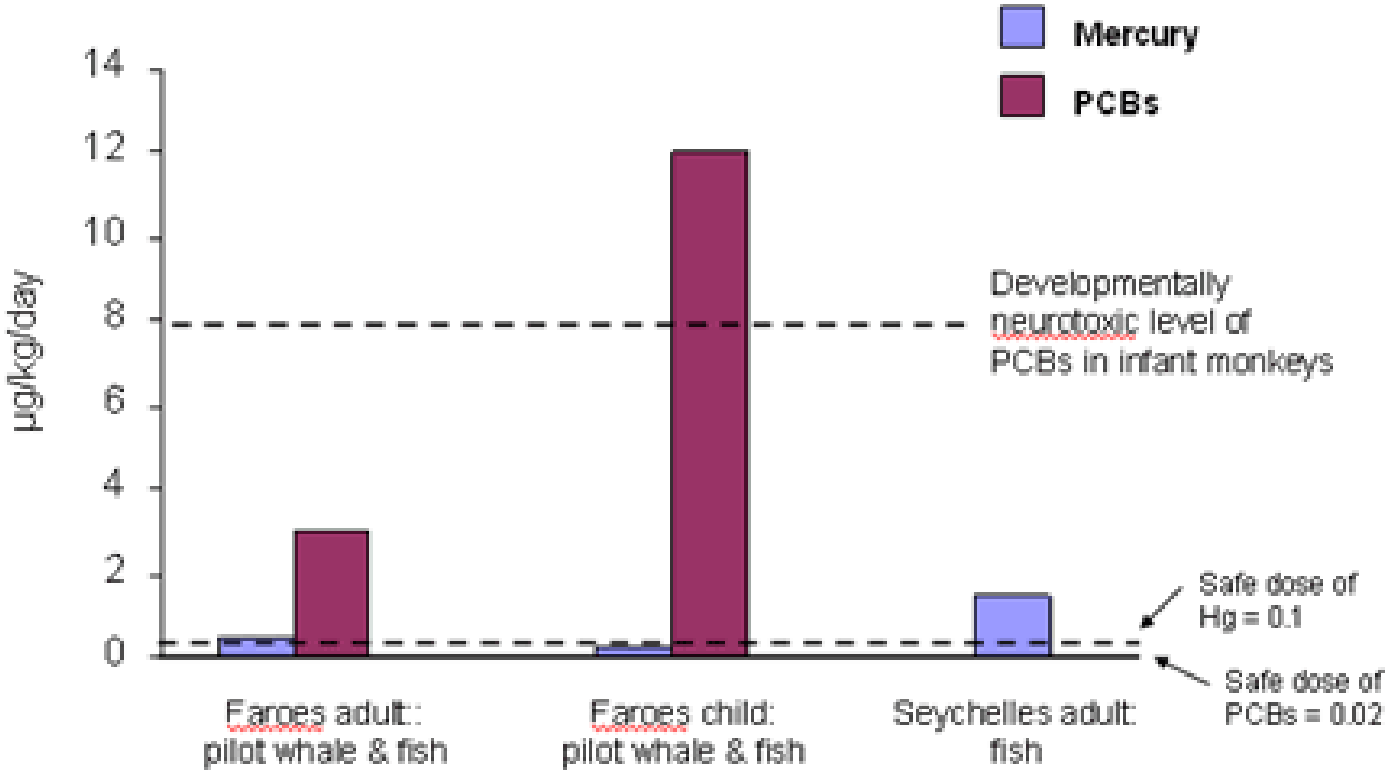
Observed: decreased attention, memory, and language skills

The Seychelles study is a prospective cohort approach based on 779 mother–infant pairs.

Neurodevelopmental and neurobehavioral examinations were performed at several ages up to 66 months (5.5 years).

Prenatal methylmercury exposure was estimated from maternal hair samples collected at birth.

At no age was significant exposure-related neurodevelopmental or neurobehavioral deficit observed in the Seychelles Islands study.



Faroes Islanders - displayed neurologic deficits

Seychelles Islanders – did not display neurologic deficits

Perhaps the combination of PCBs + mercury is important

Summary

Levels of methylmercury in food that affect cognitive function are controversial

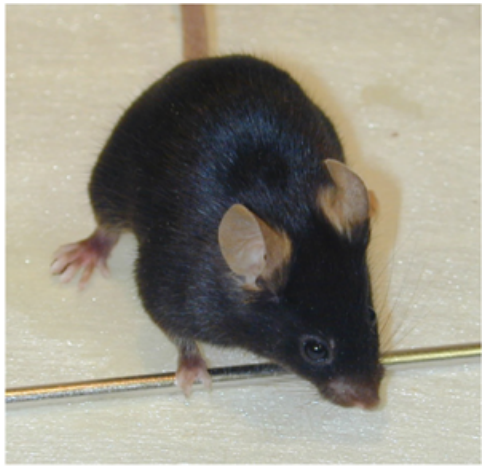
PCBs are often found with methylmercury and the combination and/or PCBS may be more toxic

Other factors may be involved (smoking; alcohol, etc.)

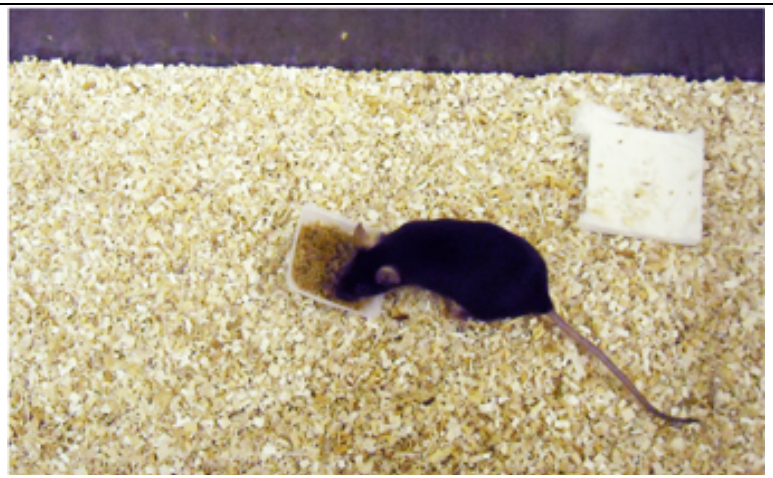
Karienn S. Montgomery, Jessica Mackey, Kerry Thuett, Stephanie Ginestra, Jennifer L. Bizon and Louise C. Abbott

Chronic, low-dose prenatal exposure to methylmercury impairs motor and mnemonic function in adult C57/B6 mice

Behavioural Brain Research Volume 191, Issue 1, Pages 55-61 (2008)

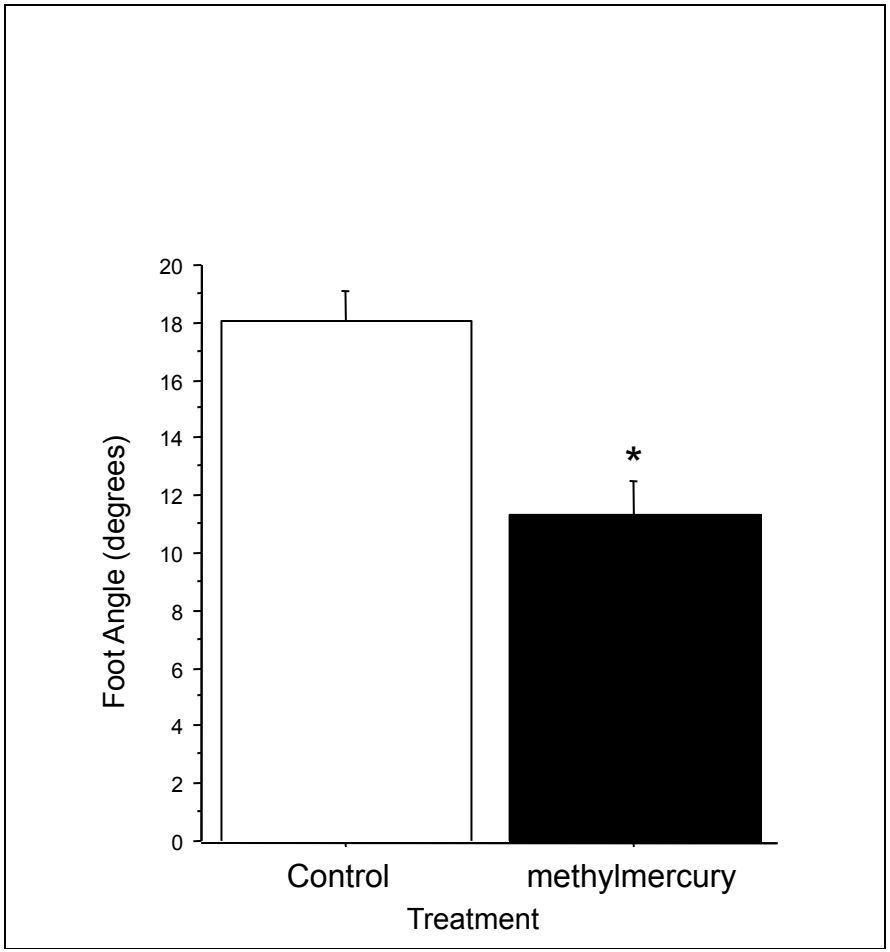


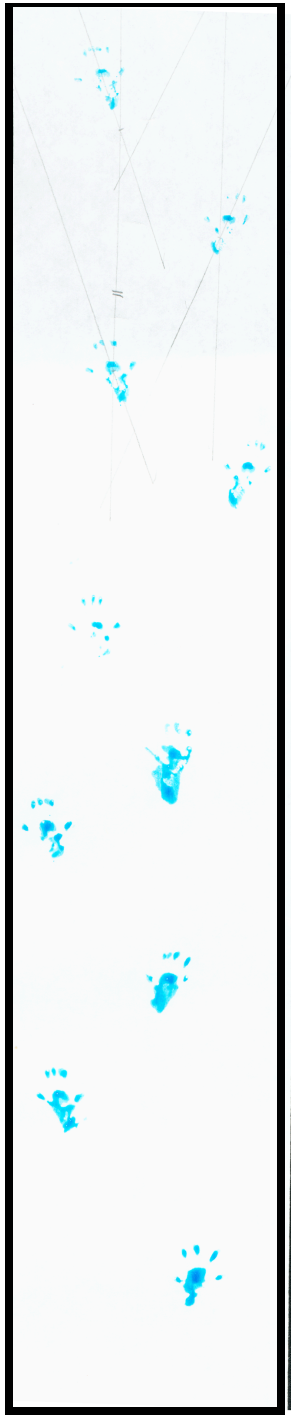
Mercury content in brains of adult and fetal mice exposed orally to a total dose of 0.1mg MeHg.	
ADULT FEMALE MICE EXPOSED AS ADULTS	**TOTAL BRAIN LEVELS**
CONTROLS (**no MeHg**) (n=6)	0.003 ppm ± .001 (SE)
TREATED **pregnant mice killed on gestational day 18** (n=4)	0.063 ppm ± 0.011 (SE)*
E18 FETUSES EXPOSED PRENATALLY	**TOTAL BRAIN LEVELS**
CONTROLS (**no MeHg**) (n=4 fetuses)	0.0015 ppm ± 3.083E-4 (SE)
TREATED MeHg given to pregnant dam (n=8 fetuses)	0.048 ppm ± 0.005 (SE)*
THREE-MONTH-OLD MICE EXPOSED PRENATALLY	**BRAIN REGION LEVELS**
CONTROLS (**no MeHg**) - cerebellum (n=3)	0.0011 ppm ± 1.946E-4 (SE)
CONTROLS (**no MeHg**) - neocortex (n=3)	0.0011 ppm ± 2.379E-4 (SE)
TREATED PRENATALLY - cerebellum (n=5)	0.0010 ppm ± 1.526E-4 (SE)
TREATED PRENATALLY – NEOCORTEX (N=5)	0.0028 ppm ± 0.002 (SE)

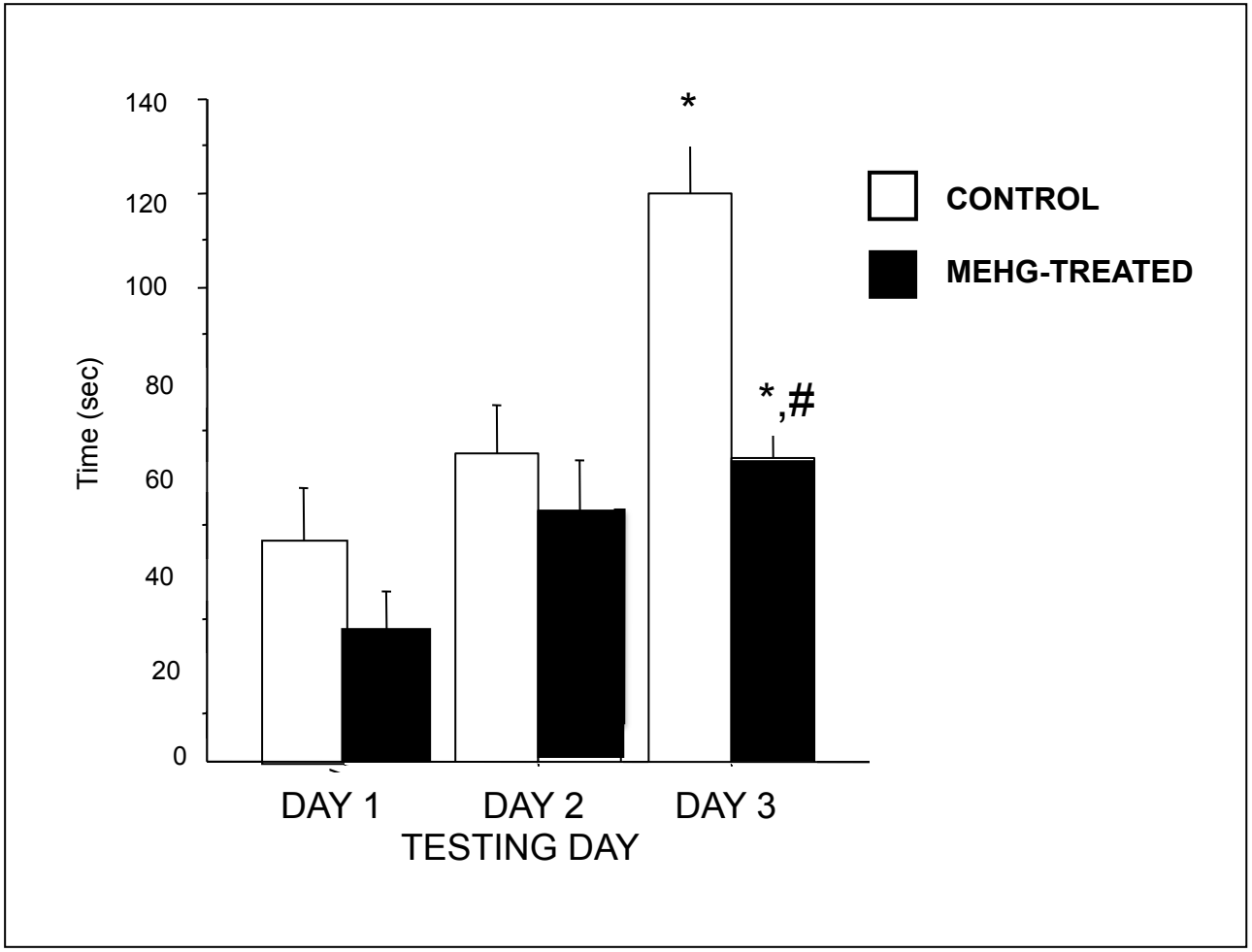


methylmercury-exposed mice demonstrated a significantly narrower foot angle (*) compared to control mice

Black bars = methylmercury-exposed mice
White bars = control mice
Error bars = standard error of the mean (S.E.M.).





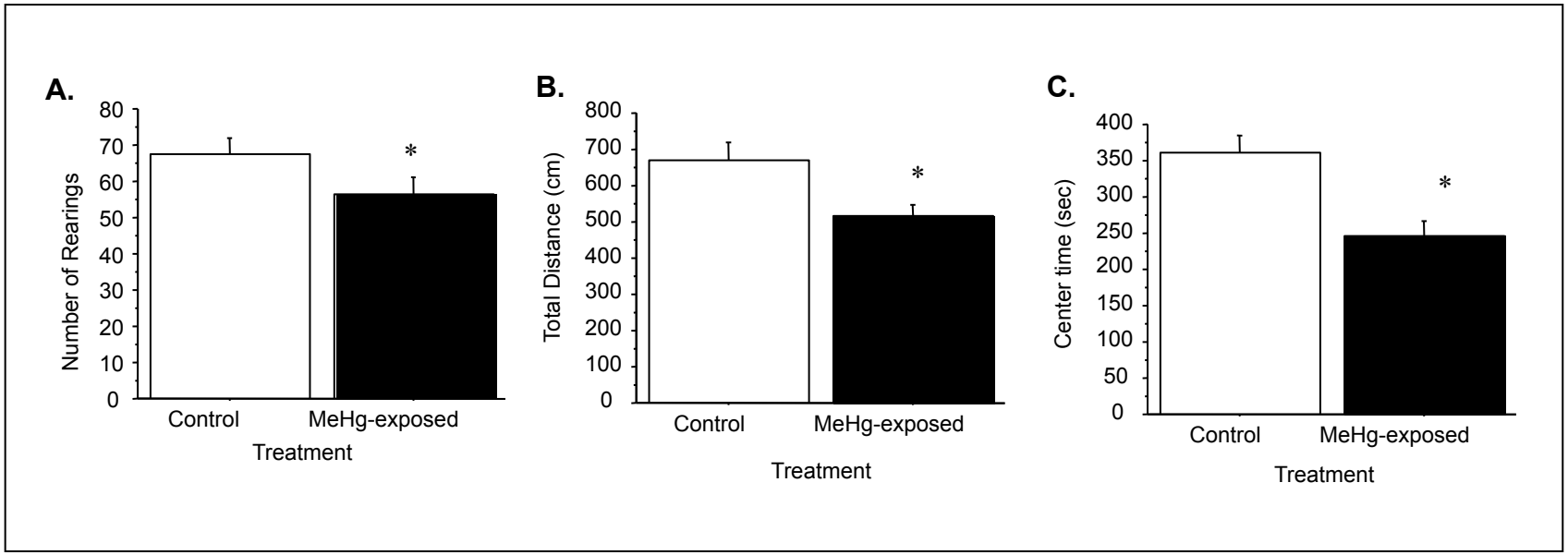


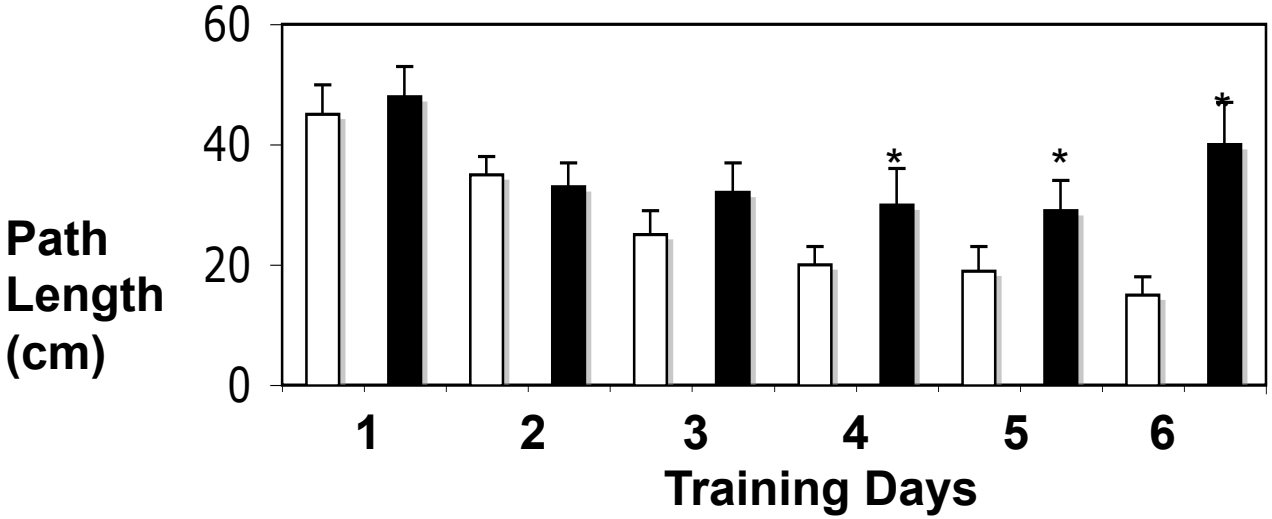
All mice spent increased time on **accelerating rotarod** over sequential days of testing. Methylmercury (MeHg)-treated mice (black bars ■) spent significantly less time on rotarod compared to control mice (white bars □).
Error bars indicate standard error of the mean (S.E.M.).

Open field activity during first 10 min.
Methylmercury (MeHg)-treated mice
Made fewer vertical (A) and fewer
horizontal (B) movements than
control mice.

Methylmercury-treated mice spent
less time in center of open field
than control mice (C).

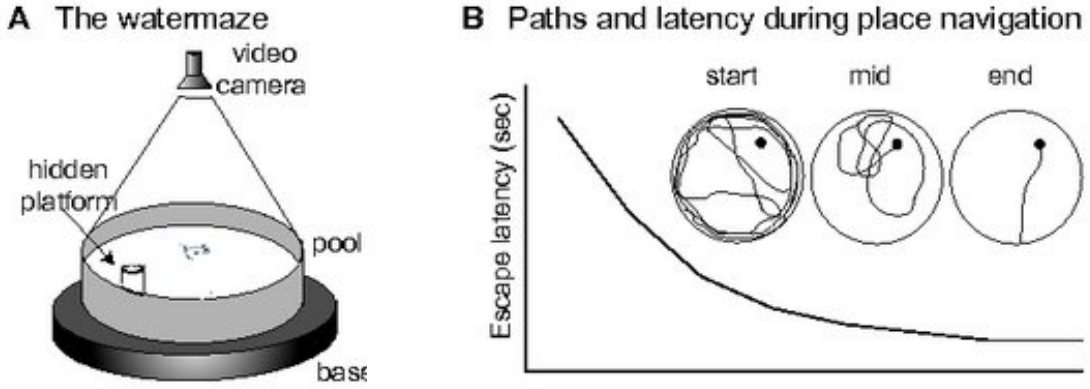
Error bars = standard error of mean (S.E.M).

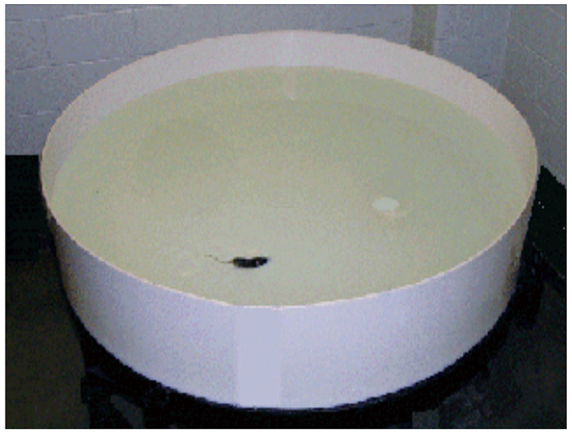


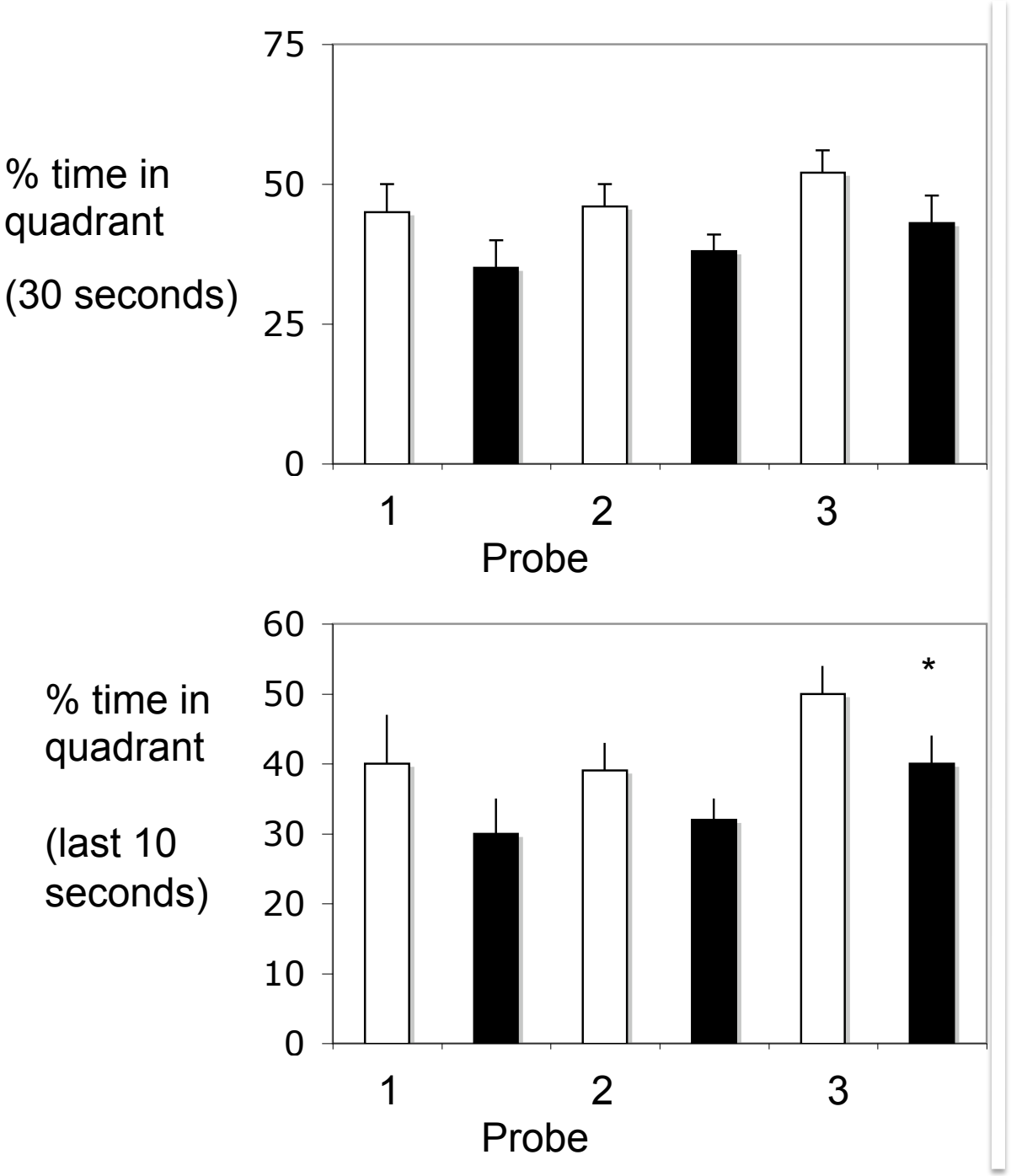


Morris water maze

- both groups improved over the course of training
- methylmercury (MeHg)-treated mice demonstrated significantly longer path lengths to hidden platform compared to control mice







- strong trend methylmercury-treated mice spent less time than control mice in target quadrant

- methylmercury-treated mice spent less time in the target quadrant than control mice during last 10 seconds of probe trials