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Mercury Exposure Assessment and Model Validation through Controlled Tuna Consumption Study

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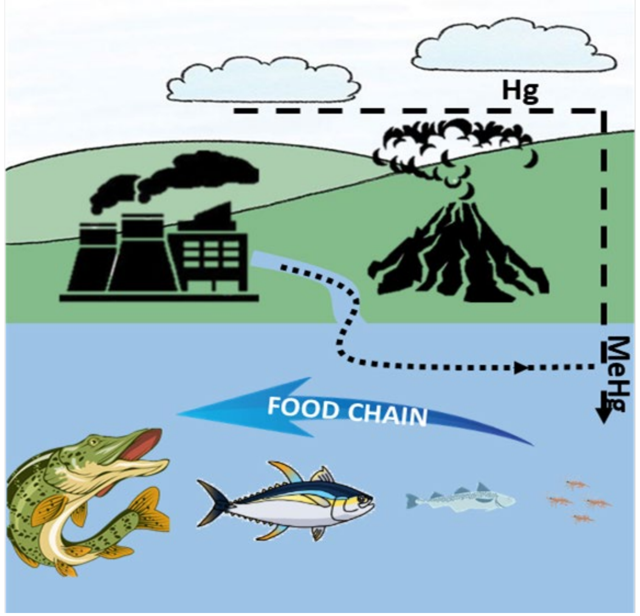
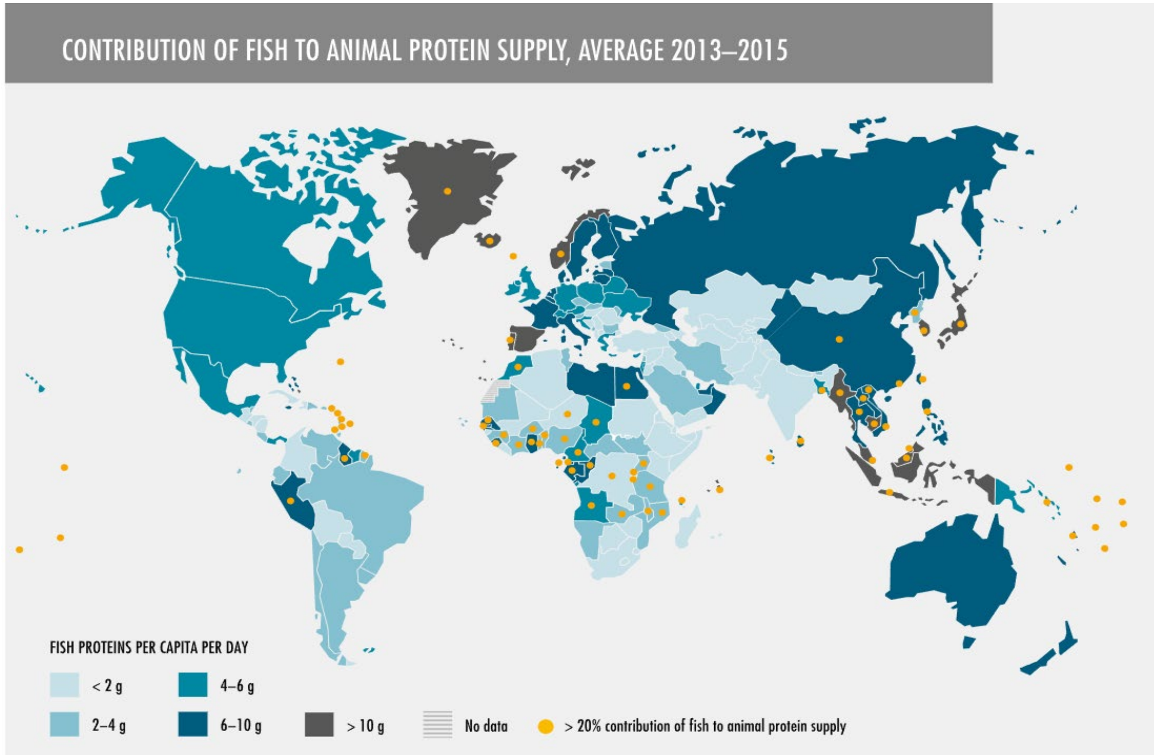
Introduction

Fish and seafood – important source of animal protein and nutrients

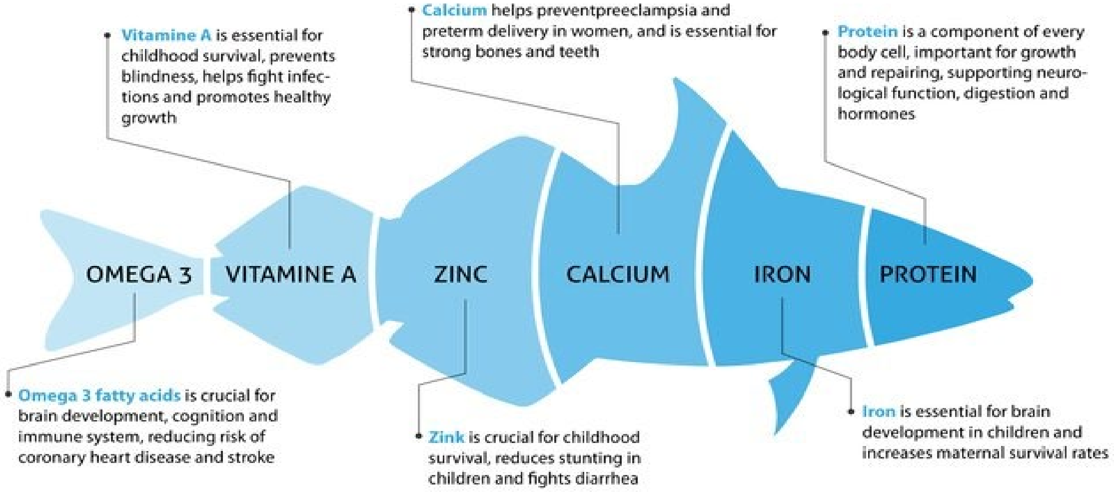
but

also the main source of the general population exposure to Hg





Source: The State of World Fisheries and Aquaculture, 2018. Food and Agriculture Organization of the United Nations (FAO)



- **Vitamine A** is essential for childhood survival, prevents blindness, helps fight infections and promotes healthy growth
- **Calcium** helps preventpreeclampsia and preterm delivery in women, and is essential for strong bones and teeth
- **Protein** is a component of every body cell, important for growth and repairing, supporting neurological function, digestion and hormones
- **Omega 3 fatty acids** is crucial for brain development, cognition and immune system, reducing risk of coronary heart disease and stroke
- **Zink** is crucial for childhood survival, reduces stunting in children and fights diarrhea
- **Iron** is essential for brain development in children and increases maternal survival rates

Source: Troell, Max & Jonell, Malin & Crona, Beatrice. (2019). The role of seafood for sustainable and healthy diets The EAT-Lancet commission report through a blue lens.

Common assumptions in health risk assessment:

- all Hg in fish is MeHg
- ingested MeHg from fish is 95-100% bioavailable

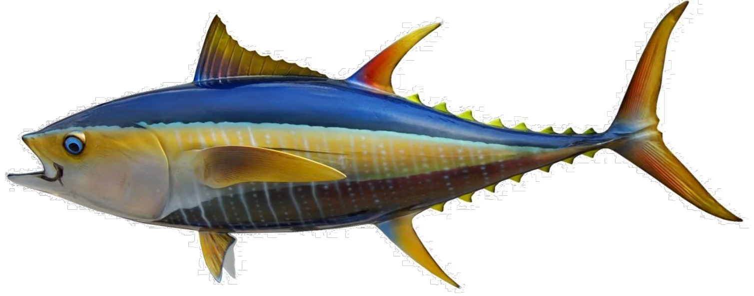
A growing body of literature challenging these assumptions!

Basis are **outdated** studies with significant **limitations:**

- small number of participants
- unrealistic exposure sources and routes (CH_3HgCl, CH_3HgNO_3 aqueous solution…instead of physiologically relevant MeHg) Aberg et al. (1969), Miettinen et al. (1971), Berntssen et al. (2004)
- unknown exposure dose, speciation
- poorly described participant characteristics
- lack of speciation in biological samples
- no data on how fish was prepared, what was consumed with it

How adequate are these models?

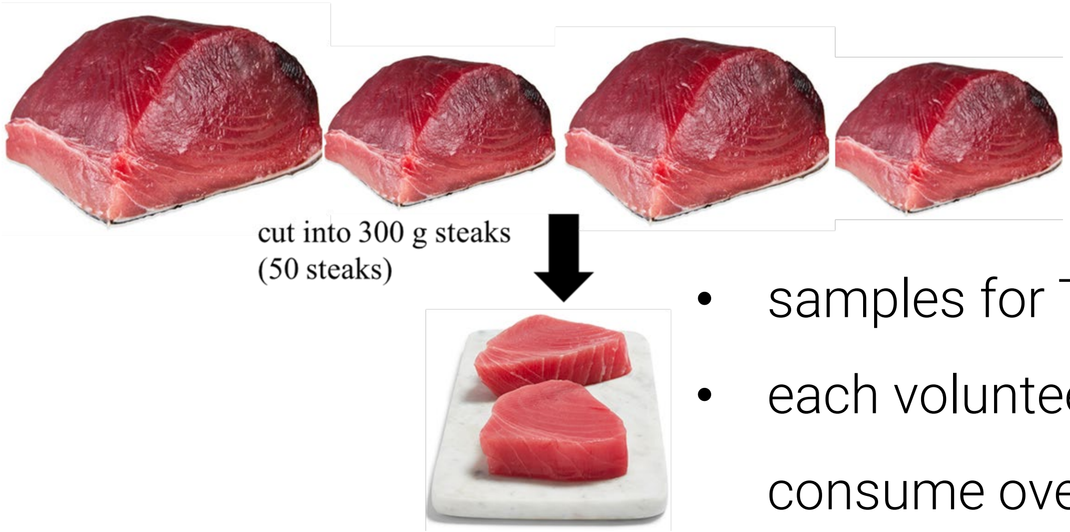
The tuna experiment



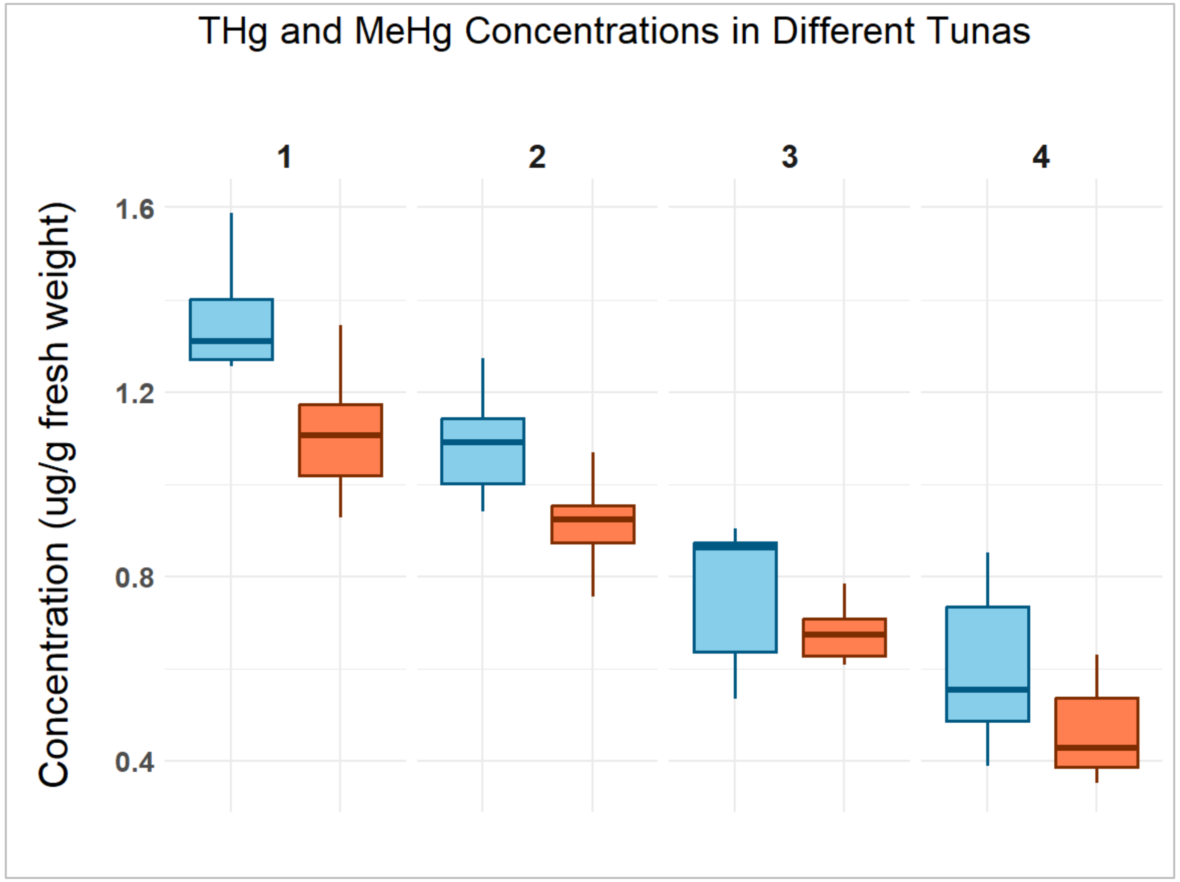
- creation of a **controlled** and realistic exposure scenario and subsequent measurements of **THg and MeHg** in **multiple** biological samples

16 volunteers (10 experimental + 6 controls)

Yellowfin tuna (Thunnus albacares)



- samples for THg and MeHg measurements taken from each steak
- each volunteer in the experimental group was given 5 steaks to consume over 5 consecutive days

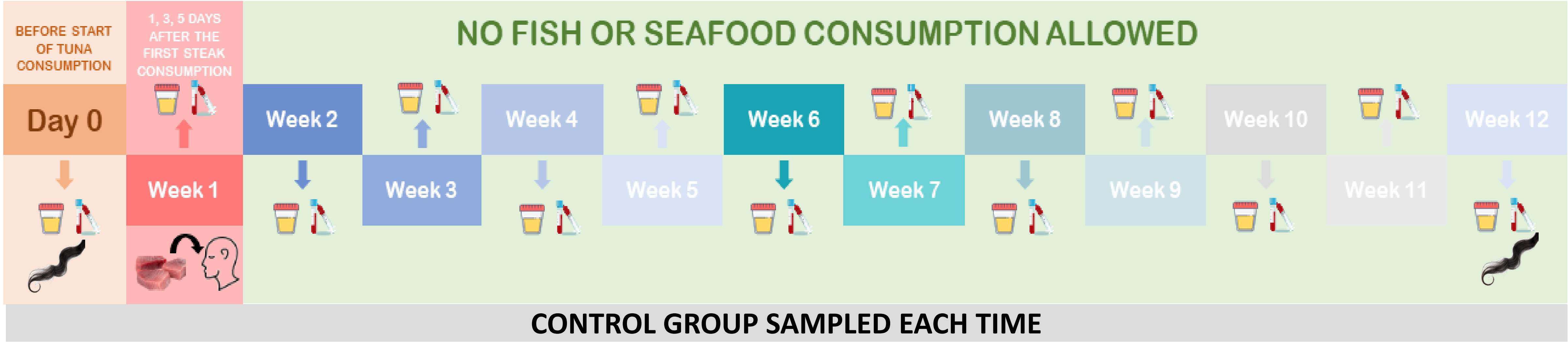


THg: 0.38 – 1.6 μg g^{-1} fresh weight

~ 80% MeHg

The sampling regimen

Dietary diary – how tuna was prepared (grilling on sunflower oil for 5 minutes on each side), foods and drinks consumed with it, time of consumption



BEFORE START OF TUNA CONSUMPTION

1, 3, 5 DAYS AFTER THE FIRST STEAK CONSUMPTION

NO FISH OR SEAFOOD CONSUMPTION ALLOWED

Day 0

Week 1

Week 2

Week 3

Week 4

Week 5

Week 6

Week 7

Week 8

Week 9

Week 10

Week 11

Week 12

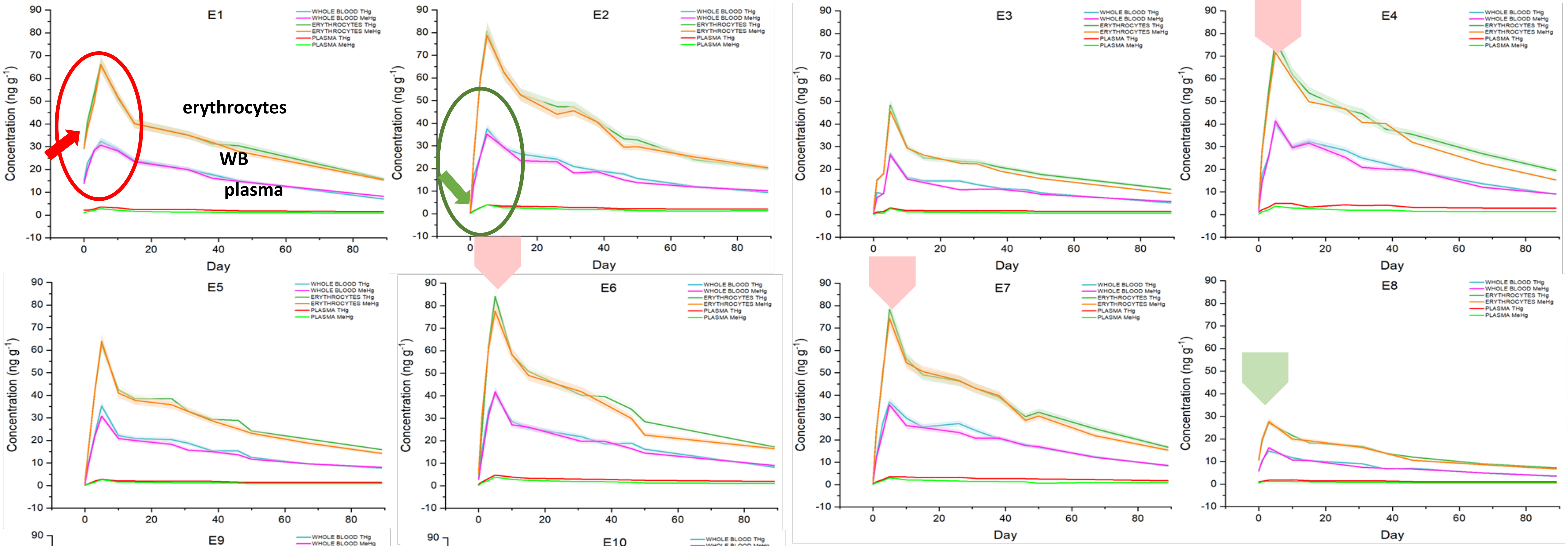
CONTROL GROUP SAMPLED EACH TIME

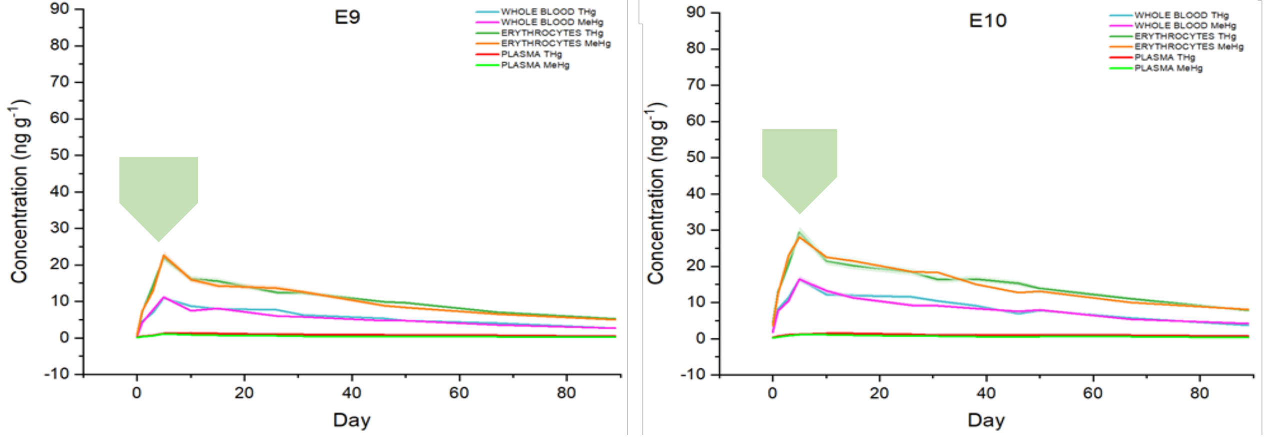
Day 0 – sampling to establish initial state of exposure

5 days of fish consumption (experimental group), 3 samplings (also control group)

No fish consumption, continuous periodical sampling until 89 days post-exposure

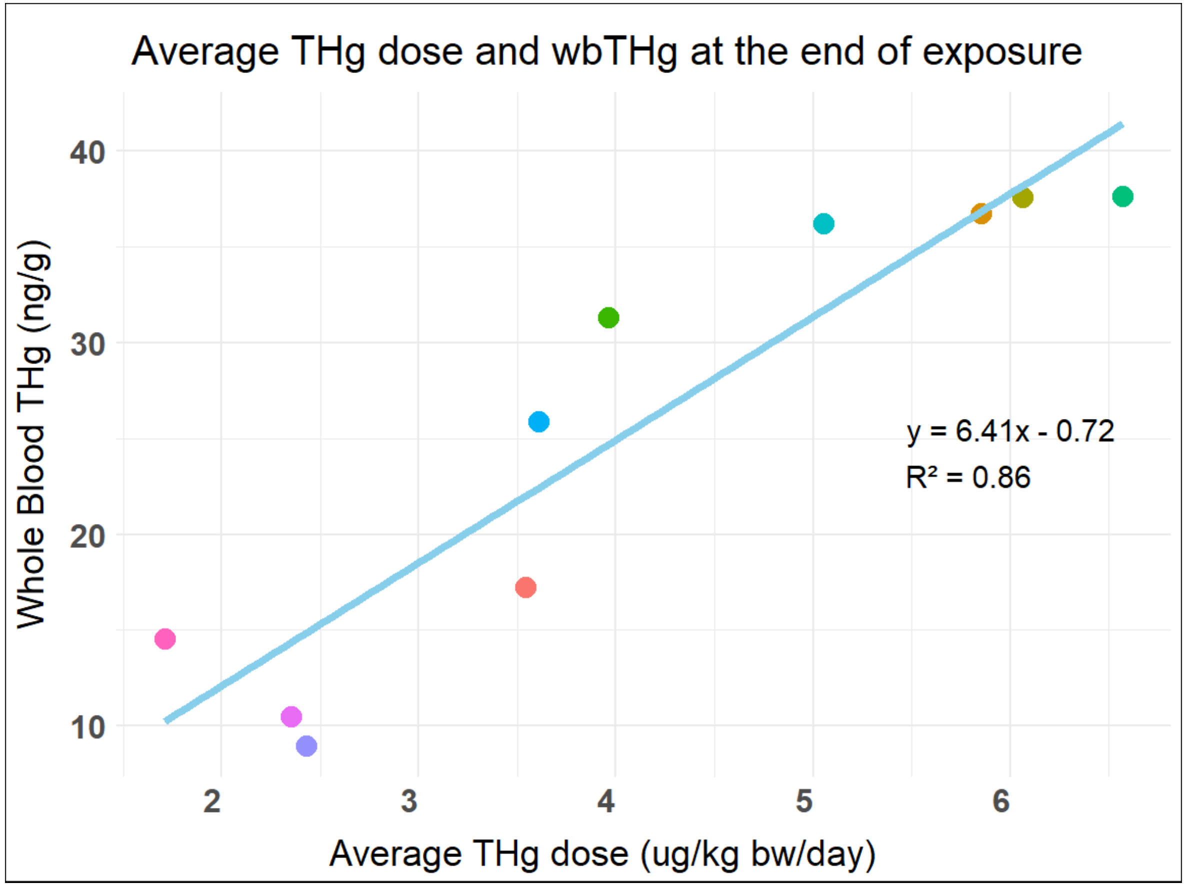
BLOOD

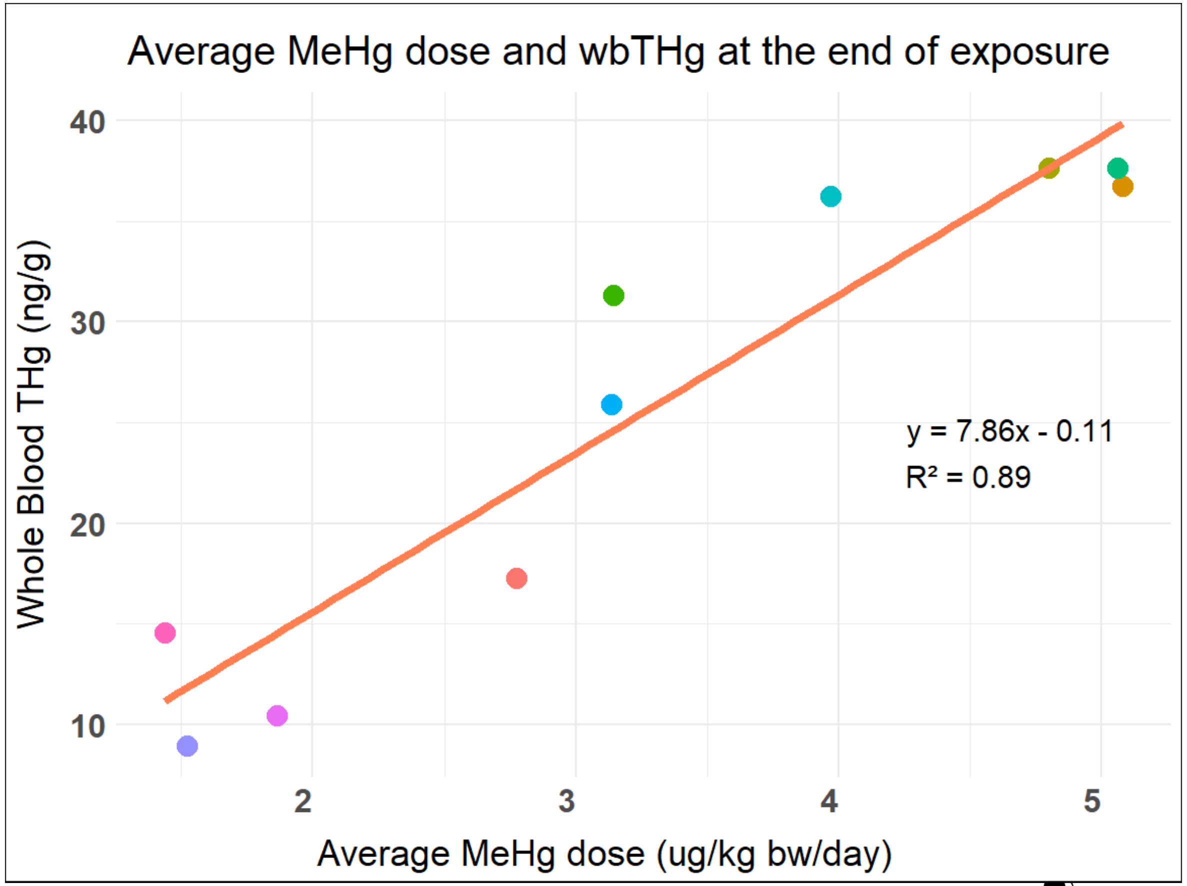




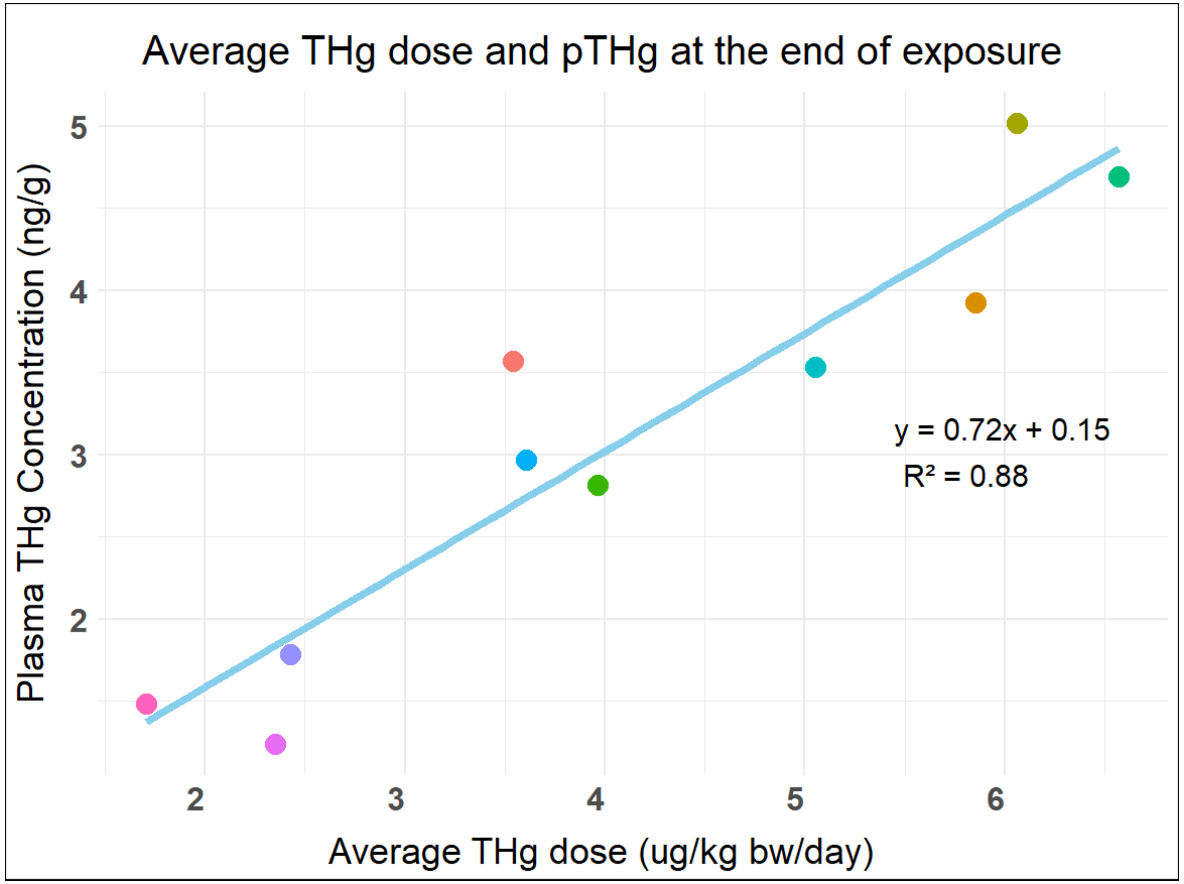
- in whole blood and erythrocytes practically all Hg is MeHg
- different starting concentrations – depend on the previous fish consumption habits
- different c_{max} reached – depend on the dose per kg bw

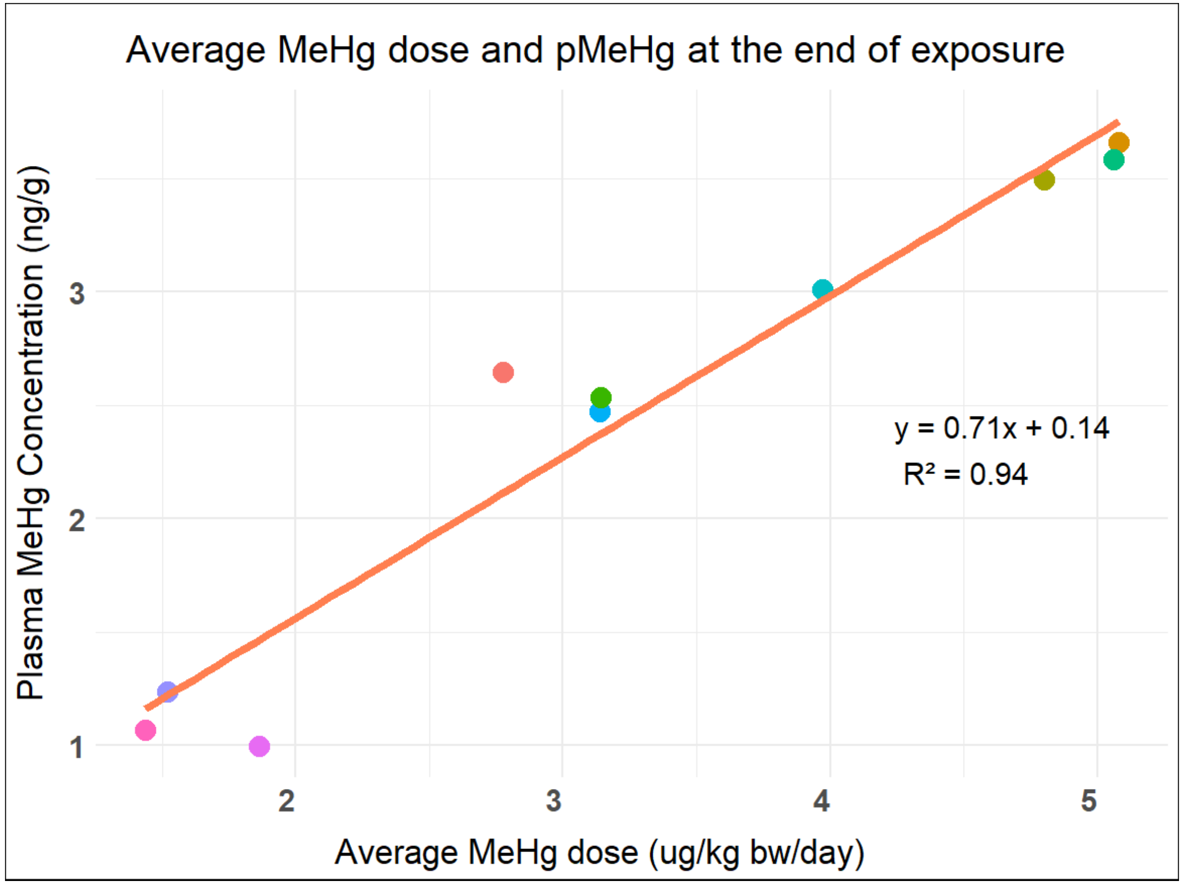
The relationship between the dose and the whole blood concentration reached



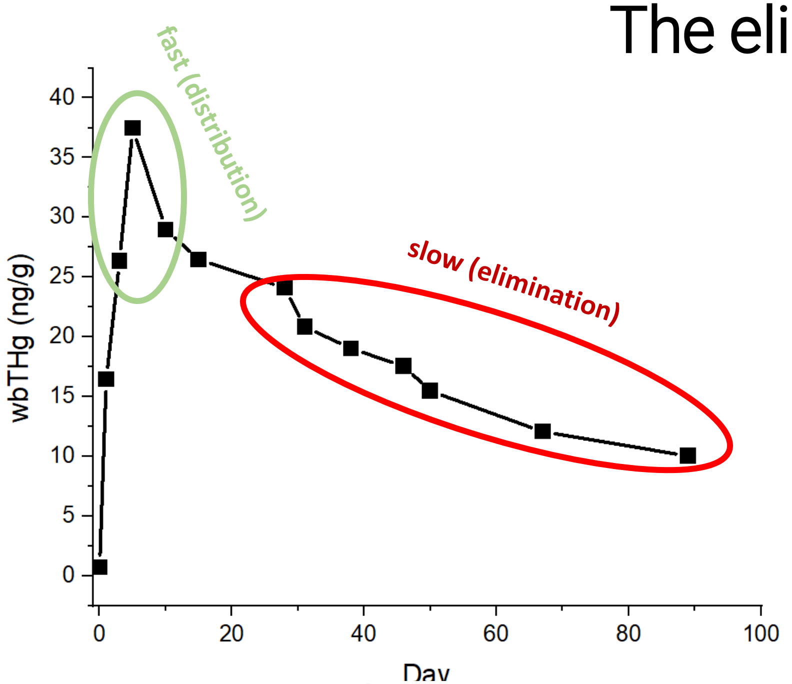


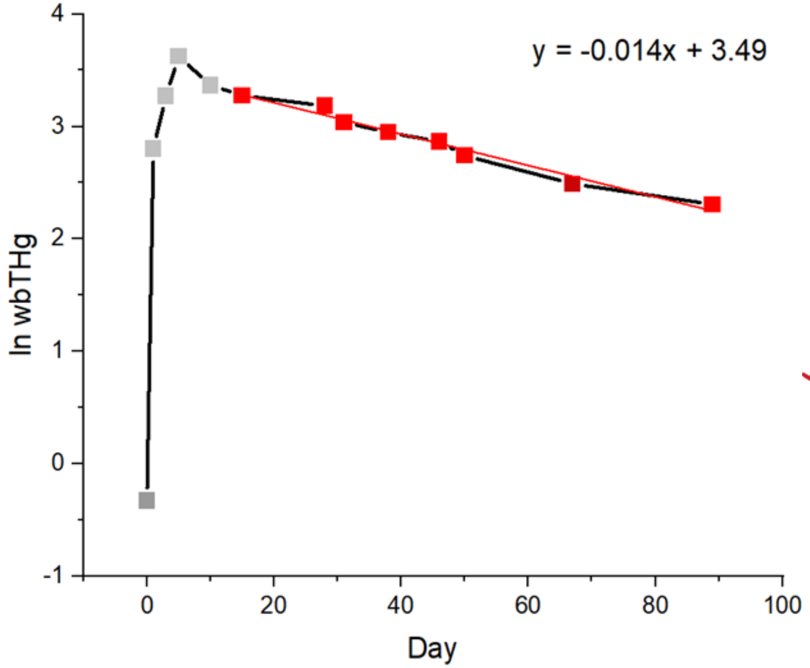
The relationship between the dose and the plasma concentration reached

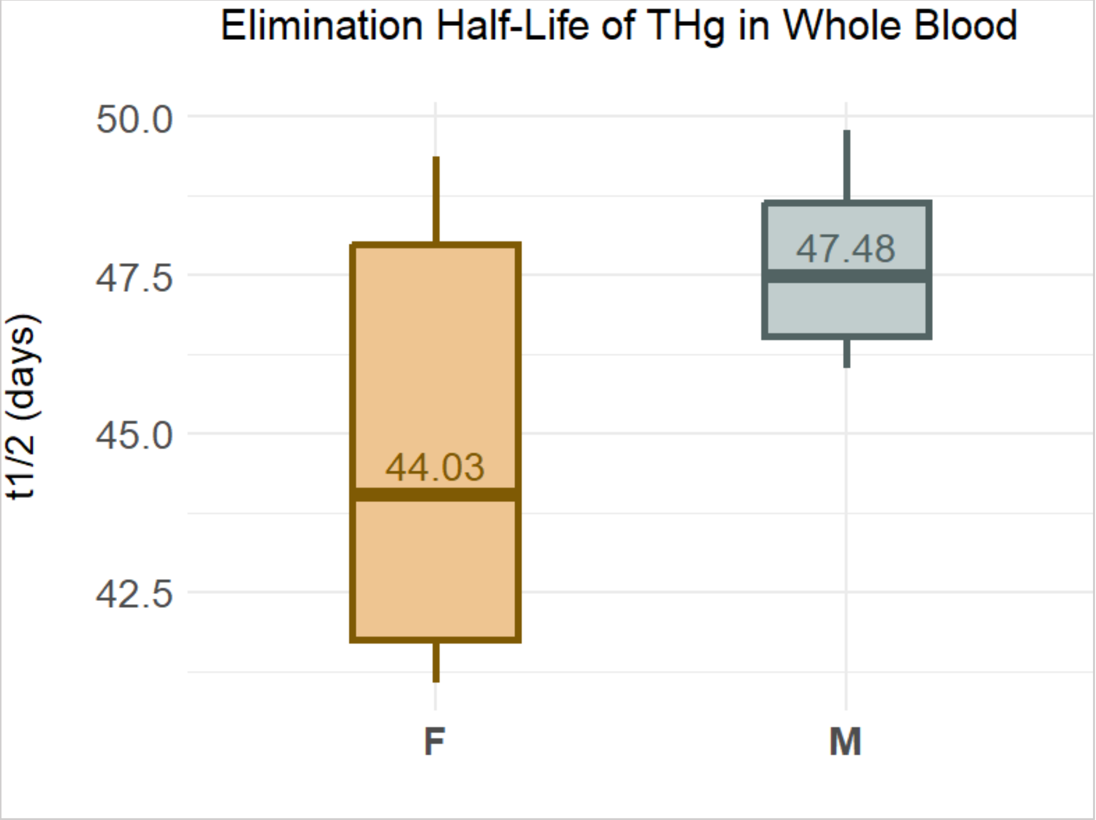




The elimination half-life of THg in blood



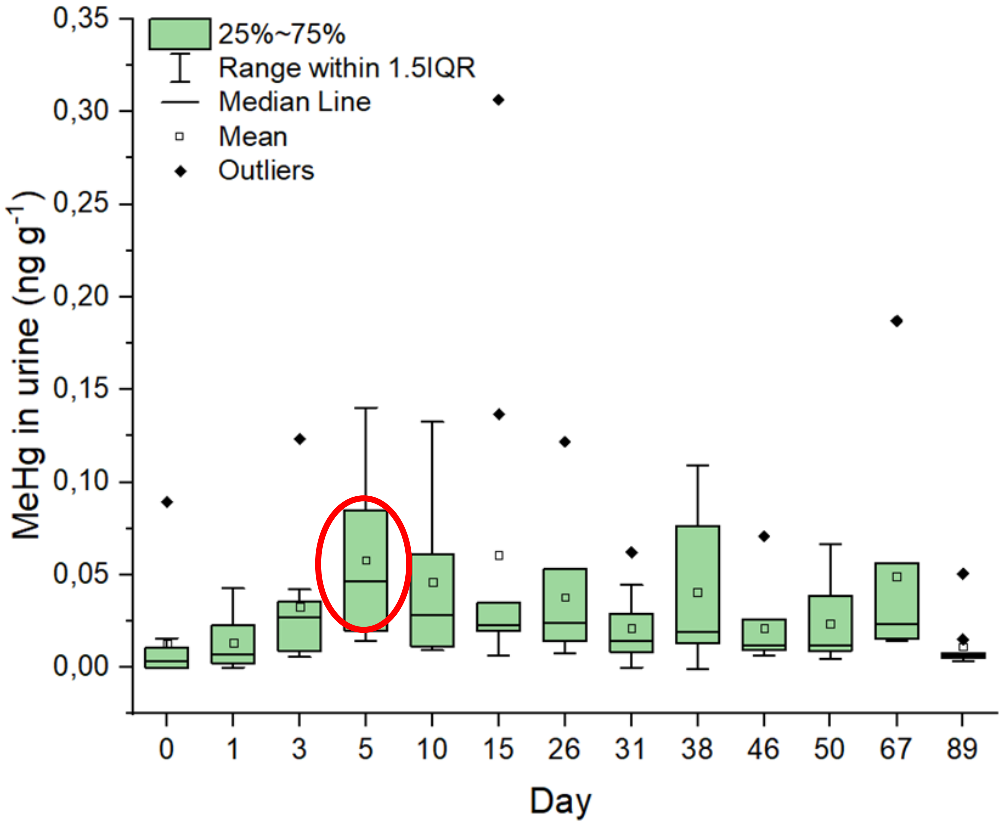


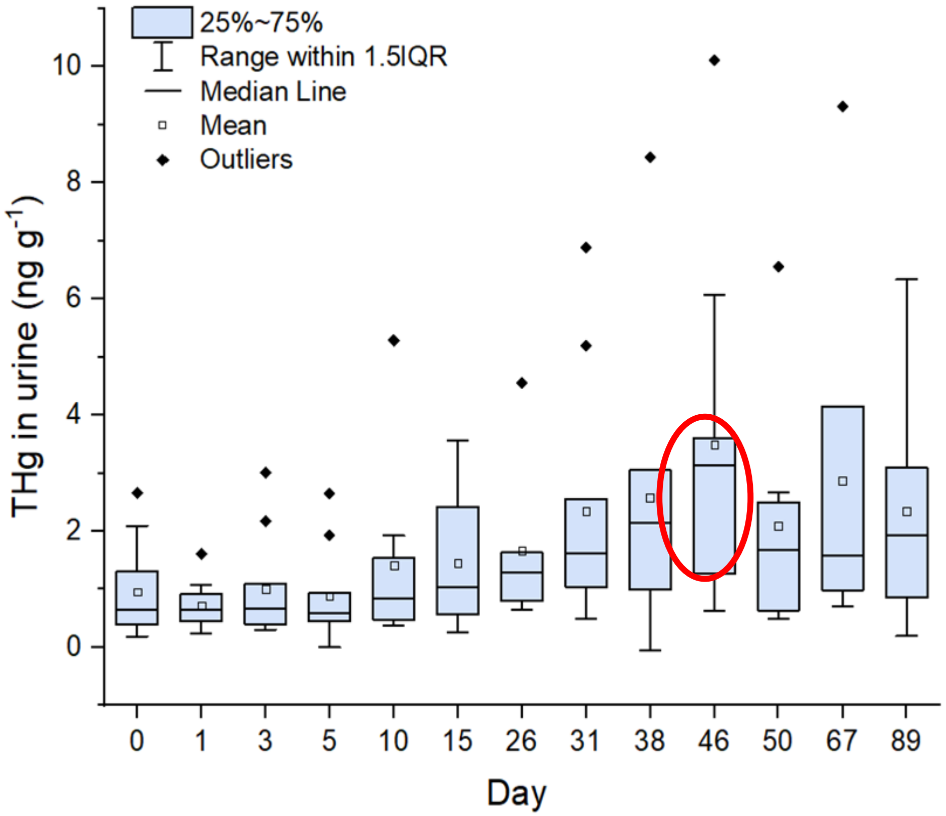

Elimination Half-Life of THg in Whole Blood

URINE

In all participants in the experimental group:

- the highest MeHg in urine was measured at the end of the exposure period
  - MeHg represented up to 13% of the total mercury
- the highest THg measured in urine was one month after the tuna consumption
  - large individual differences in mercury levels in urine – relationship with Hg dose not straightforward, different demethylation capacities?

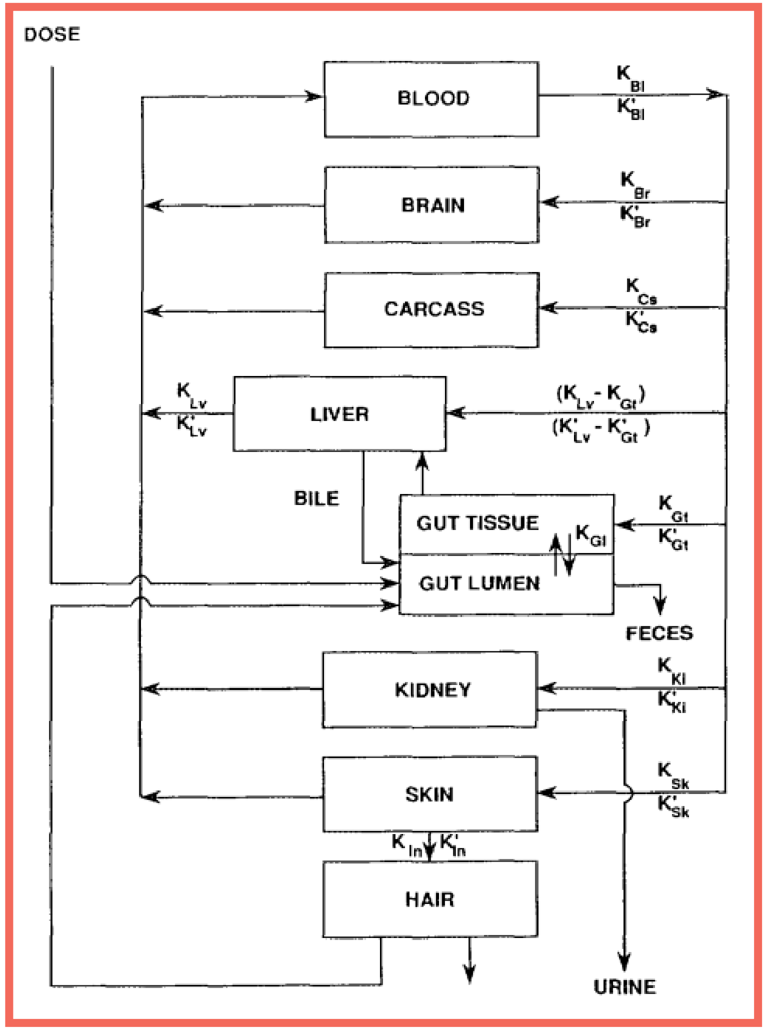




PBPK model

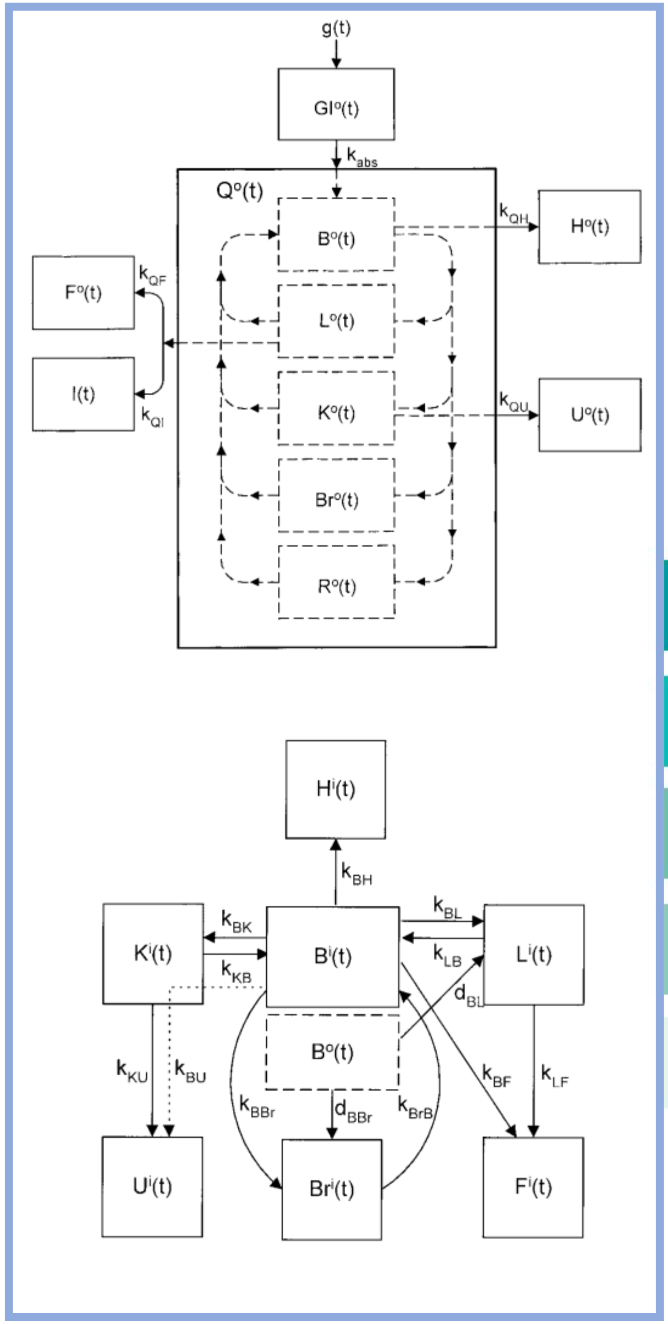
PBPK model was reconstructed based on the literature:

- **Carrier et al. (2001a):** A Toxicokinetic Model for Predicting the Tissue Distribution and Elimination of Organic and Inorganic Mercury Following Exposure to Methyl Mercury in Animals and Humans. I. Development and Validation of the Model Using Experimental Data in Rats
- **Carrier et al. (2001b):** A Toxicokinetic Model for Predicting the Tissue Distribution and Elimination of Organic and Inorganic Mercury Following Exposure to Methyl Mercury in Animals and Humans. II. Application and Validation of the Model in Humans
- **Farris et al. (1993):** Physiological Model for the Pharmacokinetics of Methyl Mercury in the Growing Rat
- **Clewell et al. (1999):** Evaluation of The Uncertainty in an Oral Reference Dose for Methylmercury Due to Interindividual Variability in Pharmacokinetics



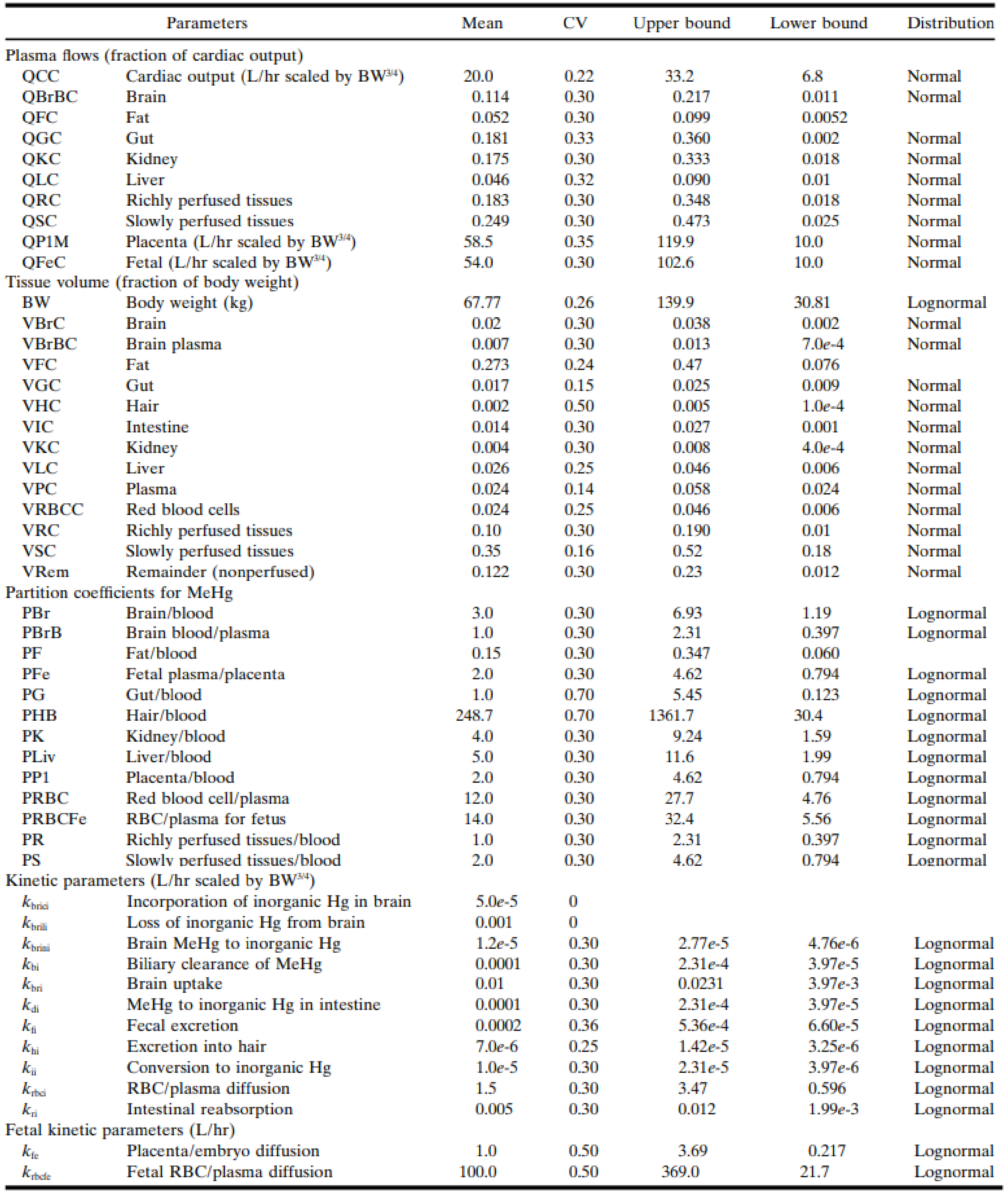
Farris et al. (1993)

Carrier et al. (2001b)



- based on Clewell et al. (1999), uncertainty analysis was introduced

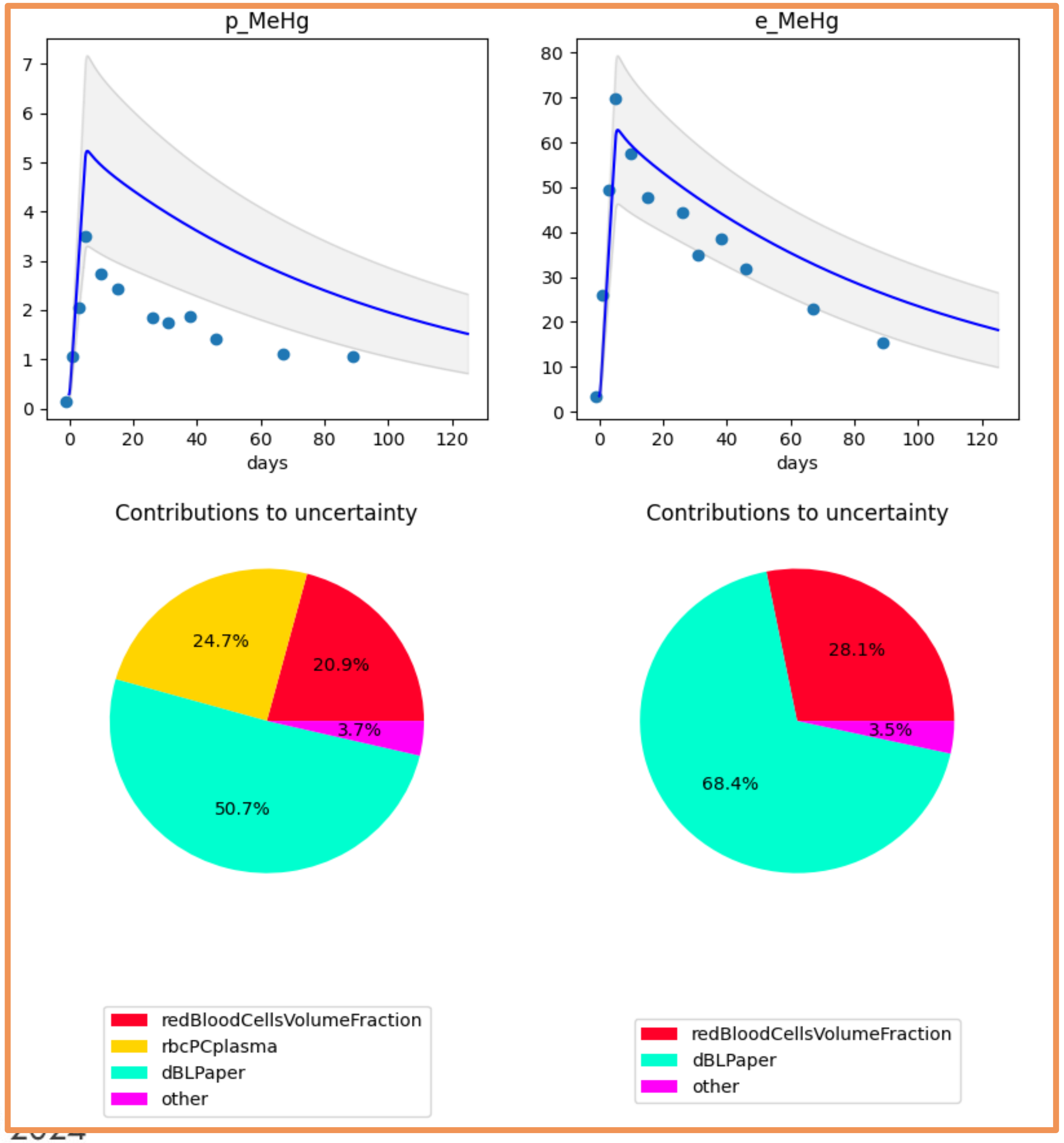
- probablity distributions of each of the parameters in the PBPK model were resampled **1000 times** and used in **MC analysis** to provide distributions of predicted internal concentrations and main uncertainty contributors

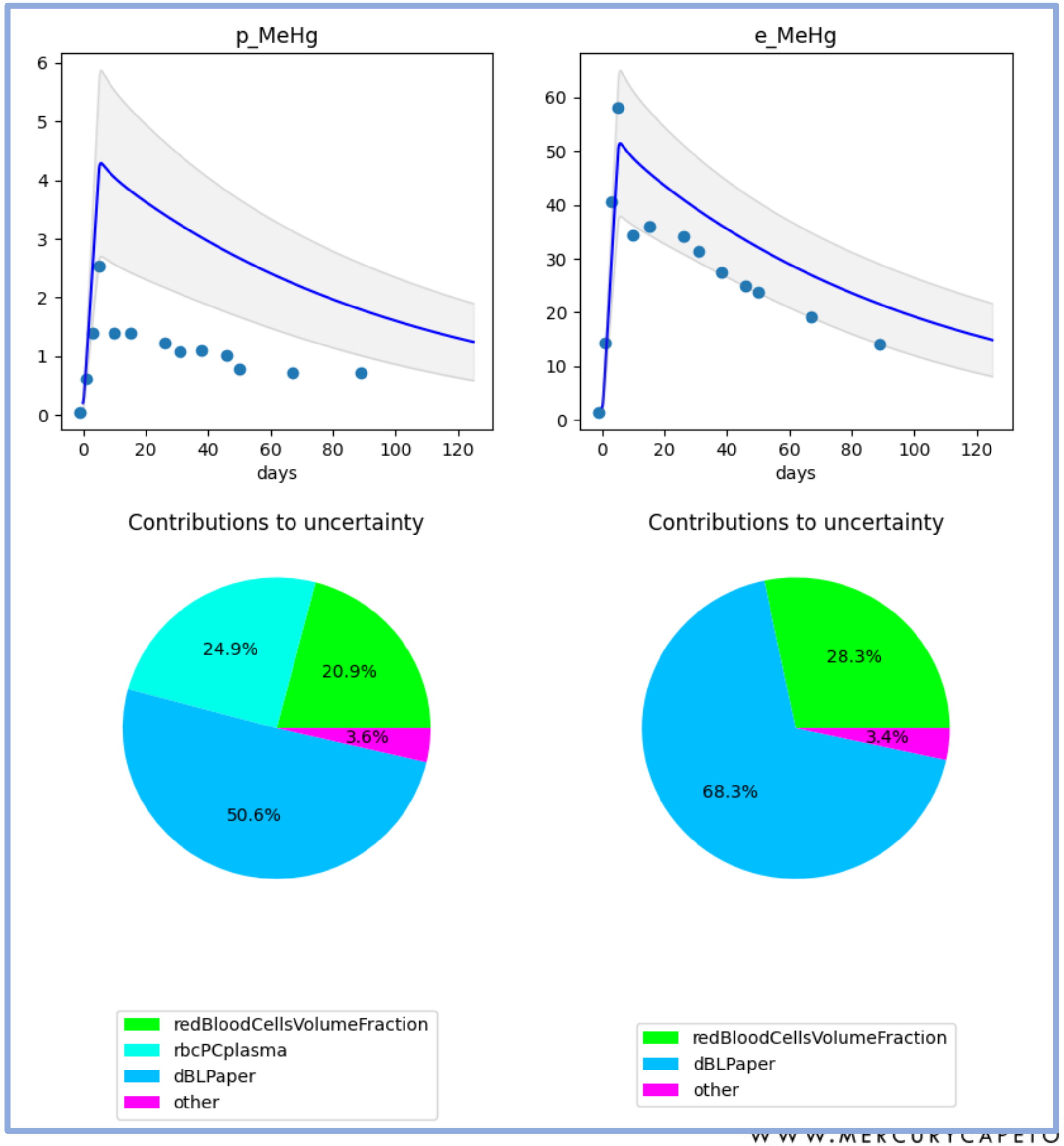


Parameters		Mean	CV	Upper bound	Lower bound	Distribution
Plasma flows (fraction of cardiac output)						
QCC	Cardiac output (L/hr scaled by $BW^{3/4}$)	20.0	0.22	33.2	6.8	Normal
QBrBC	Brain	0.114	0.30	0.217	0.011	Normal
QFC	Fat	0.052	0.30	0.099	0.0052	
QGC	Gut	0.181	0.33	0.360	0.002	Normal
QKC	Kidney	0.175	0.30	0.333	0.018	Normal
QLC	Liver	0.046	0.32	0.090	0.01	Normal
QRC	Richly perfused tissues	0.183	0.30	0.348	0.018	Normal
QSC	Slowly perfused tissues	0.249	0.30	0.473	0.025	Normal
QP1M	Placenta (L/hr scaled by $BW^{3/4}$)	58.5	0.35	119.9	10.0	Normal
QFeC	Fetal (L/hr scaled by $BW^{3/4}$)	54.0	0.30	102.6	10.0	Normal
Tissue volume (fraction of body weight)						
BW	Body weight (kg)	67.77	0.26	139.9	30.81	Lognormal
VBrC	Brain	0.02	0.30	0.038	0.002	Normal
VBrBC	Brain plasma	0.007	0.30	0.013	7.0e-4	Normal
VFC	Fat	0.273	0.24	0.47	0.076	
VGC	Gut	0.017	0.15	0.025	0.009	Normal
VHC	Hair	0.002	0.50	0.005	1.0e-4	Normal
VIC	Intestine	0.014	0.30	0.027	0.001	Normal
VKC	Kidney	0.004	0.30	0.008	4.0e-4	Normal
VLC	Liver	0.026	0.25	0.046	0.006	Normal
VPC	Plasma	0.024	0.14	0.058	0.024	Normal
VRBCC	Red blood cells	0.024	0.25	0.046	0.006	Normal
VRC	Richly perfused tissues	0.10	0.30	0.190	0.01	Normal
VSC	Slowly perfused tissues	0.35	0.16	0.52	0.18	Normal
VRem	Remainder (nonperfused)	0.122	0.30	0.23	0.012	Normal
Partition coefficients for MeHg						
PBr	Brain/blood	3.0	0.30	6.93	1.19	Lognormal
PBrB	Brain blood/plasma	1.0	0.30	2.31	0.397	Lognormal
PF	Fat/blood	0.15	0.30	0.347	0.060	
PFe	Fetal plasma/placenta	2.0	0.30	4.62	0.794	Lognormal
PG	Gut/blood	1.0	0.70	5.45	0.123	Lognormal
PHB	Hair/blood	248.7	0.70	1361.7	30.4	Lognormal
PK	Kidney/blood	4.0	0.30	9.24	1.59	Lognormal
PLiv	Liver/blood	5.0	0.30	11.6	1.99	Lognormal
PP1	Placenta/blood	2.0	0.30	4.62	0.794	Lognormal
PRBC	Red blood cell/plasma	12.0	0.30	27.7	4.76	Lognormal
PRBCFe	RBC/plasma for fetus	14.0	0.30	32.4	5.56	Lognormal
PR	Richly perfused tissues/blood	1.0	0.30	2.31	0.397	Lognormal
PS	Slowly perfused tissues/blood	2.0	0.30	4.62	0.794	Lognormal
Kinetic parameters (L/hr scaled by $BW^{3/4}$)						
k_{brici}	Incorporation of inorganic Hg in brain	5.0e-5	0			
k_{brili}	Loss of inorganic Hg from brain	0.001	0			
k_{brini}	Brain MeHg to inorganic Hg	1.2e-5	0.30	2.77e-5	4.76e-6	Lognormal
k_{bi}	Biliary clearance of MeHg	0.0001	0.30	2.31e-4	3.97e-5	Lognormal
k_{bri}	Brain uptake	0.01	0.30	0.0231	3.97e-3	Lognormal
k_{di}	MeHg to inorganic Hg in intestine	0.0001	0.30	2.31e-4	3.97e-5	Lognormal
k_{fi}	Fecal excretion	0.0002	0.36	5.36e-4	6.60e-5	Lognormal
k_{hi}	Excretion into hair	7.0e-6	0.25	1.42e-5	3.25e-6	Lognormal
k_{ii}	Conversion to inorganic Hg	1.0e-5	0.30	2.31e-5	3.97e-6	Lognormal
k_{rbci}	RBC/plasma diffusion	1.5	0.30	3.47	0.596	Lognormal
k_{ri}	Intestinal reabsorption	0.005	0.30	0.012	1.99e-3	Lognormal
Fetal kinetic parameters (L/hr)						
k_{fe}	Placenta/embryo diffusion	1.0	0.50	3.69	0.217	Lognormal
k_{rbcfe}	Fetal RBC/plasma diffusion	100.0	0.50	369.0	21.7	Lognormal

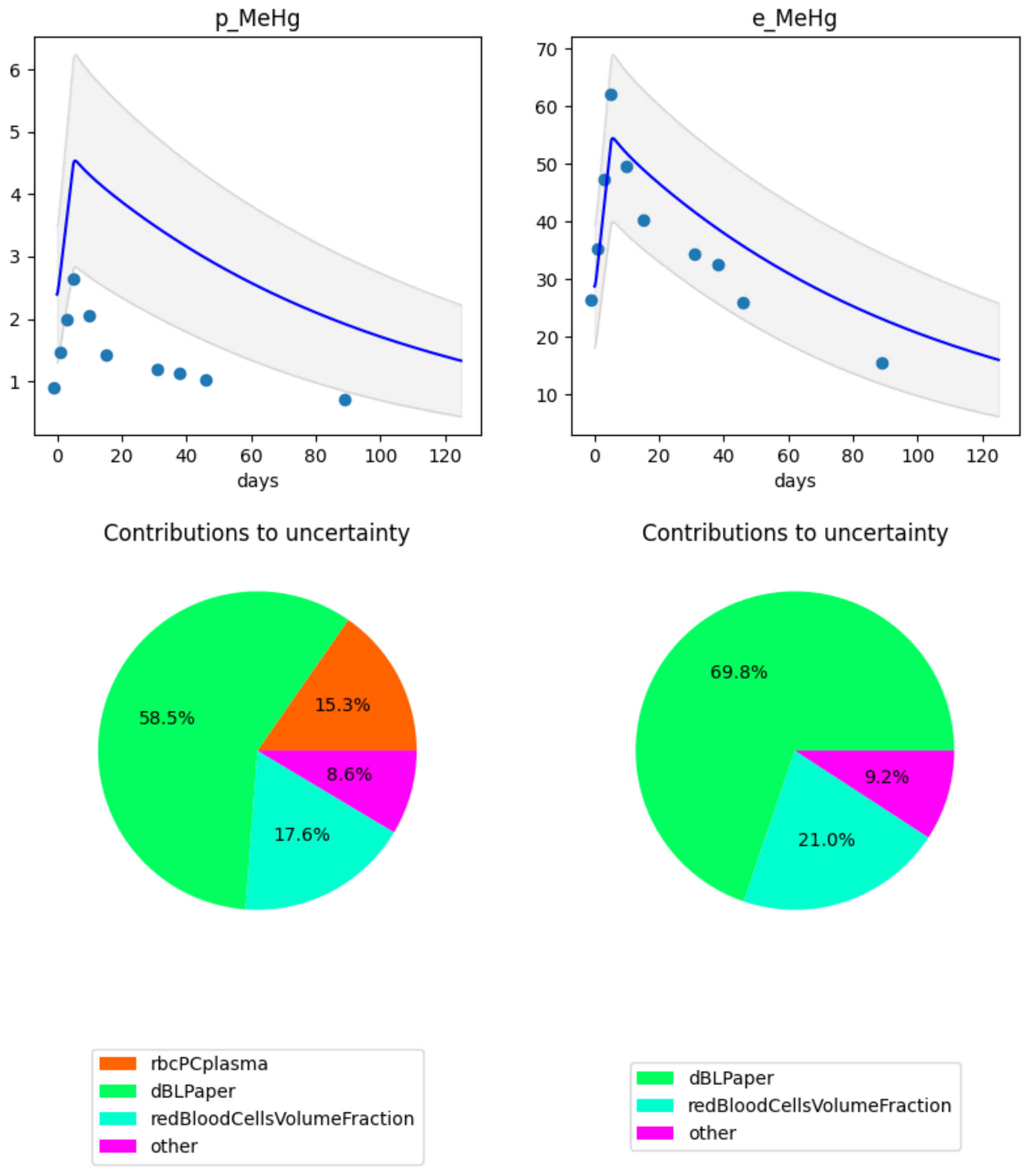
Preliminary results

- exact MeHg dose; IHg assumed to come only from demethylation of MeHg
- exact body mass – for scaling tissue volumes and kinetic parameters
- assumed 100% bioavailability of ingested MeHg





Preliminary results



- overestimation of MeHg in plasma
- slight overestimation of MeHg in erythrocytes

- Uncretainty of the modelled concentrations:
  - MeHg to IHg conversion factor in liver
  - red blood cell volume fraction
  - red blood cell-plasma partition coefficient

Conclusions

The work is still ongoing!

The PBPK model was successfully reconstructed, but improvements are needed:

- add IHg as an input, not only demethylation product
- consider variability in the absorption factor
- identify the main factors causing the discrepancy between the modeled and the measured concentrations

Thank You for Your attention!

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SLOVENIJA

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