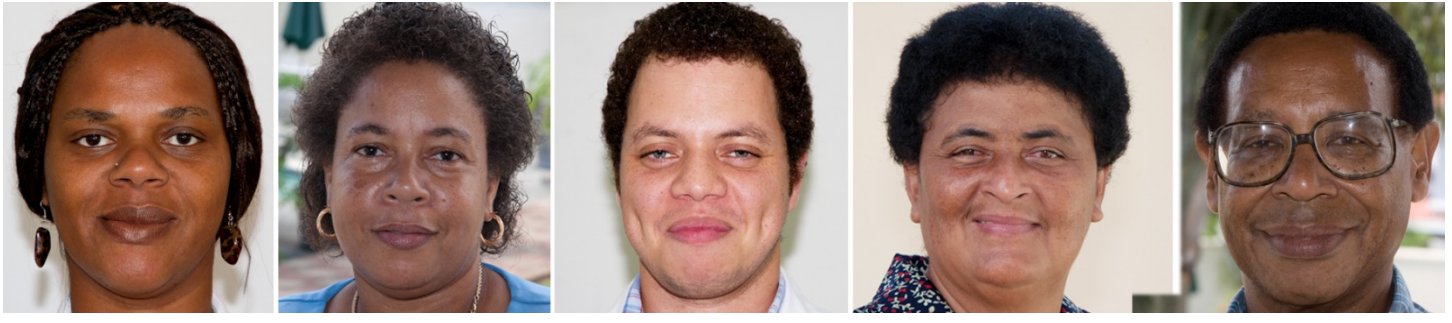
2018 UniSey ANNIVERSARY LECTURE

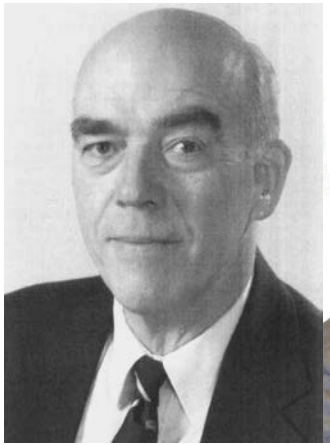
A 30 year journey of research success

Conrad Shamlaye
17 September 2018

Dedicated to all the Seychellois children and parents who are registered as participants and to all the professional and support staff involved in the Seychelles Child Development Study



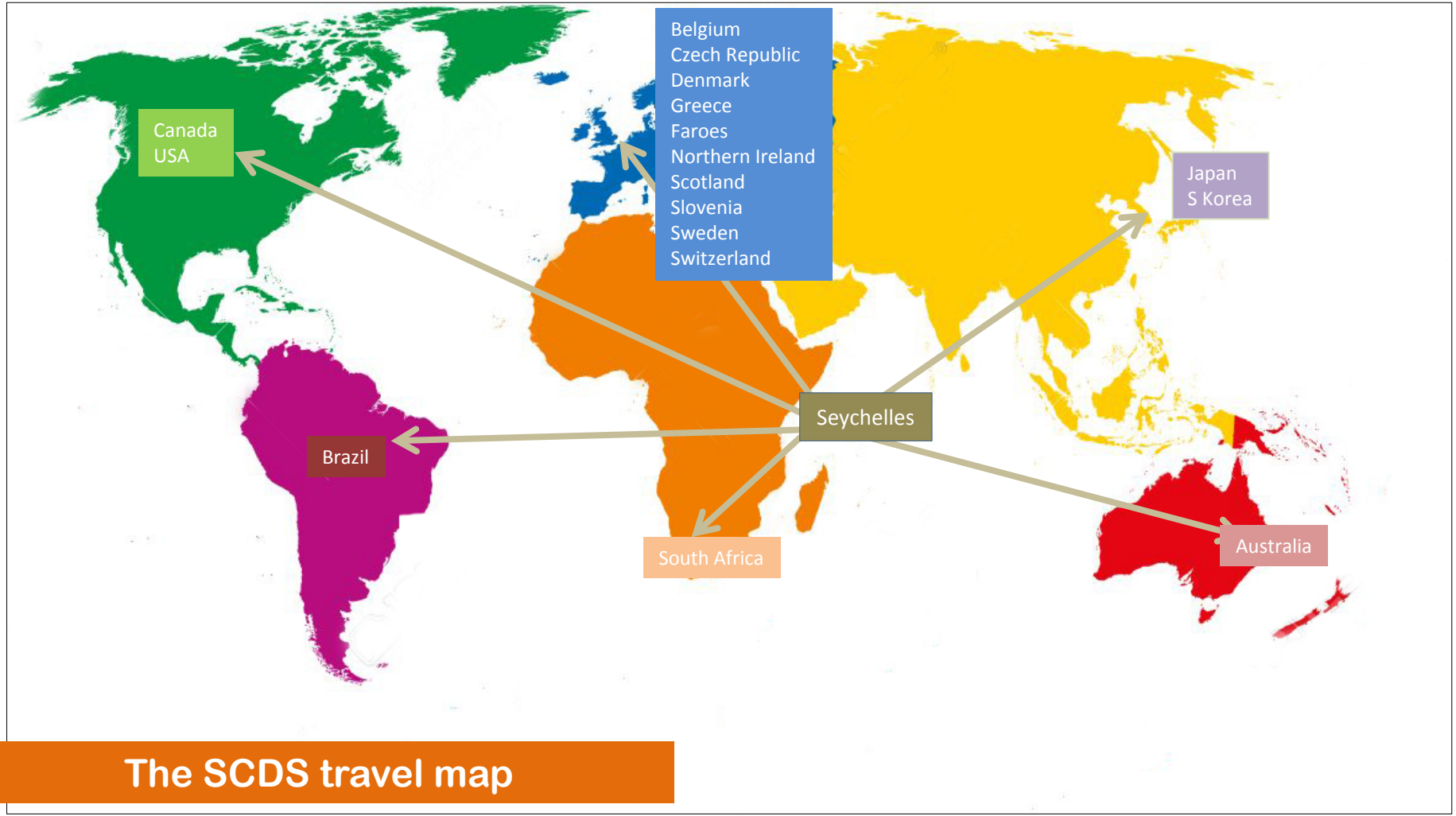
we remember



David Marsh, Elsa Cerniciari, Tristram Smith
Rochester

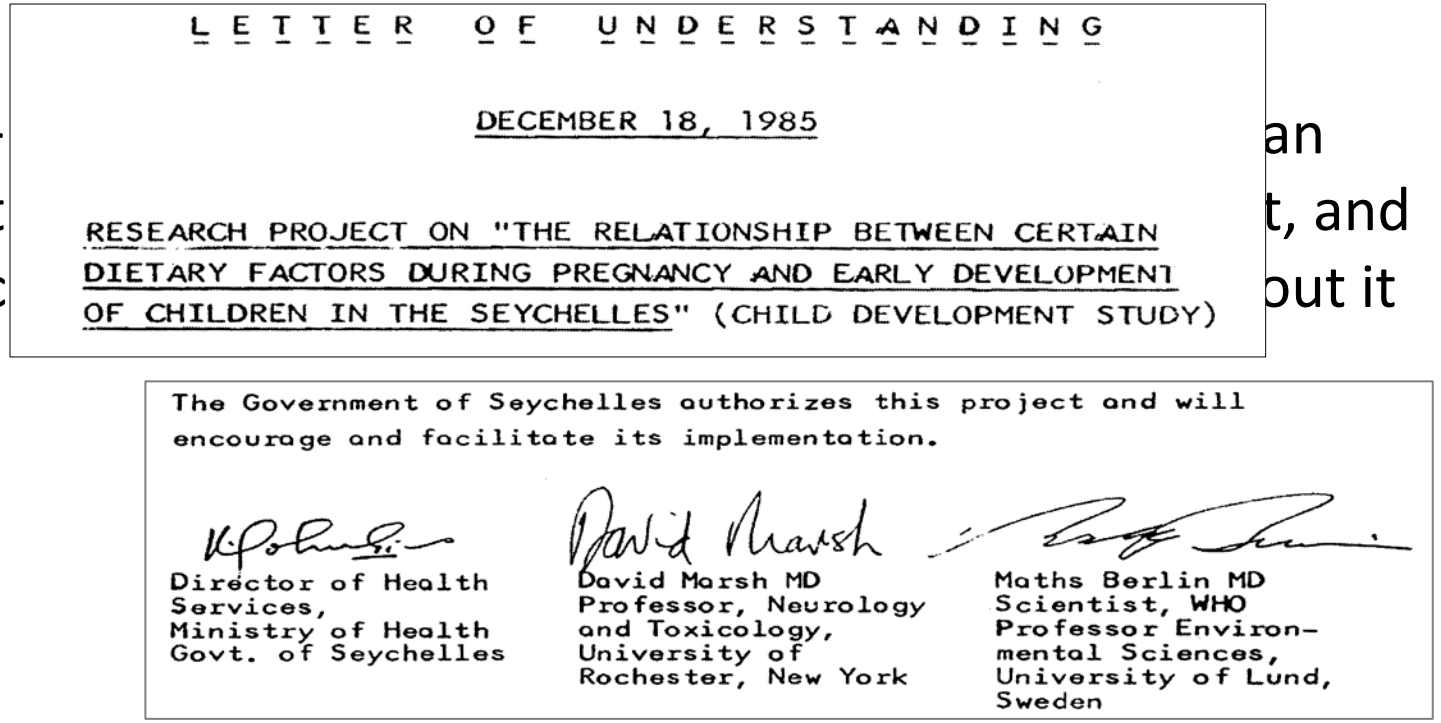
Julie Wallace
Ulster


Octavie Choisy, Heather Shamlaye
Seychelles



The SCDS travel map

- 1983 – proposal to study the possible adverse effect on infants of mercury exposure through consumption of fish during
- 1984 – an opport t, and if merc out it first



LETTER OF UNDERSTANDING

DECEMBER 18, 1985

RESEARCH PROJECT ON "THE RELATIONSHIP BETWEEN CERTAIN DIETARY FACTORS DURING PREGNANCY AND EARLY DEVELOPMENT OF CHILDREN IN THE SEYCHELLES" (CHILD DEVELOPMENT STUDY)

The Government of Seychelles authorizes this project and will encourage and facilitate its implementation.

Director of Health Services, Ministry of Health Govt. of Seychelles

David Marsh MD Professor, Neurology and Toxicology, University of Rochester, New York

Maths Berlin MD Scientist, WHO Professor Environmental Sciences, University of Lund, Sweden

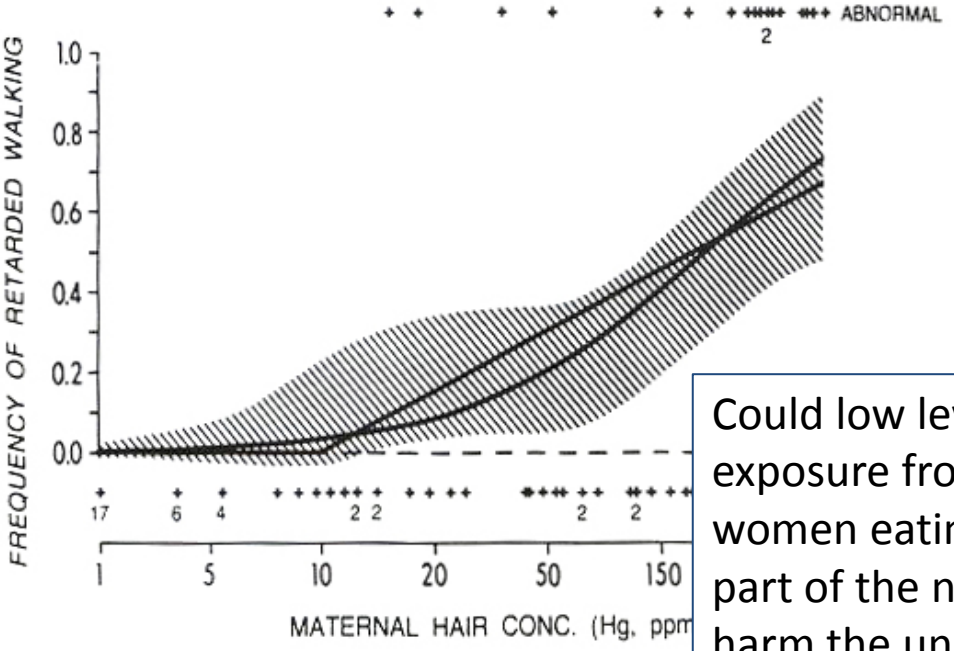
The journey that almost didn't start

Mercury poising from eating fish contaminated with industrial effluent

Minamata 1953 – 1965
Niigata 1960 - 1965

Mercury poisoning from eating seed grains treated with mercury

The observation that some children developed severe abnormalities even if the mother showed no symptoms during pregnancy suggested that the developing foetal brain is more vulnerable to mercury exposure

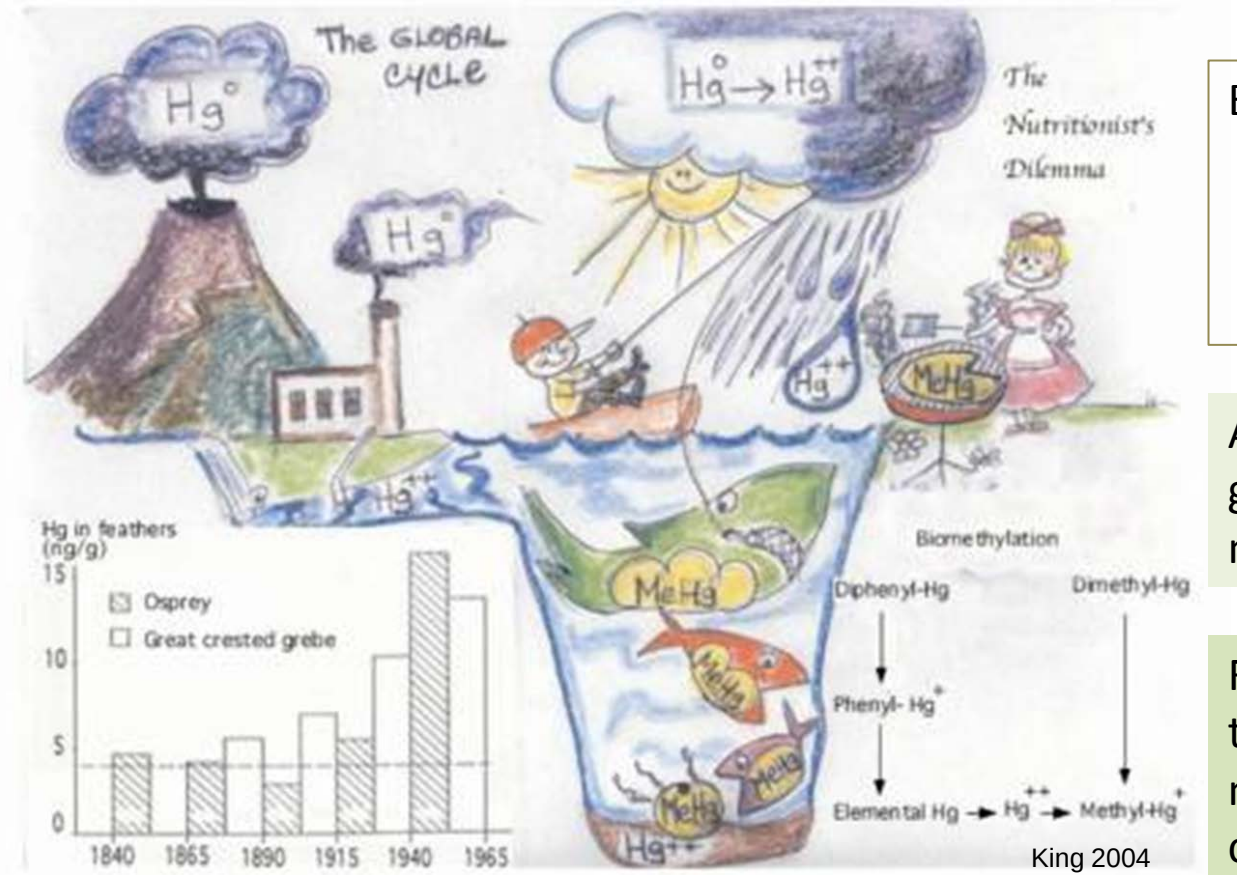


Could low level mercury exposure from pregnant women eating fish as part of the normal diet harm the unborn child

?

Why study mercury in fish?

Eugene Smith 1973



King 2004

Environmental mercury

- 10% natural sources
- 30% anthropogenic
- 60% recirculation

UNEP 2013

Artisanal and small-scale gold extraction is now the most important source

For the general population the main source of mercury exposure is the consumption of fish, and to a lesser extent dental fillings

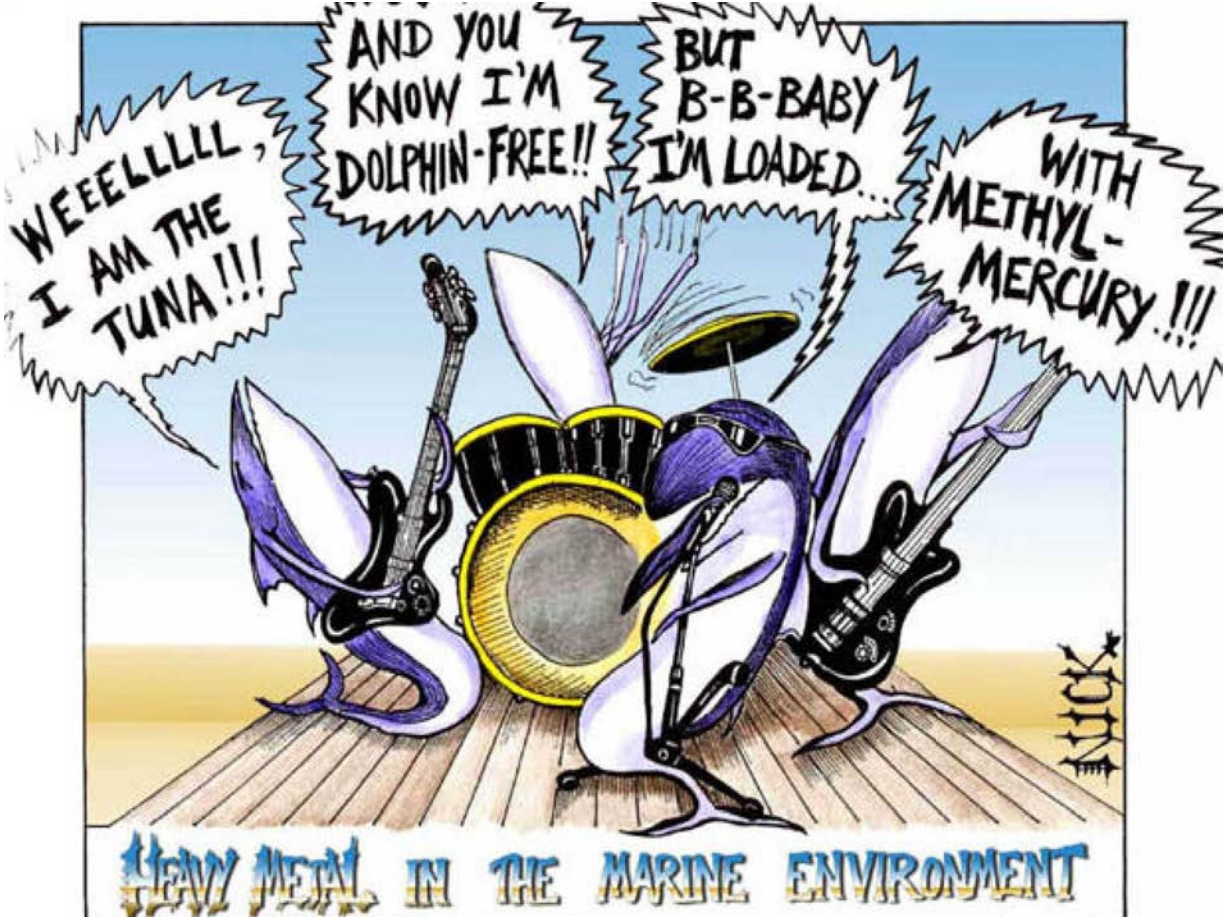
Where does mercury come from?

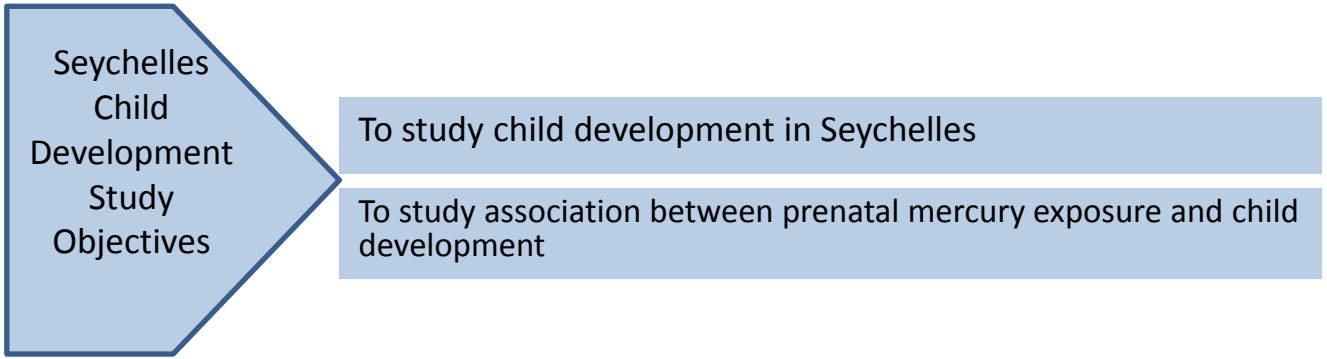
Mercury occurs naturally in ocean fish. Levels are similar in different parts of the world for the same species, and do not appear to have changed over the past 100 years

SPECIES	CREOLE COMMON NAME	MEAN (PPM)	MINIMUM (PPM)	MAXIMUM (PPM)
Carangoides gymnostethus (Bludger trevally)	Karang balo	0.70	0.27	1.11
Sphyraena jello (Pickhandle barracuda)	Bekin karo	0.66	0.44	1.58
Carangoides fulvoguttatus (Yellowspotted trevally)	Karang plat	0.40	0.14	0.71
Lethrinus microdon (Small-tooth emperor)	Bek Bek	0.32	0.25	0.52
Euthynnus affinis (Mackerel tuna)	Bonit fol	0.30	0.12	0.39
Lutjanus bohar (Two-spot red snapper)	Vara vara	0.23	0.10	0.43
Variola louti (Yellow-edged lyretail)	Krwasan/Gran ke	0.20	0.06	0.29
Lutjanus sanguineus (Humphead snapper)	Bordmar	0.20	0.07	0.28
Lethrinus mahsena (Sky emperor)	Madanm beri	0.18	0.06	0.36
Lethrinus variegatus (Varigated emperor)	Baksou	0.16	0.06	0.41
Epinephelus chlorostigma (Brown-spot grouper)	Vyey makonde	0.16	0.04	0.28
Lutjanus sebae (Emperor red snapper)	Bourzwa	0.14	0.08	0.27
Gymnocranius grandoculis (Blue-lined large-eye bream)	Kaptenn blan	0.14	0.10	0.24
Aprion virescens (Green jobfish)	Zob gri	0.09	0.04	0.18
Rastralliger kanagurta (Indian mackerel)	Makro dou	0.05	0.02	0.10
Scarus ghobban (Blue-barred parrotfish)	Kakatwa blan	0.04	0.00	0.12
Octopus vulgaris (Octopus)	Zourit	0.01	0.01	0.01
Siganus sutor (Shoemaker spinefoot)	Kordonnyen blan	0.01	0.00	0.01
Scarus rubroviolaceus (Ember parrotfish)	Kakatwa rouz	0.01	0.00	0.02
Siganus argenteus (Streamlined spinefoot)	Kordonnyen soulfanm	0.00	0.00	0.00

University of Rochester Mercury Analytical Laboratory 2010

Mercury in Seychelles fish


WEEELLLLL, I AM THE TUNA!!!
AND YOU KNOW I'M DOLPHIN-FREE!!
BUT B-B-BABY I'M LOADED...
WITH METHYL-MERCURY!!!
NICK
HEAVY METAL IN THE MARINE ENVIRONMENT



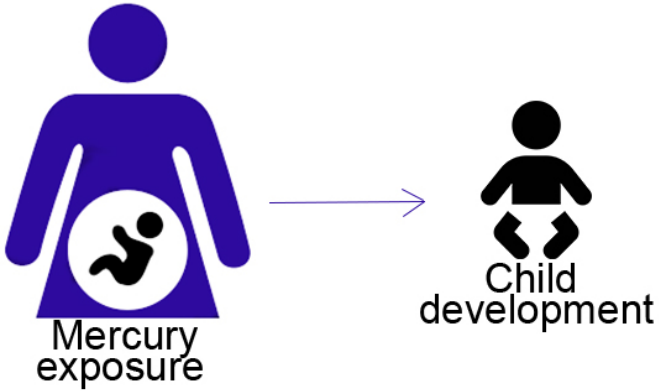
Seychelles is an ideal location for the study

- High fish consumption
- Universal health care and education
- Minimal co-exposures (no lead, PCBs)
- Stable population
- Sentinel population for the study of MeHg:
  - Fish has same level MeHg as US
  - Population has 10x the US exposure

SCDS objectives

Observational: observing the natural state with no intervention

Longitudinal: looking at events over time, waiting for the child to be born or to reach the right age



Child development is assessed by applying a battery of standard tests designed to reflect global development or specific developmental domains, although there is overlap among these. Tests should be age-appropriate and culture neutral

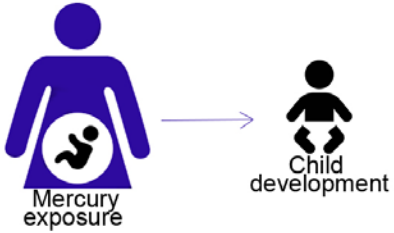
Maternal mercury exposure is measured in hair which grows at a known rate. Measuring along the strands of hair therefore captures the exposure during a defined period

Statistical analyses seek to identify and quantify association between exposure and developmental outcome. Among study participants, exposure levels will vary, as will test results. If mercury exposure has an adverse effect the test results would tend to go down with increasing exposure levels across the group.

Study design

Factors other than mercury may influence the test results. These include the age, sex and health conditions of the child, parental socioeconomic status, maternal intelligence, the home environment.

These are measured as **covariates**



There are also **confounding factors** that may be related to both the exposure and the outcome

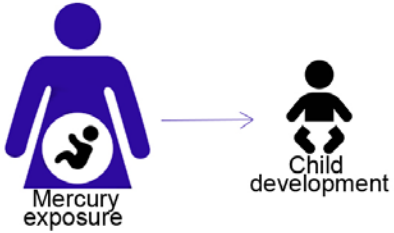
Deciding what factors are important (and therefore must be included in the study design and analysis plan) requires review of the science and careful consideration of the interplay of the potential factors

A study like the SCDS therefore requires the knowledge and skills of professionals of different disciplines, as well as a thorough knowledge and understanding of the Seychelles context and realities

Many scientific and technical issues

Ethics

- Establishment of independent Ethics Committee
- Informed consent
- Confidentiality



Logistics

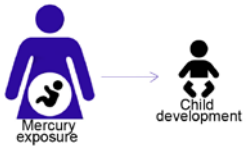
- Setting up the Child Development Centre
- Communication among collaborators and with participants
- Transfer of data and samples internationally
- Financing

Cultural issues

- Cultural perspective of participants
- Research culture versus service culture
- International and interdisciplinary interaction and collaboration

More than science

More **partners** and **collaborators**
Ministry of Health
Ministry of Education
University of Rochester
University of Ulster
Karolinska Institute/Lund Univers
University of Lausanne



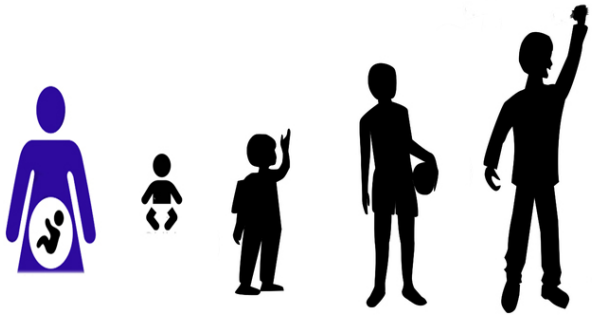
Science has expanded
Toxicology
Nutrition
Neurodevelopment
Cardiovascular
Immune system
Genetics
Animal models

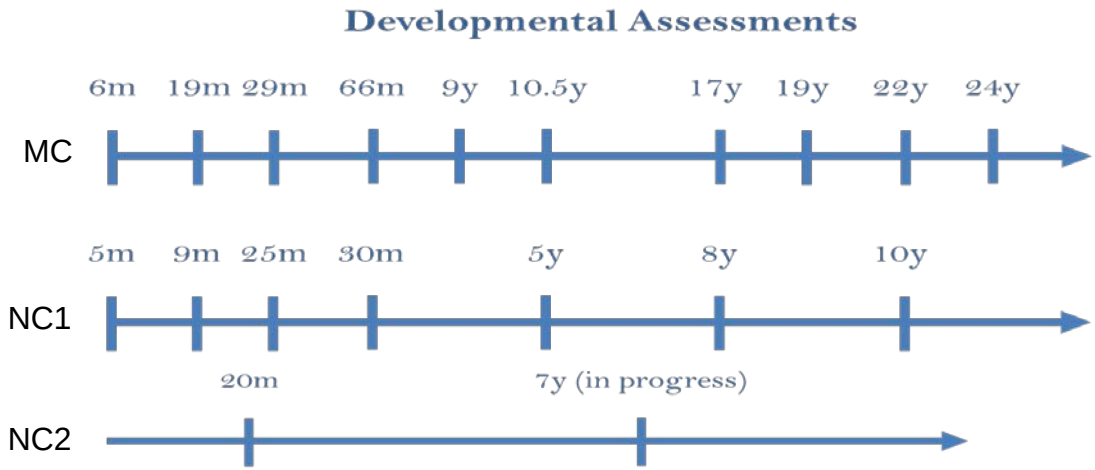
More **measurements**
Postnatal mercury exposure
Inorganic mercury exposure from dental amalgam
Other exposures such as n-3 and n-6 PUFA, amino acids, Vitamin D and E, selenium
More covariates
More developmental outcomes
Functional outcomes such as school exams

More **participants**
Pilot cohort (87-88): 789
Main Cohort (89-90): 779
NC1 (2001): 300
NC2 (08-11): 1,535
Mothers of MC (2013): 622

Evolution of SCDS over time

The **Study design** remains much the same. Study has become bigger and more complex





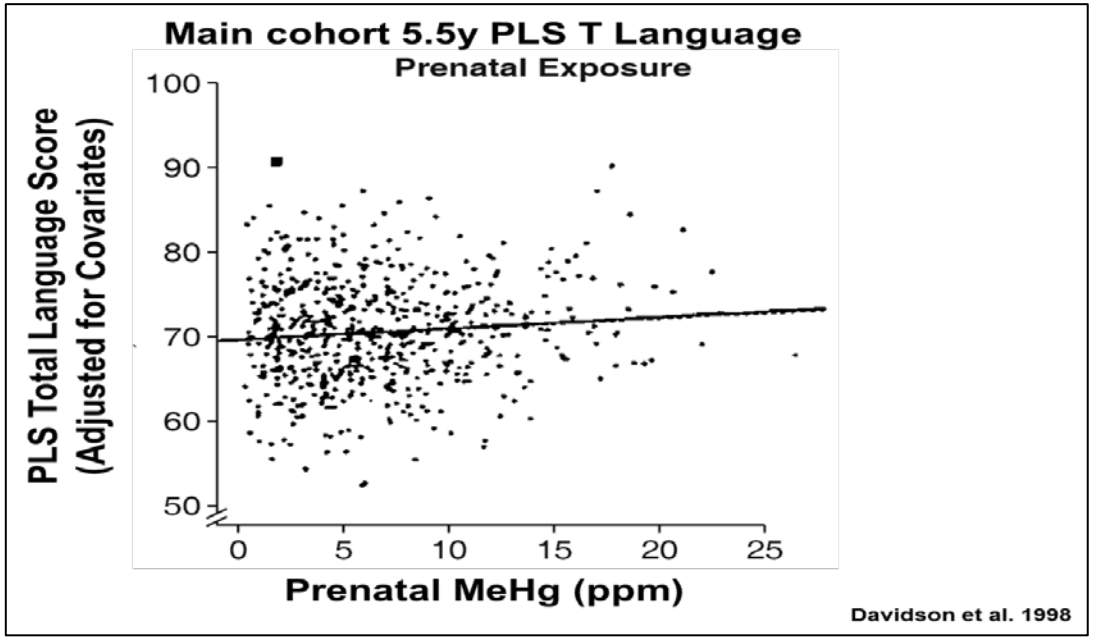
SCDS objectives

- To study child development in Seychelles
- To study associations between mercury exposure and child development
  - effects of prenatal and postnatal mercury exposure
  - exposure to organic and inorganic mercury
  - factors that may modulate these associations

Multiple assessment, refined study objectives

Main Cohort after 24 years follow up

- No consistent pattern of adverse associations between mercury and multiple outcomes
- Beneficial associations found at different ages for different outcomes

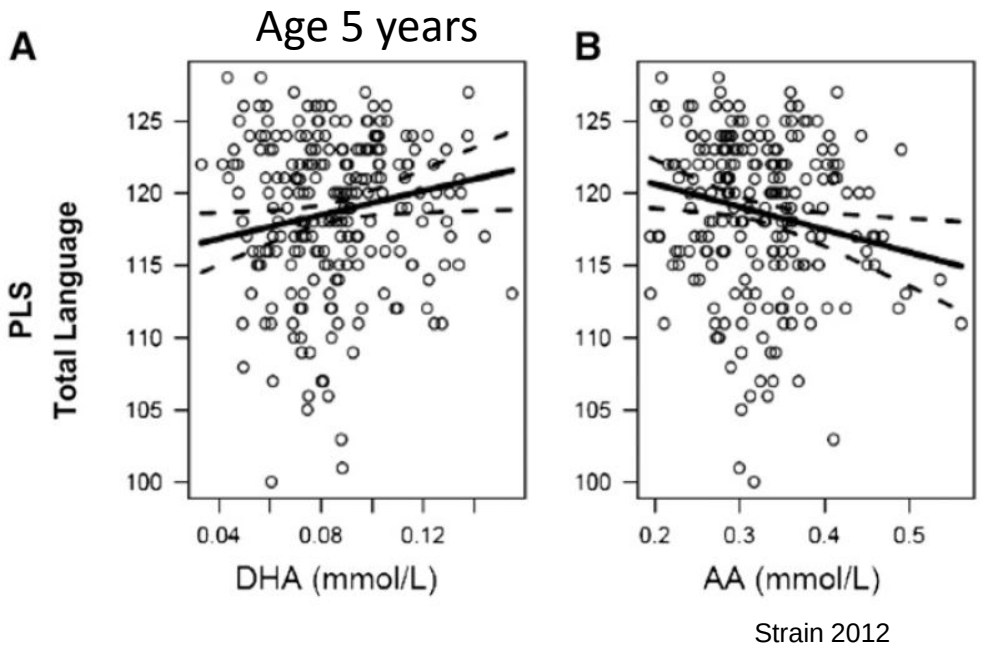


Since mercury cannot be good for child development, something that parallels mercury exposure must be responsible. **Negative confounding by nutrients?**

SCDS findings – Main Cohort

NC1 after 10 years follow up

- Beneficial n3 PUFA association
- Adverse n6 PUFA association
- No adverse association with mercury

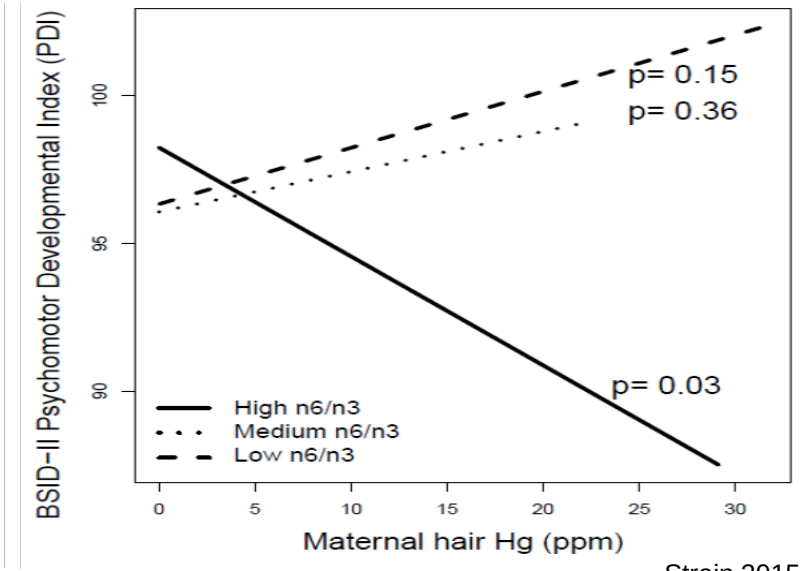


Strain 2012

Possible interaction between PUFA and mercury (effect of mercury on development may depend on level of PUFA). Cohort size is too small to evaluate this possibility

NC2 after 20 months follow up

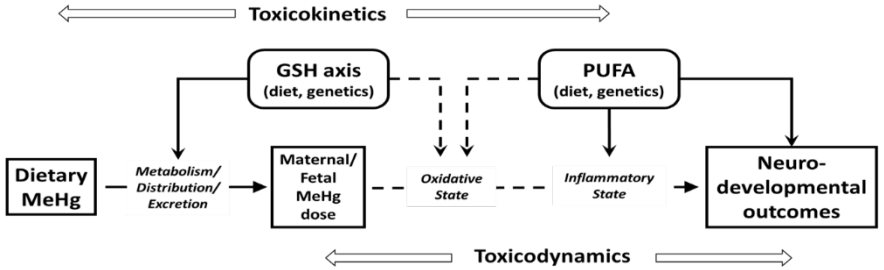
- No overall adverse association of endpoints with prenatal mercury exposure
- Higher DHA (n3 PUFA) associated with improved language development) but adversely associated with Mental Development Index
- Increasing mercury associated with lower Psychomotor Development Index but only in children of mothers with higher n–6/n–3
- Adverse association between n-6/n-3 ratio and McArthur-Bates CDI



Strain 2015

Interaction between PUFA and mercury (effect of mercury on development may depend on level of PUFA) confirmed. The impact of PUFA on development appears to be influenced by the relative amounts of n3 and n6

- No overall association between prenatal MeHg exposure and child development
- Relationship between fish nutrients and mercury far more complex than previously anticipated
- There could be an optimal balance between the different types of fatty acids
- Genetics may play a role in making some people more or less susceptible to mercury effects. How that works is likely to be complex



More research is needed!

SCDS findings – overall summary

Blood pressure

Prenatal mercury exposure is not associated with blood pressure

Thurston 2007

P6 and S3 school results

Prenatal mercury exposure is not associated with P6 and S3 national exam scores

Davidson 2010

ASD

Prenatal mercury exposure is not associated ASD symptomatology (as measured by SCQ)

Van Winjngaarden 2013

Auditory system function

Prenatal and recent postnatal mercury exposure not associated with auditory function using tests that look at the auditory system peripherally and centrally Orlando 2014

Telomere length

TL in mothers and children not associated with mercury exposure

Yeates 2017

SCDS findings – what about other ways of looking at outcomes?

Similar studies in the **Faroe Islands** have consistently found adverse effects of mercury exposure on neurodevelopment and cardiovascular outcomes

Exposure	Faroe Islands	Seychelles
Methylmercury	Pilot whale	Fish
Omega -3 LCPUFA	Fish	Fish
Selenium:mercury	Low	High
PCBs	Present	Absent

Findings	Faroe Islands	Seychelles
Methylmercury	Consistent adverse effect	No consistent adverse effect
Omega-3 LCPUFA	Beneficial	Beneficial

But the mercury and child development issue is far from resolved

Policy instruments used

- Legally enforceable maximum l
  commercialized fish
  - 1 ppm mercury in large predá
  - 0.5 ppm mercury in other fisl
- Guidelines for safe level of inta
  - EU 1.3 µg/Kg bw/week
  - USA (EPA/FDA) 0.1 µg/Kg b
  - Alaska 0.56 µg/Kg bw/day
  - Canada 0.2 µg/Kg bw/day
- Advisories on fish consumptior

Advice About Eating Fish

What Pregnant Women & Parents Should Know

Fish and other protein-rich foods have nutrients that can help your child's growth and development.

For women of childbearing age (about 16-49 years old), especially pregnant and breastfeeding women, and for parents and caregivers of young children.

- *Eat 2 to 3 servings of fish a week from the "Best Choices" list OR 1 serving from the "Good Choices" list.*
- *Eat a variety of fish.*
- *Serve 1 to 2 servings of fish a week to children, starting at age 2.*
- *If you eat fish caught by family or friends, check for fish advisories. If there is no advisory, eat only one serving and no other fish that week.**

Use this chart!

You can use this chart to help you choose which fish to eat, and how often to eat them, based on their mercury levels. The "Best Choices" have the lowest levels of mercury.

What is a serving?

To find out, use the palm of your hand!

For an adult 4 ounces

For children, ages 4 to 7 2 ounces

Best Choices EAT 2 TO 3 SERVINGS A WEEK

Anchovy
Atlantic croaker
Atlantic mackerel
Black sea bass
Butterfish
Catfish
Clam
Cod
Crab
Crawfish
Flounder
Haddock
Hake
Herring
Lobster, American and spiny
Mullet
Oyster
Pacific chub mackerel
Perch, freshwater and ocean
Pickerel
Plaice
Pollock
Salmon
Sardine
Scallop
Shad
Shrimp
Skate
Smelt
Sole
Squid
Tilapia
Trout, freshwater
Tuna, canned light (includes skipjack)
Whitefish
Whiting

OR

Good Choices EAT 1 SERVING A WEEK

Bluefish
Buffalofish
Carp
Chilean sea bass/ Patagonian toothfish
Grouper
Halibut
Mahi mahi/ dolphinfish
Monkfish
Rockfish
Sablefish
Sheepshead
Snapper
Spanish mackerel
Striped bass (ocean)
Tilefish (Atlantic Ocean)
Tuna, albacore/ white tuna, canned and fresh/frozen
Tuna, yellowfin
Weakfish/seatrout
White croaker/ Pacific croaker

Choices to Avoid HIGHEST MERCURY LEVELS

King mackerel
Marlin
Orange roughy
Shark
Swordfish
Tilefish (Gulf of Mexico)
Tuna, bigeye

*Some fish caught by family and friends, such as larger carp, catfish, trout and perch, are more likely to have fish advisories due to mercury or other contaminants. State advisories will tell you how often you can safely eat those fish.

www.FDA.gov/fishadvice
www.EPA.gov/fishadvice

EPA United States Environmental Protection Agency
FDA U.S. FOOD & DRUG ADMINISTRATION

THIS ADVICE REFERS TO FISH AND SHELLFISH COLLECTIVELY AS "FISH." / ADVICE UPDATED JANUARY 2017

Limiting exposure to mercury from fish consumption

In populations where people do not eat a lot of fish, the tendency is for people to reduce consumption as a result of the advisories

Many people depend on fish for important macro and micronutrients and do not have readily available alternative

Replacing fish by meat products has important impact on health

http://americablog.com/2013/03/mercury-fish-poisoning-salmon-us-italy-japan.html

84% of world's fish not safe to eat more than once a month

THE TIMES OF INDIA

INDIAN OCEAN TIMES

Mauritius: The rate of mercury on the island higher than standards allowed by the U.S. environmental protection agency

These limits tend to have important and widespread consequences

saicm

UNEP

INVENTORY OF MERC
RELEASES IN MAURI

36% of hair samples "exceeded the widely recognised US Environmental Protection Agency guideline"

"The study's report concluded that the levels in individuals … is enough to put life of the fetus at risk."

Ministry of Environment and Sustainable D
Ministry of Health and Quality of Life
February 2014

LAWS OF SEYCHELLES

CHAPTER 77A

EXPORT OF FISHERY PRODUCTS ACT

Act 18 of 1996
Act 2 of 2003
Act 32 of 2010

Heavy metal contaminants present in the aquatic environment

1. Batches of fishery products in which the levels of heavy metal contaminants exceed the maximum limits indicated in the following table shall be regarded as unfit for human consumption.

Substrate	Maximum Limit (ppm)		
	Lead	Cadmium	Mercury
Muscle meat of all fish except where indicated below:	0.3	0.05	0.5
Little tuna (Euthynnus app.) Tunas (thunnus spp. and katsuwonus pelamis.)	-	0.1	1.0
Marlin (Maraira spp.) Sail fish (Istiophorus platypterus) Rays (Raja species) Shark and dogfish (all species)	-	0.05	1.0

Schedule 10

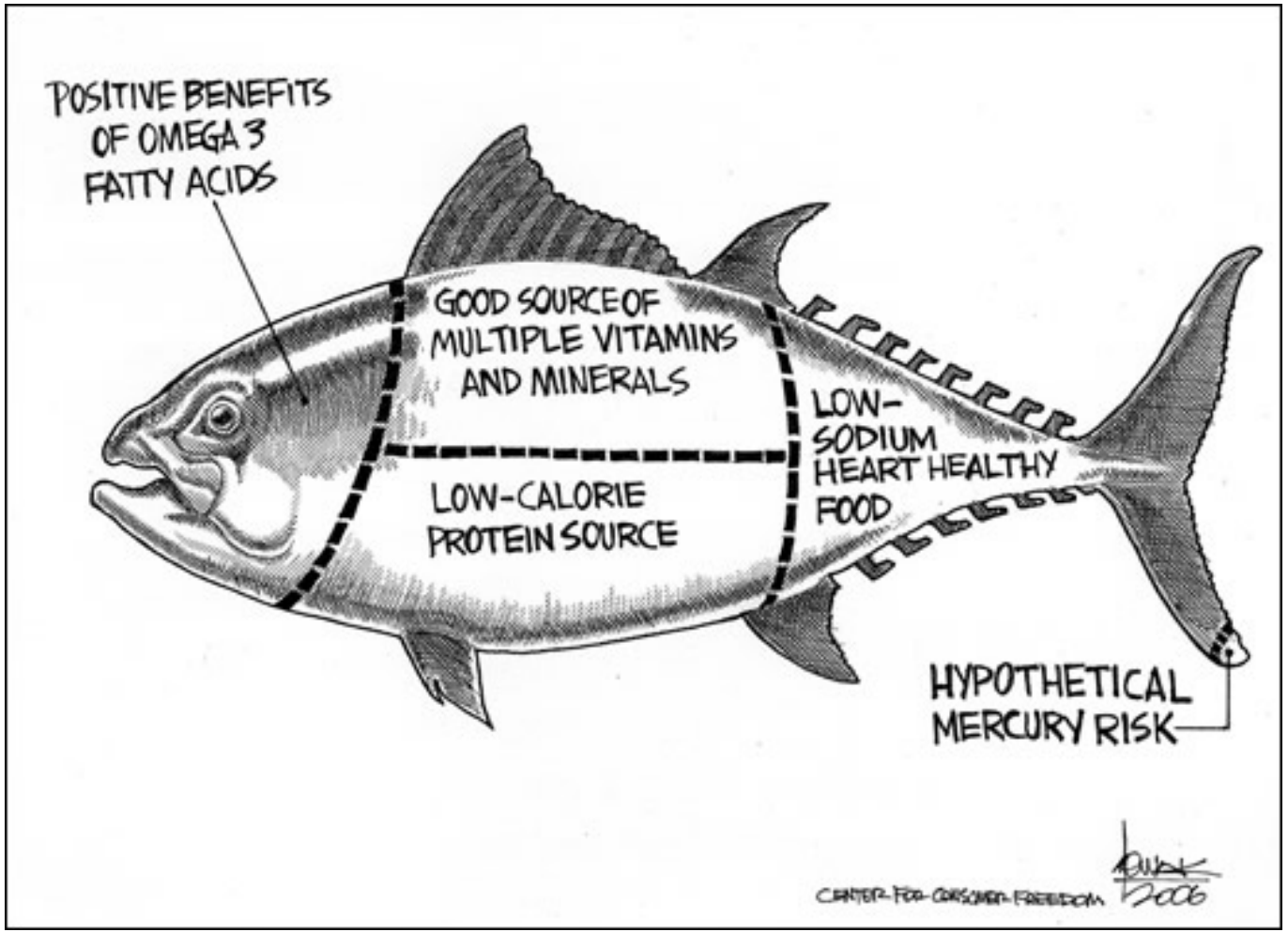
Governments can overreact

Member states should:

Emphasize the neurodevelopment benefits to offspring of fish consumption by women of childbearing age, particularly pregnant women and nursing mothers, and the neurodevelopment risks to offspring of such women not consuming fish

FAO and WHO Expert Consultation on the Risks and Benefits of Fish Consumption, January 2010

WHO/FAO expert opinion



A bit of perspective

Global response strategy to tackle the mercury problem throughout its entire life cycle

- limit mercury mining
- regulate trade
- reduce/eliminate use of mercury in gold mining
- control mercury emissions into the air and water
- promote sound waste disposal.
- reduce use of mercury in products and processes
    - eliminate use in medical devices
    - phase down use of dental amalgam

The Convention is silent on mercury exposure from fish consumption

Adopted October 2013
Came into force 16/08/2017

Seychelles signed May 2014, ratified January 2015

Minamata Convention

- The SCDS is an internationally recognized health research success
- Demonstrates the capacity to study the complex relation between mercury exposure and health better than most studies
- Provides evidence that guides fish consumption recommendations worldwide
- Guides national nutrition policy development and health promotion by emphasizing importance of fish
- Provides longitudinal data on child development and info child health and education programmes
- Promotes research and builds capacity
- Assists other projects (Autism)

At the end of a 30 year journey …

- Analysis of P6 and S3 exam scores confirms that girls outperform boys in all subjects
- The presence of the father through childhood and adolescence impacts positively on school exam performance
- Poorer performance at P6 associated with later substance abuse at 17 years in boys and girls, and more antisocial behaviour among girls

- Dental caries is more common in children whose parents have lower socioeconomic status
- Dental caries is associated with poorer outcomes measuring cognitive abilities and achievement

Analysis of NC2 mothers' food consumption identifies 4 main dietary patterns. Oily fish, bouyon bred, veg and fruit combined associated with the highest serum levels of good n3 PUFA

SCDS provides evidence on many other issues

- Numerous publications in scientific journals
- Presentation at international scientific conferences
- Participation in policy and regulatory fora
- International conferences in Seychelles 1998, 2003, 2010, 2015
- Special issue of Seychelles Medical and Dental Journal 2004

SCDS output

Promote knowledge and research culture

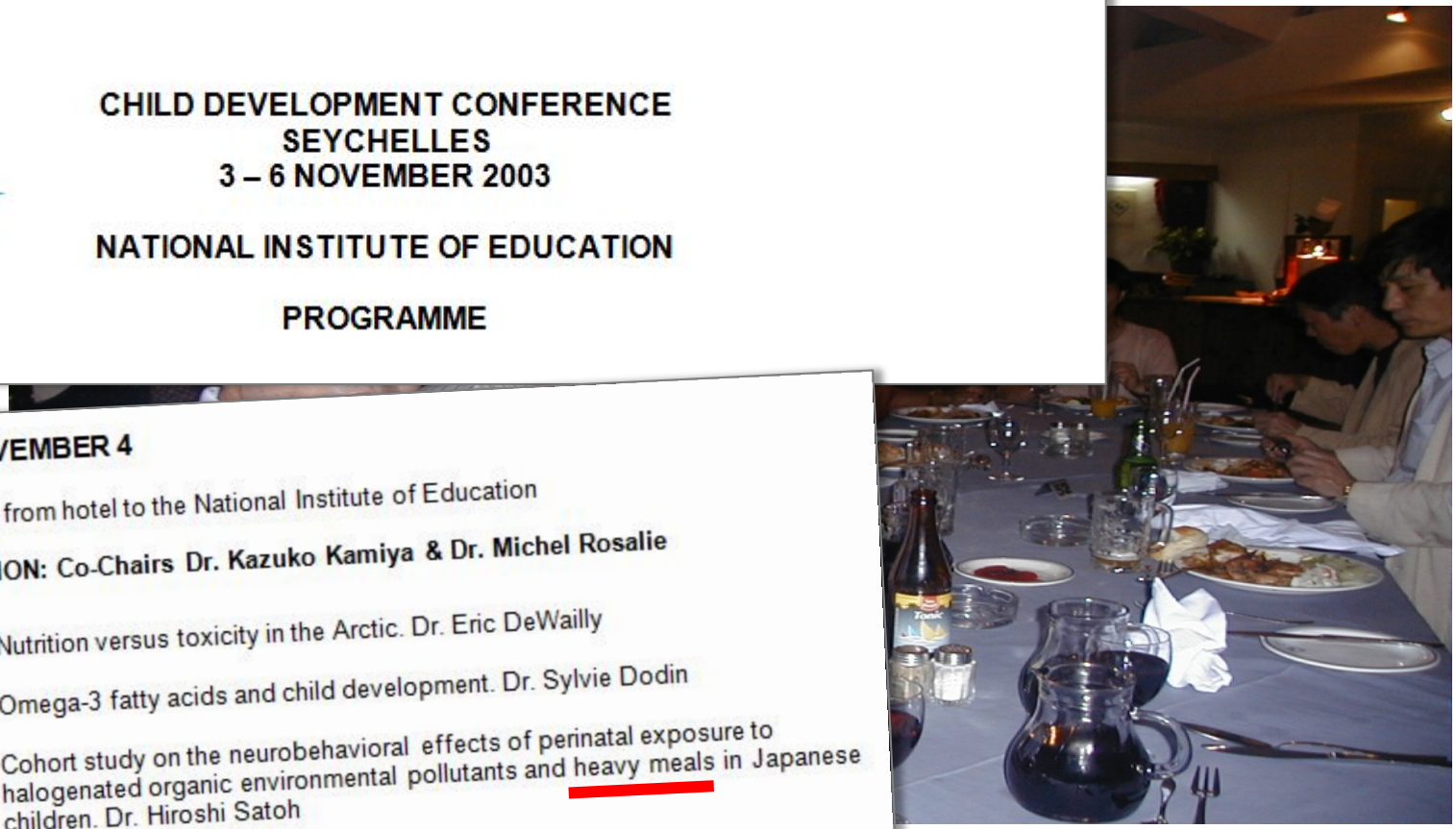
- Establish a National Research Council
- Strengthen National Data Centre
- Establish research in every Ministry
- Increase financing for research
- Train researchers and develop networking
- Promote dissemination of research findings
- Promote utilisation of research as evidence base for policies and services

CHILD DEVELOPMENT CONFERENCE
SEYCHELLES
3-6 November 2003

CHILD DEVELOPMENT CONFERENCE
SEYCHELLES
3 – 6 NOVEMBER 2003

NATIONAL INSTITUTE OF EDUCATION

PROGRAMME



TUESDAY, NOVEMBER 4

8:30 Transport from hotel to the National Institute of Education

MORNING SESSION: Co-Chairs Dr. Kazuko Kamiya & Dr. Michel Rosalie

9:00-9:30	Nutrition versus toxicity in the Arctic. Dr. Eric DeWailly
9:30-10:00	Omega-3 fatty acids and child development. Dr. Sylvie Dodin
10:00-10:30	Cohort study on the neurobehavioral effects of perinatal exposure to halogenated organic environmental pollutants and heavy meals in Japanese children. Dr. Hiroshi Satoh
10:30-11:00	BREAK

…exposure to heavy meals

on a lighter note …

What kind of data have we collected?

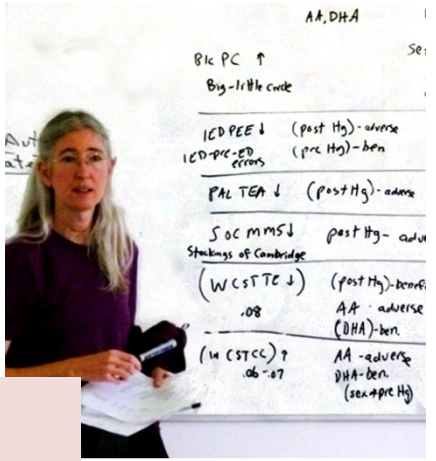
Demographic and background
Family composition and statu
Mother and father educatior
Mother and father occupatic
Home Environment
Early child-care arrangement
Food consumption
Maternal status
Antenatal, perinatal paramet

Health and Nutritional Statu
Anthropometric measureme
Vision and Hearing
Oral health status
Food consump
Health, illness,
Medication
Pregnancy
Life events

Exposure measurements
Prenatal mercury exposure
Recent mercury exposure
Dental amalgam
LCPUFA
Iron, iodine, taurine
Selenium

Developmental and other outcomes
Cognitive
Memory
Perceptual-Motor
Mood
Social Communication
Language
Problem-solving and Learning
Scholastic Achievement
Behavioural, alcohol, smoking, drugs, disciplinary issues at school
Neurophysiological: Auditory Processing
Cardiovascular Status, HRV

Genetics
Gene polymorphism
Telomere length
Mitochondrial DNA



SCDS data archives

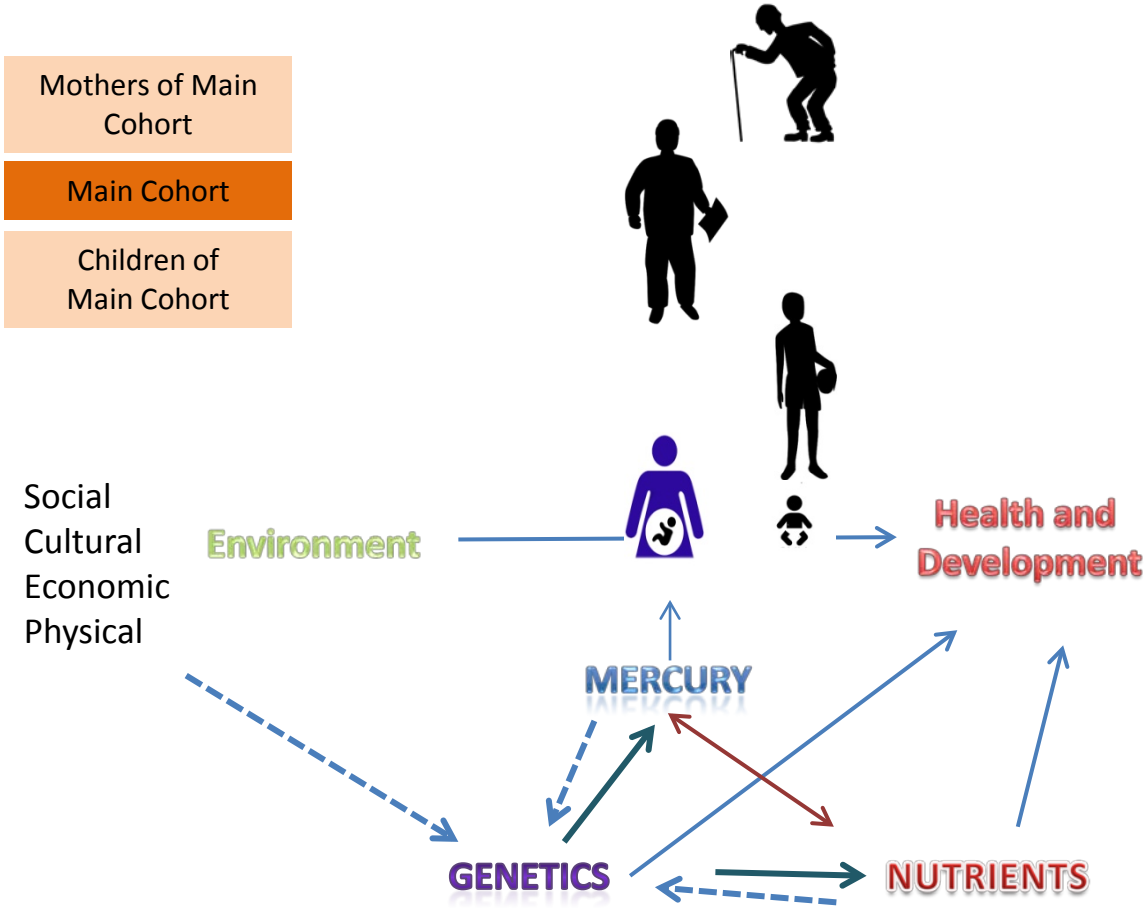
- Multinational and multidisciplinary scientific team with long and successful research track record
- Study participants reviewed many times and still going strong
- Huge amount of high quality data collected and archived
- Agility and versatility to look at issues in different ways:
  - at each time point has data on wide range of exposures and outcomes and can look at many different aspects of exposure and outcome
  - Can take longitudinal, prospective as well as restrospective view of exposure and outcome relationships
  - Can interact with other studies sharing similar designs and data sets
- Consistent approach to study design, hypothesis-driven approach and analysis planning and conduct
- Large output in terms of publications, conferences
- Good record of human resource development and careers

SCDS keeps going

Mothers of Main Cohort

Main Cohort

Children of Main Cohort



Ageing
Cardiovascular function
Neurodegenerative
Immune system function
Cancers

School performance
Risky behaviour

Cognitive
Social
Language
Motor
ASD
Immune system

The SCDS travel map

Paulette Anaou
Elizabeth Arrisol
Ghislaine Auguste
Georgie Azemia
Daniella Balette
Linda Barallon
Helene Basset
Raymonde Bellard
Daniel Belmont
Rose-May Benoit
Egbert Benstrong
Lymiah Bibi
Anne-Marie Bibi
Florida Bijoux
Jude Bijoux
Nathalie Bodin
Agnes Boniface
Pascal Bovet
Rubell Brewer
Daphnee Brice

Patricia Charlette
Betsy Chavez
Octavie Choisy
Nadia Ciseau
Jan de Broek
Johnette Denis
Joachim Didon
Marie-Helene Dogley
Lanka Dorby
Jean-Paul d'Offay
Agnes Elizabeth
Kathleen Ernesta
Christina Esther
Erica Fanchette
Jude Faure
Maxime Ferley
Agnes Florentine
Julita Fostel-William
Joanne Fred
Brigitte Gabriel

Lina Gabriel
Jude Gedeon
Leeory Gedeon
Juliette Henderson
Francoise Hoareau
Stephanie Hollanda
Hubert Innane
Meganne Jean
Sharon Jean
Rose-Mai Jolicoeur
Prosper Kinabo
Judy Labiche-Jean Baptiste
Sylvette Labrosse
Diana Laporte
Joel Lawen
Jeanne Legaie
Aubrey Lesperance
Andre Leste
Veraine Louis-Marie
Jeanne Low-Toy

Lindy Lucas
Catriona Monthy
Judy Morel
Naddy Morel
Marie-Helene Niole
Dana Padayachy
Philip Palmyre
Marie-Antoine Payet
Cyril Pillay
Brigitte Pool
Harold Pothin
Vivian Radegonde
Jan Robinson
Sarah Romain
Brian Santache
Paulette Sarah
Conrad Shamlaye
Heather Shamlaye
Emelyn Shroff
Jude Shroff

Josianne Sifflore
Graham Sims
Flavie Sinon
Jeanne-D'Arc Suzette
Bernard Valentin
Helene Valentin
Justin Valentin
Simone Victor
Sandra Vidot
Bharathi Viswanathan
Marija Zlatkovic
Child Health Nuses
Midwives
Teachers

Seychelles SCDS personnel

SCDS family album


EXIT






VISIONARY