UNITED NATIONS
ENVIRONMENT PROGRAMME

CHEMICALS

UNEP

REGIONAL AWARENESS-RAISING WORKSHOP ON MERCURY POLLUTION

A global problem that needs to be addressed

Buenos Aires, Argentina,
13 – 16 September 2004

IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

Case study - Exposure to organic and inorganic mercury: an integrated approach

by Roberto Lucchini, resource person

Slide 1

Health effects due to exposure to inorganic and organic mercury

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Slide 2

Outline

- 1 st part: multicenter Italian study on exposure and effects from integrated multiple sources of Hg
- 2 nd part: focus on a specific area with high MeHg exposure from fish eating

Slide 3

Multicenter study

Cross-sectional design on 4 geographic areas in Northern and Southern Italy

Network of Italian Institutes of Occupational Health, Industrial Hygiene, General Pathology, Biochemistry, Odontology and Biostatistics

Funded by the Italian Ministry of Reseacrh

Slide 4

Type of Hg exposure

Occupational exposure to elemental Hg° in chloroalcali, thermometer and neon lamp

Exposure to inorganic Hg through dental amalgams

Exposure to MeHg through fish consumption

Slide 5

Hg toxicity

- Central nervous system
- Immunitary system
- Renal function

Neuro-psychological evaluation

Symptoms reporting

Neurobehavioral - SPES

Neurophysiological – Tremor DPDTREMOR

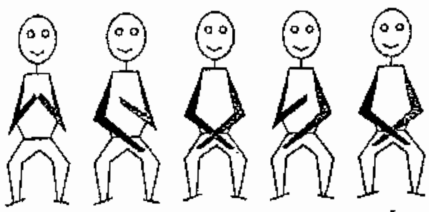
Neuroendocrine - ProlactinPR)

Slide 6

- **SPES** (Swedish Performance Evaluation System)
  1. **Simple reaction time**
  2. **Digit Span**
  3. **Finger Tapping**
  4. **Symbol Digit**
  5. **Color Word Vigilance**
  6. **Mood Rating Scale**
- **Luria Nebraska Neuropsychological Battery**

Slide 7

BAMT (Branches Alternate Movement Task)



Slide 8

Tremor Analysis - DPD

1. **Tremor intensity (m/sec²)**
2. **Median of Central frequency**
3. **Central frequency dispersion**
4. **Armonic index**
5. **Tremor index**

Slide 9

Serum Prolactin

Interferences with tubero-infundibular system:

- On the dopaminergic system (tonic inibitor)
- On the serotoninergic system (enhancer)

Prolactin secretion

Slide 10

Immunological parameters

- Few studies on cellular mediated parameters (T CD4+, CD8+, NK)
- Few studies on cytokines of T linphocytes (inteleukin, tumor necrosis factor)

Slide 11

Renal effects

- Glomerular lesion: excretion of proteins with high molecular weight
- Accumulation in proximal tube with excretion of enzymes and proteins with low molecular weight

Slide 12

Statistical analysys

1. **ANOVA comparisons according to occupational exposure, fish consumption and dental amalgams**

Multicenter study ⇒ complex interrelations between indipendent variables of exposure, socio-demographic, and confounders

2. Regression analyses (General Estimating Equations)

Slide 13

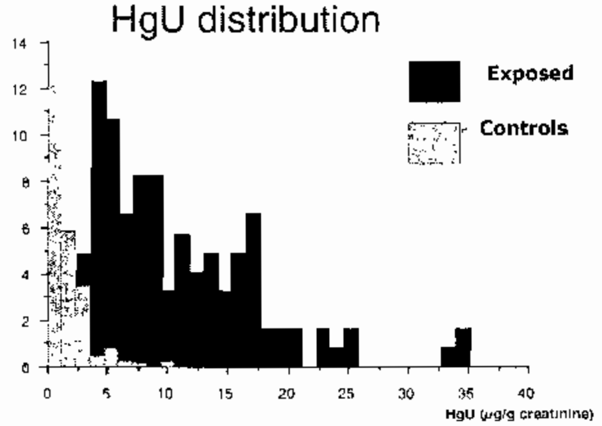
Results – HgU/creat

		N.	Mean	SD	Range	Geom mean
Brescia Thermom	Exposed	18	8	3.3	3.7-16.5	7.4
	Controls	52	1.9	1.7	0.2-10.3	1.2
Cagliari Chloroalkali	Exposed	33	14.2	9.5	4.5-35	12.7
	Controls	39	2.5	1.3	0.5-5.8	1.7
Bari Neon lamp	Exposed	33	6.1	3.6	0.2-16.5	4.9
	Controls	75	0.9	0.9	0.1-6.2	0.6
Priolo Chloroalkali	Exposed	38	11.9	9.1	1.9-35.2	9.4
	Controls	30	4.1	5.9	0.7-35.2	2.7
Total (*)	Exposed	104	10.4	6.9	0.2-35.2	8.3
	Controls	196	1.9	2.8	0.1-33.2	1.2

(*) t= 15.35 p<0.0001

Slide 14

HgU distribution



Slide 15

Group comparisons

	Exposed Mean	Exposed SD	Exposed Median	Controls Mean	Controls SD	Controls Median	
Symptoms							
Fatigue	7.08	2.59	6.00	6.59	2.13	6.00	ns
Sleep	11.10	3.99	10.00	10.79	3.13	10.00	ns
Memory	9.07	2.74	8.00	9.22	2.38	9.00	ns
Attention	7.58	2.88	7.00	7.58	2.10	7.00	ns
Psychomotor	8.25	2.55	7.00	7.87	2.11	7.00	ns
Mood	12.89	4.59	12.00	12.51	3.91	12.00	ns
Psychiatric	5.35	1.58	5.00	5.57	1.67	5.00	ns
Psycosomatic	21.70	5.31	21.00	21.54	4.99	20.00	ns
Neurological 1	11.76	3.41	11.00	11.76	3.93	10.00	ns
Neurological 2	6.60	2.08	6.00	6.07	1.41	6.00	ns
Sexual	3.37	0.96	4.00	3.27	1.02	3.00	ns

Slide 16

	EXPOSED Mean	EXPOSED SD	EXPOSED Median	CONTROLS Mean	CONTROLS SD	CONTROLS Median	
SPES							
SRT	277.01	41.61	269.50	284.13	39.71	276.00	ns
DS	10.00	1.91	10.00	10.60	1.93	10.00	ns
FT dominante	62.71	8.34	64.00	62.25	7.80	62.50	ns
FT non domin.	58.38	8.46	59.00	57.23	7.35	56.50	ns
SD	3182	692	2972	3256	764	3139	ns
CW	588.71	33.08	589	590.72	33.36	593	ns
Stress	11.63	3.38	12.00	12.61	3.54	12.00	ns
Attivazione	11.48	2.89	11.00	12.01	2.72	12.00	ns
Luria-Nebraska							
LURIA sum	80.76	20.41	76.00	75.59	17.55	74.00	ns
BAMT							
BAMT n	46.60	14.30	**46.00**	48.58	13.27	**50.00**	***

Slide 17

	EXPOSED Mean	EXPOSED SD	EXPOSED Median	CONTROLS Mean	CONTROLS SD	CONTROLS Median	
Tremor							
I dom	0.15	0.09	0.12	0.14	0.06	0.12	ns
I ndom	0.14	0.07	0.12	0.14	0.08	0.12	ns
F(50) dom	7.53	1.38	7.30	7.27	1.41	7.20	ns
F(50) ndom	7.41	1.48	7.3	7.60	1.58	7.4	ns
sF(50) dom	2.88	0.76	2.80	2.87	0.77	2.90	ns
sF(50) ndom	3.10	0.80	3.20	3.16	0.78	3.30	ns
HI dom	0.88	0.05	0.88	0.88	0.05	0.88	ns
HI ndom	0.86	0.05	0.85	0.86	0.05	0.86	ns
TI dom	88.86	31.05	90.00	90.76	28.30	88.00	ns
TI ndom	83.74	30.48	82.00	84.21	27.09	85.00	ns
Prolactin							
PRL	9.71	5.68	**9.05**	13.29	8.64	**11.87**	***

Slide 18

GEE Regressions

	Occupational exposure	Dental exposure	Fish eating	HgU
Prolactin	S** (-)	NS	NS	S** (-)
FT dom	S** (-)	NS	NS	NS
BAMT	S* (-)	NS	NS	NS
Symptoms				
Fatigue	NS	NS	S** (-)	NS
Psychiatric	NS	NS	S** (-)	NS
Attention	NS	NS	S** (-)	NS
Sleep	NS	NS	S** (-)	NS
Psychomotor	NS	NS	S** (-)	NS
Neurological	NS	NS	S** (-)	NS
IL-8	S** (-)	NS	NS	S** (-)
β2-MG	S** (-)	NS	NS	S** (-)

*(S** = p<0.01, S** = p≤0.05)*

Slide 19

MODEL: PRL as f of indipendent variables, with research center as casual effect

	β ESTIM	β SE	T-test	p
Intercept	3.780764	0.3554594	10.63608	<.0001
Sex	-0.479636	0.1636791	**-2.93034**	**0.0037**
Age	-0.016563	0.0048142	**-3.44036**	**0.0007**
Low school	-0.073698	0.1551757	-0.47492	0.6352
High school	0.005473	0.1599771	0.03421	0.9737
Diploma	0.010724	0.2269409	-0.04725	0.9633
Residency	0.084124	0.1540275	0.54616	0.5654
BMI(25, ?)	-0.195610	0.0921302	-2.12319	0.0346
BMI(29.0,41.3)	0.185337	0.1186810	1.56160	0.1195
Smoke	-0.016026	0.0871111	0.18646	0.8524
Coffee(1, 3)	-0.195267	0.1267121	-1.54102	0.1244
Coffee(4,10)	-0.068651	0.1511339	-0.45424	0.6500
Alcohol(0,...)	-0.275775	0.1262582	-2.17389	0.0306
Alcohol(10.000,110.000)	0.127359	0.1069917	1.18943	0.2353
FISH(<1 3/week)	-0.071184	0.1605486	0.44338	0.6578
FISH(sometimes)	-0.015424	0.1835052	-0.08405	0.9331
FISH(never)	-0.265447	0.3055400	-1.37902	0.1690
AMALG surface(4.0, 93)	-0.097557	0.0868329	-1.09815	0.2731
AMALG SURFACE(92.5,468)	0.013004	0.1140953	0.11397	0.9093
OCCUP EXP	-0.276520	0.0837922	**-3.30007**	**0.0011**

Slide 20

CONCLUSIONS

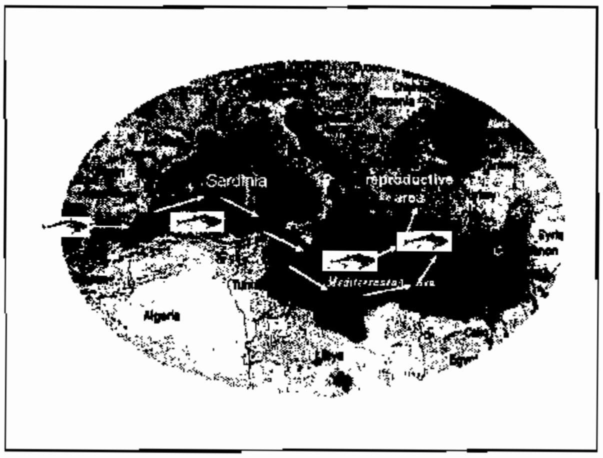
- High variability between participating centers
- Necessity of appropriate regressive analysis to minimize the influence of confounders, including the geographical data source

Slide 21

CONCLUSIONS 1

- Evidence of early neurobehavioral-endocrine changes by occupational exposure to Hg° of 8 µg/g creat HgU
- No changes induced by an average number of 2-3 dental amalgams ≅ 40-80 mm²
- Protective effect of small size fish eating (selenium – aminoacids ?)

Slide 22

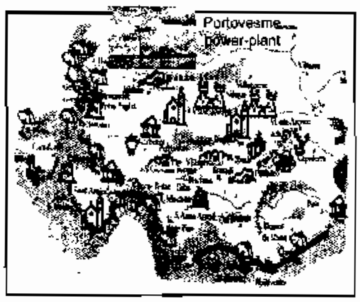


Slide 23

Town of Carloforte - Sardinia

Yellow-fin tuna

Red-fin tuna

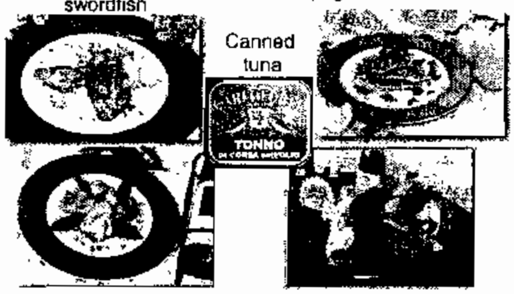


Slide 24

The "Tonnara" in Carloforte

Slide 25

Typical courses with tuna fish



Slide 26

Mercury content in local fish

		Mean	Max
Tuna fish (over 100 Kg)		1 51	2 12
Swordfish (over 50 Kg)		1.18	1.46
Red mullet		0 32	0.62
Gurnet		0.33	0.60
Weever		0.21	0.41
Octopus	U.S. FDA 1 ppm	0.13	0.23
Sarago	Health Canada 0.5 ppm	0.09	0.16

Slide 27

Subgroups comparison

Cases:

22 adult male subjects lifetime living in Carloforte

non occupationally exposed to Hg

usual eaters of local tuna fish

Controls

22 age-matched Sardinian subjects not occupationally exposed to mercury moderate eaters of small-size fish

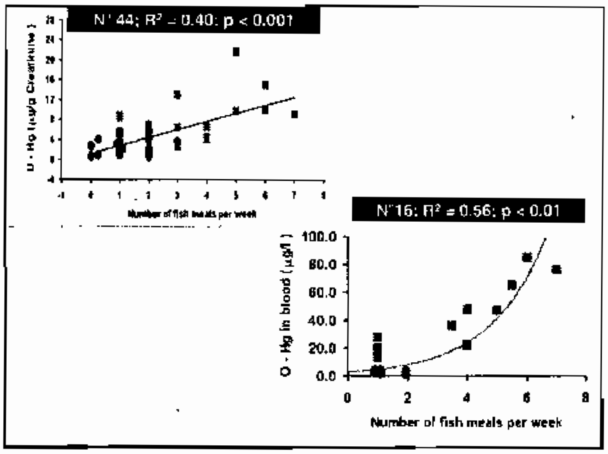
Slide 28

Hg biological measurement

		Cases		Controls		
	Units	Median	Range	Median	Range	2P
U-Hg	µg/g creat	6.5	1.8-21.5	1.5	0.5-5.3	0 001
T-Hg	µg/l	44.0	15- 93	3.9	1 2-5.4	0 000
O-Hg	µg/l	41.5	13- 85	2.8	0.8-4 0	0.000

T-Hg Total blood Hg
O-Hg Organic blood Hg

Slide 29



Slide 30

	Carloforte		Controls		
	Median	Range	Median	Range	2P *
S RT (msec)	**0.27**	0.2-0.4	**0.27**	0.2-0.5	0.401
CW (msec)	**0.61**	0.6-0 7	**0.59**	0 5-0 7	0.003
DSymb (msec)	**3.70**	2 5-5.9	**2.85**	2 2-4 4	0.000
FT (N° hits)	**112.5**	83-142	**124.0**	99-153	0.037
L-N (sum)	**71.9**	54-102	**80.0**	60-107	0.061
BAMT (score)	**40.5**	27-56	**44.0**	30-66	0.682
DSpan (sum)	**10.0**	8-15	**10.5**	7-16	0.893
Tremor Index	**90.0**	50-125	**88.0**	40-121	0 972

* General Factorial ANOVA performed on log-transformed variables (covariates age, education level, ethanol consumption, smoking)

Slide 31

Serum Prolactin (PRL)

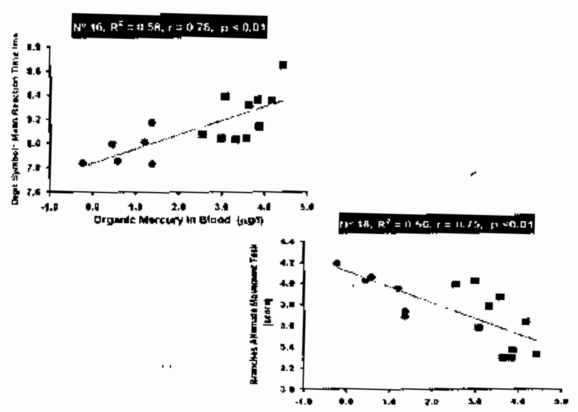
	Cases	Controls
GM	13.1	8.9
GSD	1.6	1.5
Range	4.9 - 33.8	4.3 - 22.4

2P = 0.006

Pearson's correlation:

Urinary mercury	N° 44	r = 0.51	p < 0.01
Blood organic mercury	N° 16	r = 0.58	p < 0.05

Slide 32



Slide 33

Multiple stepwise regression

Dependent variable: **Digit Symbol Reaction Time**

Multiple Regression N° 16 R^2 = 0.77, F = 19.5, p = 0.0006

Covariates		β	SE β	p	partial R^2
Blood organic mercury	(log)	0.114	0.025	0.001	**0.66**
Education level		-0.147	0.072	0.048	0.11

Dependent variable: **Branches Alternate Movement Task**

Multiple Regression N° 16 R^2 = 0.81, F = 14.6, p = 0.0005

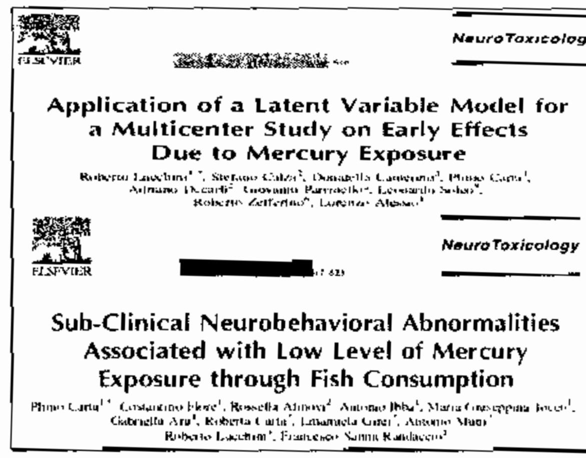
Covariates		β	SE β	p	partial R^2
Blood organic mercury	(log)	-0.107	0.036	0.010	**0.69**
Age		-0.013	0.005	0.042	0.12

Slide 34

CONCLUSION

- Big size fish rich in organic Hg induces neurobehavioral changes and increased PRL
- Organic and inorganic Hg with different effects on PRL (different neurotransmitter ?)
- Small size fish low in organic Hg with beneficial effects

Slide 35



Slide 36

In the meantime, you are all welcome to Carloforte for a nice vacation with a moderate, "safe" meal of delicious tuna-fish