

Occupational cohort study of Miteni factory workers

Long-term health effects among the employees of a chemical factory producing intermediates for crop protection chemicals, pharmaceutical products, perfluorinated derivatives (PFAS, PFOA): On going activities

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The studies have been approved by the Ethical Committee.

Designing an epidemiological study on PFAS exposed population in Veneto Region
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Aim of the presentation

To report on the activities, on going or planned, to evaluate long-term health effects among factory workers (RIMAR/MITENI, Trissino, Vicenza province) through retrospective cohort studies.

The factory has produced, since 1968, over one hundred of chemicals: intermediates for crop protection chemicals, pharmaceutical products, perfluorinated derivatives (PFAS, PFOA).

Several agents used or produced may have entailed potential health effects on factory workers.

At present, the work force is of about 130 employees.

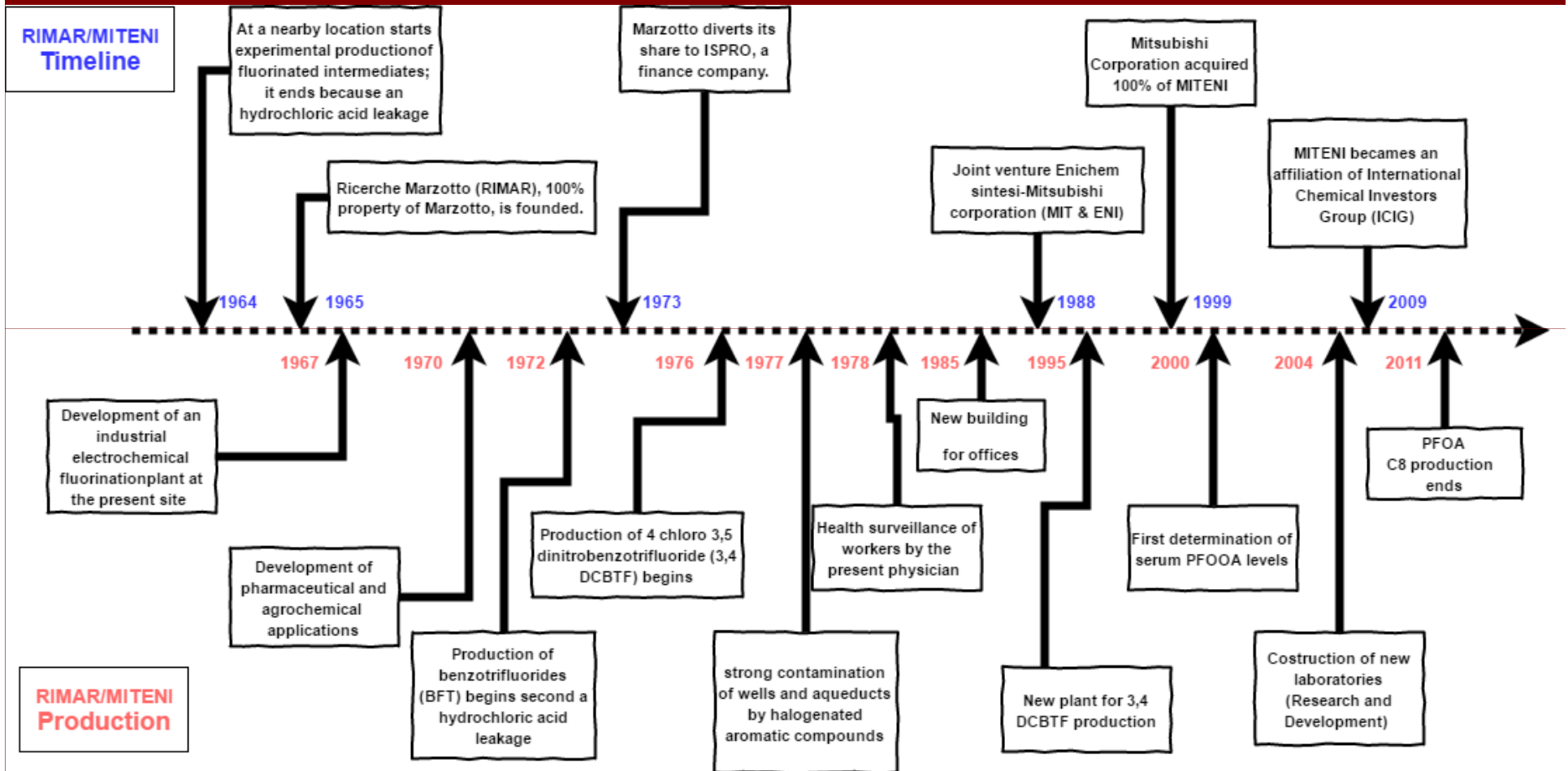
The MITENI facility nowadays

Presence of:

- 3 production departments;
- 1 pilot plant;
- laboratories;
- waste-processing, etc..



RIMAR/MITENI Timeline



Production of perfluoro compounds

Production of perfluorocarboxylic and perfluorosulfonic acids (fluoropolymers, PF) through electrochemical fluorination (nowadays in 26 modular units).

In particular:

- Perfluorooctanoic acid (CAS 335-67-1) and its ammonium salt (CAS 3825-26-1)
- Perfluorooctanesulfonyl fluoride (CAS 307-35-7) and its acid potassium salt (CAS 2795-39-3)
- Perfluorobutanesulfonyl fluoride (CAS 375-72-4) and its acid potassium salt (CAS 29420-49-3)

Production lines

1. **Fluoropolymers (PF)** by electrochemical fluorination
2. **Down stream production plant** for fluoroaromatic products (FA) starting from basic fluorotoluenes
3. **Production plant for benzotrifluorides (BTF)** by treating chloride products (benzotrichlorides) with hydrofluoric acid [i.e: the herbicide Trifuralin]
4. **Pilot plant:** includes electrochemical fluorination cells

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Polyfluoroxylylene derivatives	Pharmaceuticals Intermediates
Fluoroaromatics derivatives	Performances Products
Perfluorinated derivatives	
SF5 derivatives	
Fluorinated building blocks	
Fluorinating agents	

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The RIMAR/MITENI study.

On-going activities:

Two main studies:

- **1. A retrospective cohort mortality study on factory employees.**

Reference population: mortality of the regional population.

Results are almost complete.

- **2. A retrospective cohort incidence study on factory employees.**

Reference population: incidence comparison between RIMAR/MITENI cohort and a cohort of employees of a metallurgical factory of the same province.

Results within 2017.

Intensity of exposure

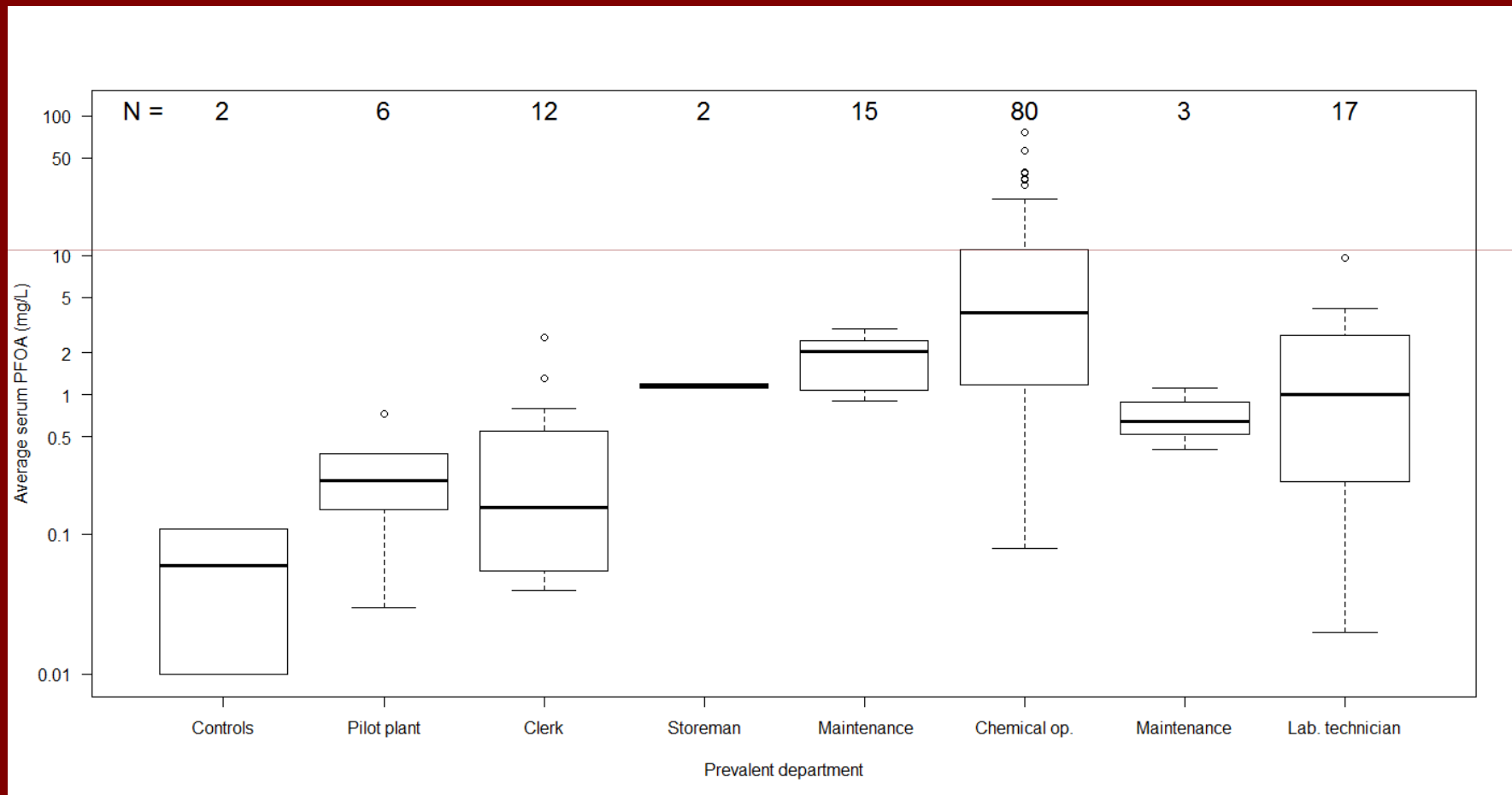
Retrospective yearly PFOA serum levels determined since year 2000 among a subset of employees.

Exposure levels or biomonitoring data on exposures other than PFOA are not available.

PFOA serum levels in mg/l (log scale)

135 workers (+2 controls) with at least one yearly serum PFOA measurement since 2000.

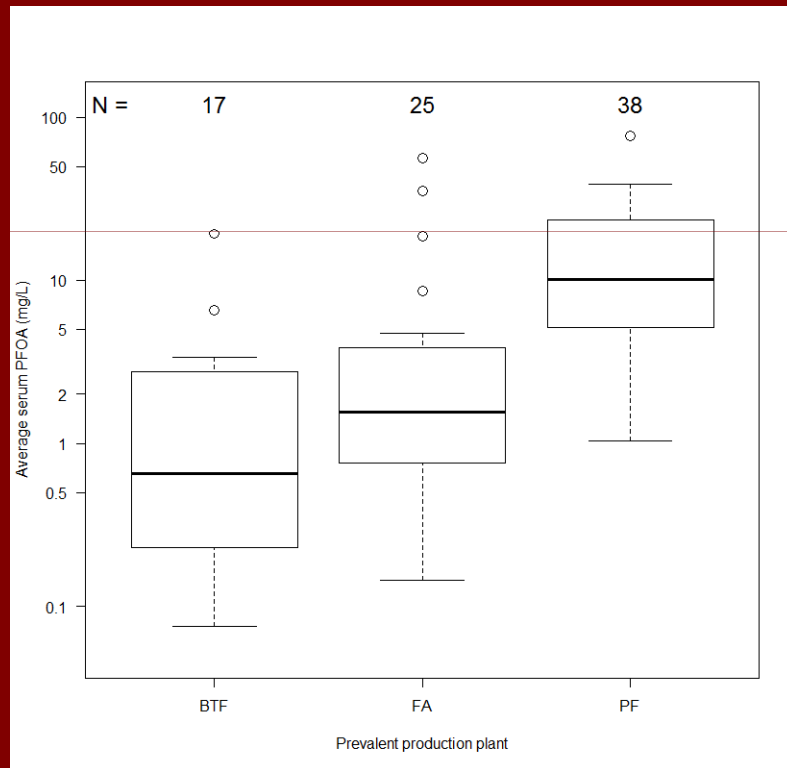
Result: PFOA levels show different values among workers by main task.



PFOA serum levels

Average PFOA (mg/l) serum levels among employees broken down by production department.

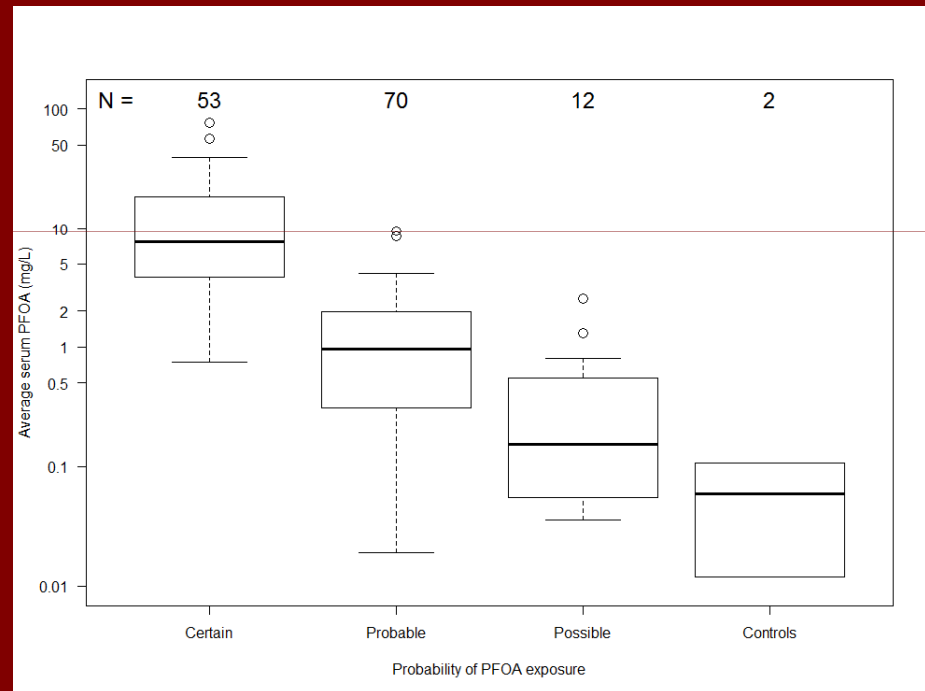
Result: the highest average is recorded among those at the PF dept.



PF= PFOA and PFOS
BTF= Benzotrifluorides
FA= Fluoroaromatics

Average PFOA serum levels among employees broken down by probability of exposure.

Result: clear differences between groups.

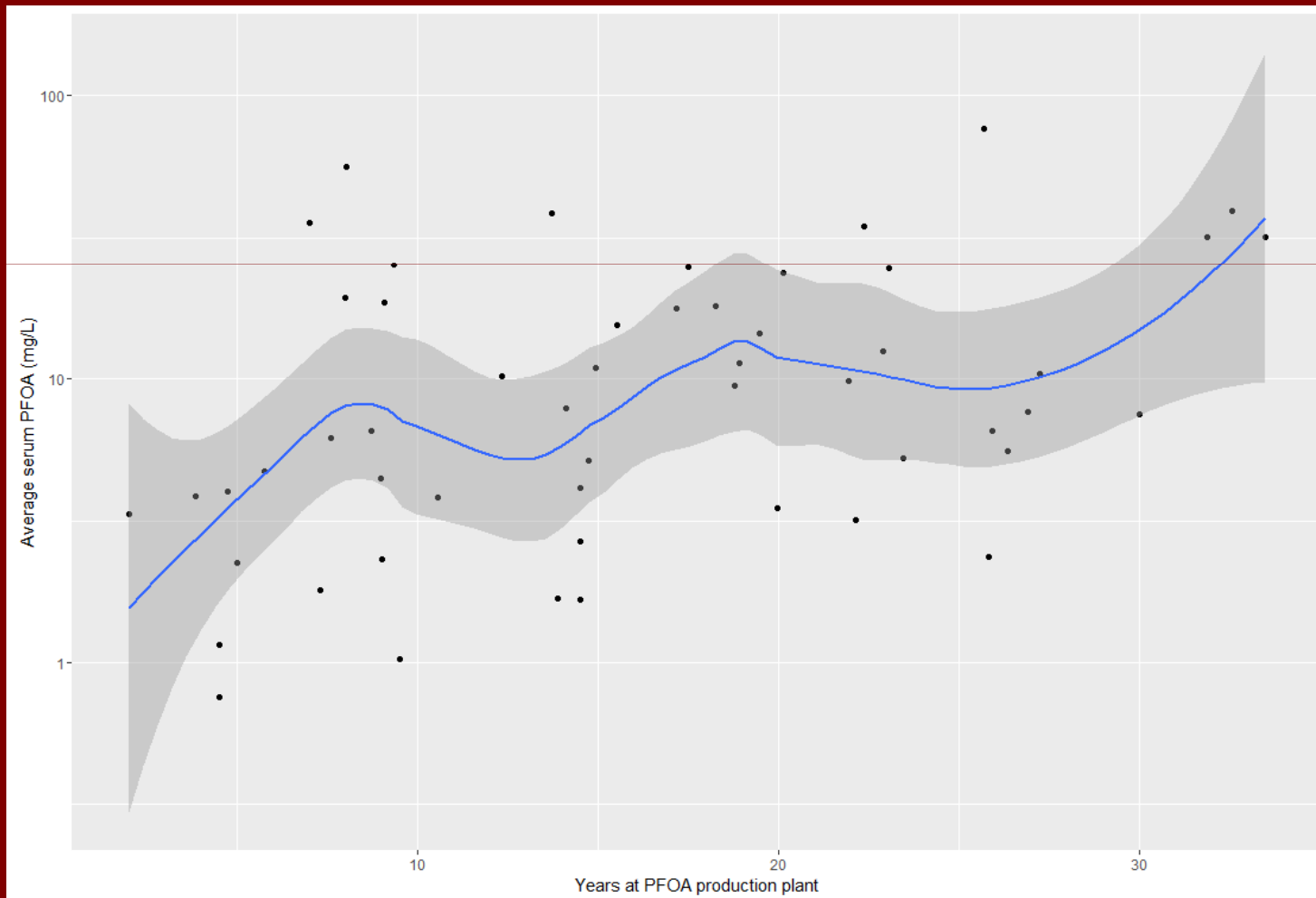


Certain = working presence at the PFOA dept
Probable = working in and around the general production
Possible = employment exclusively as clerk
Controls= subjects selected by purpose

PFOA serum levels

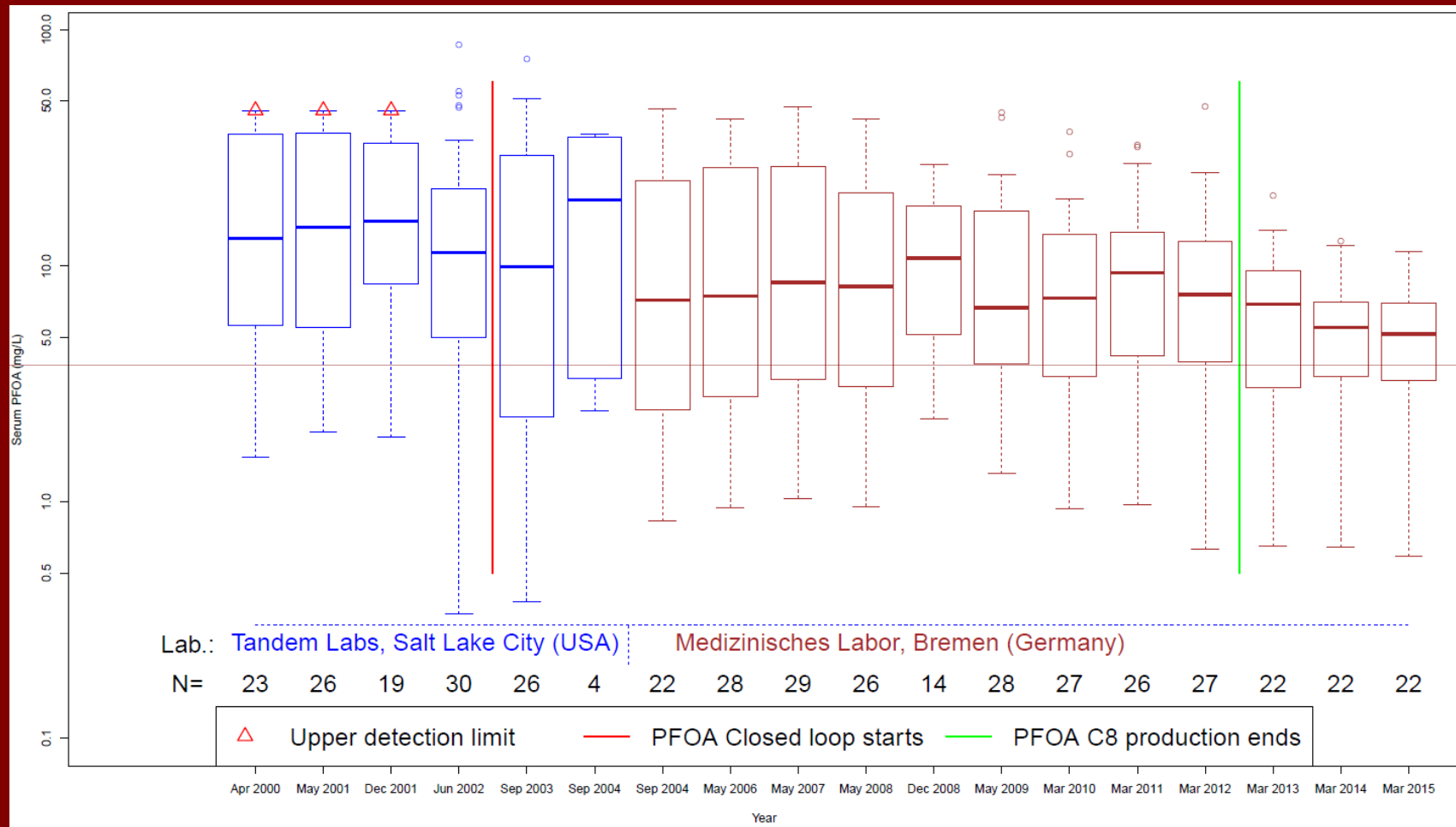
Average serum levels among 53 workers who have been (but not necessarily still are) at the PFOA dept.

Result: a dose-response between serum PFOA levels and length of work at the PF dept.



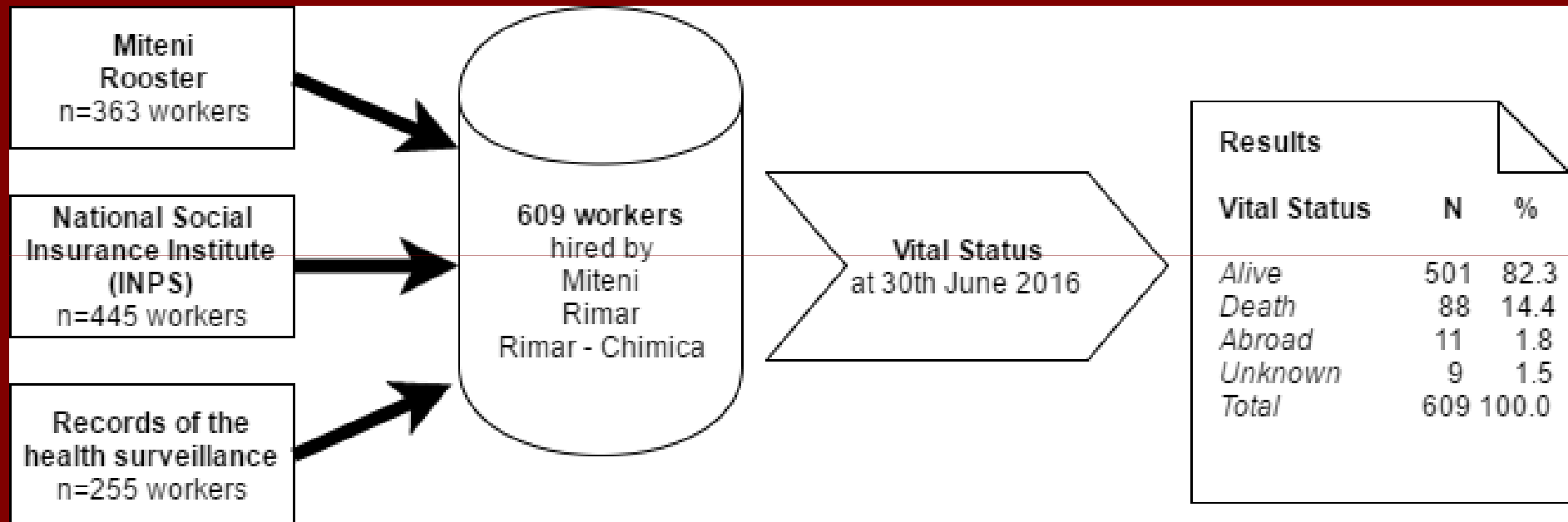
PFOA serum levels in mg/L

Concentrations among workers at the PF dept by year of work.



Result: no evidence of a decreasing trend (2004-2012) among workers₁₂ at the PF dept.

Cohort study: RIMAR/MITENI



Cohort mortality study

Exclusion criteria:

- incomplete records (n=9)
- clerks at the Milan offices (n=36);
- hired by RIMAR/MITENI, but really at work in a sister company (RIMAR meccanica/Sperotto; n=15);
- hired for less than 365 days (n=48);
- hired after the year 2004 (n=33);
- females (n=58).

415 male workers are eligible for the mortality cohort study.

Statistical analysis:

Standardized Mortality Rates (SMR) with 95% Confidence Intervals (95% CI) obtained by indirect standardization (mortality rates of the Veneto Region).

Cohort mortality study

Main characteristics	Total (n=415)
Birth date (mean, S.D.)	1954.1 (13.8)
Deaths (at 30th June 2016) (n (%))	79 (19.0)
Year of hire (n (%))	
<1975	118 (28.4)
1975-1990	172 (41.5)
>1990	125 (30.1)
Main task (n (%))	
Clerk	50 (12.1)
Storeman	14 (3.4)
Maintainer	41 (9.9)
Plant operator	216 (49.6)
Laboratory technician	28 (6.8)
Other	28 (6.8)
Missing	48 (11.6)
PFOA/PFOS exposure (n (%))	
Certain	75 (18.1)
Probable	241 (58.1)
Possible	51 (12.3)
Missing	48 (11.6)

Cohort mortality study

Preliminary results

All employees (n=415, 12,551 py)

	Obs.	Esp.	SMR	95% CI
All causes	79	73.8	1.07	0.61-1.33
Diseases of the circulatory system	25	20.2	1.24	0.84-1.84
•Ischemic heart disease	8	9.3	0.86	0.43-1.72
•Hypertension	2	1.34	1.49	0.37-5.95
Malignant Neoplasms	30	29.9	1.00	0.70-1.44
•Colon	3	2.04	1.47	0.47-4.57
•Stomach	4	1.62	2.47	0.92-6.57
•Liver	6	2.17	2.77	1.24-6.16
•Lung	5	8.81	0.57	0.24-1.69
•Bladder	2	0.74	2.70	0.67-10.76
•Kidney	2	0.90	2.22	0.55-8.86
•Lymphomas or leukemia	3	2.23	1.47	0.47-4.57
Diabetes	4	1.51	2.65	0.99-7.06
Diseases of the respiratory system	5	3.07	1.63	0.68-3.91
Cirrhosis	4	2.70	1.48	0.56-3.94
Injury, poisoning (including suicide)	6	6.51	1.08	0.51-2.25

Cohort mortality study

Preliminary results

All employees (n=415) by probability of PFOA exposure.

PFOA Exposure	All causes			Diseases of the circulatory system			Malignant neoplasms			Diabetes		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
Certain	21	1.45	0.94-2.22	7	1.67	0.80-3.50	7	1.22	0.58-2.56	2	6.89	1.73-27.54
Probable	34	0.91	0.65-1.28	10	1.03	0.55-1.91	15	0.99	0.59-1.64	1	1.32	0.19-9.37
Possible	11	1.06	0.59-1.92	3	1.00	0.32-3.12	5	1.22	0.52-2.93	0	--	-- --

Result: increased SMRs (except neoplasm) among workers with a certain exposure to PFOA.

Cohort mortality study

Preliminary results

Employees with a certain exposure to PFOA/PFOS (n=75, 2,201 py)

	Observed	Expected	SMR	IC 95%
All causes	21	14.5	1.45	0.94-2.22
Diseases of the circulatory system	7	4.19	1.67	0.80-3.50
• <i>Ischemic heart disease</i>	1	1.90	0.53	0.07-3.74
• <i>Hypertension disease</i>	2	0.27	7.31	1.83-29.25
Malignant Neoplasm	7	5.73	1.22	0.58-2.56
- <i>Liver</i>	1	0.41	2.46	0.35-17.44
- <i>Pancreas</i>	1	0.33	3.07	0.43-21.79
- <i>Lung</i>	2	1.72	1.16	0.29-4.64
- <i>Kidney</i>	1	0.17	5.97	0.84-42.42
- <i>Lymphoma</i>	1	0.42	2.40	0.33-17.05
Diseases of the respiratory system	2	0.67	3.00	0.75-11.98
Cirrhosis	2	0.55	3.67	0.92-14.67
Diabetes	2	0.29	6.89	1.72-27.54
Injury, poisoning	1	1.19	0.84	0.11-5.99

Italian cohort studies on “chemical” workers

	Production	Py	Deaths	Rates for comparison	SMR 95% CI
Bertazzi, 1981	Paints and vanishes	5,800	46	National	0.99
Bertazzi, 1986	Resins	27,000	112	Regional	0.92 0.76-1.11
Bernardinelli, 1987	Rubber	69,000	140	Local (province)	0.85 0.72-1.01
Bertazzi, 1989	Oil refinery	29,000	213	Regional	0.80 0.69-0.91
Negri, 1989	Rubber	133,000	978	Regional	0.91 0.84-0.94
Piratsu, 1991	Vinyl chloride	99,603	247	National	0.63 0.57-0.70
Pirastu, 2003	Vinyl chloride (Venice)	41,000	248	Regional	0.75 0.68-0.83
Pasetto, 2012	Petrochemical	178,000	563	Regional	0.72 0.67-0.77
Mirabelli, 2012	Tire production	224,500	891	Regional	0.93 0.86-0.99
Bena, 2016	Chimical factory	44,500	421	Regional	0.89 0.82-0.97

Occupational male cohorts of PFOA, PFAS, TFE producers

	Production	Deaths	Rates for comparison	SMR (95% CI)
Raleigh K, 2014	3M facilities producing PFOA a) Cottage Grove b) Saint Paul	1125 1829	State State	0.85 (0.80-0.90) 0.98 (0.94-1.03)
Consonni D, 2013	6 factories producing Tetrafluoroethylene (TFE)	635	National	0.77 (0.71-0.84)
Steenland K, 2012 (updates Leonard, 2008; Sark, 2009))	PFOA	1084	National	0.70 (0.66-0.74)
Lundin JI, 2009 (updates Alexander BH, 2003; Gilliland FD, 1993)	PFOA	807	Regional	0.88 (0.68-1.12)
Leonard RC, 2008	Polymer	806	Regional	0.59 (0.55-0.63)
Alexander BH, 2003	Fluoride production (PFOS)	145	Regional	0.63 (0.53-0.74)
Gilliland FD, 1993	PFOA	148	Regional	0.86 (0.72-1.01)

Mortality study

Limitations

Limited size of the population under study.

Limited size of subjects certainly exposed to PFOA.

Lack of data on intensity of exposures to chemical compounds except for PFOA, PFOS.

Mortality: end-point not appropriate for several diseases of interest (including cancers).

Confounding factors not fully investigated.

Conclusions

Overmortality among all employees, higher among exposed to PFOA

Excess of liver, bladder and kidney cancers among all employees.

Excess of cirrhosis, diabetes, hypertension among all employees, higher among exposed to PFOA.