Analysis of medical surveillance data of Campine NV and Campine recycling NV

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Population

Data of 60 employees that work or worked for Campine NV or Campine recycling NV between 1972 and 2017 were analyzed. Only workers that worked at least 2 years in antimony were included in the study. All workers were male.

Methods

Since 1972 medical surveillance of workers of Campine NV and Campine recycling NV was carried out by 4 different external services for prevention and protection at work. Medical data of workers were stored in paper files from 1999 until 2013. From 2014 data were gathered in an electronic medical file. Data of paper and electronic files were extracted and put in a database. The company provided data about seniority.

Medical surveillance for workers in antimony included pulmonary function tests, chest X-ray, liver function tests and bio monitoring of antimony in urine. The bio monitoring was carried out with a frequency between once to four times a year or more for workers who showed high biomonitoring values.

For each worker the following data were loaded in the database: FVC (ml), FEV1 (ml), smoking status, GOT and GPT level in blood (U/l) at the start and at the end of working in antimony with the year the test was performed; height and weight at the end of working in antimony; most recent chest X-ray; date of birth. For workers that started before 2000 the data of 2000 were used as value at start. For workers that are still working the data of end were from 2016 or 2017. The chest X-ray was the most recent result found in the electronic file between 2014 and 2017. The chest X-ray was not available for workers who stopped working before 2014. For each worker, all urinary antimony values that were available within the period he worked in antimony factory were recorded in the database. Urinary antimony concentration was expressed in microgram/gram creatinine. The number of antimony recordings per worker varied from 5 to 66.

A worker's mean urinary antimony concentration was calculated by adding up all urinary antimony values and dividing by the amount of antimony recordings for that worker. A high and a low exposure group for antimony was defined. The low exposure group were the

workers whose urinary antimony level never reached or exceeded 35 micrgram/ gram creatinine. The high exposure group were those who had one or more urinary antimony measures of 35 microgram/ gram creatinine or higher. This criterion for low and high exposure groups was based on a study of Bailly et al (1). They estimated that after eight hours of exposure to 500 microgram/m^3 of pentavalent antimony, the urinary antimony concentration at the end of the shift is on average 35 microgram/gram creatinine.
The pulmonary function parameters that were taken into account were FVC, FEV1 and Tiffeneau index (FEV1/FVC). For FVC and FEV1 the percentage of a person's expected value was calculated by dividing a person's result by the expected value for that person according to his gender, length and age and multiplying by 100. The equation used to calculate the expected values in liter were the EGKS-ERS equations for a male person, namely (5,76*length (m))-(0,026*age (years))-4,34 for FVC and (4,3*length (m))-(0,029*age (years))-2,49 for FEV1. "Age" in the equation was the age at the time the test was performed. Tiffeneau index was calculated by dividing FEV1 by FVC. FVC, FEV1 as percentage of the expected value and Tiffeneau index are expected to stay unchanged over lifetime. The differences of the percentages of FVC and FEV1 and of the Tiffeneau index between end and start of working in antimony were calculated and used in the analysis. A negative difference means there is a decrease in comparison to the start value.
GOT (ALT) and GPT (AST) blood levels were recorded in U/l. The time interval between the earliest and most recent data was 17 years. In this time period different laboratories were solicited to perform the tests and different methods of analysis and reference values for GOT and GPT were used. Therefore for each liver function test was also noted if it was beyond reference according to the laboratory reference at the time the test was performed. The end and start values of GOT and GPT were recoded in an outcome variable with two possible outcomes. These outcomes were: result beyond reference compared to start (All the workers with a test within reference at start and beyond reference at the end) and result not beyond reference or no change compared to start (All the workers with a test within reference at the start and at the end or a test beyond reference at both moments, or a test beyond reference at the start but within reference at the end).
Seniority of working in antimony and the mean antimony concentration in urine were considered to be measures of exposure to antimony.
Recent chest X-ray, the difference in pulmonary function and liver function tests between time of starting in antimony and at the end of working in antimony was considered as outcome parameters.
The relationship between outcome parameters and measures of exposure were investigated.

Statistical analysis

A simple linear regression was used to investigate the relationships between the differences in pulmonary function tests (FVC, FEV1 and Tiffeneau index) and seniority and mean urinary antimony level, respectively.

The relationships between liver function tests (GOT and GPT) changes and seniority and urinary antimony level (high and low exposure group) were investigated by cross tabulation and Fisher's exact test. For that purpose seniority was categorized in a lower and a higher group, based on the median value.

Results

Descriptives and frequencies

Table 1: Minimum, maximum, mean, standard deviation (SD) and median of continuous variables

Variable	n	Minimum	Maximum	Mean	SD	Median
Age at end (years)	58	21	60	44,2	9,6	45,5
Length (cm)	59	165	203	178,3	7,1	179,0
BMI at end (kg/m*m)	57	18,4	37,2	27,1	3,8	26,9
Seniority (years)	60	2,7	44,8	16,9	10,5	16,5
Mean urinary antimony concentration (microg/gcreat)	60	1,1	161,2	18,7	23,9	14,9
Difference FVC%*	58	-14,5	26,0	3,7	9,2	4,3
Difference FEV1%*	58	- 22,6	17,9	1,0	7,5	2,5
DifferenceTiffeneau*	58	- 20,5	15,0	- 4,2	6,4	-3,3

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Table 2: Frequencies of categorical variables

Variable	n		n	%
Smoking at start	54	Smokers	32	59,3
		Non-smokers	22	40,7
Smoking at end	56	Smokers	21	37,5
		Non-smokers	35	62,5
GOT	60	Beyond reference compared to start	4	6,7
		Not beyond references or no change compared to start	56	93,3
GPT	60	Beyond reference compared to start	14	23,3
		Not beyond references or no change compared to start	46	76,7
Chest X-ray	42	No pulmonary lesions	42	100
		Pulmonary lesions	0	0

Antimony exposure group	60	Low, urinary antimony always < 35 microg/gcreat	26	43,3
		High, urinary antimony at least once ≥ 35 microg/gcreat	34	56,7

Mean seniority was 16,9 years with minimum 2,7 and maximum 44,8 years. Mean urinary antimony concentration was 18,7 microgram/ gram creatinine with minimum 1,1 and maximum 161,2 microgram/ gram creatinine.

A recent chest X-ray was available for 42 of 60 employees. No pulmonary lesions were found. For 58 of the 60 employees pulmonary function tests were available at the start and at the end they worked in antimony. FVC, FEV1 and Tiffeneau index as the percentage of the expected value according to gender, length and age are supposed to stay unchanged over lifetime. The mean differences of FVC, FEV1 as the percentage of the expected values and Tiffeneau index between end and start of working in antimony were 3,7, 1,0 and -4,2 respectively. Only for Tiffeneau index a slight decrease was observed in antimony workers. GOT and GPT values were beyond reference compared to start in 6,7 %, respectively 23,3% of workers.

Relationship between change in pulmonary function and seniority

Table 3: Simple linear regression models with difference of pulmonary function parameters as dependent variables and seniority as independent variable.

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,174	0,136	0,039
Difference FEV1 %*	0,132	0,168	0,034
Difference Tiffeneau*	-0,151	0,061	0,061

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Figure 1: Scatter plot with regression line of difference of percentage of FVC with seniority

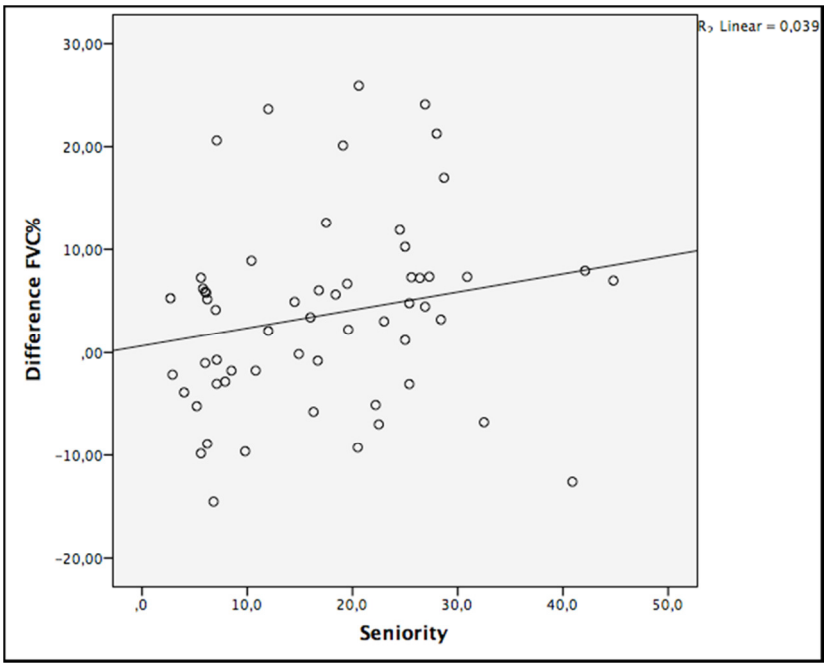


Figure 2: Scatter plot with regression line of difference of percentage of FEV1 with seniority

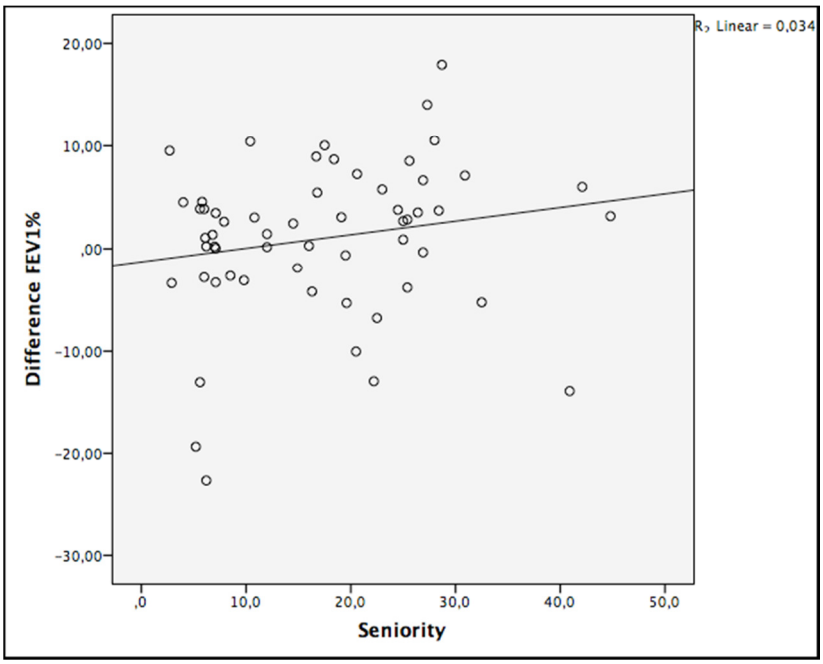
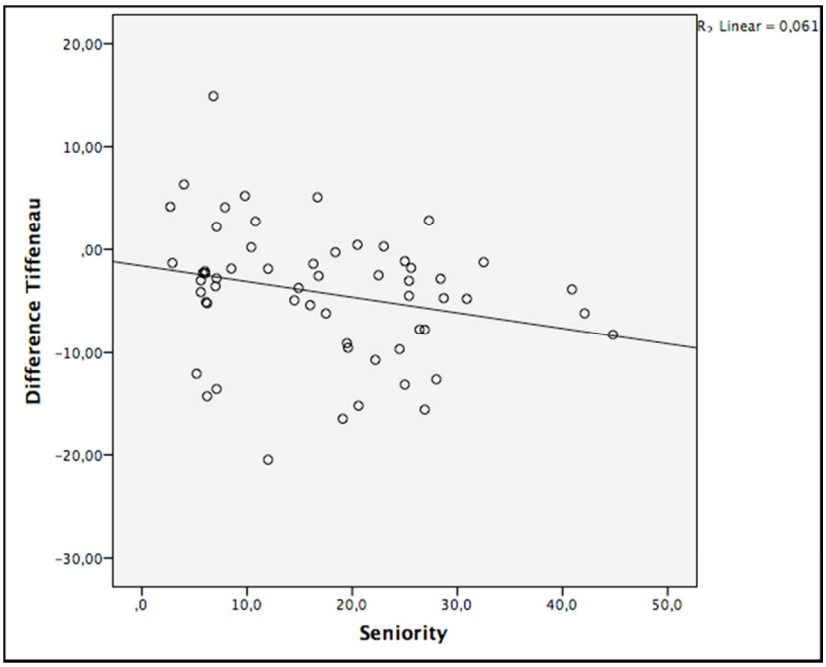


Figure 3: Scatter plot with regression line of difference of Tiffeneau index with seniority



There was a slight decrease of Tiffeneau index in relation to seniority, but this wasn't statistically significant (P> 0,05). Overall R-squared were low, the relationships between changes in pulmonary function parameters and seniority were weak.

Relationship between change in pulmonary function and seniority for smokers and non-smokers

Smokers were those workers who still smoked at the end of working in antimony and non-smokers those who never smoked or stopped.

Table 4: Simple linear regression models with difference of pulmonary function parameters as dependent variables and seniority as independent variable for smokers.

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	-0,005	0,972	0,000
Difference FEV1 %*	-0,074	0,528	0,022
Difference Tiffeneau*	-0,202	0,071	0,170

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Table 5: Simple linear regression models with difference of pulmonary function parameters as dependent variables and seniority as independent variable for non-smokers.

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,261	0,115	0,074
Difference FEV1 %*	0,234	0,101	0,079
Difference Tiffeneau*	-0,131	0,266	0,037

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Figure 4: Scatter plot with regression line of difference of percentage of FVC with seniority for smokers and non-smokers

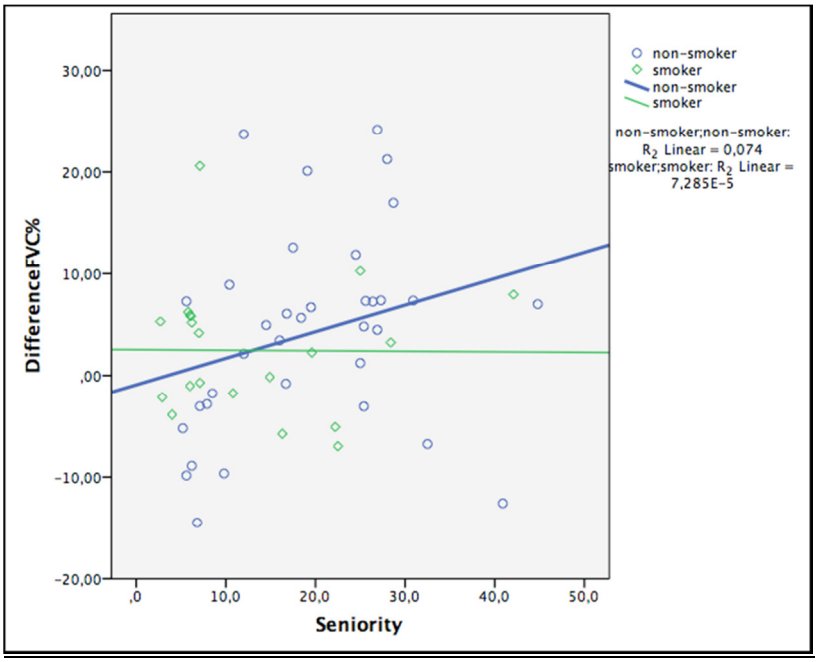


Figure 5: Scatter plot with regression line of difference of percentage of FEV1 with seniority for smokers and non-smokers

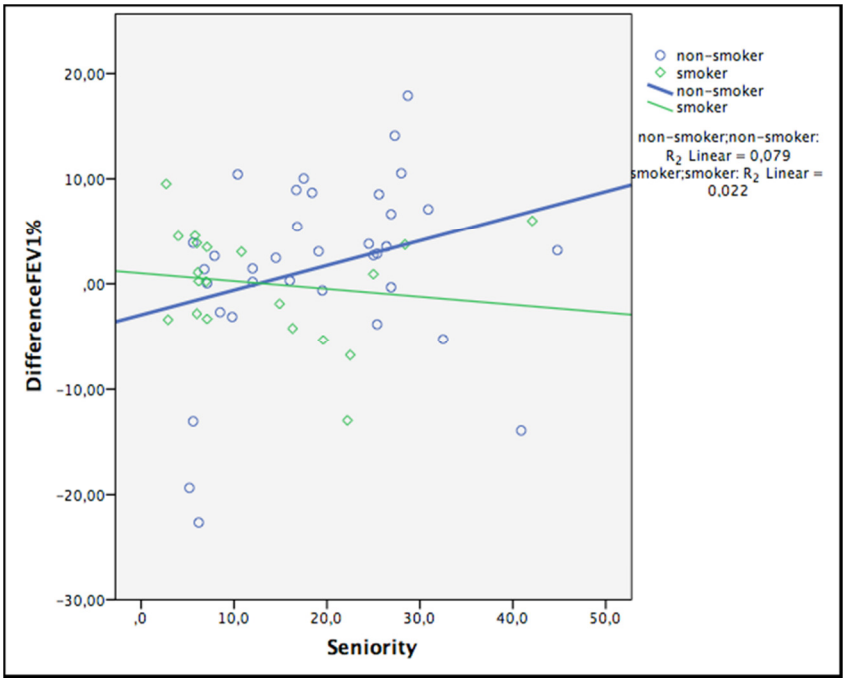
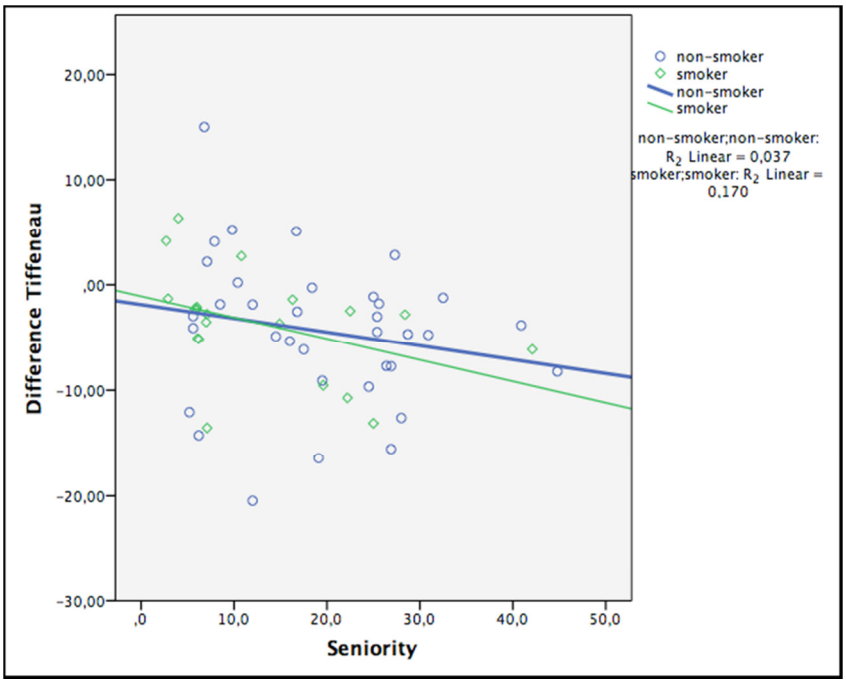


Figure 6: Scatter plot with regression line of difference of Tiffeneau index with seniority for smokers and non-smokers



After stratification in smokers and non-smokers, the decline of the Tiffeneau index in relation to seniority was more pronounced in smokers than in non-smokers. A slight decline of the percentage of FEV1 in relation to seniority was seen in smokers. These relationships weren't statistically significant ($p > 0,05$).

Relationship between change in pulmonary function and seniority for high and low exposure groups

Table 6: Simple linear regression models with difference of pulmonary function parameters as dependent variables and seniority as independent variable for the high exposure group .

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,100	0,425	0,020
Difference FEV1 %*	0,033	0,791	0,002
Difference Tiffeneau*	-0,166	0,064	0,103

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Table 7: Simple linear regression models with difference of pulmonary function parameters as dependent variables and seniority as independent variable for the low exposure group.

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,319	0,219	0,068
Difference FEV1 %*	0,288	0,097	0,120
Difference Tiffeneau*	-0,140	0,426	0,029

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Figure 7: Scatter plot with regression line of difference of percentage of FVC with seniority for the high and the low exposure group

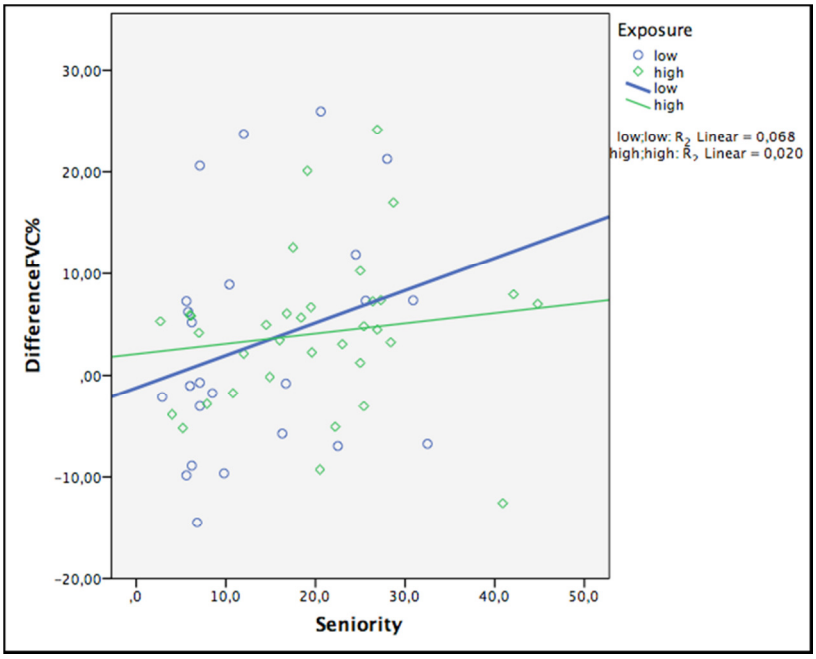


Figure 8: Scatter plot with regression line of difference of percentage of FEV1 with seniority for the high and the low exposure group

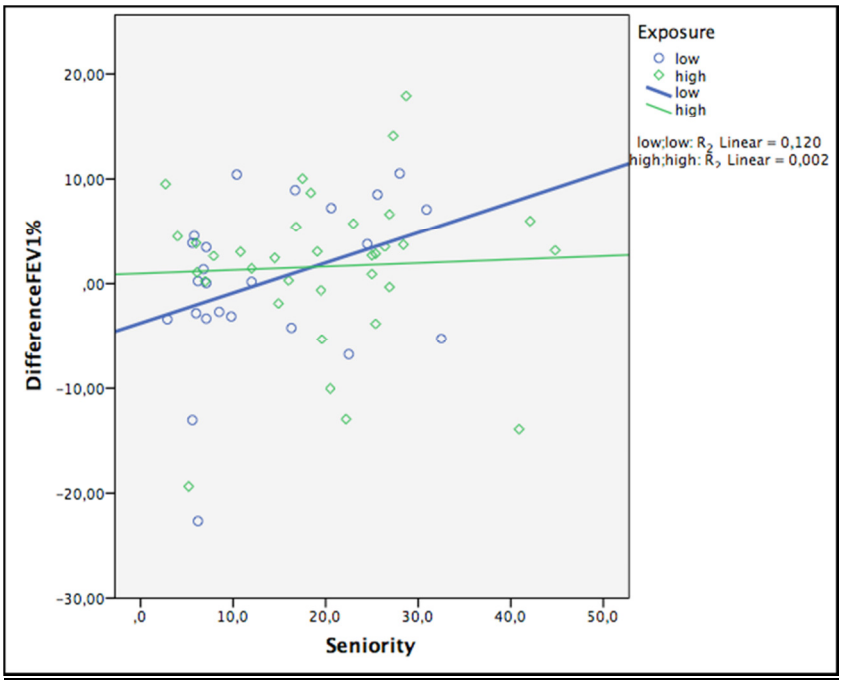
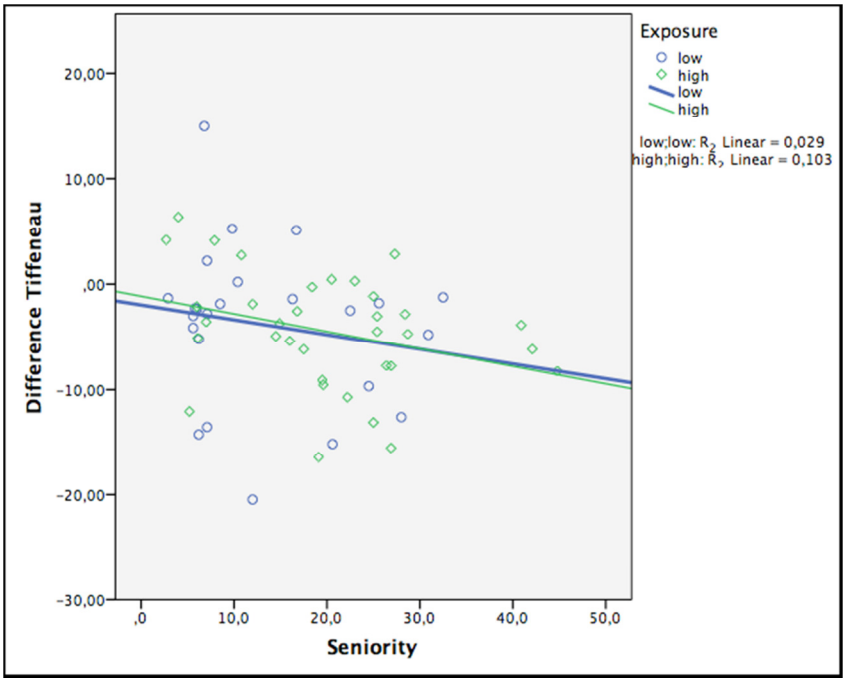


Figure 9: Scatter plot with regression line of difference of Tiffeneau index with seniority for the high and the low exposure group



The relationships between change in pulmonary function parameters and seniority weren't significantly different for the high and the low exposure group.

Relationship between change in pulmonary function and mean urinary antimony concentration

Table 8: Simple linear regression models with difference of pulmonary function parameters as dependent variables and mean urinary antimony concentration as independent variable.

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,022	0,66	0,003
Difference FEV1 %*	0,024	0,572	0,006
Difference Tiffeneau*	0,01	0,786	0,001

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Figure 10: Scatter plot with regression line of difference of percentage of FVC with mean urinary antimony concentration

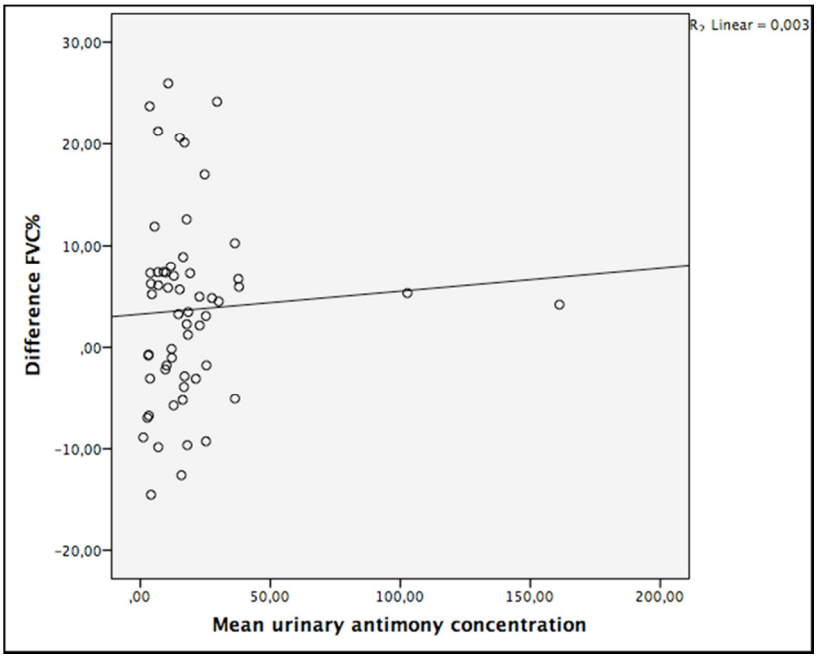


Figure 11: Scatter plot with regression line of difference of percentage of FEV1 with mean urinary antimony concentration

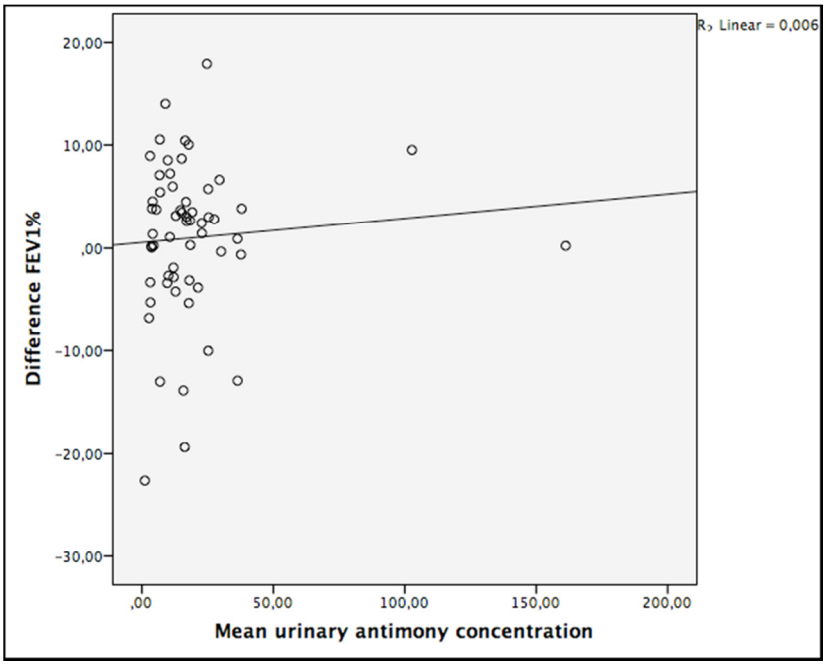
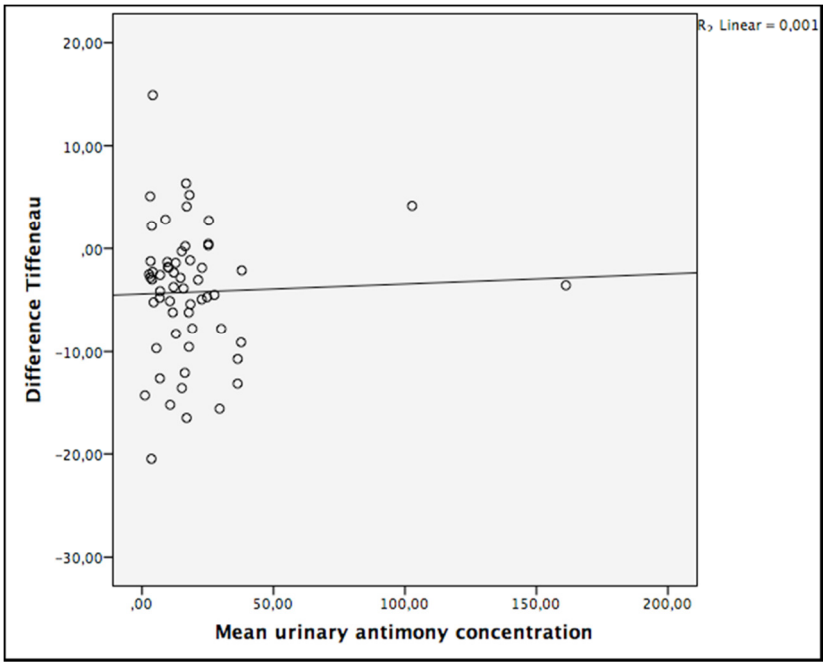


Figure 12: Scatter plot with regression line of difference of Tiffeneau index with mean urinary antimony concentration



The regressions in figure 4, 5 and 6 show 2 outliers. Because of the influence they may have on the regression models, the analyses were repeated after discarding these outliers.

Table 9: Simple linear regression models with difference of pulmonary function parameters as dependent variables and mean urinary antimony concentration **without outliers** as independent variable.

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,102	0,438	0,011
Difference FEV1 %*	0,03	0,781	0,001
Difference Tiffeneau*	-0,097	0,278	0,022

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Figure 13: Scatter plot with regression line of difference of percentage of FVC with mean urinary antimony concentration **without outliers**

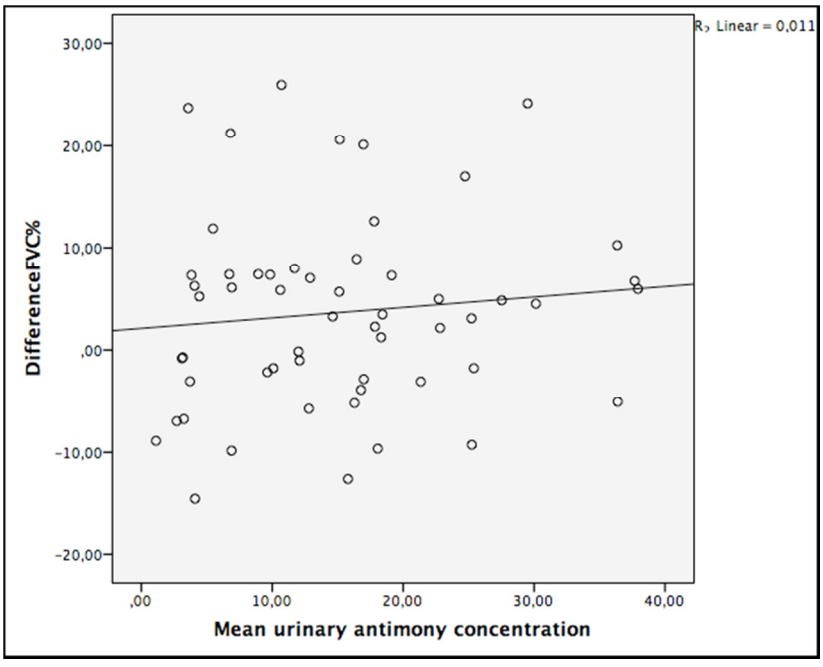


Figure 14: Scatter plot with regression line of difference of percentage of FEV1 with mean urinary antimony concentration **without outliers**

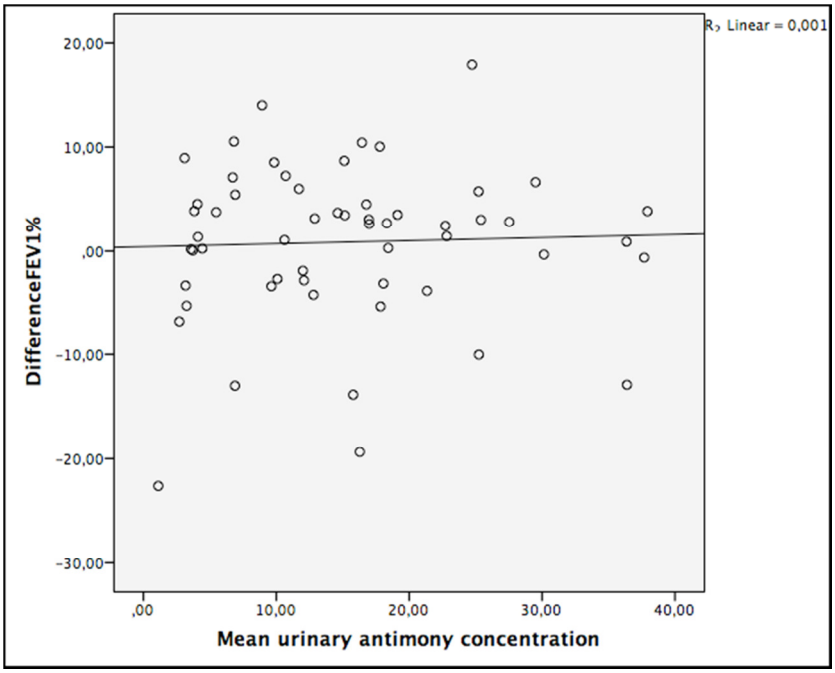
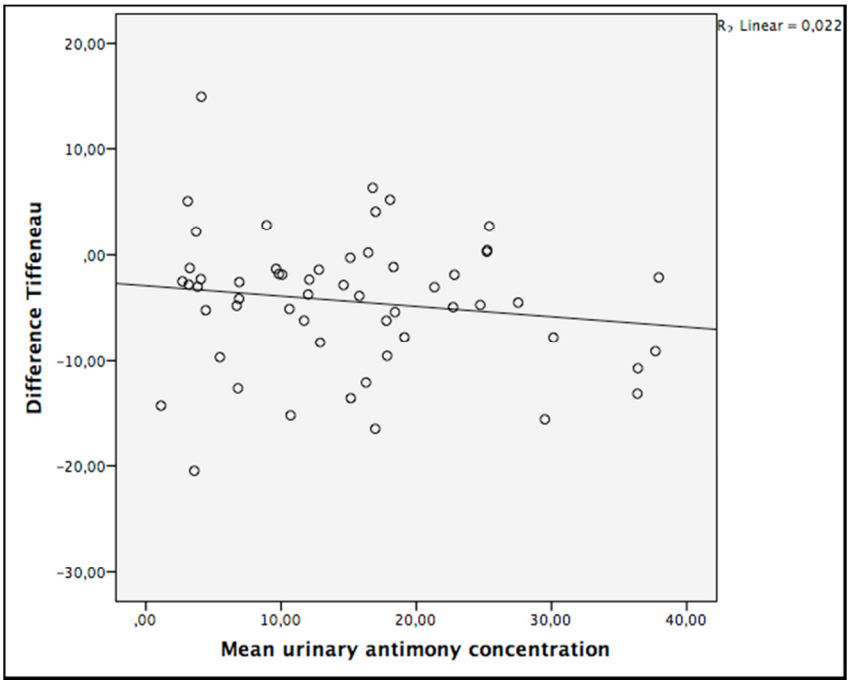


Figure 15: Scatter plot with regression line of difference of Tiffeneau index with mean urinary antimony concentration **without outliers**



There were no important relationships between changes in pulmonary function parameters and mean urinary antimony concentration. Overall R-squared were low, the relationships between changes in pulmonary function parameters and mean urinary antimony concentration were weak.

Relationship between change in pulmonary function and mean urinary antimony concentration for smokers and non-smokers

Table 10: Simple linear regression models with difference of pulmonary function parameters as dependent variables and mean urinary antimony concentration **without outliers** as independent variable for smokers

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,068	0,658	0,013
Difference FEV1 %*	-0,023	0,835	0,003
Difference Tiffeneau*	-0,128	0,254	0,081

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Table 11: Simple linear regression models with difference of pulmonary function parameters as dependent variables and mean urinary antimony concentration **without outliers** as independent variable for non-smokers

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,229	0,223	0,045
Difference FEV1 %*	0,115	0,482	0,015

Difference Tiffeneau*	-0,133	0,316	0,030

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Figure 16: Scatter plot with regression line of difference of percentage of FVC with mean urinary antimony concentration **without outliers** for smokers and non-smokers

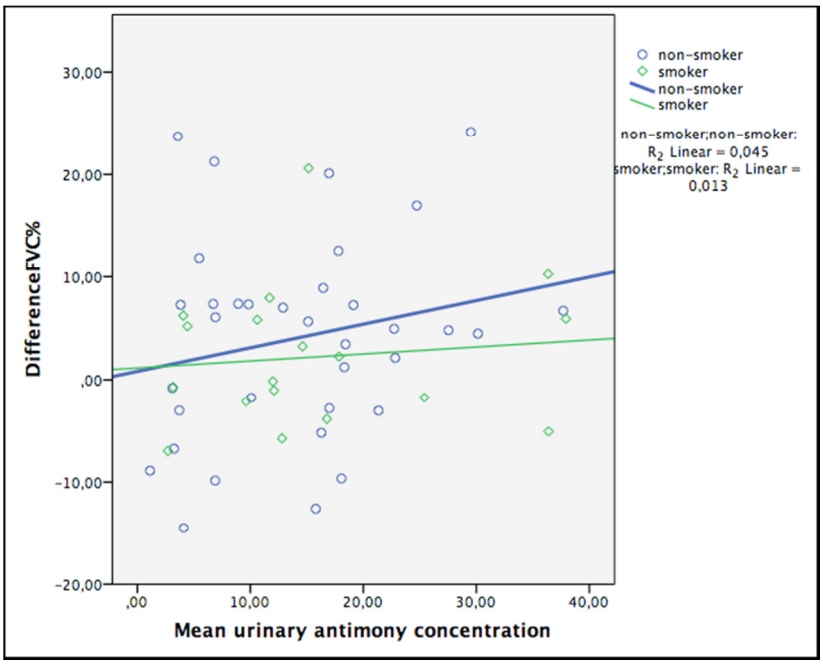


Figure 17: Scatter plot with regression line of difference of percentage of FEV1 with mean urinary antimony concentration **without outliers** for smokers and non-smokers

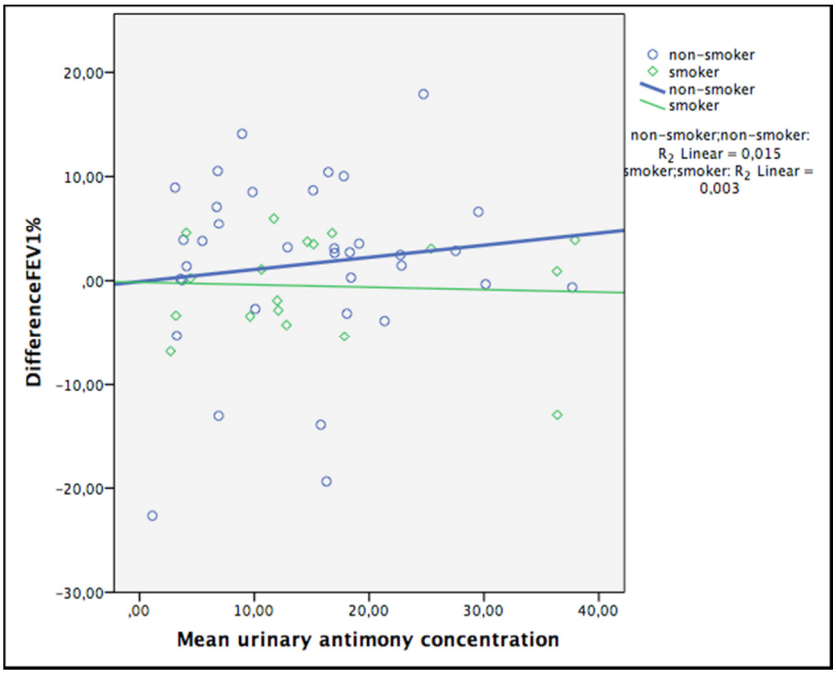
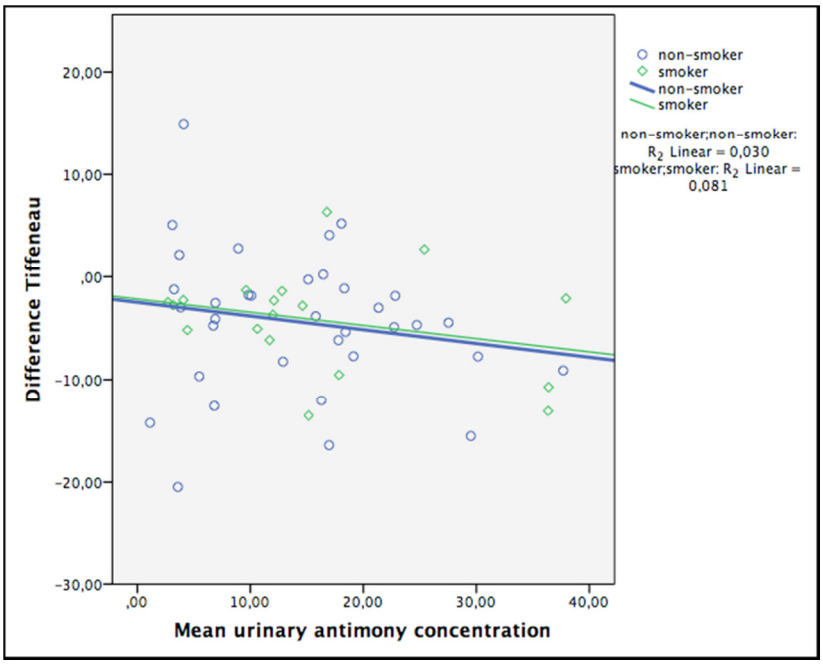


Figure 18: Scatter plot with regression line of difference of Tiffeneau index with mean urinary antimony concentration **without outliers** for smokers and non-smokers



The relationships between change in pulmonary function parameters and mean urinary antimony concentration weren't different for smokers and non-smokers.

Relationship between change in pulmonary function and mean urinary antimony concentration high and low exposure groups

Table 12: Simple linear regression models with difference of pulmonary function parameters as dependent variables and mean urinary antimony concentration **without outliers** as independent variable for the high exposure group

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,074	0,662	0,006
Difference FEV1 %*	-0,133	0,420	0,022
Difference Tiffeneau*	-0,180	0,122	0,078

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Table 13: Simple linear regression models with difference of pulmonary function parameters as dependent variables and mean urinary antimony concentration **without outliers** as independent variable for the low exposure group

Dependent variable	Unstandardized coefficient B	p	R Squared
Difference FVC %*	0,359	0,480	0,023
Difference FEV1 %*	0,391	0,251	0,059
Difference Tiffeneau*	0,103	0,763	0,004

* Difference = percentage at the end of working in antimony (or latest) – percentage at the start of working in antimony (or earliest)

Figure 19: Scatter plot with regression line of difference of percentage of FVC with mean urinary antimony concentration **without outliers** for the high and the low exposure group

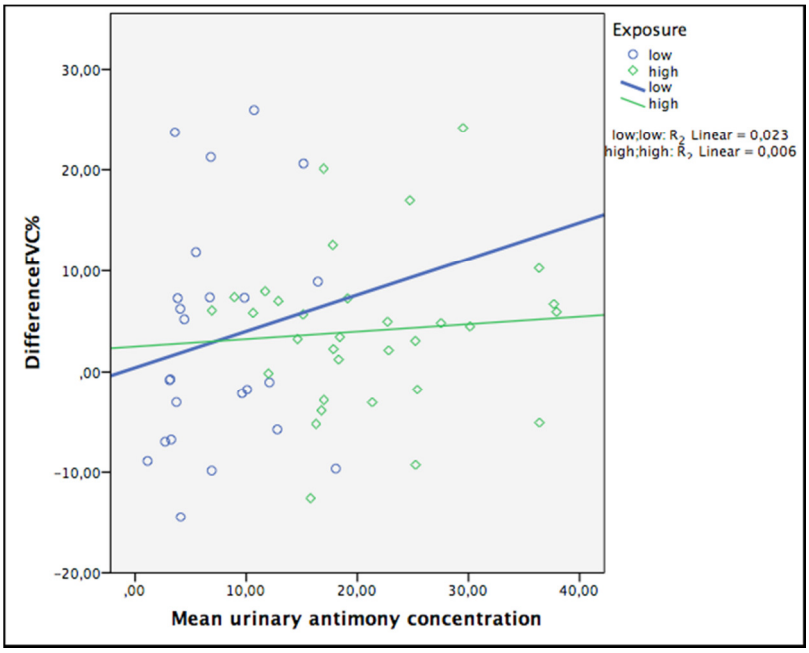


Figure 20: Scatter plot with regression line of difference of percentage of FEV1 with mean urinary antimony concentration **without outliers** for the high and the low exposure group

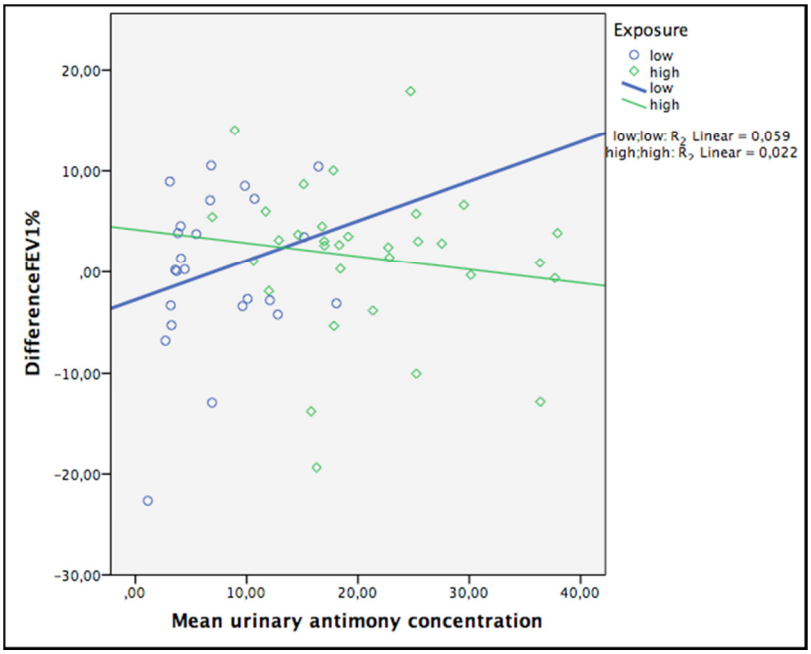
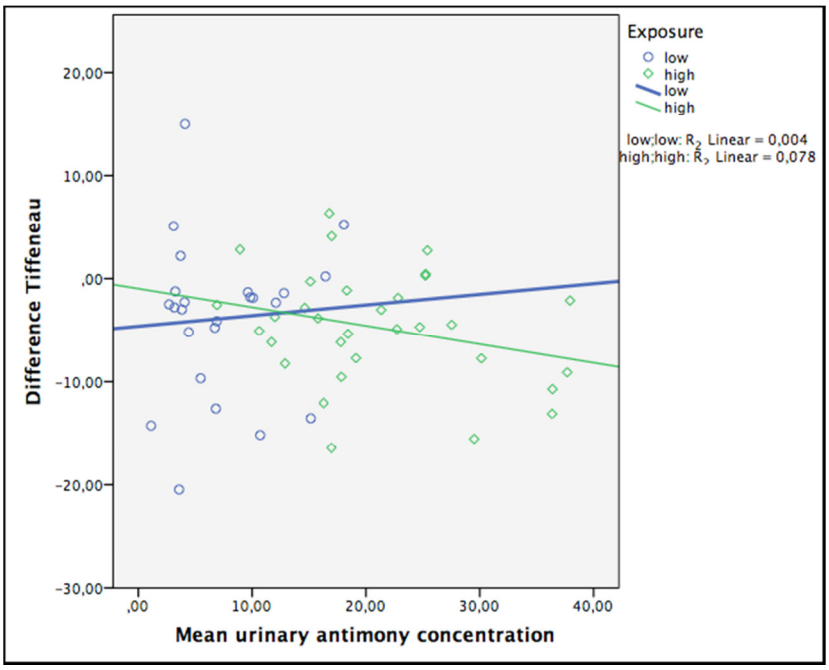


Figure 21: Scatter plot with regression line of difference of Tiffeneau index with mean urinary antimony concentration **without outliers** for the high and the low exposure group



After stratification in a high and a low exposure group to antimony, the high exposure group showed a decline of the Tiffeneau index and of the percentage of FEV1 in relation to the mean urinary antimony concentration. This decline wasn't observed in the low exposure group. These relationships weren't statistically significant.

Change in liver function according to seniority

Table 14: Cross tabulation of change of GOT and seniority

Seniority	n	% GOT not beyond reference or no change compared to start	% GOT beyond reference compared to start
< 16,5 years	30	93,3	6,7
≥ 16,5 years	30	93,3	6,7
Fisher's Exact Test 2-sided p 1,0			

Table 15: Cross tabulation of change of GPT and seniority

	n	% GPT not beyond reference or no change compared to start	% GPT beyond reference compared to start
< 16,5 years	30	83,3	16,7
≥ 16,5 years	30	70,0	30,0
Fisher's Exact Test 2-sided p 0,36			

No significant relationships between changes in GOT or GPT bloodlevel and seniority were observed.

Change in liver function according to urinary antimony concentration (high and low exposure groups)

Table 16: Cross tabulation of change of GOT and mean urinary antimony concentration

Urinary antimony concentration	n	% GOT not beyond reference or no change compared to start	% GOT beyond reference compared to start
Low exposure	26	88,5	11,5
High exposure	34	97,1	2,9
Fisher's Exact Test 2-sided p 0,307			

Table 17: Cross tabulation of change of GPT and mean urinary antimony concentration

Urinary antimony concentration	n	% GPT not beyond reference or no change compared to start	% GPT beyond reference compared to start
Low exposure	26	80,8	19,2
High exposure	34	73,5	26,5
Fisher's Exact Test 2-sided p 0,555			

No significant relationships between changes in GOT or GPT bloodlevel and high and low antimony exposure groups were observed.

References

1 Bailly R, Lauwerys R, Buchet JP et al. Experimental and human studies on antimony metabolism: their relevance for the biological monitoring of workers exposed to inorganic antimony. British Journal of Industrial Medicine 1991;48:93-97.