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Aluminium in drinking water and cognitive decline in elderly subjects: the Paquid cohort.

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Although the neurotoxicity of aluminium has been proved (1), the link between aluminium and the risk of Alzheimer's disease (AD) is still debated (2). A related hypothesis has been put forward by Birchall and Chappell (3): silicon in water could be a protective factor against aluminium toxicity.

We recently reported a significant association between the concentration of aluminium in drinking water and the incidence of dementia and AD (4). These results were based on a cohort of 3777 elderly subjects followed-up for 8 years.

In the present study we have evaluated on the Paquid cohort the association between aluminium in drinking water and the 8-year evolution of cognitive functions measured by the MMSE score, a major predictor for dementia. The study has two main methodological interests. First, the evolution of the MMSE score is not sensitive to diagnostic errors that may be present in the detection of demented or AD cases. Secondly, cognitive decline precedes by three to five years the occurrence of dementia and is less subject to competitive morbidity or mortality. In addition, this study may give insights into the influence of aluminium in normal cognitive decline and in the dementing process.

The Paquid cohort included 3,777 people aged 65 years or older at baseline, and living at home in one of the 75 randomized parishes

of the administrative areas of Gironde or Dordogne in southwestern France. Subjects were randomly selected from electoral rolls.

Subjects who agreed to participate underwent a 1-hour home interview with a specially trained psychologist. The MMSE scores were collected at the first visit in 1988-1989 and 1, 3, 5 and 8 years after the initial visit. The analyses were performed on 3401 subjects non-demented at the initial visit and for whom measurements of water were available. All these subjects completed the MMSE at least once and were included in the analysis. They have been followed-up between 0 and 8.9 years, with a mean follow-up evaluation of 5.9 years. This sample was described in the previous paper (4).

For each parish, we computed a weighted mean of all measures of aluminium and silica by using the results of chemical analyses of drinking water carried out by the sanitary administration between 1991 and 1994 (4). In order to evaluate the past exposure of subjects, the history of the water distribution network over the previous ten years (1981-1991) was evaluated.

Analyses were performed using a random effects linear regression model, including subject-specific random intercept and slope to take into account the intra-subject correlation. We also included a random intercept specific to each parish of the cohort in order to control the potential intra-parish correlation due to possibly

uncontrolled confounding factors. Since the distribution of the MMSE scores was not normal, we analysed the square root of the number of errors according to time (5). With this transformed variable, a positive coefficient indicates that the mean MMSE score decreases when the value of the covariates rises, or, for interactions with time, that the decline of the MMSE score with time is stronger for high value of the covariate. Besides the variable *time* representing the number of years after the initial visit, a binary indicator for the initial visit was introduced to account for the poor score of the subjects at the first interview. *Aluminium* was introduced as a binary variable with the threshold of 0.1 mg/l (thus, 86 subjects were considered as exposed). This threshold was already used in several studies (6) and we retained this value in our previous analysis (4). *Silica* was coded as a binary variable with the median 11.25 mg/l, as the cutoff (4). The other explanatory variables included were *age* at cohort inception, *gender*, and *educational level* in two classes: no education or primary school (ages 6 through 12 years) without diploma, and at least primary school with diploma. Parameters were estimated by the MIXED procedure of SAS software (SAS/STAT computer program, Cary, NC, SAS Institute Inc. 1999).

Table 1 presents the estimates of model parameters regarding aluminium and silica for the square root of the number of errors. Exposures to aluminium and silica interacted significantly with time. Therefore, cognitive decline with time was greater in

subjects exposed to high levels of aluminium (greater than 0.1 mg/l) and in those exposed to low levels of silica (lower than 11.25 mg/l). However, neither aluminium nor silica concentrations had any significant association with the values of the MMSE scores at inception in the cohort. As it is difficult to interpret the magnitude of the effects in our model from table 1, we have displayed in table 2 the estimated cognitive deterioration for different concentrations of aluminium and silica in drinking water and for two covariate profiles. A woman without a diploma aged 85 years, exposed to low levels of silica and not exposed to aluminium would in average lose 6.9 points on the MMSE score between the first follow-up and the 8-year follow-up; but being exposed to high levels of aluminium, she would lose 9.1 points. In this model a significant intra-parish correlation was obtained ($p=0.02$). Adjustment for occupation did not modify the results for aluminium or silica (results not shown).

When subjects diagnosed as demented during the 8-year follow-up were excluded from the analyses (253 subjects excluded), the interaction between aluminium and time was no longer significant ($p=0.67$). However, cognitive decline was still dependent on the levels of silica (silica by time, $p=0.02$).

This analysis validates our previous results which showed a link between aluminium and silica in drinking water and the risk of dementia (4). This finding was not biased by misdiagnosis. The

analysis of this cohort supports the hypothesis that aluminium concentrations in drinking water may have an effect on cognitive decline. More specifically, it suggests that when associated with a dementia process, cognitive decline with time is related to high concentrations of aluminium or low concentrations of silica in drinking water. Further work is needed to confirm these results, in particular because of the small number of subjects exposed to high concentrations of aluminium and the possibility of uncontrolled confounding factors.

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Table 1. Results of the random effects linear regression for the square root of the number of errors in the Mini-Mental State Examination (MMSE): the Paquid Study, France, 1988-1995.

Variable*	β	SE	p-value
Aluminium	-0.032	0.091	0.73
Time by aluminium	0.040	0.016	0.01
Silica	-0.012	0.036	0.73
Time by silica	-0.017	0.005	0.003

* adjusted for *time*, an indicator for the first follow-up (*indicT_0*), *age*, *time by age*, *gender*, *time by gender*, *indicT_0* by *gender*, *educational level*, *time by educational level*, *indicT_0* by *educational level*.

Table 2. Predicted differences between Mini-Mental State Examination (MMSE) scores at T8 and T1 according to levels of aluminium and silica in drinking water, for women without diploma, computed with the model of Table 1.

	Aged 65 years*	Aged 85 years*
	T8-T1	T8-T1
Aluminium (<0.1 mg/l)		
Silica (≥11.25mg/l)	-1.4	-5.9
Silica (<11.25mg/l)	-1.9	-6.9
Aluminium (≥0.1 mg/l)		
Silica (≥11.25mg/l)	-2.0	-8.1
Silica (<11.25mg/l)	-3.1	-9.1

*at cohort inception