Reply to Comment on "Environmental and Occupational Risk Factors of Amyotrophic Lateral Sclerosis: A Population-based Case-control Study"

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We much appreciate the positive comment comments and interest about our study on the environmental and occupational risk factors of amyotrophic lateral sclerosis (ALS) [1]. As correctly noted by these authors, we already acknowledged the limitations of our study they outline, including recall bias since exposure assessment relied on self-report using a questionnaire as well as the small sample size influencing the low number of exposed subjects in such categories, including the subjects working in the agricultural sector, decreasing as a consequence the statistical precision of the estimate [2].

As regards occupational exposure to lead, we also assessed the period and the duration of occupational exposures, but we did not include in our paper the corresponding estimates for the high number of non-responders and the consequent uncertainties. We are now reporting below such results: in particular analysis restricted only to subjects reporting the duration of occupational exposure to lead yielded an adjusted odds ratio (OR) of 7.48 (95% confidence interval (CI) 2.48 to 22.50), with stronger association for subjects with longer (≥20 years) duration of exposure (Table 1). [3, 4].

Based on the comment and the recent published findings on occupational solvent exposure and ALS risk, we are pleased to see the consistency of our findings with those of Dickerson et al. in the Danish population, and we strongly agree about the opportunity to further investigate this important line of research [5]. In our population, in the new analysis restricted only to subjects reporting duration of such exposure we found higher ALS risk (OR = 2.58, 95% CI 1.24-5.40) (Table 1). We also carried out an additional analysis taking into account the duration of solvent exposure, which yielded a slightly stronger association for subjects with duration ≥20 years compared with ≥10 years (Table 1).

Int. J. Environ. Res. Public Health **2020**, *x*, x

2 of 3

Table 1. Odds ratio (OR) with 95% confidence interval (CI) of ALS risk according to occupational exposure to lead and solvents and exposure duration.

Occupational exposure	Cases (y/n)	Controls (y/n)	OR [a]	OR [b]	(95% CI)
Lead					
Any duration	23/72	13/122	3.00	3.66	(1.63–8.20)
Without subjects not reporting duration	17/72	5/122	5.76	7.48	(2.48–22.50)
Duration ≥10 years	14/72	4/122	5.93	8.24	(2.44–27.82)
Duration ≥20 years	9/72	2/122	7.62	11.60	(2.29–58.81)
Solvents					
Any duration	44/51	50/85	1.47	1.46	(0.82–2.61)
Without subjects not reporting duration	27/51	19/85	2.37	2.58	(1.24–5.40)
Duration ≥10 years	20/51	16/85	2.08	2.19	(1.00–4.80)
Duration ≥20 years	11/51	9/85	2.04	2.39	(0.89–6.46)

[a] Crude model; [b] Model adjusted by sex, age, and educational attainment.

Overall, we agree about the need to take into consideration the characteristics and limitations of our study as we acknowledged in the paper, and this also with reference to the comparability of our findings with other studies and populations. In particular, the external validity of the findings of our or other studies may be influenced by the genetic background of the study participants, i.e. by the inclusion of ALS patients carrying specific gene mutations and/or the familial form of the disease, since these subjects may carry specific susceptibilities to chemicals [6, 7]. Overall, we strongly agree that the environmental risk factors of ALS, and exposure to chemicals in particular including heavy [8, 9] and selenium [10], as well as other physical and biological factors [11-14] definitely warrant further investigations, also taking into account the possible interactions between them to be assessed through advanced data analysis tools [5, 15, 16].

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Int. J. Environ. Res. Public Health **2020**, *x*, x

3 of 3

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