Reviewer’s report

Title: Pesticide exposure assessed through agricultural crop proximity and risk of amyotrophic lateral sclerosis

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Reviewer: Evelyn Talbott

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The question of whether certain environmental exposures are related to the risk of ALS is an important one as so little is presently known about the disease and its triggers. In the present investigation the authors used a matched case control study with four to one matching to consider proximity of historical and present residence to agricultural land and therefore exposures to pesticides routinely used over the years as risk factors for the disease. I believe that there are some questions that should be addressed in order to make this the best possible study for publication.

There were a reasonable number of cases (703) and surveillance and case ascertainment appears to have been exhaustive assuring a representative sample of cases to study. Four primary questions come to mind regarding the methods employed in this study:

1) The first is choice of the control group which on first read sounds reasonable; however, the issue of overmatching always comes to mind, eg. why was the control not chosen at random from the four provinces of study area instead of being matched precisely to the same province? This may have resulted in overmatching on the exposure of interest, proximity to agricultural exposure to pesticides. ? I am not sure what you do about this at this point but it should be discussed in the weaknesses and strengths section.

With regard to the exposure measure, can you say that you are confident that the residential history was captured XXX years before diagnosis, Perhaps I missed this but I ask this as the authors also indicate that the ALS disease process has an element of various forms of inflammation, oxidative stress, etc so the earlier years of exposure may be particularly important so was an effort made to capture cumulative exposures based on mobility? If not can you comment on how many of the cases and controls stayed within the one residence or is this not possible?

A timeline of exposures by residential history for cases and controls would be important.

2) Occupational exposure is also an important risk factor, was this asked as part of the study? As it may be that the risk factor, working in the adjacent agricultural location would be important to document. Please comment on availability.
3) Male versus female exposures, as women often have more home related exposures than men, please comment on a stratified analysis to the extent possible sample size wise between cases and controls.

4) A few descriptive tables would be helpful showing the age, race and gender distribution and some measure of Socioeconomic status (education, income, etc) to show the comparability distribution within cases and controls as well as a map of the four provinces.

Finally, was the rate of ALS similar in these four provinces compared to the rest of the country? In general where does Italy rank regarding the incidence rate of ALS?

With the amount of agriculture in the country, it would be helpful to have some background about the overall rate of disease and how Italy ranks say compared to the US or surrounding countries. I think the null finding is an important contribution to the literature but I believe these questions should be addressed to clarify and strengthen the findings.

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An article of importance in its field

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