Reviewer’s report

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

Version: 0 Date: 22 Mar 2017

Reviewer: Freya Kamel

Reviewer's report:

This manuscript reports a case-control study of 703 ALS patients and 2737 age- and sex-matched controls in two regions in Italy. The relationship of ALS risk to residence in proximity to agricultural land was evaluated. Little evidence of an association was observed for either residence at the time of diagnosis or historical residence. The study is large and population-based and the methods for recruiting patients and controls were good.

A major issue is exposure assessment. On the one hand, reasonable evidence indicates that individuals living in proximity to agricultural land are in fact exposed to pesticides. On the other, many features of the exposure measure used may result in substantial misclassification. First, only crops were assessed directly, and pesticide use was inferred. No information on the amounts or types of pesticides used on the land were presented, in contrast to some other studies that used residential proximity as a surrogate for exposure. Second, only data on pesticide classes were presented, but specific pesticides within classes may not have the same relationship to ALS. Third, as the authors point out, individuals living in proximity to agricultural land may be exposed occupationally as well as through proximity, but this is an ecological measure and no data on occupational exposure of individuals were available to control for potential confounding. Finally, no information on the degree of exposure were presented, for example time spent in the residence (as opposed to a workplace) or years lived in the residence; the analysis of historical exposure, although less complete, may provide some information on the latter.

Given the potential for misclassification of exposure, and the relatively small number of exposed cases in some categories, the study may not have the power to support its negative conclusion. This should be acknowledged in the Abstract and final paragraph of the Discussion, and the conclusion should be softened.

Page 5, line 39: please provide a more explicit reference for the El Escorial criteria

Page 7, lines 55 & 58: should 'filed' be 'field'?

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