Appendix I

Occupational exposures and Alzheimer´s disease.

Case-control questionnaire

Numeric values in brackets besides each answer are scores for that particular question and answer

1) selection of the cases and controls

For the cases:

1. Was the study population base sufficiently defined for the cases?

[0] No
[1] Yes

2. The cases were:

[0] Prevalent
[1] Prevalent and Incident
[2] Incident
[0] Unknown

3. The response rate among cases was:

[0] <70%
[1] 70-80%
[2] 80-90%
[3] >90%
[0] Unknown

4. Was the possible effect of selection losses for cases (not participating cases) analysed over obtained results?

[0] Selection losses were not described
[1] Selection losses were described but were not analysed
[2] Selection losses were analysed
[3] Selection losses did not exist over initially selected cases
[0] Unknown (evaluation not possible)

5. How representative were the studied cases with regard to the cases of AD in the study base?

[0] Not a random sample
[1] A random sample
[2] The entire population
[0] Unknown

For the controls:

6. Did the controls come from the same base population, this is, would have they been included in the group of cases selectable in case of having AD?

[0] No
[1] Possible, but not sure
[2] Yes

[0] Unknown (evaluation not possible)

7. Did the controls have the same exposure probability as the cases?
[0] No
[1] Possible, but not sure
[2] Yes
[0] Unknown (evaluation not possible)

8.Were the controls from the study sample representative of the study base?
[0] No
[1] Doubtful
[2] Yes
[0] Unknown (evaluation not possible)

9. Were the controls a random selection from the study base?
[0] No
[1] Possible, but not sure
[2] Yes
[0] Unknown (evaluation not possible)

10. The response rate among controls was:
[0] <70%
[1] 70-80%
[2] 80-90%
[3] >90%
[0] Unknown

11. Was the effect of selection losses for controls (not participated controls) analysed?
[0] Selection losses were not described
[1] Selection losses were described but were not analysed
[2] Selection losses were analysed
[3] Selection losses did not exist over initially selected controls
[0] Unknown (evaluation not possible)

2) Inclusion and exclusion criteria

For the cases

12. Were inclusion criteria (and exclusion criteria, if applicable) clearly described for cases?
[0] No
[1] Yes

13. The diagnostic criteria for Alzheimer´s disease (AD) was:
Note: in case of coexisting different criteria, mark them all and point the one with maximum punctuation that is applied for all the cases.

Clinical diagnosis:

[1] DSM-III-R or modified or equivalent criteria
[2] DSM-IV or modified or equivalent criteria
[2] NINCDS-ADRDA or modified or equivalent criteria
[1] ICD-9 or modified or equivalent criteria
[2] ICD-10 or modified or equivalent criteria
[1] Another type of clinical diagnosis based on standardised diagnostic protocols.
[0] Clinical diagnosis not based on standardised protocols
[3] Certain diagnosis based on autopsy.
[0] Unknown

14. In case of clinical diagnosis, the analysis included:

[1] Only cases of probable AD
[0] Also probable and possible cases of AD
[0] Unknown

For the controls

15. Were Inclusion criteria (and in its case exclusion criteria) clearly described for controls?

[0] No
[1] Yes

16. Were the same inclusion and exclusion criteria applied to cases and controls?

[0] No
[1] Yes
[0] Unknown (evaluation not possible)

3) Occupational exposure measurement

17. The information of occupational exposure used in the analysis was gathered by:

[5] Biological test
[4] Environmental test
[3] Complete questionnaire plus Job Exposure Matrix (JEM)) or evaluation of the exposure by at least one expert o hygienist.
[2] Complete questionnaire (it includes occupational history and it is designed to recall exposure to specific agents)
[1] Questionnaire not complete (not designed to recall exposures to specific agents)
[2] Registers or other indirect sources of information plus job exposure matrix or evaluation of the exposure by at least one expert o hygienist.
[0] Registers or other indirect sources only.
[0] Not sufficiently described.

18. ¿Was information about occupational exposure recalled in the same way for cases and controls, this is, was the type of measuring instrument the same?

[0] No
[1] Yes

19. Were there assessed exposures previous to the onset of AD in the cases?
Note: The onset of AD is defined as the date which informant relates the first symptom related to dementia.

[0] No
[1] Yes, without specifying
[2] Yes, and they are also at least one year before the diagnosis of AD.
[0] Unknown

20. Information about occupational exposures was recalled:

[0] Retrospectively (after onset of AD in cases)
[1] Before onset of AD in cases
[0] Unknown

21. Did people interviewed know the study hypothesis?. This is, did they know that the aim of the study was to identify risk factors for AD?:

[1] No
[0] Yes
[0] Unknown

22. Was the interviewer blindness respect to the case-control status of the interviewed person?

[0] No
[1] Yes
[0] Unknown

23. Did interviewers know the study hypothesis?. This is, did they Know that the aim of the study was to identify risk factors for AD?:

[0] No
[1] Yes
[0] Unknown

24. Was the same interviewer used for cases and controls, for the matching case-control couples at least?

[0] No
[1] Yes
[0] Unknown

25. Were the interviews independent, it is, without being surrogate informant with index subject (case or control) at the moment of the interview?

[0] No
[1] Yes
[0] Unknown

26. Were symmetrical sources of information compared in the analysis?

[1] Yes, information from relatives (or proxies) was compared for cases and controls
[2] Yes, information obtained from the cases was compared with information obtained from the controls [0] No, information from relatives (or proxies) from cases was compared with information obtained from the controls

27. Data are collected for an agreement study between sources of information?

[0] No
[1] Yes
[0] Unknown

28. If yes, is information sufficient to validate information obtained from surrogate informants?

[0] No
[1] Yes
[0] Unknown

4) control of confounding variables

29. Was confounding controlled in the study design or in the analysis of potential confounding variables?

[0] No
[1] Yes
[0] Unknown

30. Confounding variables accounted for and methods for control of confounding

[2] Age
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Sex
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Race
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Education
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Alcohol consumption
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Socio-economical status
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Other (open answer)

5) precision of the study

31. ¿Is information about precision of the study included in the statistical analysis (p values, Confidence Intervals...?

[0] No
[1] Yes

32. Was statistical power of the study analysed?

[0] No
[1] Yes

6) internal and external validity of the study

33. Internal validity of results

[0] Low
[2] Medium
[4] High
[0] Not possible to assess

34. External validity of results

[0] Low
[2] Medium
[4] High
[0] Not possible to assess

7) general assessment of the presence or absence of biases

35. Presence of selection bias:

[0] Highly probable
[2] Probable

[4] Possible
[6] Improbable
[8] Highly improbable
[2] Not possible to assess

If probable or highly probable, bias:

[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

36. Presence of disease misclassification:

[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable

If probable or highly probable, misclassification would be non-differential?:

[x] Highly probable
[x] Probable
[x] Improbable
[x] Highly improbable

If probable or highly probable, bias:

[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

37. Presence of exposure misclassification:

[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable

If probable or highly probable, misclassification would be non-differential?:

[x] Highly probable
[x] Probable
[x] Improbable
[x] Highly improbable

If probable or highly probable, bias:

[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

38. Presence of bias arising from use of surrogate informants:

[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable
[2] Not possible to assess
[0] It does not apply (registry-based information)

If probable or highly probable, bias:

[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

39. Confounding bias:

[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable

If probable or highly probable, bias:

[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

Appendix II

Occupational exposures and Alzheimer´s disease.

Cohort questionnaire

Prospective cohort studies

Numeric values in brackets besides each answer are scores for that particular question and answer

1) definition and follow-up of the cohort:

1. Were characteristics of the cohort (origin, type of cohort, data collection...) sufficiently described?

[2] Yes
[1] Doubtful
[0] No

2. Were inclusion and exclusion criteria of people of the cohort sufficiently described?

[2] Yes
[1] Doubtful (fail to reach a conclusion)
[0] No

3. The ascertainment period (follow up period) is::

[x] Retrospective
[x] Prospective
[x] Both directions
[x] Unknown

4. The INITIAL response rate at the moment when cohort was defined was?

[0] <70%
[1] 70-80%
[2] 80-90%
[3] >90%
[0] Unknown

5. Was the follow up for all people of the cohort sufficiently described?

[0] No
[1] Yes
[0] Unknown

6. ¿Was the same effort in the follow up for all the people of the cohort done?

[0] No
[1] Yes
[0] Unknown

7. Is the time of follow up sufficient to develop AD?

[0] No, is less than 5 years.
[1] Yes, at least is for 5 years.
[2] Yes, at least is for 10 years.
[0] Unknown

2) follow-up losses

8. ¿Were follow up losses sufficiently described??

[2] Yes
[1] Doubtful (fail to reach a conclusion)
[0] No

9. The follow up losses were:

[3] <10%
[2] 10-20%
[1] 20-30%
[0] >30%
[0] Unknown

10. Were follow up losses analysed?

[0] Follow up losses were not described
[1] Follow up losses were described but were not analysed
[2] Follow up losses were described and analysed
[3] Follow up losses did not exist
[0] Unknown (evaluation not possible)

11. Were losses to follow up independent of exposure?

[2] Yes
[1] Doubtful (fail to reach a conclusion)
[0] No

12. Was the possible effect of the healthy worker bias analysed?

[0] It was not described
[1] It was described but were not analysed
[2] It was described and analysed
[3] This type of bias is highly improbable due to study characteristics.

3) measurement of disease incidence

13. The initial screening criteria in order to exclude people with dementia in the cohort were:

[1] They were clearly described, and were based on validated cognitive test (MMSE or 3MS)
[0] They were not clearly described.

14. The diagnostic criteria for Alzheimer´s disease (AD) was:

Clinical diagnosis:

[1] DSM-III-R or modified or equivalent criteria
[2] DSM-IV or modified or equivalent criteria
[2] NINCDS-ADRDA or modified or equivalent criteria
[1] ICD-9 or modified or equivalent criteria
[2] ICD-10 or modified or equivalent criteria
[1] Another type of clinical diagnosis based on standardised diagnostic protocols.
[0] Clinical diagnosis not based on standardised protocols
[3] Certain diagnosis based on autopsy.

[0] It wasn´t given in the article

15. In case of clinical diagnosis, the analysis included:

[1] Only cases of probable AD
[0] Also probable and possible cases of AD
[0] Unknown

16. Was the same effort to assess information about disease done for all the people of the cohort? This is, was the intensity of search for AD independent of exposure status?

[1] Yes
[0] No
[0] Unknown

4) occupational exposure measurement

17. The information of occupational exposure used in the analysis was gathered by:

[5] Biological test
[4] Environmental test
[3] Complete questionnaire plus Job Exposure Matrix (JEM)) or evaluation of the exposure by at least one expert o hygienist.
[2] Complete questionnaire (it includes occupational history and it is designed to recall exposure to specific agents)
[1] Questionnaire, not complete (not designed to recall exposures to specific agents)
[2] Registers or other indirect sources of information plus job exposure matrix or evaluation of the exposure by at least one expert o hygienist.
[0] Registers or other indirect sources only.
[0] It wasn´t sufficiently described.

18. Was the same effort to assess information about exposure done for all the people of the cohort?.

[1] Yes
[0] No
[0] Unknown

19. Was the fact that assessed exposures were previous to the onset of AD guaranteed?
Note: The onset of AD is defined as the date which informant relates the first symptom related to dementia.

[0] No
[1] Yes, without specifying
[2] Yes, and they are also at least one year before the diagnosis of AD
[0] Unknown

20. Did people interviewed know the study hypothesis? This is, did they know that the aim of the study was to identify risk factors for AD?:

[1] No
[0] Yes
[0] Unknown

5) control of confounding variables

21. Was confounding controlled in the study design or in the analysis of potential confounding variables?

[0] No
[1] Yes

[0] Unknown

22. Confounding variables accounted for and methods for control of confounding

[2] Age
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Sex
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Race
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Education
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Alcohol consumption
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Socio-economical status
[ ] Matching
[ ] Restriction techniques
[ ] Multivariate analysis

[1] Other (open answer)

6) precision of the study

23. ¿Is information about precision of the study included in the statistical analysis (p values, Confidence Intervals...?
[0] No
[1] Yes

24. Was statistical power of the study analysed?
[0] No
[1] Yes

7) internal and external validity

25. Internal validity of results

[0] Low
[2] Medium
[4] High
[0] Not possible to assess

26. External validity of results

[0] Low
[2] Medium
[4] High
[0] Not possible to assess

8) general assessment of the presence or absence of biases

27. Presence of selection bias:

[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable
[2] Not possible to assess

If probable or highly probable, bias:
[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

28. Presence of disease misclassification:
[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable

If probable or highly probable, misclassification would be non-differential?:
[x] Highly probable
[x] Probable
[x] Improbable
[x] Highly improbable

If probable or highly probable, bias:
[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

29. Presence of exposure misclassification:
[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable

If probable or highly probable, misclassification would be non-differential?:
[x] Highly probable
[x] Probable
[x] Improbable
[x] Highly improbable

If probable or highly probable, bias:
[x] Would increase the association
[x] Would decrease the association
[x] Doubtful (fail to reach a conclusion)

30. Confounding bias:
[0] Highly probable
[2] Probable
[4] Possible
[6] Improbable
[8] Highly improbable

If probable or highly probable, bias:
[x] Would increase the association
[x] Would decrease the association

[x] Doubtful (fail to reach a conclusion)

Retrospective Cohort Studies:

(questionnaire adapted to the only one selected article of this type, a restrospective mortality study in which a expose cohort was identified and compared to general population).

1) definition and follow-up of the cohort:

1. Were characteristics of the cohort (origin, type of cohort, data collection...) sufficiently described?

[2] Yes
[1] Doubtful
[0] No

2. Were inclusion and exclusion criteria of people of the cohort sufficiently described?

[2] Yes
[1] Doubtful (fail to reach a conclusion)
[0] No

3. The ascertainment period (follow up period) is::

[x] Retrospective
[x] Prospective
[x] Both directions
[x] Unknown

4. Was the follow up for all people of the cohort sufficiently described?

[0] No
[1] Yes
[0] Unknown

5. Is the time of follow up sufficient to develop AD?

[0] No, is less than 5 years.
[1] Yes, at least is for 5 years.
[2] Yes, at least is for 10 years.
[0] Unknown

6. Were secondary sources used to collect data sufficiently described? (register, clinical records):

[4] Yes
[2] Doubtful
[0] No

7. Does information about validity of the secondary sources of information exist?

[4] Yes
[2] Doubtful
[0] No

8. Losses at the initial moment when cohort was identified were…

[3] <10%
[2] 10-20%
[1] 20-30%
[0] >30%
[0] Unknown

2) follow up losses:

9. ¿Were follow up losses sufficiently described??
[2] Yes
[1] Doubtful (fail to reach a conclusion)
[0] No

10. The follow up losses were:
[3] <10%
[2] 10-20%
[1] 20-30%
[0] >30%
[0] Unknown

11. Were follow up losses analysed?
[0] Follow up losses were not described
[1] Follow up losses were described but were not analysed
[2] Follow up losses were described and analysed
[3] Follow up losses did not exist
[0] Unknown (evaluation not possible)

12. Was the possible effect of the healthy worker bias analyzed over obtained results?
[0] It was not described
[1] It was described but were not analysed
[2] It was described and analysed
[3] This type of bias is highly improbable due to study characteristics.

3) measurement of disease incidence

13. The diagnostic criteria for Alzheimer´s disease (AD) was:

Clinical diagnosis:
[1] DSM-III-R or modified or equivalent criteria
[2] DSM-IV or modified or equivalent criteria
[2] NINCDS-ADRDA or modified or equivalent criteria
[1] ICD-9 or modified or equivalent criteria
[2] ICD-10 or modified or equivalent criteria
[1] Another type of clinical diagnosis based on standardised diagnostic protocols.
[0] Clinical diagnosis not based on standardised protocols
[3] Certain diagnosis based on autopsy.
[0] It wasn´t given in the article

14. In case of clinical diagnosis, the analysis included:

[1] Only cases of probable AD
[0] Also probable and possible cases of AD
[0] Unknown

15. In case of death certificates, besides identification of people who died of AD like the primary cause of death, was an effort done to identify also the AD in other sections of the records?
[1] Yes
[0] No
[0] Unknown

4) occupational exposure measurement

16. The information of occupational exposure used in the analysis was gathered by:

[5] Biological test
[4] Environmental test
[3] Complete questionnaire plus Job Exposure Matrix (JEM)) or evaluation of the exposure by at least one expert o hygienist.
[2] Complete questionnaire (it includes occupational history and it is designed to recall exposure to specific agents)
[1] Questionnaire, not complete (not designed to recall exposures to specific agents)
[2] Registers or other indirect sources of information plus job exposure matrix or evaluation of the exposure by at least one expert o hygienist.
[0] Registers or other indirect sources only.
[0] It wasn´t sufficiently described.

17. Was the fact that assessed exposures were previous to the onset of AD guaranteed?
Note: The onset of AD is defined as the date which informant relates the first symptom related to dementia.
[0] No
[1] Yes, without specifying
[2] Yes, and they are also at least one year before the diagnosis of AD.
[0] Unknown

18. In order to guarantee that assessed exposures were previous to the onset of AD: Do methods in the design or in data analysis exist,?
[1] Yes
[0] No
[0] Unknown

It continues with the prospective cohort questionnaire, item number 21, section 5) control of confounding variables until the end.