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Cover page

Type of article

Original article

Title

Exposure to farm animals and lung cancer risk in the AGRICAN cohort

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Footnote page

Abbreviations

HR, hazard ratio; CI, confidence interval; AGRICAN, Agriculture and Cancer Study; AHS, Agricultural Health Study; MSA, Mutualité Sociale Agricole; ADK, adenocarcinoma; SCC, squamous cell carcinoma.

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Running head

Exposure to farm animals and lung cancer risk

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24 Manuscript word count: 3951 words

25 Number of tables: 5 tables

26 Number of figures: 2 figures

27 Number of Web tables: 4 tables

28

29 Abstract

30 Epidemiological studies have found lower risks of lung cancer in farmers. However, little is
31 known about the types of agricultural activities concerned. In the AGRICAN cohort, we assessed
32 the relationship between animal farming and lung cancer by investigating the type of animals,
33 tasks and timing of exposure. Analyses included 170,834 participants from the AGRICAN
34 cohort. Incident lung cancers were identified through linkage with cancer registries from
35 enrollment (2005–2007) to 2011. A Cox model, adjusted for pack-years of cigarette smoking,
36 was used to calculate hazard ratios and 95% confidence intervals. Lung cancer risk was inversely
37 related to duration of exposure to cattle (≥ 40 years: hazard ratio=0.60, 95% confidence interval:
38 0.41, 0.89, P for trend=0.04) and to horse farming (≥ 20 years: hazard ratio=0.64, 95% confidence
39 interval: 0.35, 1.17, P for trend=0.08), especially for adenocarcinomas, but not with poultry or
40 pig farming. More pronounced decreased risks were reported among individuals who had cared
41 for animals, undertaken milking and who had been exposed to cattle in infancy. Our study
42 provides strong evidence of an inverse association between cattle and horse farming, and lung
43 cancer. Further research is warranted to identify the etiologic protective agents and biological
44 mechanisms.

45

46 Abstract word count: 194 words

47 **Key words:** animal; lung cancer; farming; occupational exposure; cohort

48

49

50 As in several other occupational settings (cotton-textile (1) and incineration (2) industries,
51 occupations with contact with water-based metalworking fluids (3)), most epidemiologic studies
52 in farming have found lower rates of lung cancer compared to the general population (4-6), as
53 supported by large cohorts of farmers from incidence data in the United States (Agricultural
54 Health Study, AHS) (7) and in Nordic European countries (8) and from mortality data in France
55 (Agriculture and Cancer study, AGRICAN) (9). Risks were decreased by 40% to 60% but the
56 estimates were not controlled for smoking, which is known to be less prevalent in farm owners
57 than in the general population (7, 9, 10). Few studies considered the types of farming associated
58 with lung cancer risk (11-22). Some of them did not control for individual smoking data (14-16,
59 19-22) or had a low statistical power to analyze specific farming activities (12-14, 18). Studies
60 were based on job title (11-15, 18, 20, 21) or on farm characteristics (16, 17, 19, 22) as a proxy
61 for individual exposure. Most studies reported lower risks for some types of animal farming (13-
62 22). The AHS cohort found lower lung cancer incidence in poultry farming and large-scale
63 livestock farming, after adjustment for smoking (17). Only one small study (23 deaths by lung
64 cancer) investigated the relation between duration of exposure of one type of animal farming and
65 lung cancer mortality, without adjustment for smoking, and found a lower mortality in long-term
66 exposed dairy farmers (14). Their updated analysis adjusted for smoking also suggested the
67 reversibility of the protective effect (18). Analyses by histological subtypes have been seldom
68 performed. After adjustment for smoking, Mastrangelo et al. found similar results between
69 squamous cell carcinomas (22 deaths) and other or unknown lung carcinomas (23 deaths) (18).
70 To date, no study has attempted to identify which tasks in animal farming could be particularly
71 protective and if early exposure to a farm environment (*in utero*, childhood) might play a role in

72 protection, as shown for other respiratory outcomes (allergic sensitization and atopic diseases)
73 (23).

74 In several occupational settings including farming, lower risks of lung cancer have been
75 previously attributed to potential exposure to endotoxins (lipopolysaccharide), a component of
76 the outer membrane of gram-negative bacteria present in organic dust (24). High levels of
77 exposure to dusts and endotoxins were measured in animal farming especially among swine and
78 poultry farming (25). Some proposed anti-carcinogenic mechanisms involve endotoxin-induced
79 inflammation leading to immune system upregulation, but they remain poorly understood and
80 evidence from human studies is limited (24). On the other hand, some recent studies did not
81 support the protective effect of endotoxins in the occurrence of lung cancer. Checkoway et al.
82 reported a possible promotion of lung cancer with increasing time since first exposure to
83 endotoxins in the cotton textile industry (26). Pooled analyses of population-based case-control
84 studies on lung cancer did not report lower risks for high exposure to endotoxins as assessed with
85 a job-exposure matrix, and they even reported increased risks of lung cancer among livestock
86 and dairy farmers (27-28). These contradictory findings reflect our lack of knowledge about the
87 possible protective effects of certain farming activities against lung cancer. A better
88 understanding of which agricultural activities, tasks and temporal courses of exposure are
89 associated with lower lung cancer risk could help in identifying protective agents and the period
90 of susceptibility to risk.

91 The prospective cohort AGRICAN offers the opportunity to evaluate the risk of lung cancer,
92 overall and by subtypes, associated with individual exposure to different types of animal farming,
93 considering periods of exposure (childhood, adulthood) and the type of tasks performed and
94 taking smoking history into account.

95

96 METHODS

97 Study population

98 The AGRICAN cohort is a prospective cohort of 181,842 active and retired agricultural subjects
99 (9). Individuals were included if they were at least 18 years old, affiliated for at least three years
100 to the *Mutualité Sociale Agricole* (MSA), the French health insurance scheme in agriculture,
101 living in one of the 11 French areas covered by a population-based cancer registry at the time of
102 enrollment (*Côte-d'Or, Doubs, Gironde, Isère, Loire-Atlantique, Manche, Bas-Rhin, Haut-Rhin,*
103 *Somme, Tarn and Vendée*) and returned a self-administered questionnaire for enrollment (1
104 November 2005–31 December 2007). The cohort was mainly composed of participants who had
105 already worked on a farm during their lifetime (87%, referred hereafter as farming population),
106 but also some participants who had never been exposed to a farming environment (such as some
107 office workers, referred hereafter as non-farming population) (12%). The study protocol was
108 reviewed and approved by the Advisory Committee on Information Processing for Health
109 Research (CCTIRS) (Reference: 01.148) and by the French data protection authority (CNIL)
110 (Reference: 05.1292). Place of residence and affiliation to the health insurance scheme are
111 checked annually by the MSA files to identify cohort members being lost to follow-up. Vital
112 status and causes of death were obtained annually using the MSA files and the French National
113 Death Index. For identification of primary incident lung tumours, the AGRICAN database is
114 matched every two years to all the general cancer registries covered by the study areas. Lung
115 cancer cases were coded according to the International Classification of Diseases for Oncology,
116 3rd edition (ICD-O-3 code: C34). We identified 768 incident lung cancer cases (619 male, 149

117 female) with a mean age at diagnosis of 72.6 years (± 10.4 years). Cases were grouped according
118 to morphology codes: 38.8% of cases were adenocarcinomas (ADK) and 28.8% were squamous
119 cell carcinomas (SCC). Other subtypes were small cell lung carcinomas (10.3%), large cell
120 carcinomas (4.3%), other carcinomas (9.9%) and cases with unknown histological types (8.2%).
121 One lung sarcoma was excluded from the analyses.

122
123 Exposure data and potential confounders

124 The enrollment questionnaire collected a complete job calendar with a lifetime history of
125 agricultural activities and information whether participants lived on a farm during their first year
126 of life (with indication of the type of animals and crops on the farm and duration of living in that
127 place). Detailed information on individual exposure was available for five types of animals:
128 cattle, poultry, pigs, horses and sheep and/or goats, and the main tasks performed for each type of
129 animal (animal care, use of insecticide, milking and disinfection of milking equipment (for cattle
130 and sheep/goats), disinfection of barns (for cattle, sheep/goats, poultry and pigs)), with year of
131 beginning and end for each task, and the number of animals concerned for care, milking and
132 insecticide use.

133 Other collected data included demographic characteristics, smoking (age at beginning, duration,
134 intensity: number of cigarettes, cigars and pipes per day), diet, some respiratory conditions (self-
135 reported diagnosis of chronic bronchitis or emphysema), weight and height.

136 Statistical analyses

137 For the present analysis, exclusion criteria were: living in an area with no registry for lung
138 tumours (*Côte-d'Or*) (n=10,875); suffering from lung cancer before the date of enrollment and

139 after the date of implementation of the most recent registry in the study area (1st January 2005)
140 (n=87) and with no follow-up (n=45). Individuals were followed from the date of enrollment
141 (date of reception of the questionnaire) until incident lung cancer diagnosis, date of death, date
142 they left the study areas covered by the cohort, date they were lost to or ended follow-up (31
143 December 2011), whichever came first. We fitted Cox proportional hazards models to estimate
144 hazard ratios (HR) and 95% confidence intervals (95% CI), adjusting for smoking history (never
145 smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, smoking of pipes and/or
146 cigars), with attained age as the underlying time metric.

147 For each type of animal, we assessed associations between lung cancer (overall and separately for
148 ADK and SCC) and each component of exposure (ever/never, duration of work, number of
149 animals, tasks). We considered two reference groups. The first, used in all the main analyses,
150 consisted of farmers not exposed to the types of animals studied. The second consisted of the
151 non-farming population. Associations were mutually adjusted for other animal exposures
152 associated with lung cancer risk in our analyses. We used categorical variables for duration of
153 exposure (10-year interval) and number of animals (quartiles). Tests for trend used median of
154 categories as a continuous variable in the model. We additionally assessed the role of
155 occupational exposure to cattle in stratified analyses by smoking (ever/never smoked), childhood
156 exposure to cattle farming in the first year of life (yes/no), and by number of years since last
157 exposure (≤5 years, 6–10 years, 11–15 years, 16–20 years, 21–25 years and ≥ 26 years).

158 To assess the robustness of associations, we performed complementary analyses adjusted for
159 other potential confounders (gender, education, body mass index, daily consumption of fruits and
160 self-reported diagnosis of chronic bronchitis or emphysema, pesticide use on crops) and using
161 other smoking metrics (duration: non-smoker, <10, 10-19, 20-29, 30-39, ≥40 years and smoking

162 status combined with tertiles of number of pack-years of cigarette smoking: never smoker, former
163 smoker and pack-years<5, former smoker and pack-years [5,15[, former smoker and pack-years
164 ≥ 15 , current smoker and pack-years <7, current smoker and pack-years [7,17[, current smoker
165 and pack-years ≥ 17). We also performed multiple imputation by chained equations (MICE) to
166 handle incomplete information (50 imputations) on smoking (missing data: 12%), job history
167 (incomplete data: 13%) and occupational exposure to cattle (ever worked in cattle farming:
168 missing data: 14%, duration of work in cattle farming: missing data: 34%) (29). Estimates of
169 parameters and variances were pooled using multiple imputation rules (30). Statistical analyses
170 were performed using SAS (version 9.3) and for multiple imputation STATA (version 13.1).

171

172 RESULTS

173 The population was mainly composed of men (54%). The median age at enrollment was 67 years.
174 Half of the population had a level of education lower than middle school. Half of the men had
175 ever smoked during their life while only 13% of women had ever smoked (Table 1). Associations
176 between smoking history (smoking status and number of pack-years of cigarette smoking) and
177 lung cancer incidence (overall, ADK and SCC) are available in Web Table 1. Smoking history
178 was significantly associated with increased lung cancer risk, for both men and women, with
179 higher risks among men for SCC than ADK. People ever worked on a farm were more often men,
180 older, less educated, never smokers, overweight or obese, born on a farm and with a higher
181 prevalence of non-cancer respiratory diseases (Table 1).

182 The most frequent type of animals raised was cattle (78% of farmers). Median duration of work
183 was higher in cattle and poultry farming. The median numbers of animals were three (for horses),
184 35 to 45 (for pig, poultry and cattle) and 50 (for sheep/goats). Care for animals was performed by

185 74% of farmers in poultry farming to 88% in cattle farming. Almost 80% of cattle farmers
186 performed milking (vs. 35% for sheep and/or goats). Insecticides on animals were used by 16%
187 of horse farmers (men: 17%, women: 12%) to 36% of cattle farmers (men: 51%, women: 16%)
188 (Table 2).

189 **Cattle farming**

190 After adjustment for smoking, occupational exposure to cattle was significantly associated with
191 an overall reduced lung cancer risk (HR=0.72, 95% CI: 0.58, 0.90) with a significant linear
192 inverse relationship with duration of exposure to cattle (P for trend=0.04), compared to farmers
193 not exposed to cattle. The deficit was more pronounced for ADK (≥ 40 years: HR=0.50, 95% CI:
194 0.26, 0.97, P for trend<0.01) than for SCC (≥ 40 years: HR=0.70, 95% CI: 0.36, 1.37, P for
195 trend=0.18). The number of cattle was not significantly associated with lung cancer risk after
196 adjustment for smoking and duration of exposure to cattle (Table 3). Lower risks associated with
197 exposure to cattle were more pronounced among non-smokers (HR=0.39, 95% CI: 0.25, 0.62)
198 than smokers (HR=0.75, 95% CI: 0.59, 0.96, P for interaction=0.01). We found a lower risk for
199 longer duration of work with cattle among non-smokers (≥ 40 years: HR=0.25, 95% CI: 0.12,
200 0.56, P for trend<0.0001) than among smokers (≥ 40 years: HR=0.59, 95% CI: 0.40, 0.87, P for
201 trend<0.001, P for interaction=0.24) (Table 4). Inverse associations with exposure to cattle and
202 overall lung cancer risk were slightly less pronounced and not statistically significant when
203 compared to the non-farming population of the cohort. Whatever the reference group (farming or
204 non-farming), associations with adenocarcinoma risk were however of the same magnitude.
205 Inverse relationships with duration of cattle farming remained significant for overall lung cancer
206 risk and for adenocarcinomas (Web Table 2). Adjustment for other potential confounders did not
207 substantially modify the associations between duration of exposure to cattle and overall lung
208 cancer risk (≥ 40 years: H=0.73, 95% CI: 0.47, 1.15, P for trend=0.04) and ADK (≥ 40 years:

209 HR=0.59, 95% CI: 0.28, 1.25, *P* for trend=0.03). Analyses using multiple imputation did not
210 provide substantial changes in prevalence of exposure to cattle and confirmed the inverse
211 relationship between duration of cattle farming and lung cancer risk (Web Table 3).

212 **Exposure to other types of animals**

213 We found a lower lung cancer risk associated with exposure to horses (≥ 20 years: HR=0.64, 95%
214 CI: 0.35, 1.17, *P* for trend=0.08), after adjustment for smoking and duration of exposure to cattle.

215 There was a significant strong inverse relation between increasing duration of exposure to horses
216 and lung ADK (≥ 10 years: HR=0.38, 95% CI: 0.15, 0.97, *P* for trend=0.03) (Table 3).

217 Associations between duration of horse farming and ADK remained unchanged, although non-
218 significant, compared to the non-farming population (Web Table 2).

219 Non-significant increased risks of lung cancer were observed for poultry and pig farming and
220 only for SCC for sheep or goats farming. We did not report significant exposure-relationships
221 with duration for these three types of animal farming. We observed significant increased risk
222 between lung cancer and number of animals only for pig farming (≥ 50 pigs: HR=1.69, 95% CI:
223 1.05, 2.73; *P* for trend=0.03), after adjustment for smoking and duration of exposure to cattle and
224 horses (Web Table 4).

225 **Associations between tasks and lung cancer risk**

226 The five tasks performed by farmers who raised cattle were inversely related to lung cancer risk,
227 but only for ADK (Table 5). Lower ADK risks were observed among those performing only care
228 (HR=0.58, 95% CI: 0.31, 1.10) or only milking (HR=0.54, 95% CI: 0.23, 1.27) or both
229 (HR=0.62, 95% CI: 0.39, 1.00). Interestingly, lung cancer risk was increased with use of
230 insecticides on cattle among those not performing care for animals or milking, overall (HR=2.71,
231 95% CI: 1.19, 6.18) and for both subtypes (data not shown). No substantial change in estimates
232 was observed after adjustment for pesticide use on crops (overall lung cancer risk: HR=2.87, 95%

233 CI: 1.16, 7.12). A decreased ADK risk was observed among farmers who provided care for
234 horses (HR=0.65, 95% CI: 0.41, 1.03) and for sheep and/or goats (HR=0.56, 95% CI: 0.30, 1.08),
235 after adjustment for cattle exposure. No clear association was found with specific tasks in poultry
236 and pig farming, apart from an increased risk for SCC associated with insecticide use on pigs
237 (Table 5).

238 **Role of exposure to cattle during early life**

239 Decreased risk of lung cancer was observed only among farmers who had been exposed to cattle
240 both in their first year of life and in their occupational life (HR=0.64, 95% CI: 0.49, 0.84,
241 compared to other farmers who had never been exposed to cattle in childhood and in their
242 occupational life (Figure 1, part A). No significant trend was observed between duration of
243 occupational exposure to cattle and lung cancer risk among those without early exposure to cattle
244 (P -trend=0.35), contrary to farmers who did (P -trend<0.0001) (Figure 1, part B).

245 **Role of time since cessation of occupational exposure to cattle**

246 Whatever the time since last exposure to cattle, decreased risks of lung cancer (HR=0.48 to 0.63)
247 were observed in relation to occupational exposure to cattle, except for participants who had
248 worked less than 20 years and stopped more than 26 years before enrollment (Figure 2).

249

250

251 DISCUSSION

252

253 This analysis in the AGRICAN cohort provides evidence of an inverse association between lung
254 cancer and duration of exposure to cattle. This inverse relationship was restricted to ADK, was
255 still present long after cessation of exposure and found only in those born on a farm with cattle,
256 after taking smoking history into account. Some tasks (care for animals and milking) were
257 associated with a greater decrease in risk. Interestingly and in contrast, insecticide use on cattle
258 increased the lung cancer risk whatever the subtypes of cancer. Decreased risks of
259 adenocarcinomas were also suggested in horse and sheep/goat farming with an inverse relation
260 with duration of work only in horse farming. Slight increased risks were observed for poultry and
261 pig farming, with a significant increased risk among pig farmers raising more than 50 pigs.

262 Our study has some strengths. First, the prospective design with collected information before
263 diagnosis based on almost 800 primary incident cases through linkage to population-based cancer
264 registries limits the differential information bias. Second, the good quality of follow-up of this
265 cohort (less than 1% of the participants lost to follow-up for cancer incidence) limits selection
266 bias. Our results, relying on an average follow-up time of 5 years, need however to be replicated
267 with longer duration of follow-up. Third, we controlled for smoking history. Associations
268 between smoking history and lung cancer risk (overall and by subtypes) were in line with
269 estimates from pooled analyses of population-based case-control studies (31) and estimates from
270 the AHS cohort (32). These smoking data allowed us to adjust or stratify our analyses on
271 different metrics of active smoking without any changes in association observed. Moreover, a
272 decreased risk seemed to be more pronounced among never smokers. Fourth, adjustment for
273 other collected potential confounders (level of education, BMI, history of chronic respiratory

274 diseases, consumption of fruits, use of pesticides on crops) did not change the results. Fifth,
275 missing information was a matter of concern particularly for the duration of farming activities.
276 However, the prevalence of exposures and associations between exposure to cattle and lung
277 cancer risk did not change after using an accurate method for imputation (29). Sixth, the
278 availability of years of beginning and ending exposures allowed us to take into account latency
279 without significant changes in the results. Seventh, since we created our cohort thanks to the
280 MSA which includes all people working in the field of agriculture, we also had a non-farming
281 population as reference category. Thus, lower risks associated to cattle farming did not seem to
282 be totally driven by potential high-risk exposure in the reference farming population as inverse
283 associations were also reported when compared to the non-farming population.

284 Few studies have estimated associations between lung cancer and some particular types of
285 farming (11-22). Some of them were large epidemiologic studies (15-17, 19-22) and based on
286 incidence data (11-13, 16, 17, 22). However, a few studies controlled for individual smoking data
287 (11-13, 17, 18). The prospective AHS cohort of North Carolina and Iowa farmers found a
288 decreased risk of lung cancer incidence associated with poultry (HR=0.6, 95% CI: 0.4, 1.0) and
289 among farmers raising more than 1000 animals (HR=0.5, 95% CI: 0.3–1.0; *P* for trend=0.04)
290 after adjusting for smoking (17). Working in dairy cattle was associated with a decreased risk
291 among men only in France (13), but with an increased risk among men in Germany (11).
292 Moreover, increased risks were observed with beef cattle farming in New Zealand (12) and
293 among animal keepers in Germany (11). Most studies in the literature did not investigate the role
294 of duration of exposure, except a small historical cohort of dairy cattle farmers in Italy that found
295 a decreased, but reversible, risk with longer duration of exposure and an increased number of
296 dairy cattle (14, 18). In Finland, lung cancer incidence was lower among dairy farmers continuing
297 this farming activity, compared to the general population, but less pronounced and statistically

298 non-significant among those who had changed to another type of farm production, suggesting the
299 reversibility of the potential protection. However, associations were not adjusted for smoking and
300 dairy farmers who had quit farming had still a lower lung cancer incidence than the general
301 population (22). Contrary to Mastrangelo's findings, exposure to cattle was still associated with a
302 decrease in risk several decades after cessation of exposure in our analyses, and we did not find
303 any inverse association with the number of cattle. Exposure to endotoxins has been proposed as a
304 potential explanation for the inverse associations found in the literature. The number of cattle has
305 not been strongly related to levels of exposure to organic dust and endotoxins which were
306 measured in a few field studies in dairy cattle farming (25). Levels of exposure to dusts and
307 endotoxins in animal farming might be much higher in poultry and pig farming than in cattle or
308 horse farming (25, 33). On the contrary, in our analyses we found lower lung cancer risks in
309 cattle and horse farming and increased risks associated with pig and poultry farming, statistically
310 significant among those raised a high number of pigs. The determinants of exposure to dusts and
311 endotoxins have not been extensively studied. They could include some tasks in cattle farming
312 (handling of feed and seeds in barns, distribution of bedding and type of bedding, milking) and
313 stable characteristics (type of slurry systems, type of milking installation) (25, 34). Whereas no
314 study to date has investigated the role of specific tasks on lung cancer risk, we found that care for
315 cattle and milking were associated with lower risks of lung cancer. From the enrollment
316 questionnaire, we could not disentangle the role of all tasks included under the heading "care for
317 animals" (feeding, distribution of bedding, use of some veterinary products). However, we found
318 an increased risk with insecticide use on cattle among farmers not performing care or milking,
319 which has received very little attention among farmers, even if some insecticides used heavily on
320 crops are also used on cattle like organochlorines (lindane), organophosphates (diazinon) and
321 pyrethroids (permethrin). The AHS cohort did not report any significant association between lung

322 cancer and permethrin use on animals (32). Our findings suggestive of lower risks in horses and
323 sheep and/or goat farming were not reported in previous studies and need to be confirmed.

324
325 Our results also suggest that exposure in early life could play a role in the occurrence of lung
326 cancer in farmers, in combination with occupational exposure. Indeed, the decrease in risk was
327 more pronounced in farmers who lived on a farm with cattle during the first year of life.
328 Interestingly, early exposure to a farm environment (*in utero* and/or during the first year of life)
329 has been shown to be inversely associated with allergic sensitization and atopic diseases through
330 exposure to endotoxins and/or other components of organic dusts such as fungal spores, glucans
331 or indicators of the diversity of microbial exposure, which were inversely related to asthma
332 among children living on a farm (23, 35).

333
334 This prospective cohort enables us to confirm some assumptions (lower risk in cattle farming,
335 including in dairy farming), to disconfirm others (reversibility of inverse associations, lower risk
336 in pig and poultry farming), and to formulate new ones (tasks of care and milking in cattle
337 farming inversely related to lung cancer risk, lower risk in horse farming, potentially protective
338 exposure in infancy, more pronounced decreased risks for adenocarcinomas, increased risk
339 associated with insecticide use on cattle).

340 Understanding the reason for the lower risk of lung cancer in farmers, which is observed
341 independently of smoking habits, could provide important clues to the etiology of this disease
342 and help for prevention. Biological mechanisms, including immunological pathways, possibly
343 related to exposure to endotoxins, need to be further elucidated. Our results suggest that the
344 farming environment appears to encompass various components that act in opposite directions:

345 some could reduce the risk while others like pesticides could increase it. The challenge for future
346 studies will be to disentangle these effects and to understand their underlying mechanisms.

347

348

ACKNOWLEDGMENTS

349 Author affiliations : INSERM, UMR 1086 Cancers et Préventions, Caen, France (Séverine Tual,
350 Clémentine Lemarchand, Mathilde Boulanger, Anne-Valérie Guizard, Bénédicte Clin, Pierre
351 Lebailly) ; Université de Caen Normandie, Caen, France (Séverine Tual, Clémentine
352 Lemarchand, Mathilde Boulanger, Bénédicte Clin, Pierre Lebailly) ; Centre de Lutte Contre le
353 Cancer François Baclesse, Caen, France (Séverine Tual, Clémentine Lemarchand, Anne-Valérie
354 Guizard, Pierre Lebailly) ; CHU de Caen, Service de Pathologie professionnelle, Caen, France
355 (Mathilde Boulanger, Bénédicte Clin) ; CHU de Besançon, Besançon, France (Jean-Charles
356 Dalphin) ; UMR-CNRS 6249 Chrono Environnement (Jean-Charles Dalphin) ; Cancer Research
357 UK Cancer Survival Group, London School of Hygiene and Tropical Medicine, London, United
358 Kingdom (Bernard Rachet) ; Caisse Centrale de la Mutualité Sociale Agricole, Echelon National
359 Santé Sécurité au travail, Bagnole, France (Elisabeth Marcotullio) ; Registre des cancers du Bas-
360 Rhin, Faculté de médecine, EA3430, Université de Strasbourg, Strasbourg, France (Michel
361 Velten) ; Registre général des Tumeurs du Calvados, Caen, France (Anne-Valérie Guizard) ;
362 EPICENE team, ISPED, Centre Inserm U1219, Bordeaux Population Health Research Center,
363 University of Bordeaux, Bordeaux, France (Isabelle Baldi) ; CHU de Bordeaux, Service de
364 Médecine du Travail, Bordeaux, France (Isabelle Baldi).

365 This work was supported by the *Ligue Contre le Cancer (Nationale and Comités du Calvados, de*
366 *l'Orne, de la Manche, du Maine et Loire et de Paris)*, the *Mutualité Sociale Agricole (caisse*
367 *centrale et caisses des Alpes du Nord, de l'Alsace, de Bourgogne, des Côtes Normandes, de*

368 *Franche Comté, de Gironde, de Loire Atlantique–Vendée, de Midi Pyrénées Nord, de la*
369 *Picardie*), the *Fondation de France* (Mr Edouard Serres), the *Agence Nationale de Sécurité*
370 *Sanitaire de l’Alimentation, de l’Environnement et du Travail* (within the call for projects 2005,
371 2006 and 2010 of the program «*Environnement Santé Travail* » of ANSES, with funding from
372 l’ONEMA in support of the Ecophyto 2018 plan), the *Institut National du Cancer* [grant number
373 InCA 8422], the *Association pour la Recherche sur le Cancer* [grant number ARC 02–010], the
374 *Conseil Régional de Basse-Normandie*, the *Institut National de Médecine Agricole*, the *Centre*
375 *François Baclesse*. Bernard Rachet was funded by the *Conseil Régional de Basse-Normandie* and
376 the European Regional Development Fund.

377 The authors thank S Deant, N Levêque-Morlais, M Niez, S Perrier, and V Tribouillard for
378 processing data from the enrollment questionnaire and C Gaultier, AS Lacauve, C Meyer and E
379 Niez for technical assistance. E Wavelet (*MSA Loire Atlantique–Vendée*), M Gagey (*Caisse*
380 *Centrale MSA*), M Delanoë (*MSA Midi Pyrénées Nord*), P Herbrecht (*MSA Alsace*), T Busquet
381 (*MSA Gironde*), JJ Laplante (*MSA Franche Comté*), D Lenoir (*MSA Bourgogne*), P Pouzet (*MSA*
382 *Côtes Normandes*), A Paumier (*MSA Picardie*), E Rigaud (*Caisse Centrale MSA*), JM
383 Thibaudier (*MSA Alpes du Nord*), who are members of the steering committee of the AGRICAN
384 cohort, and the registries in the following departments: *Doubs, Gironde, Isère, Loire–Atlantique–*
385 *Vendée, Manche, Bas–Rhin, Haut–Rhin, Somme, Tarn*. The authors also thank the *Fédération des*
386 *Registres de Cancers Bas–Normand*, gynecological tumors in *Côte–d’Or*, hematological
387 malignancies in *Gironde, Côte–d’Or* and *Basse-Normandie*, digestive tumors in *Côte–d’Or*, and
388 central nervous system tumors in *Gironde*.

389 Conflict of interest: none declared.

390

391 References

- 392 1 Astrakianakis G, Seixas NS, Ray R, et al. Lung cancer risk among female textile workers
393 exposed to endotoxin. *J Natl Cancer Inst.* 2007;99(5):357–364.
- 394 2 Rapiti E, Sperati A, Fano V, et al. Mortality among workers at municipal waste incinerators
395 in Rome: a retrospective cohort study. *Am J Ind Med.* 1997;31(5):659–661.
- 396 3 Schroeder JC, Tolbert PE, Eisen EA, et al. Mortality studies of machining fluid exposure in
397 the automobile industry. IV: A case-control study of lung cancer. *Am J Ind Med.*
398 1997;31(5):525–533.
- 399 4 Blair A, Zahm SH, Pearce NE, et al. Clues to cancer etiology from studies of farmers.
400 *Scand J Work Environ Health.* 1992;18(4):209–215.
- 401 5 Acquavella J, Olsen G, Cole P, et al. 1998. Cancer among farmers: a meta-analysis. *Ann*
402 *Epidemiol* 1998;8(1):64-74.
- 403 6 Blair A, Dosemeci M, Heinemen EF. Cancer and other causes of death among male and
404 female farmers from twenty-three states. *Am J Ind Med.* 1993;23(5):729-742.
- 405 7 Koutros S, Alavanja MC, Lubin JH, et al. An update of cancer incidence in the
406 Agricultural Health Study. *J Occup Environ Med.* 2010;52(11):1098–1105.
- 407 8 Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer - follow-up of 15 million
408 people in five Nordic countries. *Acta Oncol.* 2009;48(5):646-790.
- 409 9 Levêque–Morlais N, Tual S, Clin B, et al. The AGRiculture and CANcer (AGRICAN)
410 cohort study: enrollment and causes of death for the 2005–2009 period. *Int Arch Occup*
411 *Environ Health.* 2015;88(1):61–73.
- 412 10 Blair A, Freeman LB. Epidemiologic studies in agricultural populations: observations and
413 future directions. *J Agromedicine.* 2009;14(2):125–131.
- 414 11 Brüske–Hohlfeld I, Mohner M, Pohlabein H, et al. Occupational lung cancer risk for men in
415 Germany: results from a pooled case–control study. *Am J Epidemiol.* 2000;151(4):384–395.
- 416 12 Corbin M, McLean D, Mannelje A, et al. Lung cancer and occupation: A New Zealand
417 cancer registry–based case–control study. *Am J Ind Med.* 2011;54(2):89–101.
- 418 13 Guida F. *Occupational exposure to mineral wools and risk of lung cancer: the icare case-*
419 *control study* [dissertation]. Paris, France : University of Paris-Sud; 2012.
- 420 14 Mastrangelo G, Marzia V, Marcer G. Reduced lung cancer mortality in dairy farmers: is
421 endotoxin exposure the key factor? *Am J Ind Med.* 1996;30(5):601–609.

- 422 15 Morrison HI, Krewski D, Riedel D, et al. Cancer risks from occupational exposure to
423 agricultural chemicals in male Canadian farm operators. *J Epidemiol Biostat.* 1997;2:105–
424 120.
- 425 16 Pukkala E, Notkola V. Cancer incidence among Finnish farmers, 1979–93. *Cancer Causes*
426 *Control.* 1997;8(1):25–33.
- 427 17 Beane Freeman LE, Deroos AJ, Koutros S, et al. Poultry and livestock exposure and cancer
428 risk among farmers in the agricultural health study. *Cancer Causes Control.*
429 2012;23(5):663–670.
- 430 18 Mastrangelo G, Grange JM, Fadda E, et al. Lung Cancer Risk: Effect of Dairy Farming and
431 the Consequence of Removing that Occupational Exposure. *Am J Epidemiol.* 2005;
432 161(11):1037–1046.
- 433 19 Blair A, Sandler DP, Tarone R, et al. Mortality among participants in the agricultural health
434 study. *Ann Epidemiol.* 2005;15(4):279–285.
435
- 436 20 Lange JH, Mastrangelo G, Fedeli U, et al. Endotoxin exposure and lung cancer mortality by
437 type of farming: is there a hidden dose–response relationship? *Ann Agric Environ Med.*
438 2003;10(2):229–232.
439
- 440 21 Reif J, Pearce N, Fraser J. Cancer risks in New Zealand farmers. *Int J Epidemiol.*
441 1989;18(4):768–774.
442
- 443 22 Laakkonen A, Pukkala E. Cancer incidence among Finnish farmers, 1995–2005. *Scand J*
444 *Work Environ Health.* 2008;34(1):73–79.
- 445 23 Schuijs MJ, Willart MA, Vergote K, et al. Farm dust and endotoxin protect against allergy
446 through A20 induction in lung epithelial cells. *Science.* 2015;349(6252):1106–1110.
- 447 24 Lundin JI, Checkoway H. Endotoxin and cancer. *Environ Health Perspect.*
448 2009;117(9):1344–1350.
- 449 25 Basinas I, Sigsgaard T, Kromhout H, et al. A comprehensive review of levels and
450 determinants of personal exposure to dust and endotoxin in livestock farming. *J Expo Sci*
451 *Environ Epidemiol.* 2015;25(2):123–137.
- 452 26 Checkoway H, Lundin JI, Costello S, et al. Possible pro–carcinogenic association of
453 endotoxin on lung cancer among Shanghai women textile workers. *Br J Cancer.*
454 2014;111(3):603–607.
- 455 27 Peters S, Kromhout H, Olsson AC, et al. Occupational exposure to organic dust increases
456 lung cancer risk in the general population. *Thorax.* 2012;67(2):111–116.

- 457 28 Mastrangelo G, Rylander R, Cegolon L, et al. Lung cancer risk in subjects exposed to
458 organic dust: an unexpected and surprising story. *Thorax*. 2012;67(12):1112; author reply
459 1112-1113.
- 460 29 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and
461 guidance for practice. *Stat Med*. 2011;30(4):377–399.
- 462 30 Rubin DB. *Multiple Imputation for Non-response in Surveys* 1987. John Wiley & Sons:
463 New York.
- 464
- 465 31 Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer--relative risk
466 estimates for the major histological types from a pooled analysis of case-control studies. *Int*
467 *J Cancer*. 2012;131(5):1210-1219.
- 468
- 469 32 Alavanja MC, Dosemeci M, Samanic C, et al. Pesticides and lung cancer risk in the
470 agricultural health study cohort. *Am J Epidemiol*. 2004;160(9):876–885.
- 471
- 472 33 Samadi S, Wouters IM, Houben R, et al. Exposure to inhalable dust, endotoxins, beta(1-
473 >3)-glucans, and airborne microorganisms in horse stables. *Ann Occup Hyg*.
474 2009;53(6):595–603.
- 475
- 476 34 Basinas I, Sigsgaard T, Erlandsen M, et al. Exposure-affecting factors of dairy farmers'
477 exposure to inhalable dust and endotoxin. *Ann Occup Hyg*. 2014;58(6):707–723.
- 478
- 479 35 Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and
480 childhood asthma. *N Engl J Med*. 2011;364(8):701–709.
- 481

Table 1. General Characteristics of Study Population at Enrollment, AGRICAN, 2005-2007

	All n=170,834	Farming population n=128,387	Non-farming population n=17,528
Gender, % of men	54.2	56.1	49.8
Age, years			
	Q2 (Q1–Q3)	67 (53–76)	68 (55–77)
Education ^a , %			57 (45–66)
	Middle school or less	50.4	55.4
	High school	40.0	37.7
	More than high school	9.6	6.9
	Missing	(7.4)	
Pack–years of cigarette smoking ^a , %			
	Non-smokers	65.9	67.8
	<20	22.5	21.2
	20–39	6.3	6.0
	40–59	1.4	1.4
	≥60	0.6	0.5
	Other smokers, pipes and/or cigars	3.3	3.1
	Missing	(12.1)	
Body Mass Index, kg/m ^{2a} , %			
	<18.5	1.5	1.3
	18.5–24.9	41.9	40.2
	25–29.9	41.9	43.2
	≥30	14.7	15.2
	Missing	(15.4)	
Consumption of fruits ^a , %			
	Daily	44.6	45.1
	Missing	(8.6)	47.3
Lifetime history of chronic bronchitis or emphysema ^a , %			
	Yes	11.0	11.9
	Missing	(17.7)	6.4
Ever worked on a farm ^a , %			
	Yes (farming population)	86.7	–
	No, but ever worked in other agricultural sectors ^b	1.5	–
	No (non-farming population)	11.8	
	Incomplete job history	(13.4)	
Ever lived on a farm during 1 st year of life ^a , %			
	Yes	68.8	77.9
	Missing	(10.2)	30.5

Ever lived on a farm with cattle during 1st year of life^a, %

Yes	52.3	60.3	21.8
Missing	(13.4)		

483 ^a Missing values were excluded from percentage

484 ^b Other agricultural sectors included jobs with potential exposure to agricultural hazards (such as
485 forestry/aquaculture/service provided for agricultural work...)

486

487 **Table 2.** Description of Occupational Exposures to Animals at Enrollment Among the Farming
 488 Population, AGRICAN, 2005-2007

	Cattle	Poultry	Pig	Horse	Sheep and/or goat
N (%)	85,970 (77.5)	40,597 (37.5)	30,790 (28.1)	23,160 (21.4)	14,420 (13.2)
Nb of years, Q2 (Q1–Q3)	28 (12–40)	24 (10–40)	17 (8–32)	13 (7–24)	15 (7–28)
Nb of animals, Q2 (Q1–Q3)	45 (20–86)	45 (22–300)	35 (20–70)	3 (2–5)	50 (12–150)
Tasks, %					
Care	87.8	73.6	86.1	79.2	82.1
Insecticides	36.1	21.2	18.2	15.5	24.4
Building disinfection	35.0	34.3	35.7	NA	28.2
Milking	78.4	NA	NA	NA	34.5
Milking machine disinfection	40.8	NA	NA	NA	17.1

489 Abbreviations: NA, Not Applicable; Nb, number

Table 3. Associations Between Exposure to Cattle and Horse Farming and Lung Cancer Risk, Overall and by Subtypes, Among the Farming Population, AGRICAN, 2005-2011

			All subtypes				Adenocarcinomas				Squamous cell carcinomas			
			N	HR	95% CI	<i>P</i> for trend	N	HR	95% CI	<i>P</i> for trend	N	HR	95% CI	<i>P</i> for trend
Cattle	Ever ^a		287	0.72	0.58, 0.90		103	0.64	0.45, 0.92		90	0.97	0.63, 1.50	
	Duration ^b	Never exposed	99	1.00		0.04	39	1.00		<0.01	27	1.00		0.18
		<10 years	52	1.04	0.73, 1.49		19	1.08	0.61, 1.92		20	1.26	0.71, 2.26	
		10–19 years	33	0.85	0.57, 1.28		12	0.86	0.45, 1.65		13	1.13	0.58, 2.20	
		20–29 years	21	0.72	0.45, 1.17		9	0.77	0.37, 1.59		8	1.02	0.46, 2.25	
		30–39 years	32	0.63	0.42, 0.95		10	0.49	0.25, 1.00		12	0.90	0.45, 1.78	
		≥40 years	38	0.60	0.41, 0.89		12	0.50	0.26, 0.97		13	0.70	0.36, 1.37	
	Number of Animals ^b	Never exposed	99	1.00		0.81	39	1.00		0.91	27	1.00		0.20
		<20	26	0.83	0.51, 1.33		9	0.90	0.41, 2.00		9	1.00	0.44, 2.26	
		20–44	47	1.20	0.79, 1.83		14	1.14	0.56, 2.35		19	1.63	0.82, 3.26	
		45–84	45	1.42	0.89, 2.27		16	1.71	0.79, 3.67		19	1.98	0.92, 4.24	
		85–149	10	0.69	0.33, 1.45		9	1.32 ^c	0.52, 3.36		6	0.88 [‡]	0.31, 2.53	
≥150		10	1.14	0.54, 2.40										
Horse	Ever ^a		120	0.96	0.77, 1.21		37	0.83	0.56, 1.22		39	0.99	0.66, 1.48	
	Duration ^b	Never exposed	224	1.00		0.08	90	1.00		0.03	61	1.00		0.80
		<10 years	24	0.82	0.52, 1.30		6	0.54	0.22, 1.29		10	1.04	0.50, 2.17	
		10–19 years	15	0.80	0.46, 1.37		5	0.38^d	0.15, 0.97		7	1.08	0.47, 2.49	
		≥20 years	12	0.64	0.35, 1.17						5	0.84	0.32, 2.18	
	Number of Animals ^b	Never exposed	224	1.00		0.21	90	1.00		0.35	61	1.00		0.44
		<5	20	0.74	0.41, 1.35		4	0.60	0.16, 2.16		7	0.60	0.27, 1.34	
≥5		15	1.36	0.68, 2.72		4	1.55	0.41, 5.89		7	1.46	0.66, 3.26		

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

^a For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), exposure to cattle (ever/never), and exposure to horses (ever/never); for SCC: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco) and exposure to cattle (ever/never)

^b For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work on cattle and duration of work on horses; for SCC: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work on cattle

^c HR for the category ≥85 cattle

^d HR for the category ≥10 years

498 **Table 4.** Associations Between Occupational Exposure to Cattle and Lung Cancer Risk,
 499 Stratified by Smoking, Among the Farming Population, AGRICAN, 2005-2011

	Non-Smokers			Smokers			<i>P</i> for interaction
	N	HR	CI 95%	N	HR	CI 95%	
Ever							
Never exposed to cattle	29	1.00		88	1.00		0.01
Exposed to cattle	57	0.39	0.25, 0.62	240	0.75	0.59, 0.96	
Duration							
Never exposed to cattle	29	1.00		88	1.00		0.24
<10 years	6	0.52	0.22, 1.25	54	1.00	0.71, 1.41	
10–19 years	6	0.44	0.18, 1.06	33	0.84	0.56, 1.25	
20–29 years	7	0.56	0.24, 1.27	18	0.65	0.39, 1.08	
30–39 years	6	0.25	0.10, 0.60	28	0.59	0.39, 0.91	
≥40 years	8	0.25	0.12, 0.56	39	0.59	0.40, 0.87	
<i>P</i> for trend	<0.0001			<0.001			

500 Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

501

502

Table 5. Associations Between Tasks Performed in Animal Farming and Lung Cancer Risk, Overall and by Subtypes, Among the Farming Population, AGRICAN, 2005-2011

		All subtypes			Adenocarcinomas			Squamous cell carcinomas		
		N	HR ^a	95% CI	N	HR ^a	95% CI	N	HR ^b	95% CI
Cattle										
	Care	261	0.74	0.59, 0.93	89	0.63	0.43, 0.90	87	1.04	0.67, 1.60
	Milking	222	0.74	0.59, 0.94	79	0.65	0.44, 0.94	72	1.05	0.67, 1.64
	Insecticides on cattle	112	0.68	0.52, 0.89	43	0.66	0.43, 1.01	35	0.86	0.52, 1.43
	Barn disinfection	115	0.70	0.54, 0.92	42	0.66	0.43, 1.01	37	0.91	0.55, 1.50
	Milking machine disinfection	116	0.74	0.57, 0.96	46	0.72	0.47, 1.09	38	1.03	0.63, 1.70
Horses										
	Care	87	0.84	0.66, 1.08	24	0.65	0.41, 1.03	30	0.90	0.58, 1.39
	Insecticides on horses	20	1.04	0.66, 1.64	7	1.03	0.48, 2.23	7	1.11	0.51, 2.42
Sheep and/or goats										
	Care	43	0.86	0.62, 1.19	10	0.56	0.30, 1.08	19	1.25	0.76, 2.05
	Milking	13	0.77	0.44, 1.35	4	0.66	0.24, 1.79	4	0.83	0.31, 2.27
	Insecticides on sheep/goats	15	0.88	0.52, 1.48	7	1.18	0.55, 2.55	8	1.47	0.71, 3.03
	Barn disinfection	20	1.00	0.64, 1.58	8	1.18	0.57, 2.42	9	1.42	0.71, 2.81
	Milking machine disinfection	8	0.96	0.47, 1.94	3	1.00	0.32, 3.16	3	1.24	0.39, 3.93
Poultry										
	Care	92	0.97	0.75, 1.25	33	1.00	0.66, 1.51	24	0.90	0.56, 1.45
	Insecticides on poultry	30	0.94	0.64, 1.46	12	1.11	0.60, 2.04	12	1.23	0.67, 2.29
	Barn disinfection	43	0.86	0.62, 1.19	16	0.94	0.55, 1.61	11	0.74	0.39, 1.39
Pigs										
	Care	102	1.06	0.83, 1.37	32	1.03	0.67, 1.59	38	1.40	0.92, 2.13
	Insecticides on pigs	22	0.94	0.60, 1.46	6	0.81	0.35, 1.86	13	1.85	1.01, 3.39
	Barn disinfection	44	0.96	0.68, 1.34	13	0.90	0.49, 1.63	20	1.45	0.86, 2.42

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

^a Adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), work on cattle (ever/never) and work on horses (ever/never)

^b Adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), and work on cattle (ever/never)

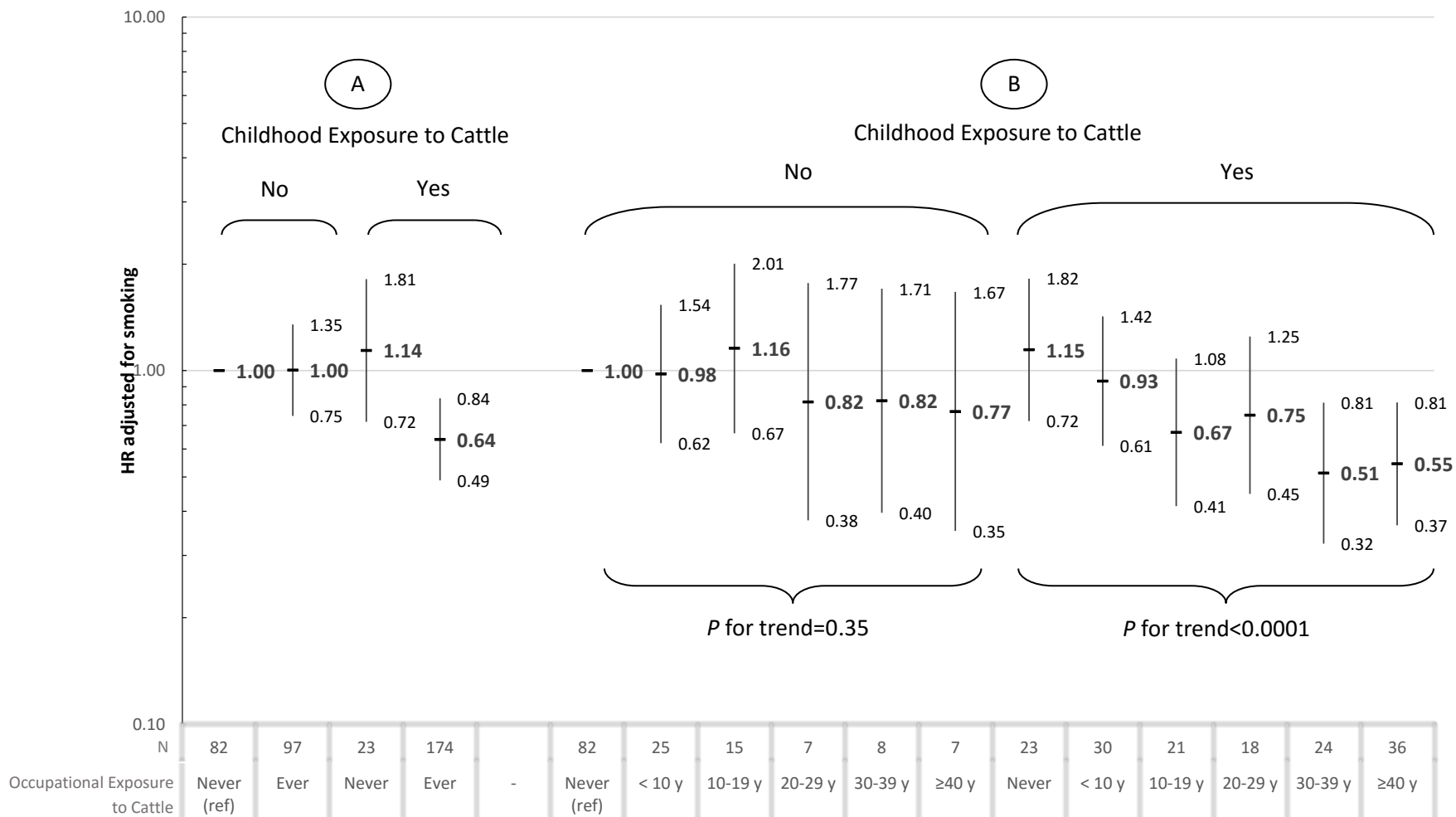


Figure 1. Associations Between Lung Cancer Risk and Occupational Exposure to Cattle (A: Ever/Never; B: Duration of Exposure), Stratified by Childhood Exposure to Cattle (First Year of Life), Among the Farming Population, AGRICAN, 2005-2011. Abbreviations: HR, hazard ratio; N, number of cases; ref, reference; y, year. Bars, 95% confidence interval.

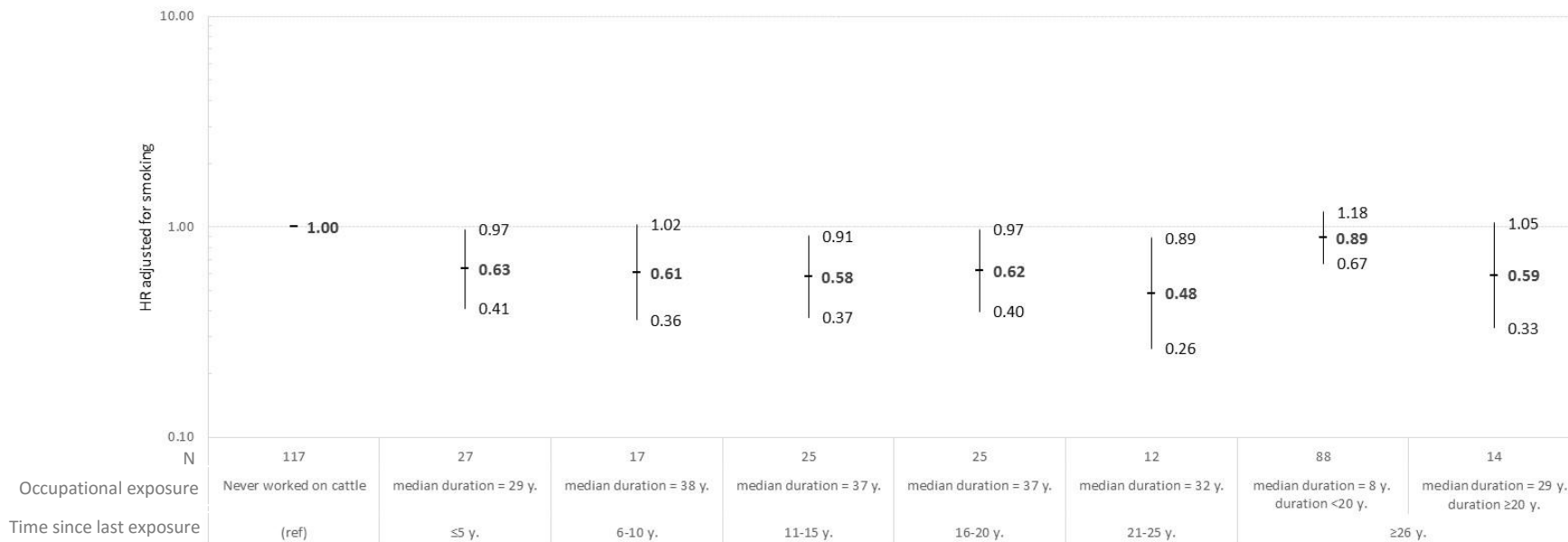


Figure 2. Impact of Time Since Last Exposure to Cattle (≤ 5 years, 6–10 years, 11–15 years, 16–20 years, 21–25 years, ≥ 26 years) on Relation Between Occupational Exposure to Cattle (for Time Since Last Exposure ≤ 25 years: Ever vs. Never Worked on Cattle; for Time Since Last Exposure ≥ 26 Years: Duration of Work < 20 Years and ≥ 20 Years vs. Never Worked on Cattle) and Lung Cancer Risk, Among the Farming Population, AGRICAN, 2005-2011. Abbreviations: HR, hazard ratio; N, number of cases; ref, reference; y, year. Bars, 95% confidence interval.

Web Tables

Web Table 1. Associations Between Smoking and Lung Cancer Risk in AGRICAN Cohort, 2005-2011

		All subtypes			ADK				SCC		
		N	HR	IC95%	N	HR	IC 95%	N	HR	IC 95%	
Smoking history											
Men											
	Non-smokers	41	1.00		17	1.00		5	1.00		
	Former smokers	275	8.66	6.24, 12.02	107	8.12	4.87, 13.55	90	23.21	9.43, 57.12	
	Current smokers	154	28.84	20.35, 40.87	45	18.36	10.42, 32.34	58	96.41	38.52, 241.32	
	Other types of smoking	71	13.07	8.90, 19.20	19	8.39	4.36, 16.14	22	33.14	12.55, 87.51	
Women											
	Non-smokers	83	1.00		53	1.00		2	1.00		
	Former smokers	14	4.34	2.39, 7.86	9	3.70	1.74, 7.87	2	-	-	-
	Current smokers	22	16.53	9.44, 28.95	11	9.85	4.56, 21.31	7	-	-	-
	Other types of smoking	4	15.34	5.58, 42.15	1	-	-	1	-	-	-
Pack-years of cigarette smoking											
Men											
	Non-smokers	41	1.00		17	1.00		5	1.00		
	<20	143	5.98	4.22, 8.46	52	5.16	2.98, 8.93	50	17.31	6.90, 43.41	
	20-39	161	17.65	12.52, 24.87	65	16.96	9.93, 28.95	49	44.08	17.56, 110.67	
	40-59	73	30.76	20.97, 45.12	22	22.42	11.89, 42.26	27	92.28	35.53, 239.73	
	≥60	37	37.40	23.97, 58.36	9	22.37	9.96, 50.25	16	132.22	48.41, 361.13	
	Other types of smoking	71	13.11	8.92, 19.26	19	8.45	4.39, 16.27	22	32.91	12.46, 86.95	
Women											
	Non-smokers	83	1.00		53	1.00		2	1.00		
	<20	17	4.21	2.36, 7.52	11	-	-	4	-	-	-
	20-39	13	19.57	10.48, 36.55	8	-	-	2	-	-	-
	40-59	3	27.96	8.70, 89.82	1	-	-	1	-	-	-
	≥60	2	56.02	13.57, 231.25	0	-	-	1	-	-	-
	Other types of smoking	4	14.56	5.30, 40.05	1	-	-	1	-	-	-

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

Web Table 2. Associations Between Exposure to Farm Animals and Lung Cancer Risk, Compared to the Non-farming Population, AGRICAN, 2005-2011

			All subtypes				ADK				SCC			
			N	HR	95% CI	<i>P</i> for trend	N	HR	95% CI	<i>P</i> for trend	N	HR	95% CI	<i>P</i> for trend
Cattle	Ever ^a	Never worked on a farm	90	1.00			36	1.00			27	1.00		
		Ever worked on cattle	287	0.86	0.66, 1.12		103	0.71	0.47, 1.07		90	0.90	0.57, 1.42	
	Duration ^b	Never worked on a farm	90	1.00		0.02	36	1.00		0.03	25	1.00		0.15
		<10 years	52	1.21	0.83, 1.76		19	1.12	0.62, 2.01		20	1.19	0.66, 2.14	
		10-19 years	33	0.99	0.64, 1.51		12	0.92	0.47, 1.80		13	1.04	0.53, 2.05	
		20-29 years	21	0.84	0.51, 1.37		9	0.79	0.38, 1.66		8	0.94	0.42, 2.09	
		30-39 years	32	0.73	0.48, 1.11		10	0.52	0.25, 1.05		12	0.82	0.41, 1.65	
		≥40 years	38	0.69	0.46, 1.04		12	0.52	0.26, 1.03		13	0.64	0.32, 1.27	
Horses	Ever ^a	Never worked on a farm	90	1.00			36	1.00			25	1.00		
		Ever worked on horses	120	1.14	0.80, 1.61		37	0.92	0.53, 1.53		39	0.88	0.46, 1.69	
	Duration ^b	Never worked on a farm	90	1.00		0.52	36	1.00		0.46	25	1.00		0.89
		<10 years	24	0.94	0.55, 1.60		6	0.55	0.21, 1.46		10	1.01	0.41, 2.49	
		10-19 years	15	0.90	0.49, 1.67		5	0.40 ^c	0.15, 1.11		7	1.02	0.38, 2.73	
		≥20 years	12	0.73	0.38, 1.42						5	0.79	0.26, 2.34	
Poultry	Ever ^a	Never worked on a farm	90	1.00			36	1.00			25	1.00		
		Ever worked on poultry	142	1.29	0.92, 1.81		55	1.31	0.78, 2.21		44	1.06	0.57, 1.99	
	Duration ^b	Never worked on a farm	90	1.00		0.99	36	1.00		0.28	25	1.00		0.37
		<10 years	15	1.04	0.55, 1.95		9	0.98 ^d	0.42, 2.26		7	0.61 ^d	0.23, 1.60	
		10-19 years	11	0.97	0.48, 1.95									
		20-29 years	6	0.99	0.41, 2.37		8	1.00 ^e	0.41, 2.39		7	0.76 ^e	0.29, 2.00	
30-39 years	8	1.25	0.57, 2.72											
≥40 years	12	1.28	0.64, 2.56											
Pigs	Ever ^a	Never worked on a farm	90	1.00			36	1.00			25	1.00		
		Ever worked on pigs	123	1.31	0.90, 1.90		45	1.34	0.75, 2.40		44	1.28	0.66, 2.48	
	Duration ^b	Never worked on a farm	90	1.00		0.83	36	1.00		0.22	25	1.00		0.69
<10 years	24	1.37	0.78, 2.41		6	0.91	0.33, 2.51		9	1.10	0.43, 2.78			

		10-19 years	12	1.04	0.52, 2.11	4	1.10	0.34, 3.53	7	1.39	0.51, 3.85
		≥20 years	23	1.48	0.84, 2.59	8	1.55	0.63, 3.83	8	1.13	0.43, 2.93
Sheep	Ever ^a	Never worked on a farm	90	1.00		36	1.00		25	1.00	
or goats		Ever worked on sheep/goats	55	1.11	0.75, 1.65	16	0.85	0.44, 1.66	20	1.03	0.51, 2.06
	Duration ^b	Never worked on a farm	90	1.00	0.53	36	1.00	0.37	25	1.00	0.80
		<20 years	13	0.88	0.47, 1.64	2	0.36	0.08, 1.55	9	1.39	0.59, 3.28
		≥20 years	10	1.21	0.60, 2.41	3	0.93	0.27, 3.16	4	1.12	0.36, 3.46

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

^a For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20-39, 40-59, ≥60, other tobacco), exposure to cattle (ever/never), and exposure to horses (ever/never); for SCC: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20-39, 40-59, ≥60, other tobacco) and exposure to cattle (ever/never)

^b For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20-39, 40-59, ≥60, other tobacco), duration of work on cattle and duration of work on horses; for SCC: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20-39, 40-59, ≥60, other tobacco), duration of work on cattle

^c HR for the category ≥10 years

^d HR for the category <20 years

^e HR for the category ≥20 years

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Web Table 3. Associations Between Exposure to Cattle Farming and Lung Cancer Risk After Multiple Imputation, Among the Farming Population, AGRICAN, 2005-2011

A. Description of Prevalence of Exposure to Cattle

	Complete case analysis	From 50 imputed datasets	
		Proportion / mean	95% CI
Work on a farm, %	86.7	86.7	86.5 86.8
Cattle farming, among those working on a farm, %	77.5	75.8	75.5 76.0
Duration of cattle farming, mean number of years	26.7	27.1	27.0 27.2
Tasks among cattle producers, %			
Care	87.9	83.3	83.0 83.6
Milking	80.2	76.7	76.5 77.0
Insecticides	36.9	39.7	39.3 40.0
Building disinfection	35.8	34.3	33.9 34.6
Milking machine disinfection	41.8	45.3	45.0 45.6

Abbreviations: CI, confidence interval.

B. Associations Between Exposure to Cattle and Lung Cancer Risk, Overall

	Complete case analysis			From 50 imputed datasets		
	HR*	95% CI	P-trend	HR*	95% CI	P-trend
Ever	0.70	0.57, 0.87		0.69	0.57, 0.84	
Duration						
Never exposed	1.00		<0.0001	1.00		<0.0001
<10 years	0.94	0.68, 1.28		0.93	0.70, 1.25	
10–19 years	0.78	0.54, 1.13		0.79	0.58, 1.07	
20–29 years	0.68	0.44, 1.05		0.70	0.51, 0.95	
30–39 years	0.54	0.36, 0.79		0.58	0.43, 0.78	
≥40 years	0.55	0.39, 0.78		0.57	0.42, 0.76	

Abbreviations: CI, confidence interval; HR, hazard ratio.

* Adjusted for pack-years of smoking

Web Table 4. Associations Between Exposure to Other Animals and Lung Cancer Risk, Overall and by Subtypes, Among the Farming Population, AGRICAN, 2005-2011

			All subtypes				Adenocarcinomas				Squamous cell carcinomas			
			N	HR	95% CI	P-trend	N	HR	95% CI	P-trend	N	HR	95% CI	P-trend
Sheep or goat	Ever/Never ^a		57	0.93	0.63, 1.23		16	0.76	0.45, 1.28		20	1.12	0.69, 1.81	
	Duration ^b	Never exposed	245	1.00		0.62	92	1.00		0.51	78	1.00		0.50
		<20 years	13	0.73	0.42, 1.30		2	0.34	0.08, 1.39		9	1.48	0.73, 3.00	
		≥20 years	10	1.03	0.54, 1.94		3	0.89	0.28, 2.82		4	1.21	0.44, 3.34	
	Number of Animals ^b	Never exposed	245	1.00		0.63	92	1.00		0.69	78	1.00		0.47
		<50	8	0.76	0.37, 1.54		1	0.30	0.00, 2.18		5	1.26	0.51, 3.14	
		50–149	6	1.00	0.44, 2.25		1	0.47	0.07, 3.41		3	1.49	0.47, 4.73	
≥150		5	0.80	0.33, 1.94		2	0.86	0.21, 3.49		3	1.42	0.45, 4.52		
Poultry	Ever ^a		148	1.10	0.88, 1.37		55	1.22	0.85, 1.73		44	1.23	0.83, 1.80	
	Duration ^b	Never exposed	188			0.84	70	1.00		0.97	60	1.00		0.64
		<10 years	15	0.91	0.52, 1.61		9	0.95 ^c	0.46, 1.97		7	0.68 ^c	0.30, 1.53	
		10–19 years	11	0.86	0.45, 1.63									
		20–29 years	6	0.88	0.38, 2.01		8	0.99 ^d	0.46, 2.14		7	0.88 ^d	0.39, 1.97	
		30–39 years	8	1.11	0.54, 2.31									
		≥40 years	12	1.16	0.62, 2.16									
Number of Animals ^b	Never exposed	188	1.00		0.90	70	1.00		0.41	60	1.00		0.24	
	<45	14	0.76	0.43, 1.33		3	0.52	0.16, 1.68		5	0.72	0.28, 1.82		
	≥45	20	0.96	0.60, 1.53		9	1.31	0.65, 2.66		4	0.54	0.19, 1.49		
Pig	Ever/Never ^a		121	1.12	0.88, 1.42		45	1.27	0.86, 1.87		44	1.42	0.95, 2.12	
	Duration ^b	Never exposed	199			0.35	75	1.00		0.30	61	1.00		0.47
		<10 years	24	1.19	0.73, 1.94		6	0.91	0.37, 2.27		9	1.15	0.53, 2.49	
		10–19 years	12	0.91	0.48, 1.73		4	1.09	0.37, 3.18		7	1.51	0.64, 3.60	
		≥20 years	23	1.30	0.80, 2.09		8	1.54	0.70, 3.37		8	1.24	0.56, 2.74	
		Number of	Never exposed	199	1.00		0.03	75	1.00		0.07	61	1.00	

Animals ^b	<49	30	1.12	0.73, 1.72	9	1.15	0.54, 2.42	10	0.93	0.46, 1.88
	≥50	19	1.69	1.05, 2.73	8	2.00	0.95, 4.19	7	1.74	0.79, 3.86

Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of cases.

^a For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), exposure to cattle (ever/never), and exposure to horses (ever/never); for SCC: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), and exposure to cattle (ever/never)

^b For all subtypes and adenocarcinomas: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), duration of work with cattle and duration of work with horses; for SCC: adjusted for smoking (never smokers, pack-years of cigarette smoking: <20, 20–39, 40–59, ≥60, other tobacco), and duration of work with cattle

^c HR for the category < 20 years

^d HR for the category ≥ 20 years