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Time to pregnancy and exposure to pesticides in Danish farmers

Solveig Brixen Larsen, Michael Joffe, Jens Peter Bonde, and the ASCLEPIOS study group

Abstract

***Objectives*—Circumstantial evidence suggests that organic farmers may have higher sperm count than other men, but comprehensive epidemiological studies of male fecundity among farmers have never been carried out. A substantial increase of sperm count is expected to translate into a shorter time to pregnancy—the number of menstrual cycles or months it takes a couple to get pregnant from discontinuation of birth control. Toxicological effects on spermatogenesis in humans and animals have been described after exposure to several pesticides. The aim of this study was to examine time to pregnancy among farmers who used pesticides (traditional farmers) and farmers who did not (organic farmers).**

***Methods*—A total of 904 (84%) men, selected from the Danish Ministry of Agriculture lists of traditional and organic farmers, participated in telephone interviews. Information was collected on time to pregnancy for the youngest child, exposure to pesticides, and potential confounders.**

***Results*—With the discrete analogue of the Cox regression model (including potential confounders: male and female smoking, female age, parity, and contraceptive method), the fecundability ratio between traditional farmers who used pesticides and organic farmers was 1.03 (95% confidence interval (95% CI) 0.75 to 1.40). In the group of farmers who sprayed with pesticides, none of the characteristics related to the use of pesticides could account for the variation in time to pregnancy.**

***Conclusions*—No overall effect of pesticides on male fecundability was found in this retrospective study among Danish farmers. Also, we found no evidence of higher male fecundability in organic farmers.**

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Keywords: time to pregnancy; pesticides; fertility

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Circumstantial evidence suggests that organic farmers may have a higher sperm count than other men,[1 2] but comprehensive epidemiological studies of male fecundity among farmers have never been carried out. A substantial increase of sperm count is expected to translate into a shorter time to pregnancy—the number of menstrual cycles or months it takes a couple to get pregnant from discontinuation of birth control.

Only a few epidemiological studies refer to the effects of pesticides on fecundability (the probability of obtaining conception in a menstrual cycle). A study of time to pregnancy and occupational exposure to pesticides in fruit growers in The Netherlands showed that several exposure variables were related to the time to pregnancy, and the effect of high exposure was mainly apparent if the couple had intended to become pregnant in the spraying season.[3] Toxicological effects on spermatogenesis in humans have been described after occupational exposure to 1,2-dibromo-3-chloropropane (DBCP),[4 5] ethylene dibromide (EDB),[6] carbaryl,[7] chlordecone,[8] and 2,4-dichlorophenoxyacetic acid (2,4-D).[9] Animal studies indicate male reproductive toxicity of several pesticides, and some of these pesticides have been used in Danish agriculture during the past decade—for example, benomyl, carbendazim,[10] iprodione,[11] isoproturon,[12] atrazine,[13] chlormequat-chloride,[14] glyphosate,[15] deltamethrin, dimethoate,[16] fenvalerate,[17] mancozeb, manep,[18 19] and dinoseb.[20] For many other pesticides, no information is available on possible reproductive toxicity.

It is well known that the fecundability among sexually active couples not using contraceptives varies. Therefore the waiting time to pregnancy differs among couples and between populations. The time to pregnancy has been proposed as a simple measure in epidemiological studies to investigate the effects of environmental exposures on fecundability.[21 22]

We hypothesised that use of pesticides in agriculture entails a risk of reduced fecundability. This paper reports the time to pregnancy among farmers who used pesticides (traditional farmers) and farmers who did not (organic farmers).

Material and methods

STUDY POPULATION

From the Danish Ministry of Agriculture lists of traditional and organic farmers we selected samples of 1146 male farmers, in the age range from 18 to 50 years. One sample included all organic farmers living in Jutland (n=441). Among traditional farmers from 26 municipalities in Jutland a random sample was taken among those expected to have agriculture as a main occupation (more than 20 hectares if they had animals, or more than 70 hectares if they had no animals, n=705). The farmers received a letter with information about the investigation, and telephone interviews were conducted between October 1995 and May 1996 by

Table 1 Study participation among traditional farmers and organic farmers (the farmers are grouped according to their occupation at the time of data collection)

	Traditional farmers		Organic farmers	
	n	*%*	*n*	*%*
Posted invitation	705		441	
Ineligible (no telephone, no contact, not Danish speaking)	53		20	
Non-responders answering a few questions	100	15.3	36	8.6
Non-responders not answering any questions	29	4.5	4	0.9
Participants	523	80.2	381	90.5

Table 2 Characteristics of participants and non-participants

	Participants (n=904)		Non-participants (n=169)	
Age (y, n (%)):				
≤30	39	(4.3)	11	(8.1)
31–35	157	(17.4)	15	(11.0)
36–40	250	(27.7)	28	(20.6)
41–45	226	(25.1)	44	(32.4)
>45	230	(25.5)	38	(27.9)
Missing	2		33	
Age (mean (SD))	40.0 (6.0)		41.2 (6.4)	
Children (n (%)):				
0	101	(11.6)	16	(17.8)
1	100	(11.5)	17	(18.9)
2–7	667	(76.9)	57	(63.3)
Missing	36		79	
Children (mean (SD))	2.3 (1.3)		2.0 (1.4)	
Married (%)	96.0		92.4	

trained female interviewers. A total of 904 men participated (84%), and table 1 shows the participation in the two groups.

DATA COLLECTION

The questionnaire was developed in English by ASCLEPIOS (A European concerted action on occupational hazards to male reproductive capability),[23] translated into Danish and pilot tested. Men not willing to provide the full information were asked to answer a few questions on age, number of children, marriage, and occupation. Table 2 shows characteristics of participants and non-participants. Non-participants were slightly older and more often unmarried and childless.

Table 3 Farm characteristics in the exposed group of traditional farmers

	Traditional farmers using pesticides (n=450)	
	n	*%*
Crop area (hectares):		
<20	23	5.1
20–29	32	7.1
30–39	55	12.2
40–59	146	32.4
≥60	194	43.1
Crop area treated solely by the father (hectares):		
<20	98	22.0
20–29	73	16.4
30–39	83	18.6
40–59	96	21.5
≥60	96	21.5
Use of manually controlled sprayer	337	75.7
Use of tractor with open cabin	138	31.0
Index groups:*		
Group 1	95	21.1
Group 2	182	40.4
Group 3	173	38.4
Years working with pesticides:		
≤5	81	18.2
6–10	149	33.4
11–15	124	27.8
16–28	92	20.6
Use of >3 pesticides with spermatoxic effects	165	45.7
Never use gloves (mixing)	96	21.4
Pesticide exposure at the starting time of unprotected coitus	149	33.5

*Firstly each farmer was assigned a score according to the number of hectares he sprayed (0: ≤ 20, 1: >20). Secondly, the farmers cultivating potatoes and beet were allocated a score to indicate that these two crops have the highest frequency of pesticide treatment. Finally, the farmers who used a manual sprayer were assigned a score. The index groups were defined as follows: group 1=0–1 scores; group 2=2 scores; group 3=3 scores.

Reproductive data

The interviews included questions on reproductive history but only detailed questions and information on covariates for the youngest child. The key question on the waiting time to pregnancy was phrased as follows: "How many months did it take your wife to get pregnant? That is, how many months were you having sexual intercourse without using any method of birth control?". Information was collected on possible confounding factors such as the last contraceptive method, male and female smoking habits 12 months before the youngest child was born, age, and female parity.

Exposure data

The participants were divided into the following groups according to use of pesticides the year before the youngest child was born: (*a*) traditional farmers spraying pesticides, (*b*) traditional farmers who did not spray pesticides themselves, (*c*) organic farmers, and (*d*) men who were not in the farming trade when the last child was conceived. Those reporting use of pesticides were asked about the number of hectares sprayed by the father himself, type of tractor and spraying equipment, use of protective equipment, and type of crops. Table 3 shows exposure characteristics of the traditional farmers. The spraying season among farmers runs from April to October, but the number of months with possible pesticide exposure depends on the type of crops. Therefore we collected information on possible exposure to pesticides (yes/no) at the starting time of time to pregnancy (the month when contraception was discontinued). The cumulative potential exposure to pesticides was assessed from information on total number of years working with pesticides. The farmers were posted a list of the most used pesticides during the past 10 years and asked to tick the pesticides used the year before the youngest child was born. The following pesticides were considered to be potentially spermatotoxic: 2,4-dichlorophenoxyacetic acid (2,4-D); benomyl; carbendazim; iprodione; isoproturon; atrazine; chlormequat-chloride; glyphosate; deltamethrin; fenvalerate; dimethoate; mancozeb; manep; and dinoseb.

The farmers who sprayed pesticides were scored into three index groups according to several exposure variables. According to experiences from exposure studies[24 25] the variables with the supposed strongest relation to exposure were selected. The scores and variables were decided before the data analysis was carried out. Firstly, each farmer was assigned a score according to the number of hectares he sprayed (zero for ≤20 hectares, one for >20 hectares). Secondly, the farmers cultivating potatoes and beet were allocated a score to

Table 4 Characteristics of the study population classified according to occupation and spraying of pesticides one year before the youngest child was born

	Traditional farmers spraying pesticides (n=450)		*Traditional farmers not spraying pesticides (n=72)*		*Organic farmers (n=94)*	
	n	*%*	*n*	*%*	*n*	*%*
Male age (y):						
⩽ 30	133	29.7	26	36.1	18	19.2
31–35	186	41.5	24	33.3	40	42.6
36–40	110	24.6	18	25.0	23	24.5
⩾ 41	19	4.2	4	5.6	13	13.8
Female age (y)						
−25	33	7.3	10	13.9	7	7.5
26–30	172	38.2	23	31.9	25	26.6
31–35	193	42.9	33	45.8	40	42.6
⩾36	52	11.6	6	8.3	22	23.4
Birth year of child:						
1969–85	104	23.1	26	36.1	7	7.5
1986–90	130	28.9	18	25.0	19	20.2
⩾1991	216	48.0	28	38.9	68	72.3
Male smoking (cigarettes/day):						
No smoking	317	70.8	44	61.1	63	67.7
1–10	41	9.2	5	6.9	11	11.8
11–20	71	15.9	17	23.6	14	15.1
>20	12	2.7	3	4.2	2	2.2
Pipe, etc	7	1.6	3	4.2	3	3.2
Female smoking (cigarettes/day):						
No smoking	329	73.4	54	75.0	74	79.6
1–10 cig/day	53	11.8	7	9.7	12	12.9
11–20 cig/day	62	13.8	10	13.9	6	6.5
>20 cig/day	4	0.9	1	1.4	1	1.1
Last contraceptive method:						
Never used any	41	9.2	9	12.7	9	9.6
OAC	164	36.9	22	31.0	24	25.5
IUD	65	14.6	10	14.1	13	13.8
Condom, etc	175	39.3	30	42.3	48	51.1
Female primiparity	62	13.9	6	8.5	12	12.8
Farming as main occupation	398	88.4	50	69.4	62	66.0
Female proportion who worked outside the farm	308	68.6	48	66.7	65	69.9

indicate that these two crops are most often treated with pesticide. Finally, the farmers who used a manual sprayer were assigned a score. The scores were added, and the farmers were grouped according to the sum of scores as follows: group 1 (zero or one score), group 2 (two scores), and group 3 (three scores).

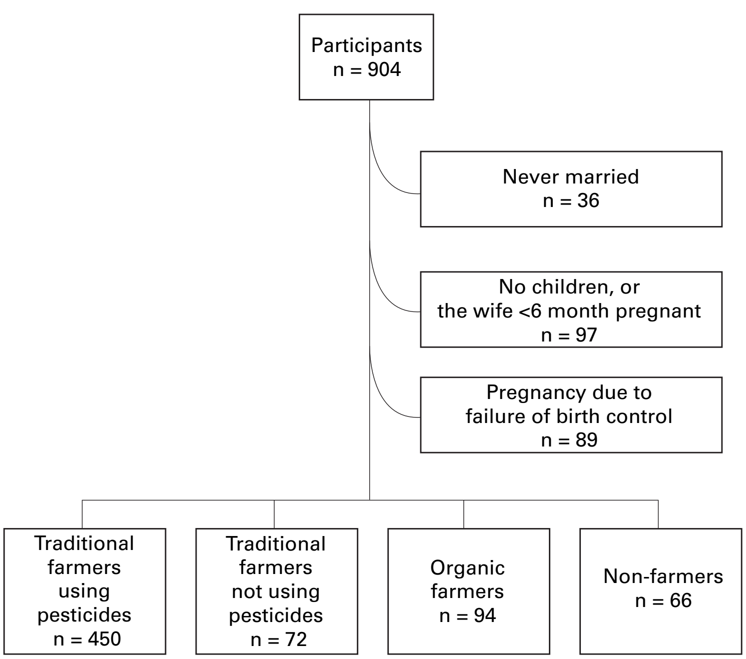

Figure 1 Study population: exposure status according to occupation one year before the youngest child was born.

STATISTICAL ANALYSIS

The following men were excluded from the data analysis: men never married (n=36), men with no children or whose wife was less than six months pregnant (n=97), men where the pregnancy was due to failure of birth control (n=89), and men without an occupation in agriculture the year before the youngest child was born (n=66). The remaining group of men (n=616) was divided into three groups according to their occupation and exposure status one year before the youngest child was born: (*a*) traditional farmers spraying pesticides (n=450), (*b*) traditional farmers who did not spray pesticides themselves (n=72), and (*c*) organic farmers (n=94, fig 1). Table 4 summarises characteristics of the participating traditional farmers and organic farmers. The organic farmers and their wives were older, the wives were less often heavy smokers and users of oral contraceptives.

Time to pregnancy data were analysed with the discrete analogue of the Cox's regression model from the SAS procedure PHREG.[26] These data are heavely tied, which is why the discrete analog method was used to handle ties. This model provides a fecundability ratio (analogous to a risk ratio or hazard ratio), representing the fecundability or conception rate of the exposed group relative to that for the control group. For example a fecundability ratio of 0.83 means that the conception rate per month of those in the exposed group is 83% of the conception rate of those in the control group (controlling for other covariates). The analysis was based on time to pregnancy data

Table 5 Unadjusted fecundability ratios for potential confounding variables

Variable	*Fecundability ratio*	*95% CI*
Male smoking (yes/no)	1.01	(0.81 to 1.26)
Female smoking (yes/no)	0.73	(0.58 to 0.92)
Female age (>30, ⩽ 30)	0.96	(0.78 to 1.18)
Recent oral contraceptive use (yes/no)	1.09	(0.88 to 1.36)
Female primipara (yes/no)	0.55	(0.41 to 0.73)

up to 13 months, and cases with time to pregnancy greater than 12 months were censored at that time.

The following potential confounding variables, selected for their biological relevance, were included in the analysis: female age (>30 years, ⩽30 years), male and female smoking (yes/no), recent use of oral contraceptives (yes/no), and female primiparity (yes/no). Table 5 shows unadjusted fecundability ratios for the confounding variables. Female smoking and primiparity were significantly related to longer waiting time.

All exposures were assessed blinded to time to pregnancy data. Firstly, we compared the group af traditional farmers who used pesticides with the group of organic farmers. Secondly, internal comparisons were made in the group of traditional farmers who used pesticides, and fecundability ratios were calculated for the different exposure variables.

Results

Figure 2 shows the unadjusted cumulative distribution of the time to pregnancy according to exposure group. The fecundability declined as the number of cycles increased. During the first year 92% of the participating men fathered a pregnancy (76% after three months and 87% after six months). The fecundability ratio between traditional farmers who had used pesticides the year before their youngest child was

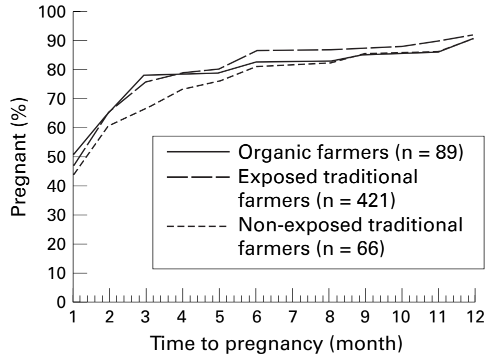

Figure 2 Cumulative distribution of time to pregnancy according to use of pesticides (missing values=40).

born and organic farmers was 1.03 (95% confidence interval (95% CI) 0.75 to 1.40). Among the organic farmers no significant difference in fecundability was found between those who started as traditional farmers (n=61) and those who were organic farmers from the beginning (n=28, fecundability ratio 0.66, 95%CI 0.33 to 1.31).

In table 6, adjusted fecundability ratios from the internal comparisons in the group of farmers who used pesticides are presented. Among farmers in the index groups 2 and 3, who were supposed to be the most exposed, a weak tendency to decreased fecundability was found, but there was no significant association. A comparison between the group of farmers who were exposed to pesticides at the starting time of unprotected coitus, and the group who were not, showed no association with time to pregnancy (fecundability ratio 1.04, 95% CI 0.78 to 1.39). The cumulative exposure, expressed as the total number of years working with pesticides, was associated with a shorter time to pregnancy, but the difference was only significant for one category. The use of more than three pesticides suspected to be

Table 6 Fecundability ratios adjusted for male and female smoking, female age, recent oral contraceptive use, and parity

Variable	*Fecundability ratio*	*(95% CI)*
Exposure group:		
Traditional farmers using pesticides *v* organic farmers	1.03	(0.75 to 1.40)
Exposure group:		
Traditional farmers using pesticides *v* traditional farmers who did not spray pesticides themselves	1.18	(0.83 to 1.66)
Pesticide exposure at the starting time of unprotected coitus	1.04	(0.78 to 1.39)
Number of years working with pesticides:		
⩽ 5	1.0 (reference)	
6–10	1.30	(0.90 to 1.88)
11–15	1.61	(1.07 to 2.40)
16	1.27	(0.83 to 1.93)
Use of ⩾ 3 pesticides with spermatoxic effects	0.88	(0.66 to 1.18)
Use of manually controlled sprayer	0.77	(0.56 to 1.05)
Use of tractor with open cabin	0.98	(0.74 to 1.31)
Not using gloves (mixing)	0.93	(0.68 to 1.27)
Crop area applicated solely by the father (hectares):		
<20	1.0 (reference)	
20–30	1.03	(0.67 to 1.58)
30–40	0.96	(0.65 to 1.43)
40–60	0.86	(0.59 to 1.27)
⩾ 60	1.29	(0.86 to 1.93)
Cultivating potatoes	1.16	(0.81 to 1.65)
Cultivating beet	0.99	(0.77 to 1.30)
Index groups:*		
Group 1	1.00 (reference)	
Group 2	0.83	(0.58 to 1.17)
Group 3	0.92	(0.64 to 1.31)

*Firstly each farmer was assigned a score according to the number of hectares he sprayed (0: ⩽ 20, 1: >20). Secondly, the farmers cultivating potatoes and beet were allocated a score to indicate that these two crops have the highest frequency of pesticide treatment. Finally, the farmers who used a manual sprayer were assigned a score (group 1=0–1 scores, group 2=2 scores, group 3=3 scores).

spermatoxic did not significantly influence the time to pregnancy, although a tendency towards a longer time to pregnancy was seen. The same tendency was found among farmers who used a manually operated tractor sprayer. Neither the use of a tractor with open cabin, nor the use of gloves when mixing the pesticides significantly influenced the time to pregnancy. We also examined whether the number of hectares sprayed by the father himself was related to fecundability, but found no relation.

Discussion

We found no significant difference in time to pregnancy between traditional farmers who used pesticides and organic farmers. In the group of traditional farmers who used pesticides, none of the characteristics relating to the use of pesticides could account for the variation in time to pregnancy. The study is one of the largest occupational studies on time to pregnancy, but it should be remembered that the control group is small (n=94). Our results are contrary to those of a study among fruit growers in The Netherlands exposed to pesticides, which showed that several exposure variables were related to time to pregnancy, and the effect of high exposure was mainly apparent if the couple had intended to become pregnant in the spraying season.[3] The difference may be due to different exposure levels or use of different types of pesticides.

MEASURES OF EXPOSURE

A limitation of our study was the lack of exact exposure measurements. It was only possible to relate the time to pregnancy to exposure variables which are supposed to indicate the exposure level and not to exposure variables with a known strong relation to the internal level of pesticide. Greenhouse workers are considered the occupational group with the highest exposure to pesticides.[27] To our knowledge no studies describe the internal concentration of pesticides among Danish farmers, but studies have described the quantity of pesticide deposited on the body of the tractor driver.[24] It was shown that tractor drivers are most often exposed to pesticides when filling the tank of the sprayer. Although this operation is only a small part of the total work process, the exposure of the spraying personnel is normally as much as 85%–90% of the total exposure involved in spraying. Furthermore, it was shown that the hands are the part of the body most exposed to pesticides. Compared with the use of conventional manually operated tractor sprayers, an exposure reduction of up to 75% can be achieved if optional spraying equipment is used (such as preparation filling equipment, hydraulic boom-lifts, equipment for hydraulic extension and retraction of the boom, non-drip valves, self cleaning filters, or nozzles for flushing tanks). In our study 67% used gloves regularly when filling the tank, 12% occasionally, and 21% never or at rare intervals. Furthermore most (75.7%) used a manually controlled sprayer, indicating that a large group of the traditional farmers may be potentially exposed.

Some of the organic farmers had worked as traditional farmers before they started as organic farmers, and if the pesticides cause irreversible effects on spermatogenesis the risk ratio between the two groups will be underestimated. However, there was no significant difference in fecundability between the group who started as traditional farmers and the group who were organic farmers from the beginning.

The spraying season runs from April to October, but the number of months with exposure to pesticides depends on the type of crops grown. There is also a large variation in the spraying days each month. In an attempt to examine the effect of spraying season, we compared the group of farmers who were exposed to pesticides when contraception was discontinued and the group who were not, but found no difference in fecundability. A possible effect of pesticides on semen quality and fecundability could be transient and reversible, and therefore not possible to detect in a retrospective time to pregnancy study.

SOURCES OF BIAS

The lack of association in our study could reflect a no effect situation or it could be due to biases hiding any true effect. Selection bias may lead to underestimation of the effect of pesticides, if traditional farmers who had difficulty conceiving were less motivated to participate than the organic farmers with fertility problems. However, experiences from a semen study among Danish farmers showed the opposite tendency.[28] The organic farmers may have an interest in reporting a high group fecundability and therefore no interest in participating if they have had trouble in conceiving. In contrast, the subfertile traditional farmers might participate to a greater extent to obtain an evaluation of possible hazardous exposures in the workplace. This would indicate a bias against the null hypothesis in this instance. Because the participation rate was high, we do not think that selection bias can explain the lack of association in our study.

When groups of couples who differ in their fecundability are excluded from analysis, there will be the opportunity for selection bias to produce underestimation or overestimation of the association between an exposure and fecundability.[29] We excluded the group of farmers for whom the pregnancy was due to failure of birth control, as it is impossible to collect time to pregnancy data in this group. The more fecund couples are more likely to have birth control failures and consequently are more likely to be excluded from analyses. If the organic farmers have a higher fecundability they are therefore more likely to be excluded from the study, and the fecundability of the control group will be artificially lowered, leading to bias in favour of the null hypothesis.

Planning bias may arise if use of more irregular or less effective methods of birth control are associated with the exposure of interest.[30] If organic farmers tend to use less efficient birth control methods the most fertile of these couples may conceive unintentionally and thus never become eligible for the study. Thus the fecundability in the exposed group will be overestimated. In our study 57.7% of the organic farmers and 44.3% among traditional farmers used less effective birth control methods. A total of 15.5% of organic farmers compared with 10.6% of the traditional farmers were excluded because of birth control failure (p=0.11), which indicates a bias in favour of the null hypothesis.

At the other extreme, the time to pregnancy approach excludes farmers without children, a group that includes infertile couples. From the organic selected sample 9% were excluded compared with 12% from the traditional sample. If the pesticides had rendered some men sterile, they would have been excluded from the analysis, and the effect of pesticides on fecundability would have been underestimated. However, it is difficult to imagine that toxicants causing sterility will not also result in a longer time to pregnancy. The recall of time to pregnancy is almost certainly better when an actual child is involved and that is the reason for restriction to births.[23]

All data, both for exposure and fecundability, are retrospective and self reported. A high validity of fecundability data from interviews is supported from other studies, although female workers' reports were somewhat more reliable than those of male workers.[21 31–35] However, we assume that this difference is the same in the different groups.

In the examination of time to pregnancy our purpose was to compare different groups of farmers similar for all variables except for exposure (use of pesticides). We adjusted for the most relevant confounders. However, confounding by other unmeasured risk factors which are more prevalent among the organic farmers than among traditional farmers cannot be ruled out. More of the organic farmers than the traditional farmers worked outside the farm, but it is difficult to imagine that outside occupational risk factors were sufficiently substantial to lower the fecundability in this group. Most of the farmers (80.0%) were educated as farmers or in another manual trade, and inclusion of educational level in the Cox's model did not change the adjusted fecundability ratio between the two groups. Although the organic pregnancies tended to occur during a different historical period (72% after 1991) we found no relation between birth year of the child and time to pregnancy. The frequency and timing of intercourse is associated with the probability of conception, but we did not collect the data because of anticipated low validity in a retrospective study, and because we assumed that the distribution was similar in the groups. If pesticides affect the libido, adjustment for frequency of intercourse would tend to obscure the effect.

In conclusion, no overall effect of pesticides on male fecundity could be found in this retrospective study among Danish farmers. Also, we found no evidence of higher male fecundity in organic farmers.

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