

Title: Association between occupational exposure to disinfectants and asthma in young adults working in cleaning or health services – results from a cross-sectional analysis in Germany.

Running title: Disinfectants exposure and asthma in young adults

Authors:

Tobias Weinmann, PhD

Felix Forster, MSc

Erika von Mutius, MD

Christian Vogelberg, MD

Jon Genuneit, MD

Doris Windstetter, MD

Dennis Nowak, MD

Katja Radon, PhD

Jessica Gerlich, PhD

Affiliations:

Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany (TW, FF, DW, DN, KR, JGer)

Comprehensive Pneumology Centre (CPC), German Centre for Lung Research (DZL), Munich, Munich, Germany (TW, FF, EvM, DW, DN, KR, JGer)

Dr. v. Haunersches Kinderspital, University Hospital, LMU Munich, Munich, Germany
(EvM)

Paediatric Department, University Hospital Carl Gustav Carus Dresden, TU Dresden,
Dresden, Germany (CV)

Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany (JGen)

Pediatric Epidemiology, Department of Pediatrics, University Medicine Leipzig, Leipzig,
Germany (JGen)

Corresponding author:

Tobias Weinmann

Institute and Clinic for Occupational, Social and Environmental Medicine

University Hospital, LMU Munich

Ziemssenstr. 1

80336 Munich, Germany

E-Mail: tobias.weinmann@med.lmu.de

Phone: +49 (89) 4400-52483

Fax: +49 (89) 4400-54954

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Author contribution: TW performed the data analysis and drafted the manuscript. FF is the fieldwork coordinator of the SOLAR study being in charge of data collection. CV, JGer, and KR are principle investigators of SOLAR and responsible for the scientific coordination of

the project. DN, DW, EvM, and JGen contributed to the conception and implementation of SOLAR. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To analyse the association of occupational disinfectants use with asthma and wheezing in young professionals.

Methods: 365 participants from the German Study on Occupational Allergy Risks II aged 20 to 24 years and working in cleaning or health services answered a questionnaire on respiratory health, occupational exposure to disinfectants, and potential confounders. By logistic regression we calculated the association between duration of occupational disinfectants exposure and doctor-diagnosed asthma, current asthma, and current wheezing.

Results: Individuals exposed to disinfectants for more than twelve months had almost three times the odds of doctor-diagnosed asthma compared to those not exposed (OR: 2.99, 95% CI: 1.36-6.55).

Conclusions: Our findings provide some further evidence for an association between occupational exposure to disinfectants and asthma, indicating that this association can be seen already after the first year of exposure.

Keywords: asthma, wheezing, disinfectants, occupational health, young adults

Asthma is a complex disease that is characterised by chronic airway inflammation, reversible airflow obstruction, and bronchial hyperreactivity.¹ It is one of the most prevalent chronic diseases worldwide and contributes substantially to the global burden of disease.^{2, 3} Asthma can lead to reduced quality of life with serious limitations in physical, social, and professional aspects of life.⁴ In addition, it causes considerable economic costs.⁵ In the US alone, taking into account factors like asthma-related mortality, healthcare costs, and reduced productivity as well as absenteeism at work or school, the total costs of asthma are estimated at more than 80 billion dollars per year.⁶

A notable contributor to the burden of asthma is occupational asthma, which until now has been linked to more than 400 different job-specific agents.⁷⁻⁹ Among those agents causing occupational asthma, cleaning products are one of the most prominent groups.^{10, 11} These products encompass irritating and sensitising agents such as disinfectants, bleach, fragrances, mixing products, or quarternary ammonium and amine compounds.^{12, 13} A sizeable number of epidemiological studies analysed the effects of occupational exposure to cleaning products on respiratory outcomes such as asthma and wheezing and provided convincing evidence for such an association.^{14, 15} The majority of the studies so far included professional cleaners as target population, while some also regarded individuals working in health services.¹⁶⁻¹⁸ To the best of our knowledge, most of those studies primarily recruited rather middle-aged adults or, when involving also younger individuals, did not differentiate between various age groups. However, we consider analysing the association between cleaning products and respiratory outcomes in early-career professionals as an interesting research question. First, previous research suggests that early years of exposure are a critical period during the development of occupationally induced asthma.^{19, 20} Evidence for the effects of cleaning products on respiratory health specifically among young adults may thus help to develop and implement prevention and intervention strategies during the crucial period right before or at the

beginning of their work life.¹⁹ This is even more important as previous studies observed knowledge gaps with respect to cleaning products and their potential detrimental health effects among hospital workers.²¹ Moreover, getting to know if health-related effects become evident early in the professionals' career, and thus after a very short period of exposure, may increase the understanding not only of the dose-response relationship between occupational exposure to cleaning products and asthma but also enhance the knowledge of the potential underlying mechanisms, which is still relatively scarce.²²

OBJECTIVES

Based upon these considerations, our primary aim was to analyse the association of occupational use of disinfectants with asthma and wheezing in young adults. As a secondary aim, we tried to further elucidate this potential association by evaluating the dose-response relationship between duration and frequency of disinfectants use and asthma and wheezing.

METHODS

Study design and sample

The present analysis used questionnaire data from the German Study on Occupational Allergy Risks II (SOLAR II). The details of the studies' methodology were described by an earlier publication.²³ In short, SOLAR builds upon the German part of Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II).^{24, 25} During the latter, parents of 6399 (85.3%) children between nine and eleven years of age living in the cities of Dresden and Munich completed a questionnaire on socio-demographic factors, symptoms of asthma, allergic rhinitis, and eczema as well as on potential risk factors for these disease entities between 1995 and 1996. In addition, a sample of the children underwent clinical examination including skin prick test, bronchial challenge with hypertonic saline, and blood sampling. When the participants were 16 to 18 years old, the first follow up was performed

(SOLAR I, 2002-2003). During SOLAR I, 3785 participants (59.1%) answered a questionnaire that was based on ISAAC II adding questions on occupational factors from the European Community Respiratory Health Survey (ECRHS). About five years later, between 2007 and 2009, 2051 individuals (response: 70.6%) aged 19 to 24 years took part in SOLAR II. They again underwent clinical examination and answered a self-administered questionnaire on socio-demographic, environmental, and occupational factors including domestic and occupational exposure to cleaning agents as well as on symptoms of asthma and allergies. As the main exposure of interest of the present analysis was occupational exposure to disinfectants, we only included individuals who during SOLAR II reported to currently work in health services or jobs involving cleaning activities (N=356; Figure 1).

Exposure assessment

Following the questions on disinfectants used by the ECRHS (which can be found at <http://www.ecrhs.org/quests.htm>), the study questionnaire asked the participants for how many hours per day they currently used disinfectants at work: never, <1h per day, 1-3h per day, or >4h per day. To additionally take into account the total duration of the exposure, we assessed the duration of participants' last job (start and end date) with job being defined as any work performed for at least one month with a minimum of eight hours per week. From these two variables (disinfectants use at work and duration of current job) we calculated our main exposure variable duration of occupational exposure to disinfectants. Those participants who reported never using disinfectants or no job with a duration of at least one month and eight hours per week were classified as not exposed. Those who indicated any use of disinfectants (<1h per day, 1-3h per day, or >4h per day) and a current job were categorised according the duration of their last job (1-12 months, more than 12 months). Thus, our main exposure variable used for primary risk analysis had three categories (no exposure, exposure 1-12 months, exposure >12 months). In secondary risk analysis, we evaluated the effect of

occupational exposure to disinfectants per day with the above-mentioned categories (never, <1h per day, 1-3h per day, or >4h per day) as exposure variable.

Outcome definition

We evaluated the effect of disinfectants use on three different binary outcome variables that were measured via the study questionnaire: doctor-diagnosed asthma, current asthma, and current wheezing. Doctor-diagnosed asthma was defined as having ever had an asthma diagnosis by a medical doctor. Current asthma was considered as present if the participants indicated doctor-diagnosed asthma and either wheezing without cold or use of asthma medication within the last twelve months prior to the survey. The third variable, current wheezing, took into account if the participants reported wheezing without cold or use of asthma medication within the last twelve months prior to the survey, independently of a doctor's diagnosis.

These outcome definitions are consistent with previous analyses from the SOLAR study and in accordance with measurement of asthma in other epidemiological studies, most prominently the ECRHS.^{26,27}

Potential confounders

The SOLAR study questionnaire collected data on a range of additional variables, such as sex, age, socio-economic status (SES), study centre, smoking, current occupation, and domestic use of disinfectants. For measurement of SES, individuals were asked for their highest educational level with at least twelve years of school attendance considered as high SES and less than twelve years as low SES. With respect to smoking, the questionnaire assessed if the study subjects have ever smoked (i.e., at least one cigarette per day for one year or longer) and if they currently smoked (i.e., within the last month). Using this information, we categorised them as never, former, or current smokers. The variable on

current occupation differentiated if the participant was apprentice, student, employed, or other (i.e., self-employed, job-seeking, or maternity/parental leave). Domestic use of disinfectants was characterised the same way as occupational use of disinfectants, i.e., by asking the participants for how many hours they currently used disinfectants at home: never, <1h per day, 1-3h per day, or >4h per day. As only few participants reported to use disinfectants at home, for further analysis this variable was dichotomised into no use vs. any use.

Statistical analysis

First, we present descriptive statistics of the participants' characteristics using absolute numbers (n) and percentages (%) for the categorical variables and arithmetical mean and standard deviation (SD) for the continuous variable age. Next, we calculated separate logistic regression models for the associations between duration of occupational exposure to disinfectants (no exposure, 1-12 months, >12 months) and the three outcome variables doctor-diagnosed asthma, current asthma, and current wheezing. Lastly, during secondary risk analyses we performed logistic regression models to assess the association between occupational exposure to disinfectants per day (never, <1h per day, 1-3h per day, or >4h per day) and the outcome variables. All regression models first calculated crude odds ratios (OR) and then adjusted odds ratios (aOR) including the respective 95% confidence intervals (95% CI) for the association between exposure and outcome variables with no exposure to disinfectants being the reference category in every model. For confounder adjustment, based on prior knowledge from other studies, we selected the following variables to be included in the models: age (continuous in years), sex (female, male), study centre (Dresden, Munich), smoking (never, former, current smoker), and domestic use of disinfectants (no, yes). Additionally, we performed chi-square-tests for trend in all models (alpha: .05). For all variables taken into account in this analysis, the percentage of missing data was below 5%.

Therefore, we considered imputation of missing data as neither necessary nor justified and performed complete case analyses.

All statistical analyses were conducted using STATA Version 12 (STATA Corp., USA) and SPSS Version 25 (IBM Corp., USA).

Ethics

The study was approved by the Ethical Committee of the Medical Faculty of the University of Dresden (Dresden, Germany), the Ethical Committee of the Bavarian Chamber of Physicians (Munich, Germany) and by the Ethical Committee of Ulm University (Ulm, Germany). Informed consent for participation was obtained from all study subjects.

RESULTS

Descriptive statistics

The mean age of the study population was 21.8 years; almost three quarters of the participants were female. Slightly more than 50% were categorised into the low SES group. With respect to their current occupation, most participants were employees (47%) while 28% did an apprenticeship and 21% went to university. Eighty-one (23%) individuals were classified as being occupationally exposed to disinfectants for more than twelve months. Concerning domestic use of disinfectants, the vast majority of the participants (82%) did not use them at home. Forty individuals (11%) ever had a doctors' diagnosis of asthma, while current asthma and current wheezing were reported by 25 (7%) and 77 (22%) participants, respectively (table 1).

Primary risk analysis

In the crude and in the adjusted models, participants that were occupationally exposed to disinfectants for more than twelve months had about three times the odds of doctor-diagnosed asthma compared to the non-exposed participants (crude OR: 2.94, 95% CI: 1.37-6.51;

adjusted OR: 2.99, 95% CI: 1.36-6.55). We observed additional evidence for an association between more than twelve months of occupational exposure to disinfectants and current asthma (crude OR: 2.88, 95% CI: 1.12-7.38; adjusted OR: 3.04, 95% CI: 1.14-8.08) while for current wheezing, we observed no evidence for an association (table 2). There was also some indication of a dose-response relationship with increasing effect estimates from the lowest to the highest exposure category for doctor-diagnosed asthma (p for trend in the adjusted model = 0.01) and current asthma (p for trend in the adjusted model = 0.03), but not for current wheezing (p for trend in the adjusted model = 0.13).

Secondary risk analysis

In the logistic regression analysis including occupational exposure to disinfectants per day as exposure variable, we observed increasing odds ratios from the lowest to the highest exposure category for doctor-diagnosed asthma as outcome variable (table 3). Nevertheless, the confidence intervals and the test for trend (p for trend in the adjusted model = 0.34) do not allow drawing any firm conclusions regarding an association.

DISCUSSION

The present paper aimed at scrutinising the association of occupational exposure to disinfectants with asthma and wheezing in young adults at the beginning of their professional career. To achieve this aim, we analysed cross-sectional data from 356 individuals aged 20 to 24 years working in health or cleaning services. In total, our results support the hypothesis of an association between exposure to disinfectants and impaired respiratory health. More specifically, we found good evidence of an almost three-fold increased risk of asthma after only at least twelve months of occupational exposure to disinfectants.

Differentiating between the three outcome definitions that we used, we observed the strongest evidence between occupational exposure to disinfectants and having ever had a doctor's

diagnosis of asthma and current asthma, i.e., a doctor's diagnosis of asthma and either wheezing without cold or use of asthma medication within the last twelve months prior to the survey, even though the confidence interval in the risk analysis on current asthma became a little bit wider due to a lower number of cases under this outcome definition and thus less statistical power. For the third outcome definition, wheezing only (i.e., irrespective of a doctor's diagnosis), our analysis provided no evidence for an association with occupational exposure to disinfectants. This may be explained by the lower specificity of wheezing alone as outcome definition.²⁸ We also did not observe much evidence for an association between the daily duration of occupational exposure to disinfectants and any of the three outcome variables. Since this variable only measured current exposure but did not take into account the total duration of exposure (i.e., since when they were in this job), this null result seems to speak in favour of the hypothesis that individuals have to accumulate a certain total level of exposure before health effects become evident. However, as this secondary analysis had four exposure categories, power issues because of the low sample size and the limited number of cases may have played an even stronger role than in the primary analysis.

Compared to the existing body of evidence, our results are in line with results from previous studies with similar research questions such as those that were included in a systematic review by Folletti et al.¹⁵ While this review dealt with cleaning agents in general, also studies specifically investigating exposure to disinfectants observed evidence for detrimental effects on respiratory health.²⁹⁻³¹ For instance, a recent analysis within the Nurses' Health Study II suggested an association between occupational exposure to disinfectants and poor asthma control.^{16, 32} A rather new and specific feature of our analysis is that our study population consisted specifically of young people early in their professional career.

Nevertheless, several caveats should be kept in mind when interpreting our findings. First, it appears rather contradictory that a certain number of our participants indicated to be currently

occupationally exposed to disinfectants but at the same time did not report to currently perform a job. Possible explanations may be that these were students doing some form of an internship, e.g., medical students in clinical traineeship, which they did not regard as a job as such, or that these were individuals who either just started their job (with the job thus not meeting the criterion of having been performed for at least one month) or who were on occasional employment (with the job thus not meeting the criterion of being performed for at least eight hours per week). As we allocated all of them into the no exposure category, the reference group in our risk analysis may not have been fully unexposed so that our effect estimates may be an underestimation of the true association between occupational exposure to disinfectants and asthma. Moreover, given the fact that the Epidemiological Study of the Genetics and Environment of Asthma (EGEA) reported significant underestimation of self-reported exposure to cleaning products in hospital staff,²¹ we cannot exclude that the self-reported exposure levels in our study population were at least partly inaccurate. In a similar manner, also measurement error with respect to the outcome might have influenced our findings. While we presume that individuals' recall of a doctor's diagnosis should not be too unreliable, our two other outcome variables current asthma and current wheezing were based on self-reported symptoms. This measurement method may have been prone to some bias through subjective and inaccurate recall and recognition of asthma symptoms.³³ Under the likely scenario that this phenomenon affected all participants irrespective of their level of exposure, this would mean a source of non-differential misclassification bias towards the null.

Furthermore, the possibility of a healthy worker effect needs to be considered. In our case, this would mean a healthy hire effect in the sense that individuals that experienced symptoms of asthma or wheezing did not choose a job in health or cleaning services right from the beginning.³⁴ This possibility is supported by the fact that in the European Community

Respiratory Health Survey exactly such an effect that asthmatic individuals were less likely to select jobs with asthma-relevant inhalation exposures became evident. Moreover, a recent study on occupational exposures and chronic respiratory disease from New Zealand regarded a healthy hire effect as a likely source of bias in their findings.³⁵ Having said that, we need to highlight that an earlier analysis in our study population did not observe much evidence for a healthy hire effect in this population.³⁶

Concerning potential confounding, we took into consideration a variety of socioeconomic and lifestyle factors. Going through the cited previous studies in the field, we did not identify additional factors that seem to be strongly associated with disinfectants use as well as with asthma and wheezing. Hence, even though by its very own nature unknown confounding can never entirely be ruled out, we do not think that uncontrolled confounding had a major impact on our findings.

Finally, we need to highlight that the cross-sectional nature of our analysis may limit drawing causal conclusions, especially as we had no information on the dates of the doctors' asthma diagnoses thus being unable to establish a temporal relationship between exposure and outcome. Besides, there is also a lack of knowledge with respect to the underlying pathophysiological mechanisms. Although disinfectants are rather seen as sensitising agents (while other agents such as bleach are rather regarded as irritants),¹³ on the whole the underlying mechanisms between cleaning agents and asthma are still considered a 'black box'.²² Upcoming research in this field may thus try to collect information on individuals' use of specific products to be able to analyse the potential effects of particular compounds of cleaning agents.

CONCLUSIONS

To conclude, our findings provide some further evidence for an association between occupational exposure to disinfectants and asthma. Moreover, our results suggest that this association can be seen already in young people at the beginning of their occupational career and after a relatively short period of exposure.

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FIGURE LEGEND

Figure 1: Flow chart of follow-up from ISAAC Phase II to SOLAR II and the present analysis indicating periods of recruitment, number of participants and response, and participants' age at each stage of follow-up.

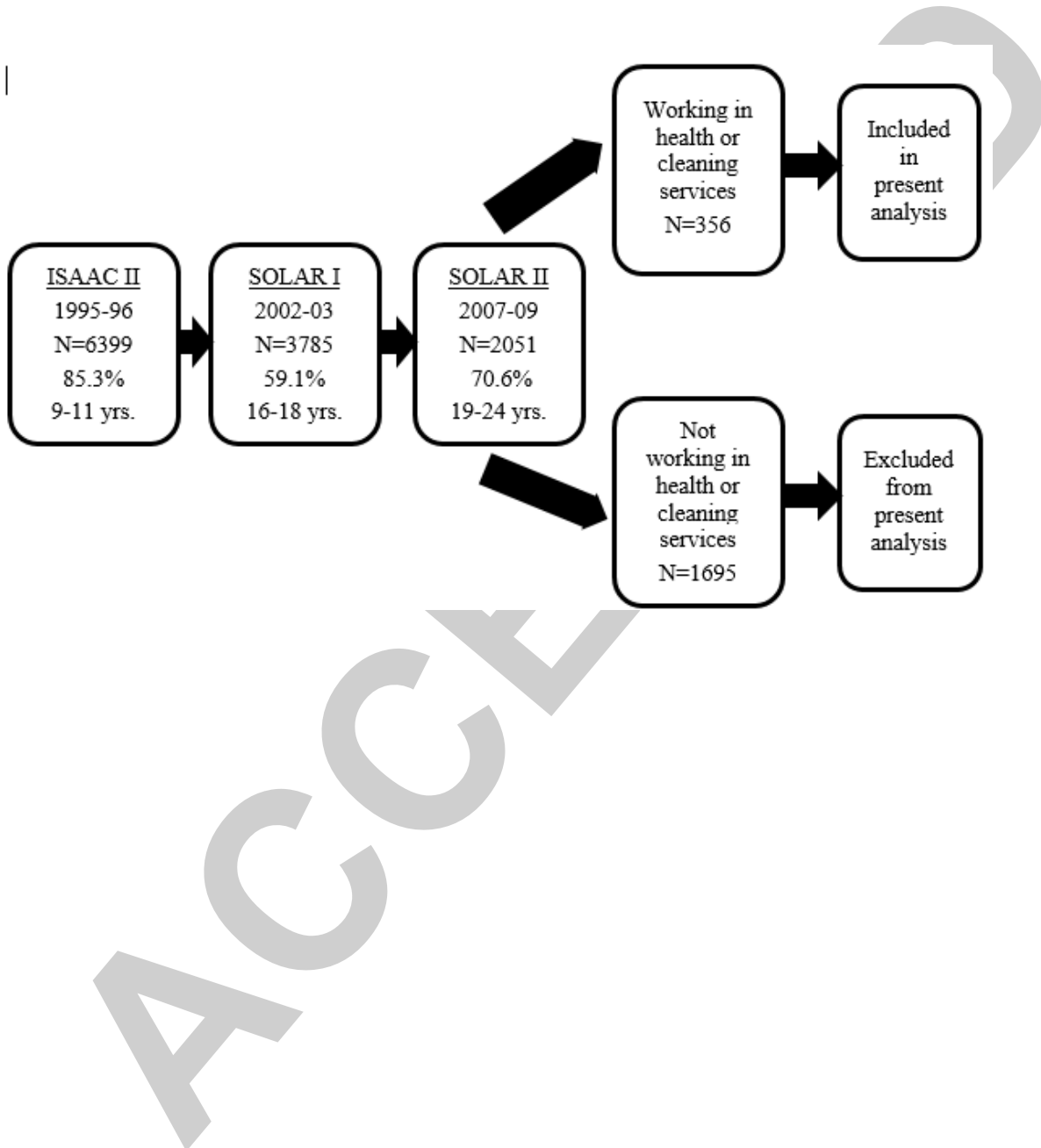


Table 1: Description of the demographic, exposure, and outcome variables in the study population (N=356)

	Missing (n)	Mean	SD
Age (years)	0	21.8	0.74
	Missing (n)	N	%
Sex	0		
Female		253	71.1
Socioeconomic status	1		
Low		182	51.2
Study centre	0		
Dresden		198	55.6
Smoking	4		
Never smoker		160	45.5
Ex-smoker		35	9.9
Current smoker		157	44.6
Current occupation	0		
Apprentice		99	28.1
Student		74	21.0
Employee		164	46.6
Other*		15	4.3
Domestic use of disinfectants	4		
Yes		65	18.5
Occupational exposure to disinfectants per day	5		
Never		94	26.8
<1h per day		114	32.5
1-3h per day		56	15.9
>4h per day		87	24.8
Duration of occupational exposure to disinfectants	5		
No exposure		195	55.5
Exposure 1-12 months		75	21.4
Exposure >12 months		81	23.1
Prevalence of asthma/wheezing			
Doctor-diagnosed asthma	2	40	11.3
Current asthma	3	25	7.1
Current wheezing	1	77	21.7

*Other occupations: self-employed, job-seeking, maternity/parental leave

SD: Standard deviation

Table 2: Results from the logistic regression analysis for the association between duration of occupational exposure to disinfectants and doctor-diagnosed asthma, current asthma, and current wheezing

	Doctor-diagnosed asthma				Current asthma				Current wheezing			
	No. of cases	No. of non-disease d	OR	95 % CI	No. of cases	No. of non-disease d	OR	95 % CI	No. of cases	No. of non-disease d	OR	95 % CI
No exposure	15	179	Reference		9	184	Reference		37	157	Reference	
1-12 months	8	66	1.45	0.59 - 3.57	5	69	1.48	0.48 - 4.58	17	58	1.24	0.65 - 2.38
>12 months	16	65	2.94	1.37 - 6.51	10	71	2.88	1.12 - 7.38	22	59	1.58	0.86 - 2.90
			aOR*	95 % CI			aOR*	95 % CI			aOR*	95 % CI
No exposure	15	179	Reference		9	184	Reference		37	157	Reference	
1-12 months	8	66	1.30	0.51 - 3.33	5	69	1.55	0.47 - 5.02	17	58	1.25	0.63 - 2.46
>12 months	16	65	2.99	1.36 - 6.55	10	71	3.04	1.14 - 8.08	22	59	1.61	0.86 - 2.99

OR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence intervals

* All analyses adjusted for age, sex, smoking, study centre, and domestic use of disinfectants

Table 3: Results from the logistic regression analysis for the association between occupational exposure to disinfectants per day and doctor-diagnosed asthma, current asthma, and current wheezing

	Doctor-diagnosed asthma				Current asthma				Current wheezing			
	No. of cases	No. of non-diseased	OR	95% CI	No. of cases	No. of non-diseased	OR	95% CI	No. of cases	No. of non-diseased	OR	95% CI
Never	8	85	Reference		6	86	Reference		18	75	Reference	
<1h/day	12	101	1.26	0.49 - 3.23	8	105	1.09	0.36 - 3.27	23	91	1.05	0.53 - 2.10
1-3h/day	7	49	1.52	0.52 - 4.44	3	53	0.81	0.19 - 3.38	14	42	1.39	0.63 - 3.07
>4h/day	12	75	1.70	0.66 - 4.38	7	80	1.25	0.40 - 3.89	21	66	1.33	0.65 - 2.70
			aOR*	95% CI			aOR*	95% CI			aOR*	95% CI
Never	8	85	Reference		6	86	Reference		18	75	Reference	
<1h/day	12	101	1.27	0.47 - 3.43	8	105	1.22	0.38 - 3.91	23	91	1.04	0.51 - 2.13
1-3h/day	7	49	1.39	0.45 - 4.34	3	53	0.85	0.19 - 3.81	14	42	1.21	0.53 - 2.79
>4h/day	12	75	1.64	0.59 - 4.53	7	80	1.35	0.40 - 4.60	21	66	1.25	0.59 - 2.65

OR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence intervals

* All models adjusted for age, sex, smoking, study centre, and domestic use of disinfectants