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RESEARCH ARTICLE

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Respiratory/allergic effects of indoor toluene exposure on Italian schoolchildren

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ABSTRACT

To assess the effects of indoor toluene on respiratory/allergic health in schoolchildren. Respiratory/allergic symptoms in the last week and related risk factors were assessed through questionnaire in 2284 schoolchildren (mean age 10 years, 50.9% males) of eight Italian cities. Measurements of pollutants were performed in 130 classrooms (44 schools). Toluene was measured by *Radiello*® passive diffusive samplers. The levels of indoor toluene were relatively low (mean 4.17 µg/m^3, median 2.70 µg/m^3). The prevalence of respiratory symptoms during the

monitored week was 32.8% (16.8% at school), including 25.7% of dry cough (11.9% at school). Nasal and skin problems were reported by 73.3% (48.1% at school) and 31.6% (13.7% at school). Multiple logistic regression, accounting for center, sex, age, diagnosis/family history of asthma or rhinitis, passive smoking at home, levels of indoor particulate and carbon dioxide, indicated significant associations between toluene concentration and all considered respiratory/allergic symptoms. The strongest association regarded dry cough (OR 1.32, 95% CI 1.15-1.52) and dry cough at school (OR 1.51, 1.23-1.85). Although toluene levels in classrooms were relatively low, the exposure to this volatile organic compound is a risk factor for respiratory/allergic health of schoolchildren.

HIGHLIGHTS BOX

1. **What is already known about this topic?** VOCs are ubiquitous in the environment and their concentration is consistently higher indoors than outdoors. VOCs indoor exposure is associated with general (such as headache and tiredness), irritant, respiratory, cardiovascular, neurological and carcinogenic effects.

2. **What does this article add to our knowledge?** Evidence regarding the health effects of VOCs exposure in schools is still limited worldwide; our study showed that indoor toluene exposure, even at relatively low concentrations, is associated with respiratory/allergic symptoms in Italian schoolchildren.

3. **How does this study impact current management guidelines?** This study highlights the importance of conducting further studies evaluating the health impact of exposure to VOCs in schools; public authorities should be aware of and intervene for abating this risk factor for children's health.

Key words
VOCs; toluene; schoolchildren; respiratory symptoms; allergic symptoms.

INTRODUCTION

Volatile Organic Compounds (VOCs) are a group of organic chemical pollutants that originate from both anthropogenic and biogenic sources. VOCs are ubiquitous in the environment since there are many sources (e.g., traffic/industrial emissions, building/furnishing materials, arts/crafts materials, cleaning agents, and personal-care products). Concentrations of many VOCs are consistently higher

indoors - up to ten times higher - than outdoors (1). Several studies have shown that indoor exposure to VOCs is associated with general (such as headache and tiredness), irritant, respiratory, cardiovascular, neurological and carcinogenic effects (2, 3).

Benzene, toluene, ethylbenzene and xylene (BTEX) are the most important toxic VOCs. Toluene is a clear, colorless liquid with a sweet, pungent odor. It can be released as a gas into the indoor air at room temperatures. Toluene can enter the indoor environments in vehicle exhaust or vapors from stored fuel. It is also a very good solvent, and it can dissolve many organic compounds. Indoor sources of toluene include building materials (e.g., solvent/water-based adhesives, floor coverings, paint, chipboard), consumer and automotive products (e.g., cleaners, polishes, adhesive products, oils, greases, lubricants), and environmental tobacco smoke (4). Exposure to toluene is generally via indoor air, through inhalation, and its average concentrations can vary considerably.

It is known the role of indoor air pollution in affecting respiratory health in both children and adults (5). Even low concentrations of indoor pollutants may have adverse biological effects when exposures are prolonged (6). Even though health-related organizations have set standard limits as unhazardous levels (e.g. Environmental Protection Agency, The European Union, The Standardisation Administration of China…), it has been observed that, within or even below these limits, constant exposure to these toxic chemicals is linked to adverse health effects. Concentrations below the VOCs reference values, including toluene, are associated with increased oxidative stress, a precursor mechanism of chronic diseases such as bronchitis, asthma, and loss of pulmonary function (7). Acute or chronic exposure to toluene vapor can irritate the mucous membranes of the upper respiratory tract (8). There is evidence on the association between occupational asthma and toluene exposure (9, 10), as well as between urinary metabolites of toluene and childhood asthma (11).

Children are most vulnerable to the ubiquitous pollution in their environment, and they not always respond to pollutants as adults do. Children are frail during their growth and, because of their physical constitution and breathing rate relative to their body size, they are more susceptible to the health effects of air pollution than adults (12).

Children spend about 5-8 hours a day at school, thus the school ranks second after the home for the length of time spent indoors. Studies regarding the school environment and related health effects in children have been performed worldwide, including Europe (13-19). Most studies concern the effects of exposure to particulate matter (PM), nitrogen dioxide (NO_2), carbon dioxide (CO_2), mold/dampness, formaldehyde or total VOCs (8, 16, 17). There are very few studies on the association between indoor toluene in schools and respiratory/allergic symptoms in schoolchildren. In the present study, we assessed how indoor toluene may affect respiratory health in schoolchildren.

MATERIAL AND METHODS

Study population

Data from the Italian project named "Exposure to indoor pollutants: guidelines for the evaluation of risk factors in the school environment and definition of measures to protect the respiratory health of schoolchildren and adolescents" (*Indoor-School*), funded by the Center for Disease Control (CCM) of the Italian Ministry of Health, were analyzed (20).

The *Indoor-School* project (2011-2014) was conducted in eight Italian cities (Udine, Sondrio, Milan, Pisa, Rome, Bari, Cagliari, Palermo) in two phases (21). The project was developed considering possible geographic differences in the three Italian macro areas (North, Centre, South) (Fig. 1). We present here data from the first phase (2011-2012), regarding 2285 schoolchildren (mean age 10.3 yrs., 50.8% males), 44 schools, and 130 classrooms.

Environmental assessments

The project included indoor/outdoor environmental measurements (i.e. temperature, relative humidity, CO_2, $PM_{2.5}$, NO_2, and VOCs). Measured VOCs were Benzene, Toluene, Ethylbenzene, Xylene (BTEX), and Formaldehyde. Indoor measurements were performed for one week in the classrooms, during normal activities (full classroom), and under representative conditions (same sampling points for all classrooms). In the same week, outdoor measurements were also carried out in the immediate vicinity of the school. The method was the same for all monitored schools. Toluene

levels (µg/m^3) were measured by *Radiello*® passive diffusive samplers (ICS Maugeri, Italy) and high-performance liquid chromatography (HPLC) at the laboratory of "Istituto Superiore di Sanità" (ISS), National Center for Research and Evaluation of Immunobiological Products (Rome). The VOCs were sampled by adsorption and extracted with carbon disulfide (CS_2) (2 mL and under stirring for approximately 30 minutes) and sent for HPLC analysis with a Flame Ionization Detector (FID).

$PM_{2.5}$ (µg/m^3) and CO_2 levels (part per million, ppm) were measured by means of direct reading analyzers (DustTrak for $PM_{2.5}$ and Q-track for CO_2) (22).

Health assessments

Information on respiratory/allergic symptoms, during the monitored week, were collected through a questionnaire administered directly to the schoolchildren. We considered the following symptoms for analyses:

- respiratory symptoms (RSs) (Question: "In the past week, have you had dry cough or breathlessness with or without whistling/wheezing in the chest or whistling/wheezing in the chest?");
- nasal problems (NPs) (Question: "In the past week, have you had runny nose or itchy/irritated nose or stuffy nose or sneezing?");
- skin problems (SPs) (Question: "In the last week, have you had rashes/itching on hands/arms/face/neck or eczema?").

The answers to the questions were as follows: "yes at home, yes at school, yes in other places, no". We considered presence/absence of symptoms in general, regardless of location, and specifically, while the children were at school.

Potential confounders

Information on children's diagnosis of asthma/rhinitis, family history of asthma/rhinitis, allergy (hay fever, allergy to pollens/damp/mold/cat/dog), and exposure at home to second-hand smoke (SHS) was collected by a questionnaire filled in by the parents. The questionnaires were derived from previous questionnaires used in studies conducted among schoolchildren in Europe: "International

Study of Asthma and Allergies in Childhood" (ISAAC) project (23), "Health Effects of School Environment" (HESE) study (24), "School Environment and Respiratory Health of Children" (SEARCH) study (25), and "Schools Indoor Pollution and Health Observatory Network in Europe" (SINPHONIE) study (26).

Moreover, we collected information on school characteristics through a questionnaire filled in by the principal.

The Indoor-School study protocol, participant information sheet, and consent form were locally approved by the Ethics Committee of each participating centre, after the approval obtained by the Clinical Manager of the study from the Ethics Committee of the University Hospital "P. Giaccone " of Palermo (N. 5/2011, 18/5/2011).

Statistical analyses

Statistical analyses were performed with the Statistical Package for Social Science (SPSS version 17). Used routines were frequency distributions, analysis of variance with post hoc Bonferroni and Waller-Duncan tests, non-parametric tests of Kolmogorov-Smirnov and Kruskal-Wallis. The association between symptoms and indoor toluene exposure was assessed by logistic regression analyses unadjusted and adjusted for city, gender, age, asthma/rhinitis diagnosis, family history of asthma/rhinitis, allergy, SHS exposure at home, and levels of indoor $PM_{2.5}$ and CO_2 as independent variables. Indoor toluene levels were not normally distributed and were log10-transformed for analyses. The significance level was set at 0.05.

RESULTS

Table 1 reports the characteristics of the sample. Table 2 and Figure 2 shows the prevalence of considered symptoms. Any RSs were reported by 32.8% of the schoolchildren, with significantly higher prevalence in Bari (76.6%) and Cagliari (69.4%); 16.8% of children reported RSs at school, with the highest prevalence in Rome (28.6%). In particular, dry cough was present in 25.7 % of cases (11.9% at school), with significantly higher prevalence in Rome (40.5%, 24.8% at school). NPs were the most frequently reported (73.3%), with significantly higher prevalence in Palermo (84.8%); with

regard to NPs at school, the prevalence was 48.1%, with the highest value in Rome (61.2%). SPs were present in 31.6% of cases with the highest prevalence in Cagliari (40.3%), and 13.7% at school (19.8% in Rome).

SHS at home was reported by 21.5% of parents, with the highest prevalence in Rome (31.0%) and Palermo (27.4%), and the lowest in Udine (14.4%) and Milan (14.5%).

As regards toluene, indoor levels were relatively low (median value 2.70 μg/m^3), and showed a significant positive correlation with outdoor levels (Sperman's rho 0.74, $p<0.001$). Mean concentrations of toluene were more elevated indoors than outdoors (4.17 vs 3.94 μg/m^3) (Tab. 3). There was a significant difference between centers ($p<0.001$, by Kruskal-Wallis test), due to the highest concentrations in Rome and Milan (Fig. 3). Indoor toluene was positively associated with vehicular traffic ($p=0.01$ by Kruskal-Wallis test): median levels in schools located near roads with low, medium, and high/very high vehicular traffic were 1.35, 3.50 and 4.70 μg/m^3, respectively.

Both bivariate and multiple regression analyses showed that indoor toluene was significantly related to all considered symptoms (Tab. 4). The strongest association was found with dry cough at school (odds ratio - OR 1.51, 95% confidence interval - 95% CI 1.23-1.85).

DISCUSSION

Despite the magnitude of the school population, the state of knowledge regarding VOCs in schools, including their association with health outcomes in schoolchildren, is still limited worldwide. A reason might be that most epidemiological research on VOC exposure has focused on occupational exposure for workers, where the exposure concentrations are much higher than those in residences, office buildings, or schools. While high concentrations of toluene are known to affect multiple human organ systems, research concerning the influence of exposure to low concentrations of indoor toluene is scarce. Schoolchildren spend approximately six to eight hours per day in various school microenvironments. Therefore, assessing their air toxics exposure is important to formulate interventions and policies for a healthier environment.

According to other authors, we found that indoor toluene was the predominant compound within the measured BTEX (mean concentrations were 4.16, 1.00, 1.13, 0.19 μg/m^3 for toluene, benzene, xylene, and ethylbenzene, respectively), and it was more elevated indoors than outdoors (26-28), indicating a double origin in indoor levels (original sources and penetration from outdoors). Indeed, we found a significant positive correlation between indoor and outdoor toluene in the study sites. Our results confirm the difference in the concentration of toluene between the schools located in areas with high traffic density and school located in areas with low vehicular traffic (12). It is not surprising that the highest levels of exposure happen in schools of Rome, near roads with medium (50%) or heavy/very heavy traffic (50%). Children attending near-road schools are more sensitive to the deleterious effects of these air toxics, thus the role of school location in children's air pollution exposure is a growing policy issue (29).

The mean indoor toluene level in our classrooms (4.17 μg/m^3) was lower than those found by Sofuoglu et al. in Turkish primary schools (18.70 μg/m^3) (28), by Martins et al. in Portugal (20.70 μg/m^3) (27), by Norbäck et al in Malaysian schools (12.3 μg/m^3) (8), and remarkably by Kim et al in Korea (81.17 μg/m^3) (30). Conversely, the median concentration (2.70 μg/m^3) was very similar to that found in the schools of the "School Health Initiative: Environment, Learning, and Disease" (SHIELD) study, performed in Minnesota (2.5 μg/m^3) (31).

With regard to adverse health effects, we found significant positive association of respiratory symptoms, nasal and skin problems with toluene exposure at school. The Agency for Toxic Substances and Disease Registry (ATSDR) (32) indicates in 1 ppm the minimal risk level for chronic exposure to toluene for the general population, which corresponds to 265 μg/m^3. Thus, the levels measured in our classrooms were low. However, our results suggest the lack of a real threshold below which there are no effects of toluene exposure on children's health. As mentioned, children are more vulnerable and susceptible to air pollution than adults.

Kim et al., in Korea, reported that schools with many students having allergic rhinitis symptoms had higher concentrations, almost double for toluene (p=0.02), compared to schools where fewer students had allergic rhinitis symptoms (30). Similarly, we found significantly higher levels of toluene for schoolchildren with allergy (including hay fever) than for those without allergy.

Most studies on the effects of toluene exposure in children report associations with asthma or reduced lung function (11, 27, 33). Indeed, in our study we found that toluene exposure was associated with typical asthma symptoms, such as dry cough, shortness of breath, and chest wheezing.

CONCLUSIONS

Our study points out that toluene exposure at school, even at relatively low concentrations, is associated with respiratory/allergic symptoms in Italian schoolchildren.

Further studies evaluating both toluene and other VOCs should be conducted in schools in order to clarify the underlying mechanisms of the adverse respiratory/allergic impacts.

Public authorities should be aware of and intervene for abating this risk factor in order to protect children's health.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

The authors have no financial or non-financial interests to disclose.

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Human studies and subjects

The Indoor-School study protocol, participant information sheet, and consent form were locally approved by the Ethics Committee of each participating centre, after the approval obtained by the Clinical Manager of the study from the Ethics Committee of the University Hospital "P. Giaccone " of Palermo (N. 5/2011, 18/5/2011).

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Table 1. Characteristics of children.

	N (valid %)
Total sample: *Males*	2285 1161 (50.8)
City: *Udine* *Sondrio* *Milan* *Pisa* *Rome* *Bari* *Cagliari* *Palermo*	 355 (15.5) 76 (3.3) 376 (16.5) 391 (17.1) 343 (15.0) 324 14.2) 62 (2.7) 358 (15.7)
Age (years): *Mean ± SD (Median)* *[range]*	10.3 ± 1.7 (10.0) [6-15]
Asthma/rhinitis diagnosis	321 (15.4)
Asthma/rhinitis family history	822 (38.6)
Allergy†	299 (13.1)
Second-hand smoke at home	446 (21.5)

† Including allergic cold, hay fever, allergy to pollens/damp/mold/cat/dog, confirmed by a physician

Table 2. Respiratory/allergic symptoms reported by schoolchildren (N=2285) in the environmental monitored week

	N (valid %)
Respiratory symptoms *(dry cough/breathlessness/wheezes)* at school Dry cough at school Nasal problems *(runny/dry nose)* at school	749 (32.8) 385 (16.8) 547 (25.7) 271 (11.9) 1612 (73.3) 1100 (48.1)

Skin problems *(rashes/itching)* at school	664 (31.6) 313 (13.7)

Table 3. Concentration of toluene inside the classroom, and outside the school in the environmental monitored week.

Region	City	Indoor toluene (μg/m^3)		Outdoor toluene (μg/m^3)	
		Mean ± SD	Median [range]	Mean ± SD	Median [range]
Friuli Venezia Giulia	Udine	2.39 ± 2.44	1.85 [0.01-7.60]	3.35 ± 5.03	1.85 [0.01-14.90]
Lombardy	Milan Sondrio	7.31 ± 5.62 0.99 ± 0.70	5.70 [3.00-29.00] 1.30 [0.01-1.70]	5.44 ± 1.69 0.01 ± 0.00	5.10 [3.00-7.90] 0.01 [0.01-0.01]
Tuscany	Pisa	2.75 ± 2.48	1.35 [0.23-7.80]	2.50 ± 2.51	1.45 [0.20-7.20]
Lazio	Rome	12.40 ± 5.53	12.63 [3.14-26.33]	11.75 ± 13.22	8.25 [3.80-44.0]
Puglia	Bari	1.99 ± 3.30	0.01 [0.01-9.80]	1.85 ± 3.64	0.01 [0.01-9.80]
Sardigna	Cagliari	0.10 ± 0.24	0.01 [0.01-1.00]	1.17 ± 1.27	1.01 [0.01-2.90]
Sicily	Palermo	3.33 ± 2.06	3.40 [0.01-8.90]	2.70 ± 1.99	2.55 [0.01-5.10]
Total		4.17 ± 5.17	2.70 [0.01-29.00]	3.94 ± 6.35	2.40 [0.01-44.00]

Table 4. Crude and adjusted associations between indoor toluene and respiratory/allergic symptoms.

	Crude OR (95% CI)	Adjusted OR (95% CI)
Dry cough/breathlessness/wheezes	**1.19 (1.10-1.29)**	**1.16 (1.03-1.29)**
Dry cough/breathlessness/wheezes at school	**1.20 (1.08-1.33)**	**1.26 (1.08-1.46)**
Dry cough	**1.24 (1.12-1.37)**	**1.32 (1.15-1.52)**
Dry cough at school	**1.40 (1.22-1.61)**	**1.51 (1.23-1.85)**
Nasal problems	**1.03 (1.00-1.13)**	**1.15 (1.03-1.29)**
Nasal problems at school	**1.08 (1.01-1.17)**	**1.17 (1.06-1.30)**
Skin rashes/itching	1.03 (0.95-1.12) †	1.17 (1.04-1.31)
Skin rashes/itching at school	**1.11 (1.00-1.24)**	**1.21 (1.03-1.40)**

Odds Ratio (OR) and 95% Confidence Interval (CI) for toluene log-unit increment. Analyses accounted for city, gender, age, asthma/rhinitis diagnosis, asthma/rhinitis familiarity, allergy, second-hand smoke at home, indoor PM2.5 (log unit increment), and indoor CO2 (100 ppm increment).
† Borderline significant.

FIGURE LEGENDS

Figure 1. Distribution of the investigated regions and participating cities throughout Italy.

Figure 2. Percent prevalence of considered symptoms by city. RSs (Respiratory symptoms): dry cough/breathlessness/wheezes; NPs (Nasal problems): runny nose or itchy/irritated nose or stuffy nose or sneezing; SPs (Skin problems): skin rashes/itching. *** $p<0.001$; ** $p=0.01$.

Figure 3. Levels of indoor toluene (($\mu g/m^3$) in the monitored classrooms, by city (Ba, Bari; CA, Cagliari; MI, Milan; PA, Palermo; PI, Pisa; RO, Rome; SO, Sondrio; UD, Udine).

Figure 1.

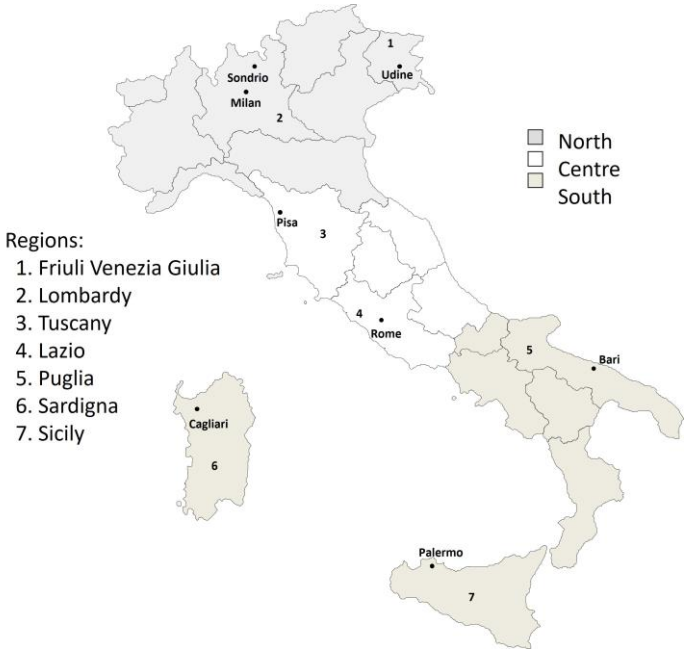

Figure 2.

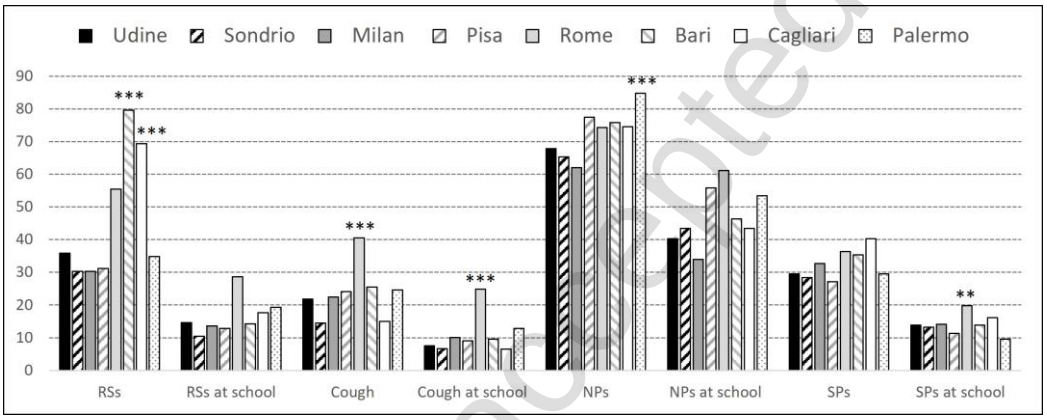

Figure 3