

Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school-children

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Summary

Background Children attending a primary school showed symptoms such as headache, cough, rhinitis and epistaxis. Assessment of specific IgE to formaldehyde gave positive results in some children.

Objective Was IgE-mediated sensitization as well as symptoms in children associated with formaldehyde exposure at school?

Methods Sixty-two 8-year-old children attending three forms at a primary school were investigated. Indoor formaldehyde concentrations were measured in classrooms of both schools (one frame construction with particleboard used extensively as panelling vs a brick building) which were consecutively attended. Assessment of specific IgE to formaldehyde was done in all children. Children were transferred to a brick building and 3 months later specific IgE to formaldehyde in pupils showing initially elevated radioallergosorbent test (RAST) values reassessed. In all children symptoms were evaluated by questionnaire before and 3 months after changing school.

Results In the school panelled with particleboard the World Health Organization (WHO) threshold for formaldehyde of 0.050 ppm was crossed in two classrooms (0.075 ppm and 0.069 ppm) whereas in one classroom 0.043 ppm was found. RAST classes of ≥ 2 were found in three children, two of them attending the classroom with 0.075 ppm formaldehyde. Elevated RAST classes of ≥ 1.3 were found in another 21 pupils. Thirty-eight pupils as well as 19 control children showed RAST classes in the normal range of ≤ 1.2 . Headache, nose bleeding, rhinitis, fatigue, cough, dry nasal mucosa and burning eyes were found in the affected children. There was a good correlation between symptoms and the formaldehyde concentrations in the classrooms. However, elevated IgE levels to formaldehyde did not correlate with symptoms. Formaldehyde concentrations in the classrooms of the brick built school were 0.029 ppm, 0.023 ppm and 0.026 ppm. After transferral specific IgE to formaldehyde decreased significantly from 1.7 ± 0.5 to 1.2 ± 0.2 ($P < 0.002$) as did the incidence of symptoms.

Conclusion Gaseous formaldehyde, besides its irritant action, leads to IgE-mediated sensitization. As children are more sensitive to toxic substances than adults, threshold levels for indoor formaldehyde should be reduced for children.

Keywords: children, formaldehyde sensitization, indoor formaldehyde exposure, specific IgE to formaldehyde, threshold levels

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Introduction

Formaldehyde resin is frequently used in the production of particleboards and urea formaldehyde foam insulations. In addition, formaldehyde is found in textiles, paper and paint [1–3]. Gaseous formaldehyde, emitted from formaldehyde-containing products, is highly soluble in water and thus irritating to mucous membranes of the eyes (starting at 0.01 ppm) and the upper respiratory tract (starting at 0.1 ppm) [1]. In high concentrations (starting at 5 ppm) gaseous formaldehyde may affect the lower part of the respiratory tract causing occupational asthma [2,4–6]. Therefore, formaldehyde has been recognized as a frequent indoor air pollutant.

In November 1992, children attending a primary school (Volksschule Breitenlee, A-1220 Vienna) showed symptoms such as headache, cough, rhinitis and epistaxis. Assessment of specific immunoglobulin E (IgE) to formaldehyde gave positive results. As IgE-mediated sensitization as well as symptoms could possibly be associated to formaldehyde exposure at school, all children were investigated and indoor formaldehyde levels were measured.

In the present study IgE-mediated sensitization to formaldehyde as well as irritant symptoms were documented in 8-year-old school-children during chronic exposure to gaseous formaldehyde in their classrooms at Volksschule Breitenlee and 3 months after cessation of exposure to formaldehyde.

Materials and methods

Patients

Our investigations involved children attending a Viennese primary school (Volksschule Breitenlee) for 2.5 years. All 62 school-children (34 boys and 28 girls, mean age 8 years) attending three different forms (3A, 3B, 3C) of this school were examined. Their school was primarily a frame construction with particleboard used extensively as panelling. In addition, the window frames were embedded into urea foam and the floor covering was pasted.

First RAST examination in December 1992

In all children specific IgE to formaldehyde was assessed using RAST (Biodiagnostics, Freiburg, Germany). Total IgE levels were measured by PRIST (Pharmacia, Uppsala, Sweden). Written informed consent by parents was obtained throughout.

In 46/62 children specific IgE to *Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium* and *Mucor* were measured by RAST (Pharmacia, Uppsala, Sweden). In

addition, mould cultures were used due to the musty odour of classrooms.

Second RAST examination in March 1993 (3 months later)

Due to the elevated indoor formaldehyde concentrations the school-children had left their previous schoolhouse in late December 1992 and had moved into a brick building at the beginning of January 1993.

Specific IgE to formaldehyde was reassessed in 20/24 children whose specific IgE levels to formaldehyde had been higher than RAST class 1.2 in December 1992. In four children we were not allowed to draw blood samples.

Evaluation of children's complaints

Children's complaints were noted from December 1992 and March 1993 as well as smoking habits of persons living in the same household by standardized questionnaires [1,7]. Parents, who filled in the questionnaire, were asked for findings such as epistaxis, rhinitis and cough and subjective symptoms such as headache.

Control children

In 19 healthy, non-atopic children (10 boys, nine girls, mean age 8.5 years, range 7–10 years) not attending this primary school, specific IgE to formaldehyde was also measured. These children showed no symptoms reported by our pupils investigated. Seven of these children lived in a household in which people smoked.

Symptom score and criteria of classification

Specific IgE to formaldehyde reaching RAST-classes ≥ 2.0 were scored as positive. In addition, we scored RAST classes 1.3–1.9 as elevated as all control children showed RAST classes below this level. RAST classes ≤ 1.2 were considered negative.

Assessment of indoor formaldehyde

Indoor formaldehyde of both schools was measured spectroscopically using the standardized 'acetyl-aceton method' (German Industry Standard; DIN 52368). Formaldehyde reacts with pentane-2,4-dione in presence of acetic acid and ammoniated acetate to 3,5-diacetyl-1,4-dihydrolutidin which is measured spectroscopically at 410 nm. This accurate measurement which is done in double assay, has a variation coefficient of $\pm 10\%$.

In order to obtain true indoor formaldehyde levels, the classrooms were not ventilated for at least 5 h. Children were not present in the classrooms on the day of

Table 1. Symptoms in 62 children before and 3 months after changing school

Classroom	December 1992				March 1993				<i>P</i> -value
	3A	3B	3C	62	3A	3B	3C	62	
Number of pupils	22	22	18		22	22	18		
Indoor formaldehyde in ppm	0.075	0.069	0.043		0.029	0.023	0.026		
At room temperature in °C	23.6	22.0	21.0		23.5	22.7	23.6		
At relative air humidity in %	37	30	31		42	41	45		
<i>Objective findings</i>									
Rhinitis	9	8	6	23	3	3	2	8	<0.01*
Cough	8	6	1	15	2	0	0	2	0.01*
Epistaxis	7	6	1	14	0	0	1	1	<0.001*
<i>Subjective symptoms</i>									
Headache	11	8	10	29	5	2	3	10	<0.02*
Dry nasal mucosa	3	5	1	9	0	0	1	1	<0.05*
Poor health	2	4	1	7	0	0	0	0	<0.05*
Burning eyes	2	0	0	2	0	0	0	0	NS*
<i>Additional findings</i>									
Fatigue	7	10	4	21	3	2	1	6	<0.01*

* McNemar test.

measurements. Indoor formaldehyde measurements using the 'acetyl-aceton method' should be done at 23°C as formaldehyde levels show an increase of +10% with each degree centigrade. Measurements done below 20°C provide falsely low results. In addition, an increase in relative air humidity by 5% causes an increase of indoor formaldehyde of +10% (Table 1).

Statistical analysis

For statistical analysis the McNemar test as well as the sign test were used.

Results

Indoor formaldehyde concentrations

Indoor formaldehyde in the school panelled with

particleboard showed levels of 0.075 ppm, 0.069 ppm and 0.043 ppm in the classrooms. In the brick school building indoor formaldehyde was 0.029 ppm, 0.023 ppm and 0.026 ppm respectively (Table 1).

Specific IgE to formaldehyde

In 24 children (40%) elevated levels of specific IgE to formaldehyde were found. Pathological RAST classes ≥ 2.0 (3.2, 3.1, 2.1) were found in three children and elevated RAST classes ranging from 1.3 to 1.9 were found in 21 pupils (Table 2). Thirty-eight pupils as well as all 19 controls showed RAST classes in the normal range ≤ 1.2 .

In the reassessment of specific IgE to formaldehyde in 20 children in March 1993 RAST mean values decreased significantly from 1.7 ± 0.5 to 1.2 ± 0.2 ($P < 0.002$)

Table 2. Specific IgE to formaldehyde in 62 children in December 1992

Classroom	3A (<i>n</i> = 22)	3B (<i>n</i> = 22)	3C (<i>n</i> = 18)
Indoor formaldehyde	0.075 ppm	0.069 ppm	0.043 ppm
RAST ≥ 2.0	2	0	1
RAST 1.3–1.9	10	6	5
RAST 1.0–1.2	10	16	12

Table 3. Decrease of specific IgE to formaldehyde in 20 children in 3 months

RAST classes	December 1992	March 1993	<i>P</i> -value
Mean $\pm$ SD	1.7 ± 0.5	1.2 ± 0.2	<0.002*
Range	1.3–3.2	1.0–1.5	

* Sign test.

(Table 3). RAST values decreased in 18/20 children, 10 out of them dropped below RAST class 1.3. One child's RAST remained constant and in one it rose marginally from 1.3 to 1.4.

Smoking habits of parents

Seven out of 24 pupils having elevated specific IgE to formaldehyde in December had a smoker living in the household (i.e. a person smoking more than 10 cigarettes/day), but also 12/38 pupils with negative IgE antibodies had a smoker in the household. One of the two children who did not show a decrease of RAST classes was living in a smoker-household [1]. There was no cumulation of symptoms found in children living in smoker households.

Children's complaints

There was a good correlation between the number of symptoms and formaldehyde concentrations in the classrooms (Table 1). However, elevated levels of specific IgE to formaldehyde did not correlate with the number and severity of symptoms.

The number of objective findings and subjective symptoms decreased significantly from December 1992 to March 1993 (Table 1), 17/62 children had a total remission.

None of the children had asthma or wheezy bronchitis.

Total IgE, specific IgE to moulds and mould cultures

Mean total IgE was 107 kU/L (range: 2–1020 kU/L). In 20/62 children (32%) total IgE levels exceeded the normal range of ≤ 70 kU/L for 8-year-old children. Nine out of 24 pupils (38%) with elevated RAST results to formaldehyde had elevated total IgE levels (mean 272 kU/L, range: 90–1020 kU/L).

Mould cultures showed negative results in all three classrooms. Only 1/46 children tested for specific IgE against moulds showed a positive RAST result for *Alternaria* (RAST class 2.6).

Discussion

This study shows exposure dependent IgE-mediated sensitization to formaldehyde and surprisingly a lack of correlation of this sensitization with clinical complaints.

Indoor formaldehyde in two classrooms of the school panelled with particleboard exceeded the threshold value of 0.050 ppm considered harmless by the WHO [9]. Buildings exceeded 0.075 ppm indoor formaldehyde

should be reconstructed according to a German threshold level for health risks (Nürnberger Gefährdungsgrenzwert) [8], indoor formaldehyde exceeding 0.080 ppm is considered harmful by WHO [9]. These threshold values for formaldehyde are suitable for adults but not for children [10].

As a remarkable aspect of our investigations, IgE-mediated sensitization to formaldehyde was found in 40% of all children. A concentration dependent correlation between indoor formaldehyde exposure and sensitization appears likely as specific IgE to formaldehyde was found in 55% of children in the classroom with the highest formaldehyde concentration of 0.075 ppm and still in 33% of children in the classroom with the lowest air concentration of 0.043 ppm. However, also the individual propensity for sensitization plays an essential role as shown in the classroom with 0.069 ppm formaldehyde.

IgE-mediated sensitization to formaldehyde is rare and a matter of controversy [11,12]. While Kramps *et al.* [13] stated that exposure to formaldehyde rarely evokes the production of specific IgE, Wilhelmson and Holmström [14] found that long-term inhalation exposure to formaldehyde may sensitize and trigger a classical IgE-mediated allergy in atopics. Formaldehyde released from tooth fillings can sensitize and may cause late onset anaphylactic reactions [15].

Although our children were exposed to only moderate concentrations of formaldehyde at school, 40% of them had specific IgE to formaldehyde indicating that a sensitization to formaldehyde by inhalation took place. Obviously, children are more susceptible to toxic substances than adults [16] and more susceptible to IgE-mediated sensitization.

It appears that sensitization to formaldehyde need not be associated with symptoms as positive RAST results neither correlated with complaints of children nor was a cumulation of symptoms observed in pupils with high RAST classes [10,13]. Our data as well as the literature [13] do not conclusively explain the clinical relevance of specific IgE against formaldehyde.

In contrast, symptoms likely to be caused by irritant actions of gaseous formaldehyde, especially headache, rhinitis, cough and epistaxis, showed a good correlation to indoor formaldehyde. Epistaxis has not been mentioned in the literature as a formaldehyde associated symptom thus far. Irritation of the nasal mucous membranes by formaldehyde may damage the superficial vessels and cause bleeding. Dryness of the nasal mucosa [1], as reported by nine children may lead to formaldehyde induced epistaxis. Headache is a common symptom of formaldehyde exposure which we found in 29/62 children. Feldmann [17] reported significant changes in the EEG in probands exposed to a formaldehyde

concentration of 0.044 ppm. Moderate doses of formaldehyde therefore may cause functional alterations in the central nervous system [1].

Although assessment of symptoms is based on subjective evaluation which may be biased by parents [18], the significant reduction of formaldehyde associated symptoms and of specific IgE to formaldehyde after cessation of exposure suggest that formaldehyde emitted in the classrooms of the first school was the causing agent of the children's complaints. The main difference between the two school buildings was that the second was a brick building without particleboards as panelling. Both schools had no air condition and were cleaned in a similar manner. Living conditions of children as a source for formaldehyde exposure did not change during the observation period. As December to March are the coldest months in Austria, children spent most of their time indoors. Infectious diseases such as rhinitis and cough may be more common in December than in March perhaps partly explaining the decrease of symptoms in children. However, children also experienced symptoms in September and October 1992 in the particleboard school, which prompted commencement of assessment. The absence of cat, house dust mite and mould sensitization as well as the absence of the most common outdoor pollutants, which were also assessed, obviously excludes other possible causative factors.

Although we cannot comment on a possible regression to the mean effect in the assessment of specific IgE to formaldehyde between December and March, the significant decrease of specific IgE to formaldehyde after changing school is good evidence that formaldehyde exposure in the first school, to what ever extent, was causing sensitization.

In conclusion, chronic formaldehyde exposure induces IgE-mediated sensitization in children already at moderate concentrations. Children are more susceptible to toxic substances than adults. Thus threshold levels for indoor formaldehyde should be reduced for children. On the basis of sensitization and symptoms present in our group of children, formaldehyde exposure should be considered more frequently.

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