Allergy to methyltetrahydrophthalic anhydride in epoxy resin workers

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Abstract

One hundred and forty four current and 26 former workers in a plant producing barrels for rocket guns from an epoxy resin containing methyltetrahydrophthalic anhydride (MTHPA; time weighted average air concentration up to 150 $\mu g/m^3$) were studied. They showed higher frequencies of work related symptoms from the eyes (31 *v* 0%; $p < 0.001$), nose (53 *v* 9%; $p < 0.001$), pharynx (26 *v* 6%; $p < 0.01$), and asthma (11 *v* 0%; $p < 0.05$) than 33 controls. Also they had higher rates of positive skin prick test to a conjugate of MTHPA and human serum albumin (16 *v* 0%; $p < 0.01$), and more had specific IgE and IgG serum antibodies (18 *v* 0%; $p < 0.01$ and 12 *v* 0%; $p < 0.05$ respectively). There were statistically significant exposure-response relations between exposure and symptoms from eyes and upper airways, dry cough, positive skin prick test, and specific IgE and IgG antibodies. There was a non-significant difference in reaction to metacholine between exposed workers and non-smoking controls. In workers with and without specific IgE antibodies, differences existed in frequency of nasal secretion (54 *v* 23%; $p < 0.05$) and dry cough (38 *v* 12%; $p < 0.05$). Workers with specific IgG had more dry cough (38 *v* 12%; $p < 0.05$), but less symptoms of non-specific bronchial hyperreactivity (0 *v* 26%; $p < 0.05$). Atopic workers sneezed more than non-atopic workers (65 *v* 30%; $p < 0.01$). In a prospective study five sensitised workers who left the factory became less reactive to metacholine, and became symptom free. In 41 workers who stayed, there was no improvement, despite a 10-fold reduction in exposure. The results show the extreme sensitising properties of MTHPA.

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Organic acid anhydrides are widely used in the production of alkyd resins and as curing agents for epoxy resins. Adverse health effects of occupational exposure to several anhydrides have earlier been described—namely, phthalic anhydride (PA), maleic anhydride (MA), himic anhydride, tetrachlorophthalic anhydride (TCPA), trimellitic anhydride (TMA), tetrahydrophthalic anhydride (THPA), and hexahydrophthalic anhydride (HHPA).[1] These have irritating effects on mucous membranes and sensitising properties, causing symptoms from the eyes and airways. Influenza-like symptoms have been described after exposure to TMA and PA.[1]

We have earlier documented a case of asthma associated with another acid anhydride, methyltetrahydrophthalic anhydride (MTHPA),[2] and shown a high prevalence of sensitised subjects among workers exposed to low air concentrations of this compound.[3] Also, a case of MTHPA sensitivity was reported by Kanerva *et al.*[4]

We report here the results from further examinations, including the frequencies of symptoms, lung function, and tests for non-specific bronchial reactivity, in workers exposed to MTHPA and, also, in subjects previously exposed in the same factory.

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Materials and methods

PRODUCTION AND EXPOSURE

The plant manufactured various plastic products. Main items were barrels for rocket guns, based on an epoxy resin. Rotating cylinders were prepared, by hand swabbing on glass fibre, with a mixture of epoxy resin (50%), MTHPA (as a hardener), and methylimidazol (0·3%). Then the cylinders were wound automatically with glass fibre cords wetted with the same mixture. The cylinders later passed through a curing oven at 90–120°C. After curing, the plastic barrels were processed mechanically.

The department was situated at one end of a big workshop. In the rest of the shop, various different thermoplastics were manufactured in forming machines. Air moved from the epoxy line to these departments. In other parts of the factory small amounts of other anhydrides (MA, THPA, HHPA,

and PA) were used in the production. The workshop and exposure have been described in detail in a previous paper.[3]

After the first medical examination, the ventilation system was improved. Thus exposure to MTHPA was reduced to one tenth of the previous exposure.

SUBJECTS

At the first examination, a total of 144 currently exposed workers were studied; 13 were women. They were divided into three MTHPA exposure categories—namely, high (group H; n = 55), low (group L; n = 70), and others (group O; n = 19).

The subjects in group H (age range 21–51) worked in the particular area where the epoxy system was handled directly. The time weighted average (TWA) exposure to MTHPA ranged from 20 to 150 $\mu g/m^3$ in the different areas where the group H members worked (personal sampling for a total of 148 hours). Their median exposure time was 2·0 years (range 0–6·0). Group L (age 18–62) consisted of persons in the adjoining departments who were manufacturing thermoplastics or occupied in mechanical processing of plastic products. Their TWA exposure to MTHPA was 5–20 $\mu g/m^3$ (personal and area sampling for 74 hours). Group O (age 18–61) had an exposure that varied considerably in intensity. Thus they could not be classified in the previously mentioned categories.

All 26 former workers (group F; age 21–47) who had worked in the "high" exposure area but who had left the factory were identified. They were asked to participate in a medical examination. Nobody refused, but five subjects had moved, and could not take part in the full investigation; one other subject was not examined fully. The median exposure time for the group was 0·9 years (range 0·2–2) and the subjects had been out of exposure for a median 2·7 years (range 1–5).

As control subjects, 33 persons (age 20–50; three women) from a nearby mechanical workshop were studied. They were not exposed to acid anhydrides and their exposure to potentially irritating or sensitising aerosols and vapours were low.

The presently exposed workers in group H and 13 of the control group were retested in a second examination three months after the work environment had been improved.

MEDICAL EXAMINATION

In each case a physician (JN) obtained a medical and occupational history. Standardised questions were asked about atopy (hay fever, asthma, atopic eczema, or urticaria during childhood or adolescence) and smoking habits (modified from Rose and Blackburn 1968).[5] Symptoms (general, including influenza-like symptoms, and local, from the eyes, nose, pharynx, and lower respiratory tract) related to work were also recorded.

For all work related symptoms, the frequency of complaints (daily; once a week or more; once a month or more; less than once a month; never) and latency time (the time from start of MTHPA exposure to the first appearance of symptoms) were recorded. Asthma was defined as attacks of wheezing breath, dyspnoea, and cough. Work related symptoms were defined as those associated with work (recovering during weekends and holidays[6]). Non-specific bronchial hyperreactivity was defined as attacks of wheezing breath, dyspnoea, or chest tightness at exposure to strong odours, dust, cold, or exercise. Chronic bronchitis was defined as daily productive cough for more than three months each year in the past two years.[7]

A physical examination was performed including pulmonary auscultation. Venous blood samples were analysed for total serum concentrations of IgE and IgG. Further, specific IgE and IgG antibodies were assayed by use of radioallergosorbent tests and enzyme linked immunosorbent assay methods, respectively, against a conjugate of MTHPA and human serum albumin (HSA) (MTHPA-HSA). Values in the exposed group higher than the highest control value were regarded as positive.[3 8]

Skin prick tests with 13 common allergens (Allergologisk Laboratorium, Copenhagen, Denmark) and with MTHPA-HSA were performed as described earlier.[3 8]

Also, Group H was skin prick tested with a 1% solution of diglycidylether of bisphenol A (DGEBA; molecular weight 340) in alcohol, and a patch test with 1% DGEBA in petrolatum was performed (read after 48 hours).

LUNG FUNCTION TESTS

Forced expiratory volume in one second (FEV_1) and vital capacity (VC) were determined in all subjects with a Vitalograph S-model spirometer (Vitalograph Ltd, Buckingham, England) in accordance with the guidelines of the American Thoracic Society.[6] One control and two exposed workers could not perform a technically sufficient spirometry (in the second examination).

A metacholine test was performed after spirometry in groups H and F and in the control group: an aerosol of 0·05% metacholine chloride solution in saline was deeply inhaled for two minutes. The aerosol was dosed by a micronebuliser (Bird asmastik model 1750) with a compressor (Bird 2088 C; Bird Corporation, California, USA). The aerosol was delivered with a pressure of 15 cm H_2O. Spirometry was again performed two and five minutes after inhalation. If FEV_1 declined by less than 15% of the initial value, the procedure was repeated two minutes after the last spirometry with higher metacholine concentrations (0·5% and 2%). Subjects who had a

Table 1 Age, sex, smoking habits, atopy, work related symptoms, chronic bronchitis, non-specific bronchial hyperreactivity, skin prick test reactivity, and specific serum antibodies in 170 workers exposed to methyltetrahydrophthalic anhydride and 33 controls

	Exposure						
	Current				*Former*		*Exposure-response relation (p Value‡)*
	High (H) (n = 55)	*Low (L) (n = 70)*	*Other (O) (n = 19)*	*Total (n = 144)*	*High (F) (n = 26)*	*Controls (n = 33)*	
Age (y (median))	27	36	42	34	24	37	—
Women (%)	4	16	0	9	0	9	—
Smokers (%)	11	44	42	31	27	24	—
Ex-smokers (%)	16	21	21	19	23	18	—
Atopy:							
History (%)	22	11	21	17	23	24	—
Standard skin prick test (%)	13	11	11	12	45†	18	—
Symptoms:							
Work related*							
Eyes and upper airway (%)	65	56	42	58	69	9	<0·001
Eyes (%)	42	23	32	31	23	0	<0·001
Nose (%)	56	53	42	53	69	9	<0·001
Secretion (%)	31	21	26	26	31	3	<0·01
Blockage (%)	45	30	42	38	50	6	<0·001
Sneezing (%)	42	30	37	35	46	3	<0·001
Pharynx (%)	31	24	21	26	19	6	<0·01
Asthma (%)	11	9	21	11	8	0	NS
Dry cough (%)	18	3	11	10	8	3	<0·01
Non-specific bronchial hyperreactivity (%)	20	20	21	20	19	12	NS
Chronic bronchitis (%)	9	4	16	8	12	9	NS
Specific skin prick test (%)	18	14	16	16	10†	0	<0·05
Specific serum antibodies:							
IgE (%)	22	16	16	18	8	0	<0·01
IgG (%)	24	4	5	12	0	0	<0·001

*Symptoms during the work at the factory.
†Twenty subjects tested.
‡Test for trend over groups H, L, C.

history of bronchial hyperreactivity were initially tested with a lower concentration of metacholine (0·005%). Subjects who had suffered from airways infection within the past three weeks before the investigation were not tested.

By taking the baseline value of FEV_1 and the lowest of the two and five minute values achieved after each inhaled concentration, we obtained points in a coordinate system (metacholine concentration as abscissa and FEV_1 as ordinate). For each worker a concentration-response curve was determined by fitting the function $y = a + b \sqrt[3]{sc}$. Thus y is the estimated FEV_1 value after inhalation of the metacholine concentration c, a the estimated baseline value of FEV_1, and b describes the decline of the curve. The value of b was used as a measure of the bronchial reactivity. Due to the limited size of the control group the b values of the non-smoking controls were transformed (change of sign, inverted, and raised up to the power of 0·2) to obtain a normal distribution, and a tolerance limit was identified. A worker with a likewise transformed b value numerically higher than that limit was defined as a reacting subject.

STATISTICAL ANALYSIS

The analysis given in tables 1 and 2 were mostly devoted to the comparisons of the two proportions and statistical tests were applied to the associated fourfold tables: a χ^2 test with Yates' correction for continuity was used when the expected cell quantities were sufficiently high; otherwise Fisher's exact test was chosen. In the investigation of dose-response relations the Cochran-Armitage test for trend of proportions was applied. In table 3 the two sample rank sum test (the Mann-Whitney U-test) was employed to test the equality of the medians of two groups. Individual changes were tested with the Wilcoxon signed rank test. This test was also applied in table 4 with due attention paid to zeros and ties. Differences were considered to be statistically significant at two sided p values smaller than 0·05.

Results

SMOKING AND ATOPY

Group H comprised a smaller proportion of smokers than the other groups (table 1). The difference was significant *v* group L ($p < 0·001$).

Group F contained more subjects with a positive standard skin prick test than the other groups. The difference between group H and group F was statistically significant ($p < 0·01$). The history of atopy showed no significant group differences.

Table 2 Work related symptoms, non-specific bronchial hyperreactivity and chronic bronchitis in sensitised (positive specific serum IgE or IgG antibodies) and unsensitised subjects among 55 workers with present high exposure to methyltetrahydrophthalic anhydride (group H)

	IgE		*IgG*	
	Sensitised (n = 12)	*Unsensitised (n = 43)*	*Sensitised (n = 13)*	*Unsensitised (n = 42)*
Smokers (%)	8	12	0	14
Atopy:				
History (%)	33	19	23	21
Standard skin prick test (%)	25	9	15	12
Symptoms:				
Work-related				
Eyes and upper airways (%)	69	63	85	60
Eyes (%)	46	40	46	40
Nose (%)	69	51	77	50
Secretion (%)	54*	23	46	26
Blockage (%)	69	37	69	38
Sneezing (%)	62	35	62	36
Pharynx (%)	31	30	31	31
Asthma (%)	8	12	0	14
Dry cough (%)	38*	12	38*	12
Non-specific bronchial hyperreactivity (%)	8	23	0*	26
Chronic bronchitis (%)	0	12	8	10

*$p < 0.05$ in tests between sensitised and unsensitised workers.

SYMPTOMS

For work related symptoms (without consideration of time frequency) the total group of currently exposed workers had more complaints from eyes and upper airways than the controls (table 1; all p values <0.01). Furthermore, there were statistically significant relations between the MTHPA-exposure (over groups H, L, and C) and all symptoms. Group F had higher frequencies for all eye and nose symptoms than the controls (all p values <0.01). When groups H and F were compared, there were no statistically significant differences.

For the 30 of the 36 subjects in group H who displayed symptoms from eyes and upper airways, latency time (start of exposure to onset of symptoms) was recorded. Nine (30%) had their symptoms "immediately", an additional 14 (47%) in the first year, and seven (23%) after more than a year (up to four years; maximum observation period six years). For the 13 of the 16 subjects in group F who had symptoms, one of them developed symptoms "immediately", 11 (69%) in the first year, and one after more than a year.

When symptoms from lower airways were studied, more exposed subjects than controls had work related asthma (table 1; $p < 0.05$). There was a statistically significant exposure-response relation for dry cough only.

Among the highly exposed workers (groups H and F), eight persons (10%) had symptoms of work related asthma. Only one of these had a history of atopy and only one was a smoker.

The latency time ranged from "immediately" to two years. No associations were found between exposure intensities and frequencies of the different symptoms (data not given). When symptoms were studied in relation to history of atopy and smoking, atopic workers generally had more work related symptoms than non-atopic workers (total symptoms from eyes and upper airways 70 *v* 58%; asthma 15 *v*

Table 3 Spirometry and metacholine test (median and range) in 55 current (group H), 21 former (group F) methyltetrahydrophthalic anhydride (MTHPA)-exposed workers, and 33 controls. In the current workers and in 13 controls, examinations were made before and after a major reduction in exposure

	Highly exposed workers (group H)				
	Current			*Controls*	
	Before	*After*	*Former*	*Before*	*After*
Spirometry (No)	55	39	21	32	13
VC (l)	5·5 (4·2 to 6·8)	5·4 (4·1 to 7·2)	5·2 (4·5 to 7·5)	4·9 (3·4 to 6·2)	5·2 (4·1 to 5·6)
FEV_1 (l)	4·5 (3·2 to 6·0)	4·5 (3·0 to 5·9)	4·4 (3·7 to 6·3)	4·3 (2·8 to 5·5)	4·3 (3·0 to 4·9)
Metacholine test (No)	47	38	19	29	13
b Values*	−0·5 (−4·3 to 0·5)	−0·5 (−1·8 to −0·1)	−0·4 (−1·5 to −0·01)	−0·5 (−3·3 to 0·1)	−0·3 (−1·0 to −0·1)

*For description, see text.
All differences were non-significant.

Table 4 Work related symptoms (number of workers) among 41 workers with current high exposure to methyltetrahydrophthalic anhydride three months after a major reduction in exposure. Number of subjects who had some symptoms before the reduction are shown in parentheses

	Symptom occurrence			
Symptoms	*More often*	*Unchanged*	*Less often*	*p Value**
Eyes	5 (1)	25 (3)	11 (11)	0·21
Nose:				
Secretion	7 (1)	24 (3)	9 (9)	0·77
Blockage	5 (1)	28 (9)	7 (7)	0·68
Sneezing	10 (5)	22 (3)	8 (8)	0·61
Pharynx	6 (2)	26 (1)	8 (8)	0·58
Asthma	6 (0)	32 (1)	3 (3)	0·24
Dry cough	2 (0)	34 (1)	5 (5)	0·36

*Change of symptoms (two tailed).

9%; dry cough 20 *v* 8%), but the difference was only significant for sneezing (65 *v* 30%, $p < 0·01$). No statistically significant differences were found between smokers and non-smokers (total symptoms from eyes and upper airways 59 *v* 59%; asthma 6 *v* 8%; dry cough 16 *v* 3%; ex-smokers excluded). Nobody complained of influenza-like symptoms related to work.

IMMUNOLOGY

None of the controls had a positive reaction in skin-prick tests with MTHPA-HSA (table 1). The currently exposed workers (groups H, L, and O combined) had more often a positive skin-prick test ($p < 0·01$), as well as positive specific IgE ($p < 0·01$) and IgG ($p < 0·05$) serum antibodies than controls. Group H contained more IgG positive workers than group F ($p < 0·01$), but no significant difference was found with regard to IgE positive workers between the two groups. Statistically significant exposure-response relations were found for all three tests.

When group H was dichotomised according to IgE sensitisation to MTHPA-HSA, no significant differences were found between the subgroups for atopy or smoking habits (table 2). More IgE positive subjects showed symptoms from the nose, but this was only statistically significant for secretion. Also, the positive workers had significantly more dry cough than the IgE negative workers.

Group H was studied with regard to IgG sensitisation against MTHPA-HSA (table 2). Significantly more positive subjects had dry cough. By contrast, none of the positive workers complained of symptoms of non-specific bronchial hyperreactivity *v* 11 (26%) in the negative subgroup.

Only two of the eight asthmatic workers in groups H and F were sensitised (positive skin prick test and positive for IgE-MTHPA-HSA). Both of them had a history of atopy and a positive standard skin prick test to common allergens. The other six were not atopic and had negative skin prick tests. None of the asthmatic workers had IgG to MTHPA-HSA. There was no positive skin prick test against DGEBA, whereas one person in group H had a positive reaction in the patch test (not in table).

LUNG FUNCTION

Groups H, F, and C were studied by spirometry and metacholine tests. There were no statistically significant differences between the groups for spirometry (table 3). For the metacholine test, different tolerance limits (ranging from 50–95%) for b values in the group of non-smoking controls, were calculated. The largest excess proportion of reactives in group H was at the tolerance limit of 75% ($b = -0·82$), but this excess was not significant (36 *v* 25%; $p = 0·08$), not even in a multivariate analysis where smoking was taken into account. For ex-smokers in group H, the proportion of reactive workers (5/7) was significantly higher than 25% ($p = 0·005$). Among the ex-smokers in the control group this relation was weaker (2 of 6; $p = 0, 64$). No current smokers among the exposed workers were reactive (0 of 6 *v* 1 of 8 among the controls). Among the five tested subjects with symptoms of work related asthma in group H, only one reacted. He was one of the two sensitised asthmatic workers. The other sensitised asthmatic worker was from group F; he had not been exposed for three months and he was still reactive.

When group H was dichotomised according to presence of specific IgE antibodies, the positives had a higher fraction of reactive workers (45 *v* 33), but the difference was not significant ($p = 0·46$); neither were they different from the controls ($p = 0·12$). There was no difference between those with and without specific IgG (33 *v* 37%; $p = 0·81$).

IMPROVEMENT OF THE WORK ENVIRONMENT

The 41 subjects in group H who participated in the examination both before and after improvement of the work environment were studied with regard to changes in frequencies of symptoms. No significant decreases were found (table 4). Neither were there differences in metacholine reactivity (table 3).

Out of the 41 workers in group H, seven sensitised workers with symptoms who continued to work in

the same workroom (but at a lower exposure), were tested twice. One of them, with symptoms from eyes and upper airways and with a productive cough, had a clear increase in reactivity (slopes: $-0{\cdot}3$ *v* $-1{\cdot}4$), but no change of symptoms. Another subject, with symptoms from upper airways, had a decrease in the slope ($-0{\cdot}9$ to $-0{\cdot}5$); he reported less symptoms. The other five had only minor changes in reactivity; one had developed more symptoms from eyes and upper airways, and the others were unchanged.

Five persons in group H (in connection with the first examination) were removed from exposure because of sensitisation to MTHPA and symptoms. They were also retested. After stopping the exposure, they had no complaints of symptoms, and all of them showed a lower bronchial reactivity in the second examination, irrespective of the degree of reactivity in the first one (slopes in first *v* second examination: $-0{\cdot}9$ *v* $-0{\cdot}8$, $-0{\cdot}4$ *v* $0{\cdot}0$, $-4{\cdot}3$ *v* $-1{\cdot}6$, $-0{\cdot}6$ *v* $-0{\cdot}1$ and $-3{\cdot}5$ *v* $-2{\cdot}2$). The relative change for this subgroup was significant ($p = 0{\cdot}02$).

Discussion

Despite the extremely low exposure to MTHPA, more than half the workers suffered symptoms from eyes and airways. The main agent responsible for the symptoms in group H was probably MTHPA although the presence of other irritating substances must also be considered. The epoxy component has a low irritating property. Hypersensitivity with airways symptoms seldom occurs in workers exposed to epoxy resin,[4] and in our study skin prick testing did not reveal signs of sensitisation to the epoxy component. Some amines have irritative effects at low doses[9]; this is probably also true for methylimidazole. In the present mixture, this compound was only a small fraction, and as it has a rather low vapour pressure, the exposure was probably minor. Also, preliminary measurements indicate that the amine concentration is lower than that of the anhydride (B Åkesson of this department, personal communication).

Response to the thermal degradation products of plastics is an unlikely explanation of the symptoms in group H because of the arrangement of the ventilation system. In group L, however, exposure to such products occurred, as well as to dust of plastics. These agents may have irritating properties on mucous membranes, and may be responsible for some of the effects in that group.

The frequency of symptoms among the past workers was not raised compared with the current ones. Hence, there was no indication of a healthy worker selection caused by work related symptoms.

The present frequency of complaints from eyes and upper airways was at the same high level as found in our earlier study of workers exposed to PA dust, although the exposure in that study was as much as three orders of magnitude higher (up to 17 mg/m^3).[10] Effects of acid anhydrides on the eyes and upper airways have also been described for TMA fumes in workers[11] and in animals exposed to MA,[12] but the exposures in these studies (1–2 mg/m^3) were higher than in the present one. Effects of a few other anhydrides have been reported,[1] but without exposure data.

The present frequency of work related asthma is lower than that found in our study of workers exposed to PA dust (10 *v* 18%) at a much higher concentration (up to 23 mg/m^3).[13] In another anhydride study, out of workers exposed to vapour of HHPA at a surprisingly high concentration (2–4 mg/m^3, 11% developed asthma.[14] In an examination of subjects exposed to TCPA powder (exposure concentration not stated), 4% had work related chest symptoms.[15]

Despite the low exposure, a high fraction of the workers developed antibodies against MTHPA-HSA. Thus MTHPA seems to be one of the most potent allergens encountered.

A high frequency of work related dry cough was found in current workers with high exposure. The pathomechanism of this symptom is not fully understood. It might indicate bronchospasm;[16] however, with regard to non-specific bronchial hyperreactivity, no significant difference was found *v* the control group (C), either by history, or by metacholine test. This indicates that exposure to MTHPA did not generally increase the bronchial reactivity, which is in accordance with the results of a study of subjects exposed to PA in which no effects were found on reactivity of the small airways.[17] On the other hand, a metacholine test may be of limited value as a diagnostic tool for bronchial hypersensitivity caused by low molecular weight compounds.[18 19] This may also be the explanation of the low number of workers reactive to metacholine among the exposed groups and asthmatic workers.

Alternatively, dry cough may be the result of the irritative effect of MTHPA on the sensory nerves in the lower airways[20] or on irritant receptors in the larynx and upper airways.[21]

When IgE sensitised and unsensitised subjects were compared, both subgroups had frequent symptoms. Only for nasal secretion and dry cough did the sensitised workers have significantly higher frequencies. The complaints in the non-sensitised group were probably of an irritative nature; the lack of difference indicates that the same could apply to the sensitised group. Thus the clinical consequence of the sensitisation is not obvious. Specific provocation tests are necessary to clarify this matter.

The same pattern was seen in IgG-sensitised and unsensitised subgroups. In the sensitised subgroup, nobody was a smoker. This is worthy of note, as it has

earlier been claimed, for other exposures, that non-smokers run a greater risk of developing specific IgG antibodies.[22] Surprisingly, nobody with specific IgG antibodies complained of symptoms of non-specific bronchial hyperreactivity, compared with a quarter of the unsensitised subjects. Of course, this may be due to chance but development of IgG antibodies is often regarded as an indicator of exposure. Thus possibly subjects with a tendency to non-specific bronchial hyperreactivity avoided high exposure and therefore did not develop IgG antibodies.

Interestingly, significantly more previous workers than current ones had a positive skin prick test with common allergens. In both groups together, however, 21% were positive, which is the same fraction as in the control group (C). Thus, atopic workers, who are more reactive in their mucous membranes, tend to disappear from the exposure at an early phase, perhaps even before clear work related symptoms or a specific sensitisation has occurred. That could be an explanation why atopic workers, in many studies of small reactive organic molecules, do not seem to run a particular risk of sensitisation.[23] Another interesting finding was the association between ex-smokers, high exposure, and reactivity to metacholine. This may indicate that the exposure to MTHPA has forced workers to stop smoking.

The five sensitised subjects who left exposure became symptom free and showed a decrease in their bronchial reactivity. It thus seems that the reversibility of the reactions in the present workers was better than has been reported for subjects exposed to TCPA.[24] In the present workers who stayed in the factory, no significant decrease in symptom frequencies and bronchial reactivity was seen even after a considerable improvement of the work environment. This confirms that the epoxy system containing MTHPA has a high biological activity. Thus methods of preventing exposure need to be extremely efficient.

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