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# OCULAR AND AIRWAY SYMPTOMS RELATED TO ORGANIC ACID ANHYDRIDE EXPOSURE - A PROSPECTIVE STUDY.

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**ABSTRACT**
*Background*: Organic acid anhydrides (OAA) are used as hardeners in epoxy resin systems. They are powerful sensitizers giving frequent rhinitis and asthma in exposed workers. Incidence of symptoms are unknown. Here we present the first prospective study on the associations between OAA exposure, symptoms and effects of confounding factors.
*Methods*: All new employees in three plants handling OAA were followed for up to 8.5 years. Before the employment, a questionnaire reporting about symptoms from eyes and airways, smoking habits and atopy was answered. The subjects were asked at regular medical examinations about work tasks and work- related symptoms. Serum was analysed for specific OAA antibodies.
*Results*: Mean exposures varied between 6 and 39 µg/$m^3$.The incidence for work-related symptoms from the eyes, nose, pharynx and lower airways was 91, 64, 46, and 31 per 1000 years of exposure respectively. Symptoms were found frequently, even at mean exposure level at < 10µg/$m^3$. Smoking and atopy increased the risk of symptoms. IgE sensitized workers had a significant increased risk for symptoms from the eyes and pharynx and for running nose/sneezing.
*Conclusions*: OAA exposure is associated with frequent ocular and airway symptoms even at mean exposure levels at < 10µg/$m^3$. There is an important need for establishment of an occupational threshold limit. A limit value of below 5µg/$m^3$ is proposed.

Key words: hexahydrophthalic anhydride, low molecular weight compounds, methylhexahydrophthalic anhydrides, methyltetrahydrophthalic anhydride,

## INTRODUCTION

Organic acid anhydrides (OAA) are used as hardeners in epoxy resin systems and in the production of alkyd or polyester- resins. They have sensitizing properties even at low exposure levels (1, 2, 3, 4) and frequent ocular and upper and lower airway symptoms have also been associated with OAA exposure, not only in sensitized subjects (1, 5, 6, 7, 8).

Effects of some confounding factors such as atopy and smoking habits on these symptoms in OAA exposed workers are not clear. In most studies, smoking did not turn out to be a risk-factor for development of work-related airway symptoms (1, 6, 9,10,11). Atopy on the other hand has been shown to increase risk for symptoms from airways in some studies (1, 6, 9,12).

However, these studies investigating risks at OAA exposure are cross sectional or retrospective and may thus be biased in different ways e.g. due to healthy worker selection (13). Furthermore, information on incidence rates of symptoms are, to our knowledge, not available. For these reasons, there is a need for prospective studies. We have earlier reported results from a prospective study concerning sensitization to OAA (4). The aim of our present work is to evaluate incidence of ocular and airway symptoms from the same study population and possible effects of modifying factors such as IgE and IgG sensitization to OAA, smoking habits and atopy.

## METHODS

*Subjects and plants*

All workers starting employment at the three chosen plants handling OAA were included in the study. They had not been exposed to OAA previously. A total of 146 subjects (84 men and 62 women) were followed for up to 8.5 years. The median calendar year of birth was 1962 (range 1926-1973). The OAAs used were methyltetrahydrophthalic(MTHPA), hexahydrophthalic(HHPA) and/or methylhexahydrophthalic (MHHPA) anhydride used as curing agents in production of epoxy resin. The investigation started in 1988 and no subjects were recruited after 1997. The study was approved by the local ethics committee.

*Plant 1* : MTHPA was used as a hardener in an epoxy resin system in the production of barrels for grenade fire arms.The mean exposure was 5.9µg/$m^3$ (116 samples, total sampling time 284 hours)(4) with an observation time of 9 years.

*Plant 2* : MTHPA was used as hardener in an epoxy resin system used for fixation and isolation of components in ignition systems. An accelerator, bensyldimetylamine, in an amount less than 1% was added. The mean exposure was 10.1µg/$m^3$ (169 samples, total sampling time 428 hours) (4) with an observation time of 4 years

*Plant 3* : HHPA and MHHPA was used as hardener in an epoxy resin system used for production of electrical capacitors. An accelerator, dimethylbenzylamine, was added to the system in an amount between 0.3-1.0%. The mean exposure for OAA (expressed as the sum of HHPA and MHHPA) was 38.7µg/$m^3$ (463 samples, total sampling time 1245 hours) (4) with an observation time of 9 years.

In plants 2 and 3 most of the work was performed in closed systems and exposure originated from leaks especially from the ovens. In Plant 3, subjects working in the highest exposure departments were equipped with supplied-air respirators most of the time. Protective devices were used at the other plants when exposures were relatively high and also their use was not consequently(4). In all three plants, the work shifts were 8 hours and the work load was light.

*Individual data*
Before the start of employment, all subjects from all three plants filled out a questionnaire regarding symptoms (see below) and serum for testing of specific antibodies was collected before employment. In plants 2 and 3, once a year, all participants went through a medical examination including blood sample. Further, at the first medical examination a standard skin-prick test was performed. In plant 1 the medical examination was performed every two years. All medical examinations were performed by the same physician, a specialist in occupational medicine (JN). From the work histories and the exposure measurements for different work tasks, individual mean exposure levels were calculated for all subjects.

*Questionnaire*
All subjects answered questions about work history, atopy, smoking habits and symptoms from eyes, nose, pharynx and the lower respiratory tract.

*Medical examination*
Extensive occupational and medical histories including atopy and smoking habits were obtained by the physician through detailed interviews.

Atopy was defined as a history of hay fever, asthma, atopic eczema or urticaria (when the association to a known allergen was convincing) in childhood and adolescence. Smoking habits were obtained according to Rose and Blackburn 1968 (14).

Eyes symptoms denote foreign body sensation, burning, and/or itching or lacrimation. Nasal symptoms denote blockage, secretion and/or itching/sneezing. Pharyngeal symptoms mean sensation of dryness, irritation and/or itching. Asthmatic symptoms are defined as recurrent attacks of dyspnea, wheezing and cough. Dry cough means recurrent attacks of cough without sputum. The term symptoms from the lower airways stand for presence of dry cough and/or asthmatic symptoms. The symptoms were considered work-related if they appeared in direct relation to a specific work-task and/or they disappeared or clearly improved during weekends or vacations.

*Skin prick tests*
At the first medical examination each subject was skin-prick tested with a panel of 12 common allergens (Allergologisk Laboratorium, Copenhagen Denmark). Persons with at least one positive reading were defined as atopics by skin-prick test. The allergen reaction was read against that of histamine 3mg/ml according to Aas and Belin 1973 (15).

*Antibody determination*
Specific antibodies of IgE and of IgG classes against the relevant OAA human serum albumin conjugate were determined according to procedures described earlier (16, 4).

*Exposure assessments*
Air measurements were carried out annually, throughout the study period and also when any changes in the production-lines were introduced. Sampling and analysis was performed according to Welinder et al 2001 (4) using personal sampling in the breathing zones, or when the work-task was stationary by area sampling. The detection limit was 0.2µg/ml toluene for MTHPA and 0.1µg/ml toluene for HHPA corresponding to 0.5 –1µg/$m^3$ at a sampling volume of 200L (4).

*Statistics*
Two different measures of exposure were used: plant affiliation and mean exposure. These two measures were not included simultaneously in the models described below. For each subject, their mean exposure (average exposure intensity) was calculated from start of employment until the symptoms of interest appeared, the employment ceased or to the end of the follow-up period, whichever occurred first. The mean exposure was categorized into three groups; 0-10, >10-15 and >15 $\mu g/m^3$. Differences in exposure among symptomatic and none symptomatic subjects were tested by Mann-Whitney U test. The effect of exposure on the risk of developing ocular and airways symptoms, respectively, was evaluated by logistic regression models, where odds ratios (OR) with 95% confidence intervals (CI) were obtained. We also adjusted for potential confounders in the multivariate models if there was a tendency to association between exposure and symptoms (lower confidence limits >0.8). Gender, smoking, atopy, development of specific IgE and IgG antibodies were considered as potential confounders. In addition, effect modification was evaluated by including interaction terms in the models.

**RESULTS**
*Descriptive data*
The mean exposures varied between 6 and 39 $\mu g/m^3$. For each symptom studied, the cohort was divided into two groups; those who developed symptoms and those who did not (table 1). Only for nasal blockage a significant difference in exposure (P= 0.01) was noticed between symptomatic and asymptomatic workers. Symptomatic subjects were more often sensitized (specific IgE) than asymptomatic ones (table 1). Workers having running nose/sneezing had the highest fraction of sensitized subjects (48%) compared to those with other work-related symptoms. There was no significant differences in latency time between the different symptoms (table 1). Ten of the workers who developed asthmatic symptoms also had rhinitis. In half of the cases rhinitis preceded the asthmatic symptoms. Also, smoking habits and atopy in symptomatic and asymptomatic workers are given in Table 1.

*Incidence rates of work-related symptoms and latency times*
The incidence rates for the different symptoms are given in table 2. Ocular symptoms were most frequent with a rate of 91 cases per 1000 person-years at risk; less frequent were symptoms from the lower airways with 31 cases per 1000 person-years at risk.

*Risk-factors*
The mean exposure level was associated with nose blockage and with symptoms from the lower airways, with significantly increased risks for individuals with mean exposure levels above 15 $\mu g/m^3$ compared with individuals with levels below 10 $\mu g/m^3$ (Table 3 and 4). After adjustment for potential confounders the significant associations were still present. For the other symptoms no statistically significant increases were noticed in the highest exposure category.

Incidence rates (cases per 1000 years) were calculated for the three exposure categories (0-10, >10-15, >15 $\mu g /m^3$) for nose blockage and lower airways symptoms. The figures found were: for blockage 31, 103, and 139 and for lower airways symptoms 20, 43 and 59 respectively.

Also, when effect of plant affiliation was studied an association between development of symptoms and plant a significant increase was seen for ocular symptoms and nose blockage in plant 3 which has by far, the highest mean exposure(table 3). The significant associations were still present when potential confounders were taken into account in a multivariate model.

Smokers had a significantly increased risk of developing symptoms from the eyes and pharynx and for nose blockage as compared with non-smokers (Tables 3 and 4). The patterns, although not significant, were similar for running nose/sneezing and lower airways.

Workers with atopy had an increased risk for all the symptoms studied. The increase was significant for ocular symptoms and running nose/sneezing as compared with individuals without atopy (Table 3 and 4). The association was still true for running nose/sneezing (data not shown) when studied in the multivariate model.

Specific IgE to OAA was a significant risk-factor for development of ocular and pharyngeal symptoms and for running nose/sneezing in the univariate analysis (table 3 and 4). These associations were still significant in multivariate analyses. Furthermore, there was a significant effect for blocked nose in the univariate but not in the multivariate analyses. The association observed between IgG and running nose/sneezing in the univariate analyses (table 4) disappeared in the multivariate analysis (data not shown).

No difference in risk was found for gender (Tables 3 and 4)

Neither smoking, atopy, specific IgE, specific IgG nor gender significantly modified the observed effects of exposure on the different symptoms

**DISCUSSION**

This study is to our knowledge the first prospective one investigating the association between OAA exposure and incidence of ocular and airway symptoms. Symptoms developed frequently in the studied exposure categories in a dose- response manner also when possible confounders were considered. Thus, a no effect level could not be identified. Asthmatic symptoms were infrequently preceded by rhinitis. IgE sensitization increased the risk and for symptoms from eyes and pharynx and for running nose the increase was significant. The influence of IgG sensitization was by far less pronounced. Furthermore, smoking and to a lesser extent atopy increased the risk.

Symptoms from the eyes and upper airways are the most frequent symptoms at occupational exposure but the incidence rates is mostly unknown (17). In this study, the incidence of symptoms from the eyes and upper airways is of the same magnitude as incidence rates found for the combined symptoms in prospective studies of workers in complex platinum salts exposure (18) and for bakers and pastry-makers (19, 20, 21) but higher than found for Swedish bakers (22). However, the last named study was a retrospective cohort investigation which may be influenced by recall and selection biases.

The results in the present study may also have been influenced by methodological problems. First, the study was running during a span of years, therefore, there is a risk of drift in clinical assessments. But as the methods were standardized and furthermore carried out by the same physician during the whole observation- time this risk may be small. Second, there was a drop out of participants during the study period between the medical examinations. Although the health care personal at the respective plants were strongly requested to interview the employees and collect a final blood sample before termination of employment some cases may inevitable have been missed. Thus, there may be a tendency to an underestimation of the risk. Third, it was not practically possible to blind the study. Therefore, the examining doctor

could have been biased. However, as the medical examination was strictly according to a protocol we think that a possible bias is of little importance for the results.

Although not statistically significant for all symptoms, dose-response relationship were found and cases frequently appeared, even in the lowest exposure category, this is in accordance with an earlier cross sectional study of HHPA and MHHPA exposed workers (8) and also supported by a cross sectional study by Yokota et al 1999 (23). The dose-response relationships in this study may have been influenced as in the highest exposure group personal protection equipment was worn. Such use may tend to flatten the dose- response curve leading to an underestimation of the risks(24). As any occupational exposure threshold levels for OAA are either missing or set at levels far higher than those seen to give adverse clinical health effects in this study, efforts should be made for a revision of the threshold levels.

The latency time was short and did not differ between the different symptoms and asthmatic symptoms were generally not preceded by rhinitis. This is in accordance with a study of apprentice bakers (21). The short latency- time indicates that a close medical surveillance during the first two years of exposure is important, but as cases appear even after a longer time, OAA exposed workers should regularly go through medical controls.

The mechanisms for respiratory symptoms in OAA exposure are not fully understood (25). In only a fraction of the symptomatic workers specific antibodies of IgE class are found. Thus, other mechanisms may also be operating (25, 27). However, we have earlier shown that the presence of specific IgE antibodies play a role in development of symptoms (27). The IgE sensitized workers in this study had an significant increased risk for all symptoms but those from the lower airways. The lack of significance in this group probably depend upon the relatively low number of cases. Thus, specific IgE may be an important marker for health effects of OAA exposure. We earlier reported a considerable risk for IgE sensitization at levels below 10µg/$m^3$ and that some workers were sensitized even at levels below 5µg/$m^3$ (4). Specific IgE may then be the critical effect in OAA exposure at occupational threshold level setting.

Specific IgG influence the outcome less than IgE having a significant effect only for running nose/sneezing. This is in accordance with the earlier study of Nielsen et al (2001) but in contrast to the finding of Grammer et al (1996), who found a close association between respiratory symptoms and specific IgE as wells IgG.

We found smoking to be a clear independent risk factor. For ocular and pharyngeal symptoms and for nasal blockage the risk was significant. This is not surprising as tobacco smoke is potentially harmful to mucous membranes. However, in the few earlier studies addressing this issue, smoking was not seen to be a significant risk for OAA- related symptoms (1,6,9,10,11). As these studies are of cross-sectional or retrospective type, biases as mentioned earlier may explain this difference. Contrary, we earlier showed that smoking was not a risk factor for IgE sensitization against OAA (4).

Atopy turned out to be an independent risk-factor only for running nose/sneezing. This is in agreement with one of our earlier cohort studies of present and former MTHPA exposed workers (1) but in contrast to the results of two other cross sectional studies (7, 8) which may have been influenced by selection bias. Only few other studies have addressed this problem. Non-significant increased risks for work-related symptoms in atopics were found by Wernfors et al (1986), Baur et al (1995) and Sikora et al. (1999).

In conclusion we found that OAA exposure is associated with frequent symptoms from the eyes and airways in a dose-response related manner. Symptoms appeared even at mean exposure levels as low as < 10µg/$m^3$. Smoking and atopy may independently affect the outcome of some of these symptoms. Specific IgE sensitized workers had an increased risk for symptoms from the eyes and airways. As we have earlier shown a clear increased risk for IgE sensitization at mean exposure levels of OAA at below 5µg/$m^3$ we propose an occupational exposure threshold level to be set at below 5µg/$m^3$.

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## Tables

**Table 1**. Median exposure levels (sum of MTHPA and HHPA/MHHPA), latency-time, smoking habits, atopy, and IgE and IgG sensitisation to MTHPA and HHPA/MHHPA in exposed symptomatic(yes) or asymptomatic(no) workers.

| | Eyes | | Nose | | | | Pharynx | | Lower airways | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Blockage | | Running/sneezing | | | | | |
| | Yes N = 30 | No N= 110 | Yes N=22 | No N= 117 | Yes N=22 | No N=118 | Yes 16 | No N=124 | Yes N=12 | No N= 132 |
| Exposure level µg/m$^3$ | 8 (2-85) | 9 (0-189) | 15 (5-85) | 9 (0-189) | 7 (0-85) | 9 (0-189) | 9 (0-25) | 9 (0-189) | 12 (5-85) | 9 (0-189) |
| Latency time (months) (N;min-max) | 11 (1-53) | - | 9 (1-80) | - | 7 (1-42) | - | 6 (1-56) | | 16 (1-68) | |
| Smoker (N;%) | 22(73) | 35(32) | 15(62) | 44(38) | 14(61) | 45(39) | 11(68) | 45(36) | 8(67) | 50(38) |
| Females (N;%) | 8(27) | 75(68) | 8(35) | 72(62) | 9(39) | 72(62) | 6(38) | 52(42) | 4(33) | 57(43) |
| Atopy (N;%) | 7(23) | 25(23) | 3(14) | 29(25) | 4(17) | 29(25) | 1(6) | 32(26) | 1(8) | 31(24) |
| Standard skin prick-test positive (N;%) | 10(33) | 16(16) | 8(36)1 | 19(18) | 11(52) | 16(15) | 5(33) | 22(19) | 4(36) | 22(18) |
| IgE sensitised (N;%) | 9(30) | 12(11) | 8(35) | 13(11) | 11(48) | 10(9) | 7(44) | 14(11) | 4(33) | 17(13) |
| IgG sensitised (N;%) | 8(27) | 18(16) | 7(30) | 19(16) | 8(35) | 18(15) | 5(31) | 21(17) | 3(25) | 23(17) |

The distribution of phenotypes N;(%)
1 one missing

**Table 2**. Incidence rates (number of new cases per 1000 person-years at risk) for ocular and airways symptoms in workers exposed to MTHPA and HHPA/MHHPA.

| Symptom | Incidence |
|---|---|
| Eyes | 91 |
| Nose | |
| - Blocked | 64 |
| - Running/sneezing | 64 |
| Pharynx | 46 |
| Lower airways | 31 |

**Table 3.** The meaning of plant affiliation, mean exposure, smoking, atopy, specific IgG and IgE and gender, respectively, on ocular symptoms and nose blockage obtained from logistic regression analysis (Odds ratios (OR) with 95% confidence intervals (CI) in univariate and multivariate models).

| | Eyes | | | | Nose blockage | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate estimates | | Multivariate model I | | Univariate estimates | | Multivariate model I | | Multivariate model II | |
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Plant | | | | | | | | | | |
| I | 1.0 | | 1.0 | | 1.0 | | 1.0 | | | |
| II | 3.7 | 0.8-17.1 | 4.3 | 0.8-21.7 | 3.2 | 0.4-27.0 | 3.2 | 0.4-27.5 | | Not |
| III | 6.7 | 1.4-33.2 | 6.0 | 1.1-32.3 | 15.3 | 1.9-126 | 13.3 | 1.6-113 | | Included |
| Mean exposure ($\mu g/m^3$) | | | | | | | | | | |
| 0-10 | 1.0 | | | | 1.0 | | | | 1.0 | |
| >10-15 | 0.9 | 0.3-3.1 | | Not | 2.9 | 0.8-11.2 | | Not | 4.2 | 1.0-18.0 |
| >15 | 1.5 | 0.6-4.0 | | Included | 6.8 | 2.3-19.8 | | Included | 6.6 | 2.1-20.7 |
| Smoking | | | | | | | | | | |
| No | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Yes | 5.9 | 2.4-14.5 | 5.7 | 2.2-14.6 | 2.8 | 1.1-7.2 | 2.6 | 0.9-7.2 | 3.3 | 1.2-9.6 |
| Atopy | | | | | | | | | | |
| No | 1.0 | | | Not | 1.0 | | | Not | | Not |
| Yes | 2.6 | 1.0-6.6 | | Included[1] | 2.2 | 0.8-6.0 | | Included | | Included |
| Specific IgG | | | | | | | | | | |
| No | 1.0 | | | | 1.0 | | | Not | | Not |
| Yes | 1.9 | 0.7-4.8 | | Not | 2.4 | 0.9-6.7 | | Included | | Included |
| Specific IgE | | | | Included | | | | | | |
| No | 1.0 | | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Yes | 3.5 | 1.3-9.4 | 3.2 | 1.0-9.9 | 3.4 | 1.2-9.9 | 2.4 | 0.7-7.8 | 2.4 | 0.7-7.7 |
| Gender | | | | | | | | | | |
| Women | 1.0 | | | Not | 1.0 | | | Not | | Not |
| Men | 1.1 | 0.5-2.5 | | Included | 1.4 | 0.5-3.5 | | Included | | Included |

1. Not included because of significant association to specific IgE

**Table 4.** The meaning of plant affiliation, mean exposure, smoking, atopy, specific IgG and IgE and gender, respectively, on running nose/sneezing and symptoms from pharynx and lower airways obtained from logistic regression analysis (Odds ratios (OR) with 95% confidence intervals (CI), shown in univariate and multivariate models).

| | Running nose /sneezing | | Pharynx | | Lower airways | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate estimates | | Univariate estimates | | Univariate estimates | | Multivariate model | |
| | OR | 95% CI | OR | 95% CI | OR | 95%CI | OR | 95%CI |
| Plant | | | | | | | | |
| I | 1.0 | | 1.0 | | 1.0 | | | |
| II | 0.6 | 0.2-2.0 | 0.8 | 0.2-3.5 | 1.5 | 0.2-13.9 | | Not |
| III | 1.3 | 0.4-4.6 | 1.7 | 0.4-7.4 | 6.8 | 0.8-58.8 | | Included |
| Mean exposure ($\mu g/m^3$) | | | | | | | | |
| 0-10 | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| >10-15 | 0.4 | 0.1-3.1 | 2.2 | 0.5-9.4 | 2.1 | 0.4-12.0 | 3.5 | 0.5-24.2 |
| >15 | 2.1 | 0.8-5.7 | 1.9 | 0.6-6.4 | 3.8 | 1.0-14.2 | 4.8 | 1.0-21.6 |
| Smoking | | | | | | | | |
| No | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Yes | 2.3 | 0.9-5.7 | 3.9 | 1.3-11.8 | 3.3 | 0.9-11.5 | 3.3 | 0.9-12.2 |
| Atopy | | | | | | | | |
| No | 1.0 | | 1.0 | | 1.0 | | | Not |
| Yes | 5.4 | 1.9-14.8 | 2.1 | 0.6-6.7 | 2.6 | 0.7-9.6 | | Included |
| Specific IgG | | | | | | | | |
| No | 1.0 | | 1.0 | | 1.0 | | | Not |
| Yes | 3.2 | 1.2-8.7 | 2.2 | 0.7-7.1 | 1.6 | 0.4-6.3 | | Included |
| Specific IgE | | | | | | | | |
| No | 1.0 | | 1.0 | | 1.0 | | 1.0 | |
| Yes | 8.1 | 2.9-23.0 | 6.1 | 2.0-19.0 | 3.4 | 0.9-12.5 | 2.3 | 0.6-9.3 |
| Gender | | | | | | | | |
| Women | 1.0 | | 1.0 | | 1.0 | | | Not |
| Men | 1.4 | 0.5-3.5 | 1.2 | 0.4-3.5 | 1.5 | 0.4-5.3 | | Included |