Exacerbation of asthma

by ETS exposure

Chamber studies of ETS

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EXECUTIVE SUMMARY

About 25 experimental chamber studies have been conducted in which asthmatic subjects have been exposed to ETS for between 1 and 6 hours, many of the studies being conducted by two groups, one in New Orleans and one in Hamburg. The studies generally involve an exposure which is much higher than encountered even in extreme environmental conditions, with typical particulate concentrations in the range 1000-3000 $\mu g/m^3$ and CO concentrations exceeding 20 ppm. Some of the studies involve multiple dose levels with the lowest levels tested more typical of high environmental exposure. The majority of the studies involve a sham exposure. Although three papers report results (possibly from the same study) in groups of 100 or more asthmatics, the great majority of the studies reported results from small groups, in about half with 12 subjects or less. Most studies were of adults, though four involved children, and were restricted to nonsmokers.

The series of studies in New Orleans, and particularly the largest and most recent data, provide strong evidence that there is a proportion of asthmatics who react to ETS exposure by a drop in FEV_1 of 20% or more. Reaction (and non-reaction) could be consistently demonstrated, and reaction was shown to be dose- and time-related. While some subjects only reacted at high doses, a few reacted at all the dose levels tested. Though some subjects also react to sham exposure (implying that in these subject ETS itself may not be causing the reaction), there are a proportion of subjects who react to ETS but not sham exposure. While the design of the New Orleans studies does not allow one to assess how many subjects react to sham but not ETS exposure, other studies with relevant data suggest that this is a much rarer event. The actual proportion of asthmatics who react to ETS in this way cannot be estimated precisely due to non-random selection of study asthmatics (e.g. as smoke-sensitive by self report in the New Orleans studies, and as mild to moderate in the Hamburg studies), but is likely to be quite low. Thus, in the latest New Orleans study, 15% of the smoke-sensitive subjects reacted to ETS (and not sham exposure) at the highest exposure level tested, and the proportion reacting at typical environmental levels would be substantially less than this. While some studies did not report finding any reactors, this may be due to the few subjects tested and/or to insufficient length of ETS exposure.

The evidence relating symptoms to ETS exposure is somewhat variable, perhaps due to small sample sizes and differences in methodology, but the data taken as a whole clearly indicates that ETS exposure can induce those symptoms (cough, chest tightness, wheezing, difficulty in breathing) which occur during an attack of asthma.

The data do not show any clear effect of ETS exposure on airway responsiveness. Nor do they show any relation between reaction (FEV_1 decline), and the presence of Ige serum antibodies or a positive wheal-and-flare skin test.

The California EPA report (National Cancer Institute, 1999) concluded their evaluation of the evidence then available with the paragraph:

"In summary, although the design constraints of the chamber studies limit the interpretation of the results, they do suggest that there is likely to be a subpopulation of asthmatics who are especially susceptible to ETS exposure. The physiological responses observed in these investigations appear to be reproducible in both 'reactors' and 'nonreactors.' It is unlikely that the physiological and symptomatic responses reported are due exclusively to either stress or suggestion."

This conclusion seems a valid one and the newer evidence from the New Orleans group makes it much clearer that ETS can exacerbate asthma in a subset of susceptible individuals. For the great majority of asthmatics, however, ETS exposure, even at extremely high concentrations, does not appear to cause asthmatic attacks.

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Abbreviations used

BHR	Bronchial hyperreactivity
CO	Carbon monoxide
COHb	Carboxyhaemoglobin
cpm	Counts per minute
ETS	Environmental tobacco smoke
$FEF_{x\%}$	Forced expiratory flow at x% of forced vital capacity
$FEF_{x\%iso}$	Forced expiratory flow at x% of forced vital capacity as measured pre-exposure
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
IgE	Immunoglobulin E
MEF	Mid-expiratory flow
MMEFR	Mid-maximal expiratory flow rate
PC_{20}	Provocative concentration of histamine or methacholine to produce a 20% fall in FEV_1
$PC_{100}SRAW$	Provocative concentration of histamine or methacholine to produce a 100% increase in specific airway resistance
PEFR	Peak expiratory flow rate
ppm	Parts per million
RV	Residual volume
RVC	Relaxed vital capacity
SRAW	Specific airway resistance
TLC	Total lung capacity
VC	Vital capacity
$VMAX_{x\%}$	Maximum volume at x% of vital capacity

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Summary of study design and results for 25 papers describing chamber studies of ETS exposure 29

1. Introduction

25 papers were identified which described the results of experimental chamber studies of the effects of ETS exposure on asthma in asthmatics (Shephard et al., 1979; Dahms et al., 1981; Ing & Breslin, 1983; Ben Hassine et al., 1984; Knight & Breslin, 1985; Wiedemann et al., 1986; Stankus et al., 1988; Urch et al., 1988; Menon et al., 1989; Ortega Gonzalez et al., 1989; Jörres et al., 1990; Menon et al., 1990; Gurk et al., 1991; Menon et al., 1991a; Menon et al., 1991b; Oldigs et al., 1991; Jörres & Magnussen, 1992; Lehrer, 1992; Magnussen et al., 1992; Menon et al., 1992; Danuser et al., 1993; Magnussen et al., 1993; Lehrer et al., 1997; Nowak et al., 1997a; Nowak et al., 1997b). In Appendix A a single page summary is provided based on each paper, giving the authors, location, subjects, exposure and study design, summarizing the effects seen on certain symptoms, airway responsiveness and lung function, and giving relevant comments, both of the authors and of these reviewers. Appendix A also points out those six studies where the results were only reported in an abstract, limiting details of the data that could be extracted.

As noted in Appendix A, there are also additional references for some of the 25 studies summarized there.

In section 2 various aspects of the data are summarized, in section 3 the main results are described and in section 4 conclusions are drawn.

2. Summary of the studies

2.1 Location

Of the 25 papers, eight were published by a group from Tulane Medical School, New Orleans, USA (Stankus et al., 1988; Menon et al., 1989; Menon et al., 1990; Menon et al., 1991a; Menon et al., 1991b; Lehrer, 1992; Menon et al., 1992; Lehrer et al., 1997), while seven were published by a group from the Krankenhaus Grosshansdorf, Hamburg, Germany (Jörres et al., 1990; Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1992; Magnussen et al., 1993; Nowak et al., 1997a; Nowak et al., 1997b). There were also two each from groups in Toronto, Canada (Shephard et al., 1979; Urch et al., 1988) and in Sydney, Australia (Ing & Breslin, 1983; Knight & Breslin, 1985). Other papers were from St Louis, USA (Dahms et al., 1981), Tunis (Ben Hassine et al., 1984), Yale, USA (Wiedemann et al., 1986), Munster, Germany (Gurk et al., 1991), Zurich, Switzerland (Danuser et al., 1993), and from Mexico (Ortega Gonzalez et al., 1989).

2.2 Possible overlaps

It is possible that the first paper from Sydney (Ing & Breslin, 1983) may be an abstract describing the results of the same study later described in more detail (Knight & Breslin, 1985).

It is also possible that a short report in 1992 from the New Orleans group (Lehrer, 1992) may be a description of the same study described more fully in 1997 (Lehrer et al., 1997). The numbers of subjects differ between the two reports, but it is possible the later report excluded some of the subjects originally referred to.

It is reasonably clear that the 11 children referred to in a 1992 paper from the Hamburg group (Magnussen et al., 1992) are the same as those referred to in a 1991 paper from the same group (Oldigs et al., 1991). The 1992 paper also includes results for adults.

2.3 Number of subjects

The papers citing the largest number of subjects are three from the New Orleans Group: Lehrer, 1992 involving 163 asthmatics; Lehrer et al., 1997 involving 130 asthmatics and 28 non-asthmatics; and Menon et al., 1991a involving 100 asthmatics. As noted above, these may not be different subjects totally.

The next highest is the 62 children study in Mexico (Ortega Gonzalez et al., 1989).

Other papers all describe small studies ranging from six subjects in the Sydney studies (Ing & Breslin, 1983; Knight & Breslin, 1985) to 31 in one of the other New Orleans studies (Menon et al., 1992).

2.4 Asthma status

Subjects were generally mild to moderate asthmatics, and had been free of respiratory infections or asthma exacerbations for at least several weeks before the study.

2.5 Age

Four of the studies were of children (Ortega Gonzalez et al., 1989; Menon et al., 1990; Oldigs et al., 1991; Magnussen et al., 1993), with one (Magnussen et al., 1992) involving both adults and children. Other studies were of adults.

2.6 Gender

Six studies (Dahms et al., 1981; Ing & Breslin, 1983; Menon et al., 1989; Menon et al., 1990; Gurk et al., 1991; Menon et al., 1991a) gave no details on the gender of the subjects. One study (Ben Hassine et al., 1984) was of females only. Other studies included both males and females. (In general, results were not presented separately by age or gender.)

2.7 Smoking status

Most studies were restricted to nonsmokers, although the definition of nonsmoker was not always clear and may have included former smokers. Indeed it was stated to do so in some of the New Orleans studies (Stankus et al., 1988; Menon et al., 1991b; Menon et al., 1992), and also in one of the Toronto studies (Urch et al., 1988) and one of the Hamburg studies (Jörres & Magnussen, 1992). One New Orleans study (Lehrer et al., 1997) included a few smokers and some where smoking status was not known – of the total of 158 subjects, 111 were stated never to have smoked and 30 were stated to have been ex-smokers for at least four years. A number of studies did not define the smoking status of their subjects.

2.8 Sensitivity to smoking

The New Orleans group restricted attention to subjects with a perceived sensitivity to smoking. Other studies generally included only a proportion who considered themselves sensitive, though this was not always known.

2.9 Healthy controls

Thirteen of the papers did not refer to any healthy control group. A further two studies (Dahms et al., 1981; Urch et al., 1988) used controls of very different ages from the asthmatics, while the remaining ten studies (Ben Hassine et al., 1984; Menon et al., 1989; Menon et al., 1990; Gurk et al., 1991; Menon et al., 1991b; Jörres & Magnussen, 1992; Magnussen et al., 1992; Menon et al., 1992; Danuser et al., 1993; Lehrer et al., 1997) used control groups which were either directly matched on age and gender or at least of a comparable distribution.

2.10 Exposure

In the Zurich study (Danuser et al., 1993) a smoking machine was kept in a small room not visible to the participants, the subjects wore nose clips and had the ETS administered by mouthpiece. In the other studies subjects breathed normally in the chamber. In two studies (Ben Hassine et al., 1984; Ortega Gonzalez et al., 1989) smokers smoked in the chamber, while in others

a smoking machine was used, in some cases the cigarettes being burnt in the room, in others the cigarettes being burnt outside with the smoke piped through. Though from the material presented in the papers this was not always clear, it appears that in most studies exposure was to a mixture of sidestream and mainstream smoke. However in six studies (Dahms et al., 1981; Gurk et al., 1991; Menon et al., 1991a; Lehrer, 1992; Danuser et al., 1993; Lehrer et al., 1997) it was made clear that the subjects were only exposed to sidestream smoke. In some studies the chamber was remarkably small, 4.25 m^3 (Wiedemann et al., 1986) and 7 m^3 (Knight & Breslin, 1985). The New Orleans and Hamburg groups used larger chambers of about 25 m^3.

Subjects appear to have been seated during exposure, with two exceptions: in Urch et al., 1988 the healthy control group exercised and in Magnussen et al., 1993 the subjects exercised for the last 6 minutes.

2.11 Level of smoke constituents

Levels of particulate matter and/or CO were reported in all but two studies (Menon et al., 1989; Ortega Gonzalez et al., 1989). Concentrations of particulate matter in homes where smokers are present are typically less than 100 $\mu g/m^3$ (National Cancer Institute, 1993) and though levels may be higher in some restaurants and bars, reported mean levels rarely exceed 300 $\mu g/m^3$ or so (National Cancer Institute, 1993). Particulate matter concentrations were reported in 15 of the 25 papers summarized and always exceeded 1000 $\mu g/m^3$ and in the Hamburg studies were typically around 3000 $\mu g/m^3$ for maximum dose levels tested. It was clear, therefore that what was generally being tested was not typical but quite extreme exposure. The same is true for CO, where levels of 20 to 30 ppm were usually reported, perhaps 10 times higher than those found in everyday environments where real-life exposure to ETS may occur (Scherer et al., 1992).

2.12 Sham exposure

16 of the 25 papers described using a sham exposure. The exceptions were the studies in St. Louis (Dahms et al., 1981), Tunis (Ben Hassine et al., 1984), Munster (Gurk et al., 1991), Yale (Wiedemann et al., 1986) and

Mexico (Ortega Gonzalez et al., 1989), and four of the studies in New Orleans (Stankus et al., 1988; Menon et al., 1989; Menon et al., 1990; Menon et al., 1992) although this last study briefly mentioned an extra group of 10 subjects not exposed to ETS who may have been sham-exposed.

2.13 Time of exposure

Exposure was for 1 hour in the first five Hamburg reports (Jörres et al., 1990; Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1992; Magnussen et al., 1993) and in eight other studies (Dahms et al., 1981; Ing & Breslin, 1983; Ben Hassine et al., 1984; Knight & Breslin, 1985; Wiedemann et al., 1986; Urch et al., 1988; Ortega Gonzalez et al., 1989; Gurk et al., 1991). Apart from the Zurich study, which only exposed through a mouthpiece for 2 minutes at each dose level (Danuser et al., 1993), other studies had longer exposure. Thus, the two final Hamburg studies (Nowak et al., 1997a; Nowak et al., 1997b) involved 3 hours exposure, four New Orleans studies (Menon et al., 1990; Lehrer, 1992; Menon et al., 1992; Lehrer et al., 1997) involved 4 hours exposure, and two other New Orleans studies (Menon et al., 1991a; Menon et al., 1991b) up to 6 hours exposure.

2.14 Variation in exposure levels

Most of the studies only tested a single exposure level of ETS. However, three of the New Orleans studies (Menon et al., 1991a; Lehrer, 1992; Lehrer et al., 1997) involved a high exposure of around 1500 $\mu g/m^3$ particles and exposures of about and 1/2, 1/4 and 1/8 of this, while another New Orleans study (Stankus et al., 1988) had a 1/2 exposure and, for selected subjects, an exposure of twice the standard level. One of the Toronto studies (Urch et al., 1988) had 2 exposure levels, producing 31 and 17 ppm CO, while the mouthpiece study in Zurich (Danuser et al., 1993) started with a dose producing 32 ppm, and then successively reduced the exposure to 1/2, 1/4, 1/8 and 1/16 of this. The low exposures in some of the studies with varying levels will be more typical of real-life high level scenarios.

2.15 Stopping of medication by the subjects

Where stated, the procedure in the Hamburg series of studies was to discontinue inhalation therapy for at least 6 hours (Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1992) or at least 12 hours (Nowak et al., 1997a; Nowak et al., 1997b) before exposure. In the earlier New Orleans studies (Stankus et al., 1988; Menon et al., 1992), inhaled bronchodilators were stopped 8 to 12 hours before each test, with participants instructed to avoid theophylline oral sympathomimetic medications for 24 hours before. In the last one (Lehrer et al., 1997), medications were withheld for 24 hours prior to the challenge, with antihistamines withheld for 48 to 72 hours. In only 3 studies (Shephard et al., 1979; Dahms et al., 1981; Urch et al., 1988) was medication stated to be continued, though not all studies reported details of this.

2.16 Statistical methods

Suppose that a lung function (or other) variable has values measured for a particular subject of:

E_o baseline measurement for ETS exposure

E_t time t measurement for ETS exposure

S_o baseline measurement for sham exposure

S_t time t measurement for sham exposure

A correct statistical analysis of the data would then involve calculating a response to ETS (e.g. E_t-E_o or E_t/E_o) and a response to sham exposure (e.g. S_t-S_o or S_t/S_o) and using a paired statistical test to determine whether the responses to ETS and sham exposure differ. In practice, a number of the papers considered here have not used (or been able to use) appropriate statistical tests.

In some studies (e.g. Dahms et al., 1981; Wiedemann et al., 1986; Stankus et al., 1988; Ortega Gonzalez et al., 1989) sham exposure has not been tested at all, in some (e.g. Ing & Breslin, 1983) sham exposure data have not been reported, while in others (e.g. Lehrer, 1992; Lehrer et al., 1997) being sham exposed depended on the subject having a previous reaction to ETS exposure, with further dose-response studies being restricted to those who did

not react to sham exposure. Furthermore others have not always used appropriate statistical tests. Thus, for example, one paper (Shephard et al., 1979) separately tested whether E_t/E_o differed from 1 and whether S_t/S_o differed from 1, a procedure which may miss an effect if, for example, the data show a non-significant decrease for E_t/E_o and a non-significant increase for S_t/S_o. Similarly, another paper (Knight & Breslin, 1985) tested for significance within each subject (by a procedure which was not clearly described) but did not perform any proper overall test based on the differences in response for each subject. In this paper, it was easy enough to do the appropriate test as the individual subject data were available, but this is not always so.

For any differences in response seen not to be attributed to other causes it is also important for the ordering of the sham exposure visit and the ETS exposure visit to be randomized, or at least to be approximately equally divided between subjects. However, it was clear that this was far from the general situation. Varying the ordering of the two exposures was carried out in some studies (Shephard et al., 1979; Urch et al., 1988; Jörres & Magnussen, 1992; Nowak et al., 1997a; Nowak et al., 1997b) but not in others (Ing & Breslin, 1983; Knight & Breslin, 1985; Oldigs et al., 1991; Danuser et al., 1993; Magnussen et al., 1993).

3. Results

3.1 Effect on symptoms

A number of studies did not report results for symptoms, or only discussed results for symptoms such as eye and nasal irritation, which is not indicative of asthma. Studies which clearly determined cough, chest tightness, wheezing or difficulty in breathing, all symptoms associated with an attack of asthma (National Cancer Institute, 1999), and which reported results were as follows:

Shephard et al., 1979 : Symptoms of asthma reported by some subjects following ETS exposure, but no results reported following sham exposure.

Ing & Breslin, 1983 : All 6 subjects reported chest tightness following ETS exposure but not following sham exposure ($p<0.05$).

Knight & Breslin, 1985 : All 6 subjects reported some symptoms of asthma following ETS exposure, but no results presented for sham exposure.

Wiedemann et al., 1986 : 3 exposed subjects reported a mild cough. No sham exposure.

Stankus et al., 1988 : All 7 subjects in whom a significant decline in FEV_1 was seen also reported some symptoms of asthma following ETS exposure. No sham exposure.

Menon et al., 1990 : Subjects complained of cough, wheezing or chest tightness following ETS exposure. No sham exposure.

Oldigs et al., 1991 : No significant difference between ETS and sham exposure on respiratory symptoms.

Jörres & Magnussen, 1992 : Significant difference between ETS and sham exposure on tightness of the chest but not cough.

Magnussen et al., 1992 : Some excess in cough and chest tightness following ETS exposure in adults but not in children.

Danuser et al., 1993 : An apparent dose-related increase in cough and chest tightness.

Magnussen et al., 1993 : Symptoms of asthma non-significantly higher following ETS exposure than following sham exposure.

Nowak et al., 1997a : ETS significantly increased a generalized score for symptoms of the throat and chest.

Nowak et al., 1997b : ETS significantly increased a generalized score for symptoms of the throat and chest, though this increase was not seen some hours following exposure.

Though the evidence is somewhat variable, perhaps due to small sample sizes and differences in methodology, the data taken as a whole clearly indicate that ETS exposure can induce those symptoms which occur during an attack of asthma.

3.2 Effect on airway responsiveness

Of 11 studies that have reported results following challenge by methacholine or histamine, four reported an increase in airway responsiveness following ETS exposure.

In the first study (Knight & Breslin, 1985), PC_{20}, in all six subjects, fell more over the four hour period of exposure than on the sham exposure day ($p<0.05$). The changes were still detectable four hours after ETS exposure.

In the three other studies (Menon et al., 1989; Menon et al., 1990; Menon et al., 1992) a proportion of asthmatics (5/10, 3/10 and 5/31 respectively) were reported to show an increase in bronchial responsiveness that was regarded as clinically significant. However clinically significant

increases were also seen in some non-asthmatic controls (1/5, 4/11 and 0/31 respectively), and there was no sham exposure.

In contrast, one study (Wiedemann et al., 1986) with no sham exposure reported a significant ($p = 0.04$) decrease in airway responsiveness following ETS exposure.

All the remaining studies (Jörres et al., 1990; Gurk et al., 1991; Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1992; Nowak et al., 1997b) found no significant effect of ETS, although one of these (Gurk et al., 1991) reported a mild increase in bronchial reactivity ($p=0.038$) in those asthmatics with more than a 5% decrease in FEV_1. Another study (Magnussen et al., 1993) found no effect on exercise induced bronchoconstriction.

Overall, the data do not show any very clear effect of ETS exposure on airway responsiveness in asthmatics.

3.3 Effect on lung function

FEV_1 is the lung function variable that has been the most studied. Some studies have carried out statistical analyses based on the average change in FEV_1 following ETS exposure, while others (notably the New Orleans group) have investigated the proportion of subjects 'reacting' (showing a defined drop of 20% or more in FEV_1).

Table 1 summarizes the results for average FEV_1 while Table 2 summarizes the results for the proportion reacting.

Of the 16 studies considered in Table 1, significant effects on overall FEV were reported in seven (Dahms et al., 1981; Knight & Breslin, 1985; Urch et al., 1988; Gurk et al., 1991; Danuser et al., 1993; Magnussen et al., 1993; Nowak et al., 1997b). The studies which found no significant effect were all small (ranging from 6 to 24 subjects) and it is possible that a lack of significance might occur due to lack of power. This may be particularly relevant if an effect is only seen in a small proportion of reactive subjects, who

might not even be present at all in some of the studies. Note that results for the New Orleans studies are not included in Table 1 as their principal endpoint was reaction, and mean FEVs were not presented.

The series of eight studies in New Orleans (Stankus et al., 1988; Menon et al., 1989; Menon et al., 1990; Menon et al., 1991a; Menon et al., 1991b; Lehrer, 1992; Menon et al., 1992; Lehrer et al., 1997) reported results which were together consistent with the following conclusions:

(i) There are a proportion of asthmatics who react to ETS exposure;
(ii) Some of these also react to sham exposure;
(iii) Disregarding those who also react to sham exposure, asthmatics who react tend to react again following rechallenge to the same exposure;
(iv) Reaction is dose-related. Some asthmatics who react at high doses do not react at lower doses, but others react consistently at all the doses tested, down to levels similar to high environmental exposure;
(v) Reaction is also time-related, and may not be seen until after a few hours of exposure especially at lower dose levels; and
(vi) Non-asthmatics rarely, if ever, show such reactions.

Occasional reactions following exposure were also seen in the studies in St. Louis (Dahms et al., 1981), Mexico (Ortega Gonzalez et al., 1989) and Zurich (Danuser et al., 1993) and in one of the studies in Sydney (Knight & Breslin, 1985). The other Sydney study (Ing & Breslin, 1983) and the Yale study (Wiedemann et al., 1986) did not have any reactors, but included only 6 and 9 subjects, respectively.

Two early studies in Hamburg (Oldigs et al., 1991; Jörres & Magnussen, 1992), which claimed no effect of ETS on FEV_1, did in fact include some reactors (as can be seen from the individual subject data), as did a later study (Magnussen et al., 1993) which reported a marginally significant effect. These studies were of 1 hour duration, less than the period of exposure which produced many of the reactions seen in the New Orleans studies. Of two later studies in Hamburg, involving a 3 hour exposure period, one (Nowak

et al., 1997a), of 10 subjects, found no reactors, while the other did (Nowak et al., 1997b).

The question as to the relative effects of ETS and sham exposure on the probability of reaction is an important one. Though the New Orleans studies found that only some subjects who reacted to ETS also reacted to sham exposure, they did not test all subjects for the effects of sham exposure, and one does not know how many subjects might have reacted to sham exposure and not ETS. The other studies, however, cast some light on this. Thus four studies (Knight & Breslin, 1985; Oldigs et al., 1991; Jörres & Magnussen, 1992; Magnussen et al., 1993) found reactions only with ETS exposure, while one study (Nowak et al., 1997b) found more reactions to ETS exposure only than to sham exposure only.

Results for lung function variables other than FEV_1 were reported in 11 studies and are summarized in Table 3. As in Table 1, results for the New Orleans studies are not included as only FEV_1 was studied. In general, the results summarized in Table 3 are very similar to those summarized in Table 1. Overall the data for lung function variables other than FEV_1 do not materially assist further in deciding whether or not the overall data show that ETS exacerbates asthma.

3.4 A physiological or a psychological response?

For the purposes of deciding whether or not ETS exacerbates asthma, it does not particularly matter whether the response is a physiological or a psychological one. However some of the studies report data relating to this issue.

In the second Toronto study (Urch et al., 1988) subjects viewed a bank of burning cigarettes during each of sham, moderate and heavy ETS exposure, and data on psychological and subjective response variables were recorded. The authors concluded from their findings (not considered here in detail) that "while suggestibility may augment physiological responses to passive smoking,

any effect is relatively weak". It seems to us that if the sight of the burning cigarettes during sham exposure was supposed "to provide an element of suggestion" it should have been controlled for by a visit involving sham exposure and no sight of the burning cigarettes.

The fact that in the large studies in New Orleans (Lehrer, 1992; Lehrer et al., 1997) some asthmatics reacted to sham exposure with a 20%+ drop in FEV_1 indicates that responses may not always be due to a physiological reaction to cigarette smoke constituents.

Reports of a lack of association between a positive smoke challenge and the presence of serum IgE antibodies and/or a positive immediate wheal-and-flare skin test to a tobacco leaf extract (Stankus et al., 1988; Ortega Gonzalez et al., 1989; Lehrer, 1992) indicate that the response is not a clinical allergic response.

4. Summary and conclusions

About 25 experimental chamber studies have been conducted in which asthmatic subjects have been exposed to ETS for between 1 and 6 hours, many of the studies being conducted by two groups, one in New Orleans and one in Hamburg. The studies generally involve exposure which is much higher than encountered even in extreme environmental conditions, with typical particulate concentrations in the range 1000-3000 $\mu g/m^3$ and CO concentrations exceeding 20 ppm. Some of the studies involve multiple dose levels with the lowest levels tested more typical of high environmental exposure. The majority of the studies involve a sham exposure. Although three papers report results (possibly from the same study) in groups of 100 or more asthmatics, the great majority of the studies reported results from small groups, about half with 12 subjects or less. Most studies were of adults, though four involved children, and were restricted to nonsmokers.

The series of studies in New Orleans, and particularly the largest and most recent data, provide strong evidence that there is a proportion of asthmatics who react to ETS exposure by a drop in FEV_1 of 20% or more. Reaction (and non-reaction) could be consistently demonstrated, and reaction was shown to be dose- and time-related. While some subjects only reacted at high doses, a few reacted at all the dose levels tested. Though some subjects also react to sham exposure (implying that in these subject ETS itself may not be causing the reaction), there are a proportion of subjects who react to ETS but not sham exposure. While the design of the New Orleans studies does not allow one to assess how many subjects react to sham but not ETS exposure, other studies with relevant data suggest that this is a much rarer event. The actual proportion of asthmatics who react to ETS in this way cannot be estimated precisely due to non-random selection of study asthmatics (e.g. as smoke-sensitive by self report in the New Orleans studies, and as mild to moderate in the Hamburg studies), but is likely to be quite low. Thus, in the latest New Orleans study, 15% of the smoke-sensitive subjects reacted to ETS (and not sham exposure) at the highest exposure level tested, and the proportion reacting at typical environmental levels would be substantially less

than this. While some studies did not report finding any reactors, this may be due to the few subjects tested and/or to insufficient length of ETS exposure.

The evidence relating symptoms to ETS exposure is somewhat variable, perhaps due to small sample sizes and differences in methodology, but the data taken as a whole clearly indicates that ETS exposure can induce those symptoms (cough, chest tightness, wheezing, difficulty in breathing) which occur during an attack of asthma.

The data do not show any clear effect of ETS exposure on airway responsiveness. Nor do they show any relation between reaction (FEV_1 decline), and the presence of IgE serum antibodies or to a positive wheal-and-flare skin test.

The California EPA report (National Cancer Institute, 1999) concluded their evaluation of the evidence then available with the paragraph:

"In summary, although the design constraints of the chamber studies limit the interpretation of the results, they do suggest that there is likely to be a subpopulation of asthmatics who are especially susceptible to ETS exposure. The physiological responses observed in these investigations appear to be reproducible in both 'reactors' and 'nonreactors.' It is unlikely that the physiological and symptomatic responses reported are due exclusively to either stress or suggestion."

This conclusion seems a valid one and the newer evidence from the New Orleans group makes it much clearer that ETS can exacerbate asthma in a subset of susceptible individuals. For the great majority of asthmatics, however, ETS exposure, even at extremely high concentrations, does not appear to cause asthmatic attacks.

TABLE 1

Change in FEV_1 in relation to ETS exposure*

Study	Result
Shephard et al., 1979 (Toronto)	Ratio of exposed to sham FEV_1 1.031 at baseline, 1.021 after 30 mins, 0.992 after 1 hour, 1.021 after 90 mins and 1.014 after 2 hours. No significant variation.
Dahms et al., 1981 (St Louis)	Percent reduction in FEV_1 following ETS exposure 8.6% after 15 mins (NS), 12.9% after 30 mins ($p<0.01$), 17.5% after 45 mins ($p<0.01$) and 21.4% after 1 hour ($p<0.01$). [No sham exposure.]
Ing & Breslin, 1983 (Sydney)	No significant changes in FEV_1 when compared to baseline values. [Sham exposure data not reported.]
Ben Hassine et al., 1984 (Tunis)	Percent change in FEV_1 following ETS exposure +1.2% after 15 mins (NS), +2% after 30 mins (NS), -1.2% after 45 mins (NS) and +1.1% after 60 mins (NS). [No sham exposure.]
Knight & Breslin, 1985 (Sydney)	All 6 subjects showed a fall in FEV_1 following ETS but none did following sham exposure ($p<0.05$).
Wiedemann et al., 1986 (Yale)	FEV_1 was similar on day 1 at baseline (3.43ℓ), on day 2 pre-smoke (3.48ℓ) and on day 2 post-smoke (3.45ℓ). [No sham exposure.]
Urch et al., 1988 (Toronto)	Change in FEV_1 from pre-exposure levels after 30 mins exposure were +23 ml for sham, +4 ml for moderate ETS (17 ppm CO) and – 71 ml for heavy ETS (31 ppm CO). The dose-response was significant ($p<0.05$).

TABLE 1 (continued 1)

Jörres et al., 1990 (Hamburg)	Mean change in FEV_1 following ETS exposure (+0.12ℓ) and following sham exposure (-0.03ℓ) did not differ significantly.
Gurk et al., 1991 (Munster)	Significant decline in FEV_1 from 3.02ℓ to 2.89ℓ ($p<0.025$) following ETS exposure. [No sham exposure.]
Oldigs et al., 1991 (Hamburg)	There was no difference (in children) between pre- and post-exposure FEV_1 following either ETS exposure (1.95ℓ vs 1.94ℓ) or sham exposure (1.97ℓ vs 1.98ℓ).
Jörres & Magnussen, 1992 (Hamburg)	Changes following ETS exposure (3.34ℓ pre to 3.21ℓ post) did not differ significantly from those following sham exposure (3.28ℓ pre to 3.24ℓ post).
Magnussen et al., 1992 (Hamburg)	Changes following ETS exposure (3.31ℓ pre to 3.21ℓ post) did not differ significantly from those following sham exposure (3.18ℓ pre to 3.14ℓ post). These are results for adults. Results for children as reported in Oldigs et al., 1991.
Danuser et al., 1993 (Zurich)	Following exposure at 2, 4, 8, 16 and 32 ppm CO percent reductions in FEV_1 were, respectively, 6.5, 5.6, 7.1, 8.2 and 8.7%. The effect of ETS was highly significant ($p<0.001$) but not clearly dose-related.
Magnussen et al., 1993 (Hamburg)	The change in FEV_1 in the children during ETS exposure (1.68ℓ pre to 1.56ℓ during) was significantly ($p = 0.043$) greater than the change during sham exposure (1.66ℓ pre to 1.61ℓ during).

TABLE 1 (continued 2)

Nowak et al., 1997a (Hamburg)	There was no significant change in FEV_1 during or after ETS exposure as compared with sham or pre-exposure levels (e.g. 3.79ℓ, 3.63ℓ, 3.72ℓ at start, end and 1 hour after ETS exposure, and 3.66ℓ, 3.63ℓ, 3.59ℓ for sham exposure.
Nowak et al., 1997b (Hamburg)	There was a greater fall with ETS than sham both during exposure (5.6% vs 3.0%, p = 0.013) and after exposure (9.1% vs 5.9%, p = 0.026).

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* Details of the exposures are given in Appendix A.

TABLE 2

Proportion of asthmatics 'reacting' (showing a 20% or more fall in FEV_1) in relation to ETS exposure*

Study	Result
Dahms et al., 1981 (St Louis)	Proportion not reported, but as average changes are around 20% after 45 mins and 1 hour exposure it is clear that many subjects, perhaps at least 50%, reacted. [No sham exposure.]
Ing & Breslin, 1983 (Sydney)	No subjects reacted, the largest fall noted being 12.55%. [Sham exposure data not reported.]
Knight & Breslin, 1985 (Sydney)	1 of the 6 subjects (16.7%) reacted following ETS exposure. No falls following sham exposure.
Wiedemann et al., 1986 (Yale)	None of the 9 subjects reacted following exposure. [No sham exposure.]
Stankus et al., 1988 (New Orleans)	Of 21 subjects, 2 (9.5%) reacted to low exposure (852 $\mu g/m^3$ particulates) and a further 5 (23.8%) reacted to high exposure (1421 $\mu g/m^3$ particulates). All the reactions were reproducible on re-challenge. Of the remaining 14, 5 claiming a strong history of smoke sensitivity were tested at an ultra-high exposure level (about twice the high exposure) and none reacted. [No sham exposure.]
Ortega Gonzalez et al., 1989 (Mexico)	Reactions following exposure were seen in 2/62 of the children (3.2%). [No sham exposure.]

TABLE 2 (continued 1)

Menon et al., 1990 (New Orleans)	None of the 10 children reacted following exposure. [No sham exposure.]
Menon et al., 1991a (New Orleans)	7/100 subjects (7.0%) reacted at high exposure (1392 $\mu g/m^3$ particulates). Of these, 3 did not react to any of the 3 lower dose levels (804, 289, 242 $\mu g/m^3$ particulates), 1 reacted only to the highest of these doses, and 3 reacted to all 3 doses.
Menon et al., 1991b (New Orleans)	6 subjects had been shown to react to ETS 2 years earlier. Of these, 5 again reacted on re-challenge after 1 to 2 hours exposure. None of the 5 reacted to sham challenge. The sixth subject did react on a subsequent occasion after 2½ hours. The other 9 subjects had previously not reacted and did not react again after challenges of 2 and 6 hours duration on 2 separate days 4 weeks apart.
Oldigs et al., 1991 (Hamburg)	Of 11 children, 1 (9.1%) reacted to ETS exposure. None reacted to sham exposure.
Jörres & Magnussen, 1992 (Hamburg)	Of 24 adults, 1 (4.2%) reacted to ETS exposure. None reacted to sham exposure.
Menon et al., 1992 (New Orleans)	5 of 31 asthmatics (13%) reacted to ETS. None of the 10 asthmatic controls reacted to sham exposure.
Danuser et al., 1993 (Zurich)	1 of 10 subjects (10%) reacted to 16 ppm CO. [Sham exposure data not reported.]
Magnussen et al., 1993 (Hamburg)	Of 13 children, 2 (15.4%) reacted to ETS exposure. None reacted following sham exposure.

TABLE 2 (continued 2)

Lehrer et al., 1997 (New Orleans)	26 of 130 asthmatics (20%) reacted to the high exposure (1553 μg/m^3 particulates). 6 of the 26 reactors (23%) reacted to sham exposure also. Of the 20 who reacted to ETS only, 7 underwent a dose-response study at lower levels of 621, 337 and 121 μg/m^3 particulates. 3 did not react at all, 1 reacted only at the highest of these 3 doses and 1 reacted at the highest 2 of these doses and 2 reacted at all 3 lower doses.
Nowak et al., 1997a (Hamburg)	None of the 10 subjects reacted to ETS exposure during the 3 hour exposure period or 9 hours afterwards.
Nowak et al., 1997b (Hamburg)	5 of the 17 subjects (29%) reacted between 1 and 9 hours following ETS exposure. 1 of these also reacted to sham exposure. 1 subject reacted only to sham exposure, but 9 hours after the end of exposure.

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* Details of the exposures are given in Appendix A.

TABLE 3

Summary of findings for lung function measurements other than FEV_1 in relation to ETS exposure*

Study	Report
Shephard et al., 1979 (Toronto)	No significant differences between ETS and sham exposure after 2 hours for RVC, RV, FRC, FVC, $VMAX_{25\%}$ or $VMAX_{50\%}$. Only significant effect on TLC (ratio of ETS to sham 0.965, $p<0.02$). Ratios also not significant for the dynamic lung volumes after 30, 60 and 90 minutes, except for FVC (ratio of ETS to sham 1.039, $p<0.05$). Changes in pulmonary function considered to be "slight".
Dahms et al., 1981 (St Louis)	Following ETS exposure percent reductions in FVC and $FEF_{25-7\%}$ similar to those noted for FEV_1 (see Table 1) and significant ($p<0.05$ or $p<0.01$). [No sham exposure.]
Ing & Breslin, 1983 (Sydney)	Falls of 20% or more in FVC and PEFR and of 30% in MMEFR were defined as "significant" but none were observed. One subject showed a 26.8% fall in MMEFR. [Sham exposure data not reported.]
Ben Hassine et al., 1984 (Tunis)	Compared to pre-exposure levels, levels following exposure after 15, 30, 45 and 60 minutes were, respectively, -0.5%, +0.7%, +0.5% and –0.5% for VC and +2.0%, -11.7%, -4.2% and –5.4% for $FEF_{25-75\%}$. Statistical tests not conducted. [No sham exposure.]
Knight & Breslin, 1985 (Sydney)	Trends in VC, MMEFR and PEFR were noted to be "similar" to those seen for FEV_1. [Data not reported.]

TABLE 3 (continued 1)

Wiedemann et al., 1986 (Yale)

$VMAX_{50\%}$ was similar on day 1 at baseline (3.46), on day 2 pre-smoke (3.46) and on day 2 post-smoke (3.42). Corresponding FVC values were 4.57, 4.65 and 4.56. The decrease (2%) following exposure was statistically significant ($p<0.01$). [No sham exposure.]

Urch et al., 1988 (Toronto)

Changes from pre-exposure levels after 30 minutes exposure were as follows:

	FVC	FEF_{50}	FEF_{75}	FEF_{60iso}
Sham	0	+56	+16	+24
Moderate	-41	+69	+59	+29
Heavy	-105	0	-4	-104
Trend p	<0.05	NS	NS	NS

Ortega Gonzalez et al., 1989 (Mexico)

20%+ declines in MMEFR were seen in 8/62 of the children (13%), with 10-20% declines in a further 6 (9.7%). For FVC 20%+ declines were seen in 1 (1.6%), with 10-20% declines in a further 2 (3.2%). [No sham exposure.]

Jörres et al., 1990 (Hamburg)

No significant effects on SRAW following exposure.

Gurk et al., 1991 (Munster)

Significant increase in SRAW from 5.29 to 5.96 ($p=0.033$) following ETS exposure. [No sham exposure.]

Oldigs et al., 1991 (Hamburg)

There was no difference (in children) between pre- and post-exposure SRAW following either ETS exposure (10.4 vs 9.4) or sham exposure (8.7 vs 9.0).

TABLE 3 (continued 2)

Jörres & Magnussen, 1992 (Hamburg)	Changes in SRAW following ETS exposure (7.9 pre to 7.4 post) did not differ significantly from those following sham exposure (8.2 pre to 7.9 post).
Magnussen et al., 1992 (Hamburg)	Changes in SRAW following ETS exposure (7.5 pre to 7.2 post) did not differ significantly from those following sham exposure (8.8 pre to 8.4 post). These are results for adults. Results for children as reported in Oldigs et al., 1991.
Danuser et al., 1993 (Zurich)	Following exposure at 2, 4, 8, 16 and 32 ppm CO reductions in FVC and MEF_{50} were seen which were evident, and highly significant $p<0.001$) at all dose levels but only slightly greater at higher than at lower doses.

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* Details of the exposures are given in Appendix A.

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APPENDIX A

Summary of study design and results for 25 papers describing chamber studies of ETS exposure

Notes

Exposure : Smoke was mechanically generated unless stated otherwise.

Effects on symptoms : Only symptoms classically associated with asthma (e.g. shortness of breath, wheezing, tightness in chest, cough) are mentioned in this appendix.

Authors:	Shephard et al., 1979
Location:	Toronto, Canada
Subjects:	14 asthmatics aged 19 to 65 years, 9 men and 5 women. 4 subjects claimed sensitivity to cigarette smoke.
Exposure:	In a closed room of 14.6m^3 capacity, with a CO concentration 24 ppm above ambient and a suspended particulate concentration of 2-4 mg/m^3. Sidestream and mainstream smoke.
Design:	Subjects in room for two hours on two occasions – ambient air or smoke exposed. Order of two tests randomized. Subjects continued with their normal medication on experimental days.
Effects on symptoms:	Symptoms only recorded on smoke exposed occasion. 3 subjects reported shortness of breath, 5 wheezing, 6 tightness in chest and 5 cough. Severity was never more than moderate.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	Based on ratio of values at end of two hours in exposed and ambient conditions, no significant differences seen for relaxed VC, RV, FRC, FVC, FEV_1, $VMAX_{25\%}$ or $VMAX_{50\%}$. There was a statistically significant ($p<0.02$) lower reduction in TLC, by 3.5%, under the test condition. In four subjects with claimed sensitivity, there was a small increase in FEV_1.
Comments of authors:	"Changes of pulmonary function were slight." "Our data thus do not suggest that asthmatic subjects have an unusual sensitivity to cigarette smoke."
Comments:	Smoking habits of subjects not reported.

Authors:	Dahms et al., 1981
Location:	St Louis, USA
Subjects:	10 nonsmoking asthmatic men and women aged 18 to 26 years, five of whom reported being smoke-sensitive. Also 10 nonsmoking healthy control men and women aged 24 to 53 years.
Exposure:	In a $30m^3$ chamber which produced an average increase in COHb of 0.40%, taken to indicate an environmental CO concentration of 15 to 20 ppm. Sidestream smoke.
Design:	Subjects in both groups exposed in the chamber for 1 hour with lung function measured before exposure and at 15 minute intervals during exposure. The asthmatic subjects continued taking their medication but refrained from using any bronchodilators for four hours before exposure.
Effects on symptoms:	Not studied.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	There was a significant linear decrease in lung function during the exposure in the asthmatic group, with FEV_1 decreased 21.4%, FVC decreased 20% and $FEF_{25-75\%}$ decreased 19.2%, after an hour. The control subjects showed no decline in lung function.
Comments of authors:	"These data show that nonsmokers with bronchial asthma are at risk when exposed to sidestream cigarette smoke in an environmental chamber."
Comments:	No comparisons made of asthmatics who did or did not report being smoke-sensitive. Smoke exposure concentrations not measured directly. No sham exposure. Ages of controls and asthmatics totally different.

Authors:	Ing & Breslin, 1983
Location:	Sydney, Australia
Subjects:	6 subjects with mild to moderate asthma. All had sensitivity to cigarette smoke. Sex and age not given.
Exposure:	In $7m^3$ room, from mechanical device producing smoke from cigarettes at a rate of approximately 100 mls of smoke every two minutes in same room as subject. Concentrations of smoke were in range 20-25 ppm CO with rises in COHb of 0.5%.
Design:	Each subject in room for one hour on two occasions – ambient air or smoke exposed. Smoke exposure always second. Subjects abstained from medications for 6 to 48 hours prior to tests, the time depending on the medication.
Effects on symptoms:	Chest tightness, described as an average asthmatic attack, produced in all six subjects on smoke exposure but not on sham exposure. The sensation started within 15 minutes of exposure and continued for up to 1 hour post challenge.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	FEV_1, FVC, MMEFR and peak flow measurements showed no significant change compared with baseline levels.
Comments of authors:	"Passive exposure to cigarette smoke in these subjects produced marked symptoms described as usual asthma but not significant evidence of airways obstruction."
Comments:	Only reported as abstract. Smoking habits of subjects not reported. Changes in lung function following smoke exposure not reported relative to changes seen following sham exposure.

Authors:	Ben Hassine et al., 1984
Location:	Tunis
Subjects:	11 female nonsmoking asthmatics (in- or out-patients) of mean age 32. Also 9 female nonsmoking control subjects hospitalised but with no lung pathology, of the same mean age.
Exposure:	In a $34m^3$ unventilated room. Smoke generated by two smokers smoking continuously in the room. COHb levels rose from 0.71 to 1.2% in the asthmatics following exposure, and from 0.84 to 1.1% in the controls.
Design:	Two subjects were exposed at a time for an hour. Spirometry was conducted at the start of exposure, after 15, 30, 45 and 60 minutes of exposure, and also 10 minutes after the end of exposure after a dose of an adrenergic bronchodilator (salbutamol). Medication had been ceased for at least 12 hours before the start of exposure.
Effects on symptoms:	Stated to be available on request.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	There were no significant differences pre and post exposure in FEV_1, VC or $FEF_{25-75\%}$. Nor was there any difference between asthmatics and the controls. There were reactions in individuals, particularly in $FEF_{25-75\%}$, but these were seen in both asthmatics and the controls, and were cured by inhaling salbutamol.
Comments of authors:	"In summary, our conventional spirometric measures were incapable of detecting a systematic bronchomotor reaction of ETS inhalation on the bronchi of either asthmatics or control subjects with undamaged lung pathology. Clinically one suspects nevertheless an aggravating effect of passive smoking in asthmatics. More precise measures of breathing are probably necessary to verify this interaction." (Translated from French original.)
Comments:	Neither individual data nor results of significance tests are presented. No sham exposure.

Authors:	Knight & Breslin, 1985
Location:	Sydney, Australia
Subjects:	6 nonsmoking subjects with mild to moderate asthma. Aged 22 to 39 years. 4 men and 2 women. 4 subjects gave a positive history of asthma induced by ETS.
Exposure:	"Exposed to the air of a provocation room in which smoke was produced mechanically from one cigarette after another, continuously, over one hour." No further details are given, though these were stated to be available on request. Exposure may be as described by Ing & Breslin, 1983.
Design:	Each subject in room for one hour on two occasions – ambient air or smoke exposed. Smoke exposure always second.
Effects on symptoms:	All 6 patients were stated in the abstract to develop "chest tightness and symptoms similar to an attack of asthma" following smoke exposure. However the results section of the paper only states that all 6 patients experienced some symptoms and that, of the 4 subjects with a positive history of asthma, 2 experienced chest tightness, 1 wheezing and 1 both symptoms. No results are given for the sham exposure.
Effects on airway responsiveness:	A histamine inhalation test was conducted at baseline and four hours after leaving the room on both days, and for each test PC_{20} was calculated. In all six subjects PC_{20} fell more over the four hour period on the exposed day ($p<0.05$).*
Effects on lung function:	All subjects showed a fall in FEV_1 on the smoke exposed day, but none showed a fall on the control day ($p<0.05$).* "Similar trends" were noted for VC, MMEFR and PEFR, though results were not presented.
Comments of authors:	"Our findings suggest that passive smoke inhalation may produce asthma attacks in subjects who suffer from asthma and may lead to increased bronchial reactivity to histamine for a time after such inhalation."
Comments:	Paper is very short, subjects and methods are poorly described, and exposure is not well characterized. No comparison made of asthmatics who reported history of asthma induced by ETS. No details given as to whether medications for asthma were stopped pre-test.

*p values computed by PNL.

Authors:	Wiedemann et al., 1986
Location:	Yale, United States
Subjects:	9 nonsmoking asthmatics aged 19 to 30, 5 men and 4 women. 6 subjects claimed sensitivity to cigarette smoke. None currently taking oral asthma medication. 5 previously hospitalised (>1 year ago).
Exposure:	Exposure in 4.25m^3 chamber with mean CO level of 40 to 50 ppm. Sidestream and mainstream smoke. Subjects given option to wear goggles to reduce eye irritation.
Design:	Methacholine inhalation challenge and spirometry on day 1. On day 2 spirometry before 1 hour ETS exposure, with methacholine inhalation challenge and spirometry immediately after. Subjects refrained from using inhaled bronchodilators for 6-8 hours before exposure.
Effects on symptoms:	3 subjects experienced mild, transient cough.
Effects on airway responsiveness:	On day 1 each subject, as expected from their asthmatic status, had a high degree of bronchial responsiveness compared to a normal population. 8 of the 9 subjects showed a small decrease following ETS exposure ($p<0.05$).
Effects on lung function:	There was no difference in FEV_1 or $VMAX_{50\%}$ on day 2 before or after ETS exposure. FVC showed a small decrease of 2% ($p=0.01$).
Comments of authors:	"Although the finding of decreased airway reactivity might suggest that passive smoking produces a 'protective' effect on the underlying asthma, the observed change in reactivity was slight and of uncertain clinical significance. We conclude that passive smoking presents no acute respiratory risk to young asymptomatic asthmatic patients."
Comments:	No sham exposure. No test of delayed airway hyper-responsiveness. No comparison made of asthmatics who did or did not report being smoke-sensitive.

Authors: Stankus et al., 1988

Location: New Orleans, USA

Subjects: 21 subjects with asthma exacerbated by ETS exposure. Aged 21 to 50 years. 5 men and 16 women. 13 were never smokers and 8 ex-smokers for at least 1 year. 19 were atopic.

Exposure: Subjects were exposed in a static chamber (12 by 7 by 11 feet = 26m^3) to up to three increasing levels of cigarette smoke (sidestream and mainstream):

Level	Aerosol (cpm)	Aerosol ($\mu g/m^3$)	CO (ppm)
Low	439	852	8.7
High	895	1421	13.3
Ultra high	1742	Not done	14.1

Design: Subjects exposed to the low level for 2 hours. If a 20% FEV reduction not induced, exposed to the high level for 2 hours, following a 30 minute rest period. Some subjects then exposed later to the ultra high level if no 20% FEV reduction. Medication withheld before testing (oral medication 24 hours, inhaled bronchodilators 8-12 hours, steroids on morning of challenge).

Effects on symptoms: Cough, dyspnoea and/or chest tightness in all 7 subjects with significant declines in FEV_1. Results for these symptoms not given for subjects without declines.

Effects on airway responsiveness: Not studied.

Effects on lung function: Of the 21 subjects 2 reported a 20% decline in FEV_1 following low level exposure. A further 5 reacted to the high level exposure. Of the remaining 14, 5 with a strong history of cigarette smoke sensitivity were challenged with the ultra high level on a separate day, but none experienced a significant fall in FEV_1. The 7 subjects with a 20% decline in FEV_1 did not differ from the other 14 as regards IgE antibodies or a positive immediate wheal-and-flare skin test to a tobacco leaf extract.

Comments of authors: "Collectively, these studies document a significant decline in pulmonary function in a substantial percentage (33%) of a population of 'smoke-sensitive' subjects with asthma exposed to environmental tobacco smoke."

Comments No sham exposure. Essentially the same results were reported elsewhere in a conference paper (Stankus & Lehrer, 1988). Although few details are given, this reports reproducibility of reaction (20% decline in FEV_1) and non-reaction in 6 reactors and 10 non-reactors on rechallenge up to two years later. Also no reactors in a group of 15 atopic non-asthmatic subjects on identical challenge.

Authors:	Urch et al., 1988
Location:	Toronto, Canada
Subjects:	16 asthmatic nonsmokers aged 19 to 63 years, 8 males and 8 females. 13 had never smoked and 3 were exsmokers (for at least 2 years), 6 were assessed as sensitive to cigarette smoke and 6 as insensitive/indifferent (others not reported). Also 24 non-asthmatic nonsmokers aged 18 to 34 years, 12 males and 12 females. 20 had never smoked and 4 were exsmokers (at least 6 years).
Exposure:	In 14.6m^3 chamber to "moderate" smoke (17 ppm CO) or "heavy" smoke (31 ppm CO). Not stated whether mainstream/sidestream, but smoking machine was outside chamber.
Design:	On Visit 1 baseline physiological and psychological data were obtained but there was no exposure. On Visits 2 to 4 subjects were exposed for 65 mins to either heavy, moderate or sham exposure, with order of treatments balanced. On these 3 visits, subjects shown a similar bank of burning cigarettes. Asthmatics rested during exposures, but non-asthmatics exercised intermittently on bicycle. Asthmatics continued usual medication, except during exposure.
Effects on symptoms:	Not studied.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	FVC, FEV_1, $FEF_{50\%}$, $FEF_{75\%}$ and $FEF_{60\%iso}$ were determined after 5, 30 and 60 minutes relative to pre-exposure values. In asthmatics, significant ($p<0.05$) dose-response relationships were noted for $FEF_{50\%}$ after 5 minutes, and for FVC and FEV_1 after 30 minutes, with no significant changes after 60 minutes. For non-asthmatics the only significant difference noted was for $FEF_{50\%}$ after 30 minutes.
Comments of authors:	"Significant dose-response relationships … observed for reported symptoms, deterioration of pulmonary function … could reflect either a pure physiological response, or an interaction between physiological and psychological responses."
Comments:	The paper is more concerned with trying to determine whether suggestibility may augment physiological response to ETS, concluding that "any effect is relatively weak". The authors noted it was obvious little smoke was present during sham exposure, but not as to whether heavy or moderate exposure was occurring. If the sight of the burning cigarettes during sham exposure was supposed "to provide an element of suggestion" why was it not controlled for by a no exposure/no sight visit? No comparisons made of asthmatics assessed as smoke sensitive or not.

Authors:	Menon et al., 1989
Location:	New Orleans, USA
Subjects:	11 "smoke sensitive" asthmatics and 5 age and sex matched non-asthmatic controls.
Exposure:	In static inhalation chamber.
Design:	Serial methacholine challenges were performed and PC_{20} was determined one day prior to, at 6 hrs, at 24 hrs and as necessary up to 14 days post-ETS challenge. A two-fold or greater decline from baseline following ETS challenge was considered significant.
Effects on symptoms:	Not studied.
Effects on airway responsiveness:	A significant increase was demonstrated at 6 hrs post-ETS challenge in 5 of 10 asthmatics and 1 of 5 controls. One asthmatic experienced a 7-fold increase in airway reactivity and a second asthmatic had increased reactivity for up to 14 days.
Effects on lung function:	Not studied.
Comments of authors:	"These results identify ETS as an important influence on airway reactivity and support our previous findings which documented significant declines in pulmonary functions in a substantial proportion of asthmatics after exposure to ETS."
Comments:	Only reported as an abstract. No details given of extent or duration of ETS exposure. No sham exposure. No details as to whether medications were stopped.

Authors:	Ortega Gonzalez et al., 1989
Location:	Mexico
Subjects:	62 nonsmoking asthmatic children aged 6 to 16, 48 boys and 14 girls
Exposure:	In $35m^3$ furnished room where two volunteers smoked a total of five cigarettes. No measurement of smoke constituent levels.
Design:	Exposed for an hour, with lung function measured before and after exposure. Bronchodilator medication was suspended 8 hours before the study, with anti histamines suspended by as much as 72 hours in some cases.
Effects on symptoms:	Not studied
Effects on airway responsiveness:	Not studied
Effects on lung function:	Declines of at least 20% were seen in 8 children (13%) for MMEFR, in 2 children (3.2%) for FEV_1 and 1 child (1.6%) for FVC. Declines of 10-20% were seen in a further 6 children (9.7%) for MMEFR, 1 child (1.6%) for FEV_1 and 2 children (3.2%) for FVC. Changes were seen in some aspect of lung function in 20 children (32.2%).
Comments of authors:	"The results obtained for the effects of passive smoking should not be considered conclusive" … "The most sensitive parameter of the spirometry test was the MMEFR" [translation from Spanish].
Comments:	The study also reported no correlation between changes in MMEFR and either parental cigarette smoking habits or skin test sensitivity to tobacco antigen. No sham exposure. Smoke constituent levels not reported.

Authors:	Jörres et al., 1990
Location:	Hamburg, Germany
Subjects:	11 mild asthmatics, mean age 36 years, 5 men and 6 women.
Exposure:	In a chamber with a particulate matter concentration of 2800 $\mu g/m^3$, and a CO of 20 ppm.
Design:	Subjects exposed for 1 hour on separate days to either ambient air or ETS. On each day, symptoms and lung function were measured before and after exposure and a methacholine inhalation challenge was started 20 mins after exposure.
Effects on symptoms:	It is not stated what symptoms were recorded. Only eye irritation was noted to occur during ETS.
Effects on airway responsiveness:	There was no significant difference between ETS and ambient air on airway responsiveness (PC_{20} or PC_{100} SRAW).
Effects on lung function:	There was no significant effect of ETS on FEV_1 or SRAW.
Comments of authors:	"We conclude that in mild asthmatics short-term exposure to ETS does not exert a consistent effect on lung function and bronchial responsiveness."
Comments:	These results are only reported in an abstract. This gives the means and standard errors of the responses in individual groups, but does not actually give the means and standard errors of the relevant ETS-sham differences. No details as to whether medications were stopped.

Authors:	Menon et al., 1990
Location:	New Orleans, USA
Subjects:	10 smoke sensitive asthmatics aged 12-18 years and 11 matched non-asthmatic controls.
Exposure:	In a static inhalation chamber (12 by 7 by 11 feet = 26m^3) to produce a total suspended particulate concentration of 1394 μg/m^3.
Design:	4 hours exposure. Methacholine challenges at 6, 24 and 72 hours and weekly post exposure. A two-fold or greater decline from baseline following ETS exposure was considered significant.
Effects on symptoms:	The asthmatics complained of cough, wheezing or chest tightness, while the non-asthmatics had upper airway irritation on exposure to ETS.
Effects on airway responsiveness:	A significant increase in bronchial hyperresponsiveness was seen after 6 hours in 3/10 (30%) asthmatics and in 4/11 (36%) controls and after 24 hours in 3/10 (30%) asthmatics and in 2/11 (18%) controls. 2 asthmatics and 2 non-asthmatics had a long-term increase.
Effects on lung function:	None of the 21 children had a decline in FEV_1 of 20% or more following exposure.
Comments of authors:	"Although none of the 21 SS children had a significant decline in FEV_1, a significant number demonstrated increased sensitivity to methacholine, suggesting prolonged airway hyper-reactivity following ETSC."
Comments:	Only presented as an abstract. Smoking habits of the subjects not reported. No sham exposure. No details as to whether medications were stopped.

Authors:	Gurk et al., 1991
Location:	Münster, Germany
Subjects:	20 patients with bronchial asthma, mean age 36 years, and 9 control subjects, mean age 34 years.
Exposure:	In a chamber to produce 35-40 ppm CO. Sidestream smoke.
Design:	Lung function measured before and immediately after ETS exposure for an hour. Histamine challenge performed on the day before and 20 minutes after exposure in all asthmatics to determine PC_{100}SRAW.
Effects on symptoms:	Not studied.
Effects on airway responsiveness:	ETS produced no change in bronchial reactivity among asthmatics as a whole. However a subgroup of the asthmatics with a more than 5% decrease in FEV_1 showed a mild increase in bronchial reactivity ($p=0.038$).
Effects on lung function:	The controls showed no change in pulmonary function. The asthmatics showed a significant ($p<0.025$) decline in FEV_1, from 3.02 to 2.89, and a significant ($p=0.033$) increase in SRAW, from 5.29 to 5.96.
Comments of authors:	"We conclude that passive exposure to sidestream cigarette smoke may reduce lung function in sensitive asthmatics. Furthermore these subjects are at risk of developing an increase in airway reactivity to histamine."
Comments:	Only reported as an abstract. No sham exposure. Smoking habits of subjects not reported. No details as to whether the medications were stopped.

Authors:	Menon et al., 1991a
Location:	New Orleans, USA
Subjects:	100 smoke sensitive asthmatics.
Exposure:	In a chamber, up to 6 hours with levels of sidestream ETS producing suspended particulate levels of 1392, 804, 289 or 242 $\mu g/m^3$ (800, 400, 200 or 100 cpm).
Design:	Reactors ($\geq$20% fall in FEV1) were sham challenged (no details given) and challenged sequentially at 4 week intervals to the decreasing dose levels.
Effects on symptoms:	Not studied.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	7/100 subjects reacted to 800 cpm. All the reactors were negative to sham challenge. 3 subjects did not react at lower dose levels, 3 reacted at 400, 200 and 100 cpm (after 90 mins to 4 hours) and one reacted at 400 cpm (after 5½ hours) but not at 200 cpm.
Comments of authors:	"This study suggests that the level and duration of exposure play an important role in the development of asthmatic reactions following ETS exposure."
Comments:	Only published as an abstract. Sex, age and smoking habits of subjects not reported. No details as to whether medications were stopped. The seven reactors were atopic, but this is not reported for the non-reactors. A later abstract (Musmand et al., 1993) describes a study of allergy testing on 58 asthmatics, 7 of whom reacted to ETS but not sham challenge. It seems likely that the 7 reactors were the same as reported here, and the non-reactors a subset of the non-reactors, though this is unclear.

Authors:	Menon et al., 1991b
Location:	New Orleans, USA
Subjects:	Group I consisted of 15 subjects with asthma who claimed symptoms of asthma on exposure to ETS; - aged 25 to 51 years, with 3 male and 12 female subjects, 13 atopic and 2 non-atopic, and 7 never smokers and 8 ex-smokers for more than 5 years. Group II consisted of 15 atopic subjects without asthma claiming upper respiratory tract symptoms on exposure to ETS; - aged 21 to 48 years, with 5 male and 10 female subjects, and 12 never smokers and 3 ex-smokers for more than 5 years.
Exposure:	In a static chamber (12 by 7 by 11 feet = $26m^3$) to produce a mean total suspended particulate concentration of 1145 $\mu g/m^3$ (800 cpm). Sidestream and mainstream smoke.
Design:	Group I had a 2- to 6-hour exposure. Those who "reacted" (with a 20% fall in FEV_1) were subjected to a sham challenge for 6 hours. Those who did not react were subjected to a 6-hour challenge at the same smoke exposure 4 weeks later. Group II also underwent a 6-hour smoke challenge. "Reactors" were subsequently retested after pre-treatment with a bronchodilator, an anti-inflammatory medication, or both on 3 occasions 4 weeks apart. Subjects avoided medication before exposures.
Effects on symptoms:	Respiratory symptoms were not reported.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	6 subjects in group I had, 24 months earlier, been shown to react to smoke exposure. Of these, 5 again reacted on re-challenge with ETS after 1 to 2 hours exposure. None of these 5 reacted during sham challenge. The sixth subject did react when subjected to the 6-hour challenge. The other 9 subjects in Group I had previously not reacted. All of these again did not react, after challenges of 2-hour and 6-hour duration on 2 separate days 4 weeks apart. No reactions were seen in Group II subjects, either 24 months earlier, or at the time of the current study. In the reactors pre-treatment with drugs blocked the decline in FEV_1.
Comments of authors:	"These studies demonstrate the persistence of ETS reactivity during a 2-year period."
Comments:	The reproducible results suggest the existence of a susceptible group of asthmatics. Although statistical tests were not reported, it is clear that the consistency of the results is not due to chance. Essentially the same results were reported earlier in an abstract (Menon et al., 1988), and later (Lehrer et al., 1999).

Authors:	Oldigs et al., 1991
Location:	Hamburg, Germany
Subjects:	11 children with allergic asthma aged 8 to 13 years, 10 boys and 1 girl. Not selected on basis of smoke sensitivity. All were never smokers.
Exposure:	In $24m^3$ chamber, with a mean total suspended particulate concentration of 2743 $\mu g/m^3$ and a mean CO of 20.5 ppm.
Design:	Each subject studied on three days within a two week period, with all investigations performed at least six hours after last inhalation therapy. On the first day lung function and airway hyper-responsiveness was measured but there was no exposure. Day two was sham exposure and day three ETS exposure, each of 1 hour, with lung function measured before and immediately after each exposure and histamine inhalation challenge started 15 minutes after exposure. Except for one subject, medication was withheld for 6h before exposure.
Effects on symptoms:	The frequency of asthma symptoms did not differ between cigarette smoke and sham exposure.
Effects on airway responsiveness:	The concentration of histamine to cause a 100% increase in SRAW or a 20% fall in FEV_1 did not differ significantly between sham and ETS exposure.
Effects on lung function:	There were no significant differences in SRAW or FEV_1 following ETS exposure or following sham exposure. (Nor in additional statistical tests by PNL were there any significant differences in change in lung function pre to post exposure between ETS exposure and sham exposure.)
Comments of authors:	"Our observations suggest that in children with mild bronchial asthma 1 hour of passive cigarette smoking does not cause consistent changes of lung function and bronchial responsiveness."
Comments:	No test of delayed airway hyperresponsiveness. The children in this study seem to be the same as in the paper reported by Magnussen et al., 1992.

Authors:	Jörres & Magnussen, 1992
Location:	Hamburg, Germany
Subjects:	24 mild to moderate non-smoking asthmatics, age 15 to 66 years, 11 men and 13 women. 16 of the 24 had a history of ETS induced respiratory symptoms and 22 were atopic. 16 nonsmoking healthy controls, age 21-51 years, 7 men and 9 women. 5 of the 15 had a history of ETS-induced respiratory symptoms, 8 were atopic and 4 were moderately hyperresponsive to inhaled methacholine; 3 were exsmokers.
Exposure:	In a $24m^3$ chamber vented to ambient air with a particulate matter concentration of 3095 $\mu g/m^3$, and a CO of 20.3 ppm.
Design:	Subjects exposed for 1 hour on separate days to either ambient air or ETS, in random order. On each day, symptoms and lung mechanics were measured before and immediately after exposure and a methacholine inhalation challenge was started 20 mins after exposure. Inhaled bronchodilators were withheld for 6h before exposure but other medication continued.
Effects on symptoms:	Comparing responses to ETS and ambient air, there was a significant increase in tightness of the chest ($p = 0.002$) but not cough in the asthmatics, and a significant increase in cough but not tightness of the chest in the controls.
Effects on airway responsiveness:	There was no significant difference between ETS and ambient air on airway responsiveness to methacholine, as measured by PC_{20} or PC_{100}SRAW in either asthmatic or control subjects.
Effects on lung function:	In asthmatics, there was no significant effects of ETS on FEV_1 or SRAW, when adjusted for the effect of sham exposure. Nor were any effects seen in the controls.
Comments of authors:	"Our observations suggest that in healthy subjects and in patients with mild to moderate asthma, symptoms induced by one hour of passive smoking are not explained by changes in lung mechanics and airway responsiveness."
Comments:	Tables 2 and 3 give the means and standard errors of the responses in the asthmatic group at individual times, but do not actually give the means and standard errors of the relevant ETS-sham differences. These can be calculated from the individual person data. Similarly for comparisons of subjects with and without history of ETS induced respiratory symptoms.

Authors:	Lehrer, 1992
Location:	New Orleans, USA
Subjects:	163 smoke-sensitive asthmatics
Exposure:	In 16.9m^3 chamber to sidestream smoke to give a total suspended particle concentration of 750-2000 $\mu g/m^3$.
Design:	Subjects were first challenged with sidestream-ETS for up to 4 hr. Those who "reacted" with a 20% or greater drop in FEV_1 then underwent a 4 hr sham challenge. Some of those who reacted again were selected for dose-response challenge with decreasing levels of sidestream-ETS 804, 289 and 242 $\mu g/m^3$ UV-absorbing particulate matter) for up to 6 hrs at 4 wk intervals.
Effects on symptoms:	Not studied.
Effects on airway responsiveness:	Not studied
Effects on lung function:	Reaction seen in 28 asthmatics (17%). 11 of these 28 reactors (39%) also reacted to sham challenge but 17 (10% of asthmatics) did not. 7 of these 17 underwent a dose-response study. Of the 7, 3 did not react at all at any of the 3 lower doses, 1 reacted only to the 804 $\mu g/m^3$ dose after 5½ hours, and 3 reacted to all the lower doses after between 1½ and 4 hours. No significant drops in PEFR were seen when subjects were monitored overnight.
Comments of authors:	"Our studies showed that about 10% of asthmatics claiming to be smoke sensitive actually demonstrated objective changes in their pulmonary function from high level SS-ETS exposure. These responses do not appear to be related to IgE antibody reactivity to tobacco allergens."
Comments:	Only a short report. Smoking status, age and sex of patients not given. Study does not test for possibility of reaction to sham exposure only. It is possible that a fuller report summarized later (Lehrer et al., 1997) may be based on some of these subjects, though this is unclear.

Authors:	Magnussen et al., 1992
Location:	Hamburg, Germany
Subjects:	18 mild to moderate nonsmoking asthmatic adults, age 21 to 51 years, 10 women and 8 men, 11 asthmatic children, aged 8 to 13 years, 10 boys and 1 girl, and 16 healthy nonsmoking controls, age 17 to 66 years, 9 men and 7 women. 11 of the asthmatic adults reported previous symptoms induced by ETS.
Exposure:	In a $24m^3$ chamber with a man particulate matter concentration of 2743 $\mu g/m^3$ and a mean CO of 20.5 ppm.
Design:	Each subject studied in a 2 week period. On two different days they were exposed for 1 hour to either ETS or ambient air. On each day, symptoms and lung function were measured before and immediately after exposure, and a methacholine (adults) or histamine (children) inhalation challenge was started 20 mins after exposure. The asthmatic subjects continued corticosteroid medication as usual but refrained from using inhalation therapy for 6 hours before exposure.
Effects on symptoms:	A figure suggests that in adults, but not in children, there are somewhat higher levels of cough and chest tightness following ETS exposure than following sham exposure.
Effects on airway responsiveness:	There were no significant differences between ETS exposure and ambient air in airway responsiveness to methacholine or histamine as determined by PC_{20} or PC_{100}SRAW.
Effects on lung function:	"Neither in children nor in adult asthmatics did the spirometric and plethysmographic results show any significant differences after exposure to AA [ambient air] or ETS".
Comments of authors:	"Our observations suggest that in children and adults with mild to moderate bronchial asthma, 1 h of passive cigarette smoking does not cause airway obstruction or consistent changes in bronchial responsiveness".
Comments:	No test of delayed hyperresponsiveness. The children in this study seem to be the same as in the paper reported by Oldigs et al., 1991. No comparisons made of asthmatics who did or did not report previous ETS induced symptoms.

Authors: Menon et al., 1992

Location: New Orleans, USA

Subjects: Group I consisted of 31 subjects with asthma who claimed symptoms of asthma on exposure to ETS; aged 12 to 50 years, with 11 male and 20 female subjects and 26 never smokers and 5 ex-smokers for at least four years. Group II consisted of 39 subjects without asthma claiming upper respiratory tract symptoms on exposure to ETS; aged 12 to 50 years, with 17 male and 22 female subjects, and 36 never smokers and 3 ex-smokers for at least four years. Group III (controls) consisted of 10 subjects with asthma.

Exposure: In a static inhalation chamber ($26m^3$) to produce a mean total suspended particulate concentration of 1266 $\mu g/m^3$. (800 cpm). Mainstream and sidestream.

Design: Following withholding of asthma medication (12-24 hours depending on type), subjects underwent methacholine challenge. Next day, Groups I and II were exposed for four hours. Study subjects demonstrating a $\geq$20% drop in FEV_1 were considered a reactor and allowed to exit from the chamber. Lung function monitoring continued for 24 hours after exposure, and serial methacholine challenges were done after 6h and 24h, and in subjects showing an increase at 24h, at 3 days and then weekly. Group III were not exposed to ETS, but no details are given whether this was "sham" exposure in the chamber or not.

Effects on symptoms: Respiratory symptoms were not reported

Effects on airway responsiveness: The percent (number) of subjects demonstrating increased bronchial hyperreactivity following methacholine challenge was as follows:

		Time after ETS challenge				
Group	n	6 hrs	24 hrs	3 days	1 week	2 weeks
I	31	32% (10)	29% (9)	16% (5)	16% (5)	13% (4)
II	39	18% (7)	10% (4)	$\geq$5% ($\geq$2)	$\geq$5% ($\geq$2)	5% (2)
III	10	0% (0)	0% (0)			

(The data above are as given in the paper. However, for Group I it is stated that four subjects requested inhaled albuterol at 6 and/or 24 hours and were not further methacholine challenged. The later percentages should therefore be somewhat higher, based on a smaller denominator.)

Effects on lung function: 5 Group I asthmatics (13%) vs 0 Group II non-asthmatics demonstrated a 20%+ decline in FEV_1 following the ETS exposure ($p<0.05$)* Group III not reported.

Comments of authors: "Our studies of passive cigarette-smoke challenge in nonsmokers demonstrate that almost 1/3 of smoke-sensitive subjects with asthma and 1/5 of smoke-sensitive subjects without asthma have a marked increase in BHR 6 hours after ETS exposure."

Comments: No description of whether controls were sham-exposed. No statistical analysis to compare groups I and II. Differences in rates not in fact statistically significant.

*p values computed by PNL.

Authors:	Danuser et al., 1993
Location:	Zurich, Switzerland
Subjects:	10 subjects with hyperreactive airways and 10 age and sex matched healthy subjects. Aged 24 to 52, 8 men and 12 women. All subjects were nonsmokers. 5 of the hyperreactive subjects had asthma and a further 4 had symptoms suggestive of asthma. 8 of the hyperreactive subjects and 2 of the healthy subjects reported ETS-induced respiratory symptoms.
Exposure:	Serially increasing 2 minute exposure to sidestream smoke delivered via a mouthpiece. CO concentrations of 0, 2, 4, 8, 16 and 32 ppm (± 5%). 5-7 minutes rest between successive exposures. Subjects wore nose-clips during exposure. Subjects could not see the smoking machine and were not told about the increasing dose.
Design:	Lung function measurement and methacholine challenge test carried out on day 1 (pretest). On day 2 (experimental; within 4 days of the pretest), lung function was measured 30 and 90 seconds after each exposure and provocation terminated if there was a fall in FEV_1 of 20% or more from the value after 0 ppm inhalation. Symptom questionnaire completed after each level of exposure. Subjects refrained from taking oral medication for 48h and inhaled bronchodilators for 12h before test.
Effects on symptoms:	Weak symptomatic responses, though chest tightness and dyspnoea showed an apparent dose-related increase in a figure. This was more marked in the hyperreactive subjects, with dyspnoea not seen in the healthy subjects.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	The lung function of the normoreactive subjects not altered by exposure. In the hyperreactive subjects, significant decreases were seen in FEV_1, FVC and MEF50. The decreases were evident at 2 ppm CO and were generally not markedly altered at higher doses. Thus FEV_1 was decreased by 6.5%, 5.6% 7.1%, 8.2% and 8.7% at the 5 successive doses. Only one subject had a decrease of 20+% FEV_1.
Comments of authors:	"Even short exposure to low concentrations of cigarette sidestream smoke causes significant impairment of lung function in sensitive persons."
Comments:	Hyperreactive group not all asthmatic. Statistical testing not conducted on symptom data. No comparisons made of those reporting prior ETS-induced symptoms.

Authors:	Magnussen et al., 1993
Location:	Hamburg, Germany
Subjects:	13 atopic mildly asthmatic never-smoking children aged 8 to 13 years, 8 boys and 5 girls. Exercise-induced asthma was confirmed by a $\geq$20% fall in FEV_1 after a 6 minute cold air exercise challenge on day 2 compared with pretest/day 1.
Exposure:	In a $24m^3$ chamber, with a mean particulate concentration of 3197 $\mu g/m^3$ and a mean CO concentration of 20.2 ppm. Goggles were worn to prevent eye irritation.
Design:	On separate days, the children were exposed to ETS or ambient air for 1 hour, with the order randomised. During the first 54 minutes, the children were at rest, and during the last 6 minutes they exercised on a bicycle ergometer. In seven children, the experiments with ambient air and ETS were done in duplicate. Symptoms were assessed before and 30 mins after exposure. Lung function was measured serially during rest, during exercise and up to 25 minutes after. Bronchoactive medication was not used for 8h before exposure.
Effects on symptoms:	Upper respiratory symptoms and chest tightness were nonsignificantly higher during the ETS exposure than during ambient air exposure. (This was only reported for the seven children who underwent duplicate experiments.)
Effects on airway responsiveness:	Exercise-induced bronchoconstriction did not differ significantly between ETS and ambient air exposure.
Effects on lung function:	With both exposures, there was an initial fall in FEV_1 after 5 minutes that did not significantly change with ongoing at-rest exposure. The reduction after 5 minutes was significantly ($p = 0.04$) greater in the ETS group (7.2% vs 3.2%). Analysis of individual data revealed that the mean changes during ETS were mainly affected by 3 children with a significant fall and one child with a significant improvement in FEV_1.
Comments of authors:	"In children with mild asthma, short-term exposure to ETS can be associated with a transient fall in FEV_1 in sensitive subjects but does not increase exercise-induced bronchoconstriction."
Comments:	No test of delayed airway hyperreactivity.

Authors:	Lehrer et al., 1997
Location:	New Orleans, USA
Subjects:	130 asthmatics aged 18-60 years, 37 male and 93 female, and 28 non-asthmatics aged 18-50 years, 8 male and 20 female. 71% of the asthmatics were assessed as hyperreactive by methacholine challenge. 86% of the asthmatics and 79% of the non-asthmatics were atopic. Of the total of 158 subjects, 111 never smoked and 30 were ex-smokers for at least 4 years, with some smokers and some not known.
Exposure:	In 16.9m^3 dynamic chamber to sidestream-ETS at a smoke index corresponding to a UV particulate matter concentration of 1553 µg/m^3 and a CO level of about 12 ppm. Selected challenges were conducted at smoke indices of ½, ¼ and ⅛ of this. These produced UV particulate matter concentrations of 621, 337 and 121 µg/m^3 and CO concentrations of 7.8, 6 and 0.8 ppm, respectively.
Design:	Subjects were first challenged with the high dose of sidestream-ETS for up to 4 hrs. Those who "reacted" with a 20% or greater drop in FEV_1 were allowed to leave the chamber, and then underwent a 4 hr sham challenge. Seven selected positive reactors (i.e. did not react to the sham challenge) were then exposed for up to 4 hrs to decreasing levels of sidestream-ETS. Medications were withheld for 24 h prior to the challenge.
Effects on symptoms:	Not studied.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	At the high exposure none of the non-asthmatic controls reacted, but 26 (20%) of the asthmatics did, mostly between 1½ and 2 hrs. The reactors tended to be more likely to have perceived smoke allergy ($p<0.05$). 6 of the 26 reacted to sham exposure. Of 7 who reacted to sidestream-ETS only, 3 did not react at lower doses, 1 reacted at the ½ dose only, 1 at the ½ and ¼ doses and 2 at all 3 lower doses.
Comments of authors:	"Responses to diminishing levels of SS-ETS demonstrated that some asthmatics can react to levels as low as 0.0128 cigarette-min/m^3 (comparable to ETS levels in the homes of many smokers)."
Comments:	It is possible that a report summarized earlier (Lehrer, 1992) may be based on some of these subjects, though this is unclear. These data are also cited elsewhere (Lehrer et al., 1999). Study does not test for possibility of reaction to sham exposure only.

Authors:	Nowak et al., 1997a
Location:	Hamburg, Germany
Subjects:	10 mild asthmatics, aged 22 to 29, 6 male and 4 female, all atopic and nonsmokers. 8 had a history of ETS induced symptoms. None currently taking regular medication.
Exposure:	In a $24m^3$ chamber vented to ambient air with particulate concentration of 3141 $\mu g/m^3$ and a CO level of 22.4 ppm.
Design:	Subjects studied on two different occasions at least 7 days apart, within a 2 week period. No ETS exposure had occurred at least 12 h before the test. Exposed to ETS or ambient air in random order, for 3 h in the evening. On-demand medications withheld for 12h before test. Symptoms assessed at start and end of exposure. Spirometry before, during and at end of exposure, then after 1h, 5h (i.e. 3 am) and 9h (i.e. 7 am next morning).
Effects on symptoms:	ETS induced a significant increase in general symptoms of the throat and chest (itchy throat, sore throat, hoarseness, cough, breathing difficulty, chest tightness, dyspnea, chest pain), but results were not reported for individual symptoms.
Effects on airway responsiveness:	Not studied.
Effects on lung function:	No significant changes in FEV_1 occurred during or after ETS exposure as compared with sham or pre-exposure spirometric values. Nor were results different for patients with and without a history of ETS-induced symptoms.
Comments of authors:	"Our data demonstrate that a single ETS exposure in subjects with mild asthma causes symptoms which were not accompanied by detectable changes in lung function or inflammatory changes immediately and several hours after exposure".
Comments:	No individual subject shows even a 15% decline in FEV_1 following exposure. Paper also presents results for effects of ETS on bronchoscopy, bronchoalveolar and nasal lavage. These results were reported previously in an abstract (Nowak et al., 1995).

Authors:	Nowak et al., 1997b
Location:	Hamburg, Germany
Subjects:	17 mild-moderate asthmatics, aged 19 to 38, 10 men and 7 women, all atopic and nonsmokers. 7 had a history of ETS induced symptoms. None currently taking regular medication.
Exposure:	In a $24m^3$ chamber vented to ambient air with a particulate concentration of 3196 $\mu g/m^3$ and a CO of 22.4 ppm.
Design:	Subjects studied on two occasions at least 7 days apart, within a 2 week period. No ETS exposure had occurred at least 12 h before the test. Exposed to ETS or ambient air in random order, for 3 hours between 7:00 and 10:00 pm. Serial measurements (spirometry, methacholine challenge and symptom assessment) made up to 9h (i.e. 7.00 am next day). Final symptom assessment at 24h. On-demand medications withheld for 12h before test.
Effects on symptoms:	ETS increased general symptoms of throat and chest, significant ($p=0.02$) during but not after exposure. Results were not reported for individual symptoms (as listed under Nowak et al., 1997a).
Effects on airway responsiveness:	$PC_{20}FEV_1$ was assessed at 5:00 pm, 11:00 pm, 3:00 am and 7:00 am. Comparing ETS to sham exposure, more subjects experienced an ETS-induced increase than a decrease in bronchial responsiveness, but the difference was not statistically significant.
Effects on lung function:	There was a greater fall in FEV_1 with ETS than with sham both during exposure (5.6% vs 3.0%, $p=0.013$) and after exposure (9.1% vs 5.9%, $p=0.026$. 5 subjects were considered ETS sensitive during exposure, and 3 of these continued after exposure. No significant difference was found between patients with and without history of ETS-induced symptoms.
Comments of authors:	"Our data show that in some subjects with mild asthma, exposure to a high concentration of passive smoke in the evening can induce nocturnal symptoms and lung function changes compared to a control exposure. These changes are largely independent of each other and appear not to be associated with a history of ETS-induced symptoms."
Comments:	Changes in FEV_1 are shown graphically in individual subjects. Of the 5 showing the largest decline following ETS, 4 had a very similar decline following sham exposure. These results were reported previously in an abstract (Nowak et al., 1993).