Exacerbation of asthma

by ETS exposure

A review of the epidemiological evidence

Part I – Literature up to 1997

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EXECUTIVE SUMMARY

This document reviews epidemiological evidence published up to 1997 relating exacerbation of asthma to ETS exposure.

Only three relevant studies of nonsmoking adult asthmatics were identified. One study in India reported a significant association of ETS exposure with various indices of asthma severity but did not control for differences in age and other potential confounding variables that differed between ETS-exposed and ETS-unexposed individuals, and included a number of obvious errors in its statistical analyses. A later study in India reported a significantly higher ETS exposure in patients with acute than non-acute asthma, but only in an abstract with little detail. A study in the USA also reported associations of ETS exposure with various indices of asthma severity, but for only one (restricted activity) was the association significant when the repeated measures design was taken into account in analysis.

While the overall evidence for adults suggests a possible relationship, it is too limited and poorly reported to allow a confidence conclusion.

There is far more evidence on exacerbation and ETS exposure in studies in children.

Fifteen studies related ETS exposure to various indices of asthma severity. These included emergency room visits, hospitalisations requiring intubation, hospital admissions for asthma in general, acute episodes or exacerbations, symptom scores, severity grades, or use of therapy. One of these studies compared ETS exposure within-child at times when the child was acutely ill or was well, finding no significant difference in urine cotinine (or cotinine/creatinine ratio) but some evidence of a higher reported ETS exposure when ill.

The other 14 studies based their conclusions on between-child comparisons. Of these, eight reported significant associations of increased ETS exposure with increased asthma severity, the strongest being the very much higher frequency of intubation with ETS exposure in the study in Davis. In another of these studies (conducted in Vancouver) a significant positive association was noted in children

admitted in the first period of the study, and a significant negative association in children admitted in the second period.

Overall, the data relating to asthma severity in children show considerable evidence of an association. However interpretation of this association is not straightforward for a number of reasons. These include the lack of clear evidence that increases in ETS exposure within child are associated with exacerbations of asthma, limited reporting of relevant study details by many authors (including information on active smoking by the child) and failure to separate out results by sex and by age. Most importantly, failure to control for potential confounding variables is a feature of the studies. No studies adjusted for maternal smoking in pregnancy, only one for any social class related variables, only one for infections in the child (and none for infections in the parent) and very few even take the sex or age of the child into account. Furthermore, some of the various endpoints used may not be very direct or reliable measures of asthma severity.

Eight studies relate ETS exposure to lung function in asthmatic children. Although there are occasional reports of statistically significant decreases in FEV_1, FVC and $FEF_{25-75\%}$ or increases in PEFR amplitude associated with ETS exposure, most analyses show no significant effect, with associations weak and sometimes in the opposite direction. Overall the data do not conclusively demonstrate an association of lung function with ETS exposure.

Data relating ETS exposure to bronchial responsiveness in asthmatic children are limited and no clear conclusions can be reached.

This document also considers other reviews of this evidence. The California EPA report, which concludes that ETS exposure exacerbates asthma in children, is limited by failing to detect obvious flaws in some of the evidence, not discussing any sources of potential bias at all and not even describing how its conclusion had been reached from the data available. The review by the group from the St George's Hospital Medical School are far more thorough but also contain deficiencies. Notably a mechanism is postulated by which ETS is considered a co-factor, operating with intercurrent infection, to exacerbate asthma, but no consideration is given to the

possibility of bias resulting if exposure to infections is greater in households with smokers. There is also no emphasis on the absence of data to distinguish effects of ETS exposure and of smoking in pregnancy. Two reviews of the evidence in asthmatic adults agree that the data available are very limited and inconclusive.

Overall the epidemiological data published in 1997 must be considered as quite highly suggestive that ETS exposure exacerbates asthma in children, but not conclusive.

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Abbreviations used

CCR	Cotinine/creatinine ratio
CI	Confidence interval
COHb	Carboxyhaemoglobin
EPA	Environmental Protection Agency (USA)
ER	Emergency room
ETS	Environmental tobacco smoke
$FEF_{x\%}$	Forced expiratory flow at x% of forced vital capacity
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HDM	House dust mite
ICS	Inhaled corticosteroids
OR	Odds ratio
NIH	National Institutes of Health (USA)
NS	Not significant
PC_{20}	Provocative concentration of histamine or methacholine to produce a 20% fall in FEV_1
PEFR	Peak expiratory flow rate
RR	Relative risk
SE	Standard error
$VMAX_{x\%}$	Maximum volume at x% of vital capacity

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1. Introduction

Individuals may be asthmatic or non-asthmatic, the asthmatic state implying the propensity for an asthmatic attack. An agent may "induce" the asthmatic state, causing an individual previously classified as non-asthmatic to be reclassified as asthmatic. An agent may also "exacerbate" asthma, by causing an attack in a known asthmatic or by increasing the severity of symptoms of asthma.

This report is one of a series of documents relating ETS to asthma. A first draft of a review of the epidemiological evidence relating ETS to asthma induction in children has already been prepared, and a similar review relating ETS to asthma induction in adults is currently being prepared.

The evidence relating ETS to asthma exacerbation can be divided into two major areas. One concerns experimental chamber studies in which asthmatics are exposed to high concentrations of ETS and their reactions (in terms of symptoms, lung function and/or bronchial responsiveness) assessed, usually in contrast to those resulting from sham exposure. A draft review of the evidence here is also available.

The other area of the evidence on ETS and asthma exacerbation is epidemiological, relating ETS exposure in asthmatics to various endpoints indicative of asthma attacks or increased severity of asthma. For convenience, this evidence is split into two parts – studies published up to 1997 and studies published subsequently. The evidence published up to 1997 broadly corresponds to that considered by the California EPA in the report released around that time and formally published in 1999 (National Cancer Institute, 1999), and by the St George's Hospital Medical School group in their series of reviews published in 1998 and 1999 (summarized in Cook & Strachan, 1999).

The studies included in this document concern asthmatic children and adults. Attention is in principle restricted to studies of nonsmokers. However, when considering children, we include studies of younger children that do not refer to active smoking (as presumably the frequency of smokers would be

quite low), and also studies that only include a very small proportion of smokers.

A requirement for a study to be included in this review is that it specifically relates indices of ETS exposure (such as smoking by parents) to endpoints that concern asthma severity or exacerbation. Studies that simply state that x% of asthmatics report that ETS exposure aggravates their asthma do not qualify for inclusion. We also included studies that presented results relating only to smoking in pregnancy.

Appendix A lists 16 papers that described studies that seemed possibly relevant, but in fact did not meet the inclusion criteria that had been specified. A brief description of each study is given, and the reasons for rejection are summarized.

Section 2 of this document describes the various studies that are considered relevant, giving details of the main results and, where appropriate, pointing out apparent weaknesses specific to the study. The section is laid out in chronological order of publication (and in alphabetical order of first author within year). Not only are papers describing results of specific studies considered, but reference is also made in section 2 to relevant review papers published up to 1997.

Section 3 then summarizes various features of the studies considered, while section 4 brings together the main findings, and draws conclusions. Section 5 compares and contrasts the findings of this review with that of other major reviews published in 1998 and 1999 which concern data presented in publications up to about 1997. Finally, section 6 summarizes the report.

2. The evidence

In a study in Minnesota, USA (O'Connell & Logan, 1974) information as to whether smoking induced or aggravated their asthma was collected for 400 asthmatic children aged 2 to 16 years (60% male). For 37 children whose parents' smoking was considered to have a significantly adverse effect on their asthma, it was recommended as a part of treatment that this exposure be eliminated, and 35 were available for follow-up six months to two years later. By then, the asthma had improved in 90% (18/20) of children where parents had stopped smoking and in 27% (4/15) where parents had continued. The relative risk can be estimated as 3.38 (1.44-7.91). Results on whether smoking irritated the respiratory tract were also presented for 228 children without asthma, allergic rhinitis or atopic dermatitis and whose siblings had no allergic disease. This study has a number of weaknesses. It uses endpoints which are soft. They are also poorly defined, it being hard to tell whether responses relate to tobacco smoke in general or to the parents' smoking. No statistical tests have been conducted, though, as shown above, differences by stopping smoking are statistically significant.

A study in Ibadan, Nigeria (Aderele, 1982) involved 380 asthmatic children aged between 10 months and 13 years, with 62% male. 107 of the children had severe asthma, 87 had moderate asthma and 186 had mild disease. None of the children were known to be smokers. From the data presented one can calculate the following relative risk estimates (95% CI) for severe and moderate asthma compared to mild asthma.

Smoking by household members	Mild	Moderate	Severe
No	143	64	74
Adult	43	23	33
RR (95% CI)	1.00	1.20 (0.67-2.15)	1.48 (0.87-2.53)
Father and older siblings	20	16	27
RR (95% CI)	1.00	1.79 (0.87-3.67)	2.61 (1.37-4.96)
Other smoking (not father/siblings)	23	7	6
RR (95% CI)	1.00	0.68 (0.28-1.67)	0.50 (0.20-1.29)
Total	186	87	107

The author notes the significance ($p<0.01$) of the trend in relation to severity where the fathers and older siblings smoked, but does not discuss the implied negative relationship with severity in other households where there is a smoker. There is no adjustment for any confounding factors although data were collected on a wide variety of variables. The author also notes that 80 (34%) of the 234 children aged 5 years and above admitted they usually coughed on passively inhaling cigarette smoke.

Random population surveys of children aged 0-17 conducted in an urban county in Michigan and in a rural county in Massachusetts, USA (Gortmaker et al., 1982) collected data on the prevalence of asthma, functionally impairing asthma and on parental smoking, but not on smoking by the child. Although much of the paper is concerned with prediction of asthma and of function-impairing asthma by various factors including parental smoking, these analyses are not relevant to exacerbation of asthma. However data in Table 1 of the paper allow one to relate maternal smoking to the probability, among asthmatic children, of the asthma being functionally impairing. This analysis, summarized below, shows a non-significant tendency for the probability to be higher if the mother smokes.

Sample	Functional impairment	Mother nonsmoker	Mother smoker	Odds ratio (95% CI)
Michigan	No	71	69	
	Yes	20	28	1.44 (0.74-2.79)
Massachusetts	No	11	11	
	Yes	3	4	1.33 (0.24-7.40)
Total (adjusted for sample)	No	82	80	
	Yes	23	32	1.43 (0.79-2.65)

In a study conducted in the region of Christchurch, New Zealand (Fergusson & Horwood, 1985) 1115 of an original 1265 children born in mid-1977 were followed up to age 6 years. The relationship between parental smoking and respiratory illnesses during this period was studied. Tables present the joint relationship of maternal and paternal smoking among the

whole population to ever having had an asthmatic episode and to the rate of asthmatic attacks per 100 children. 134 children had a diagnosis of asthma or wheezy bronchitis, while 141 had a maternal report of an asthmatic attack. From the data presented it is possible to estimate the annual rates per asthmatic child, separately for medical consultations and for maternal reports. The results show no apparent trend with paternal smoking, but some with maternal smoking, though it is impossible to assess statistical significance from the data provided.

Exposure	Source of information on asthma	Smoking (cigs/day) 0	1-10	11+
Mother	Medical consultation	0.80	0.53	0.96
	Maternal report	1.59	0.96	2.03
Father	Medical consultation	0.82	0.64	0.85
	Maternal report	1.55	1.60	1.46

(Note that these data have been estimated by dividing rates per 100 children aged 0-6 by 6 times the risks per 100 children of having at least one episode by the age of 6 years. Strictly the rates per asthmatic child should be estimated during the period the child was asthmatic, but this cannot be done from the data available. Parental smoking was assessed on eight occasions, but it is unclear how parents who changed their smoking habits have been categorised.)

In a study in Vancouver, Canada (Murray & Morrison, 1986), the effect of parental smoking was assessed in 94 children with a history of asthmatic wheezing. The children ranged in age from 7 to 17, with 65% male. Only two of the children admitted to smoking. There were 24 children whose mother smoked and 70 where the mother was a nonsmoker. These two groups were similar as regards age, gender and various confounding variables. Children whose mothers smoked had, on average, a 47% higher asthma history severity score ($p=0.001$), a 13% lower FEV_1 ($p=0.004$), a 23% lower $FEF_{25-75\%}$ ($p=0.005$) and, in a subgroup of 41 children whose values were not influenced by recent bronchodilator medications or by respiratory infections,

an almost five-fold greater responsiveness to histamine (p=0.002). FVC was not significantly related to maternal smoking in all the children, but was 12.6% lower (p=0.002) in the subgroup. In all 94 children and in the subgroup, there was a significant dose-response to the number of cigarettes smoked by the mother at home for FVC, FEV_1, $FEF_{25-75\%}$, symptoms and responsiveness to histamine. The differences between the children of smoking and nonsmoking mothers were greater in older than in younger subjects. In contrast there was no significant relationship of father's smoking to any of these indices of asthma severity, there being 28 children whose father smoked.

A review published by the Canadian Paediatric Society (Canadian Paediatric Society, 1986) is entitled "Secondhand cigarette smoke worsens symptoms in children with asthma". Although its conclusions are consistent with its title, only two of the 25 references it cites actually concern exacerbation of asthma. One is an experimental chamber study of 10 subjects (Dahms et al., 1981), the other the study in Vancouver cited above (Murray & Morrison, 1986) which reported that severity of asthma was increased if the mother smoked, but not if the father did. Much of the evidence cited related to healthy children, not asthmatics. The conclusion that "There is little doubt that cigarette smoke worsens asthma" seems premature, based on the evidence presented.

In a study in New York, USA (Evans et al., 1987) data were collected relating to 276 asthmatic children from low income families on smoking by the parents (and by the children themselves), on pulmonary function (at a random clinic visit up to 1 year after interview), on emergency health care use in the year prior to the interview and on various other potential confounding variables. The children were of average age 9.9 years, with 60% male. The analyses carried out involved 191 children, having eliminated 77 with some missing data and 8 who reported being smokers. Compared to children with no smokers in the household, there was no evidence of a significant reduction in pulmonary function in children in households where one or more parents smoked. Indeed mean pulmonary function scores were somewhat higher

where a smoker was present (FEV_1 1.60ℓ vs 1.49ℓ; PEFR 3.19ℓ/sec vs 2.74ℓ/sec; $FEF_{25-75\%}$ 1.60ℓ/sec vs 1.42ℓ/sec). There was also no significant association of household smoking with the mean number of hospitalisations in the year prior to enrolment. Household smoking was, however, significantly associated with an increase in the mean frequency of visits to the emergency room over the last year. The difference was significant whether or not adjustment for the mean number of days with asthma symptoms per month was made (3.46 vs 2.12, $p=0.008$) or was not made (3.09 vs 1.83, $p<0.05$). Frequency of asthma symptoms was not itself associated with household smoking. The strength of the association of household smoking with emergency room visits was not affected by counting only households with 2 or more smokers as exposed. It is not clear why parental smoking might increase the frequency of emergency room visits without actually affecting lung function, symptom prevalence or the frequency of hospitalisation.

In a study in Boston, USA (O'Connor et al., 1987) the relationship between parental smoking and airway reactivity was studied in 286 children. The sample included 21 asthmatics (mean age 12 years, 62% male) none of whom smoked themselves. 9 had a mother who smoked. Compared to the remaining 12 asthmatics, those with a smoking mother had a lower mean FEV_1 (100.8% vs 102.9%) and $FEF_{25-75\%}$ (76.1% vs 85.8%) and a higher mean FVC (107.8% vs 104.0%) as a percentage of predicted, none of these differences being statistically significant. Following cold air challenge, the response (fall in FEV_1 following challenge expressed as a percentage of predicted FEV_1) was almost significantly higher when the mother smoked (24.0 vs 11.9, $p=0.07$). Using linear regression to adjust for predicted FEV_1 the p-value became significant, at $p=0.02$. Adjustment for other independent variables in a multiple regression analysis did not affect this conclusion. Paternal smoking was unrelated to bronchial responsiveness to cold air. The small sample size and the marginal nature of the significance reported limit interpretation of these findings.

In a study in Viterbo province, Italy (Martinez et al., 1988) the relationship between parental smoking, asthmatic status, atopy and bronchial

responsiveness was studied in 170 unselected schoolchildren aged 9, 49% of whom were boys. The relationship between bronchial responsiveness (as determined by a carbachol inhalation test to obtain a drop in FEV_1 of 20% or more) and parental smoking in the whole population was significant (p=0.036) after controlling for sex and atopy. In the 22 asthmatic children, the same relationship was significantly (p=0.02) stronger, with the odds ratio for bronchial responsiveness for parental smoking estimated as 18.7 (1.5-232.3), based on 14/17 responders where a parent smoked and 1/5 responders where no parent smoked.

In an increased sample from the study in Vancouver (Murray & Morrison, 1988), the effect of parental smoking was measured in 240 nonsmoking children with a history of asthmatic wheezing. The children were of age 7 to 17, with 68% male. As with the data analysed in their previous paper (Murray & Morrison, 1986), the overall data showed a strong relationship of maternal smoking to pulmonary function and bronchial responsiveness (symptom data not being reported this time) but little relationship to paternal smoking. There were 56 children with a mother who smoked and 183 with a nonsmoking mother. Apart from the size of mite reaction being smaller if the mother smoked ($p<0.01$), there was little difference between the two groups in potential confounding variables. Children with a smoking mother had a lower FEV_1 (76% vs 85%, $p<0.01$), a lower $FEF_{25-75\%}$ (59% vs 73%, $p<0.01$) and a lower PC_{20} (0.91 vs 2.03, p=0.01). There was also a strong correlation with the number of cigarettes smoked by the mother. Smaller differences were seen in relation to father's smoking and they were not statistically significant.

An interesting feature of the study is the separate analyses conducted according to whether or not the readings were taken in the cold, wet season (October-May), when windows would tend to be closed and ETS exposure higher, or in the warm, dry season (July-September), when windows tend to be open and exposure lower. The analyses showed a clear association of maternal smoking with pulmonary function (FEV_1 and $FEF_{25-75\%}$), bronchial responsiveness (PC_{20}) and recent use of bronchodilator medication in the cold,

wet season, but no such association in the warm, dry season. These results were confirmed by analyses adjusting for a range of potential confounding variables.

A third paper from the study in Vancouver (Murray & Morrison, 1989) was based on 414 nonsmoking asthmatic children aged 1 to 17 (70% male) who had a mother with known smoking status. Only children aged 6+ underwent lung function testing, 294 producing an acceptable spirogram. As in the previous study (Murray & Morrison, 1988) children of nonsmoking mothers (n=322) and of smoking mothers (n=92) were comparable apart from the latter group of children having a smaller mite test wheal. Children of smoking mothers had a significantly higher asthma symptom score (8.8 vs 6.4, $p<0.01$), lower FEV_1 (77.3% vs 84.4%, $p<0.01$) lower $FEF_{25-75\%}$ (59.5% vs 71.7%, $p<0.01$) and lower log PC_{20} (-0.14 vs 0.71, $p=0.01$) and a non-significantly lower FVC (91.2% vs 93.8%, $p=0.2$). Although the differences were in the same direction in relation to smoking by the father, they were not statistically significant at $p<0.05$.

The main purpose of this paper was to investigate how the association with maternal smoking varied by the sex and age of the child. Associations tended to be stronger in boys than in girls and stronger in older than younger children. Although on some occasions differences according to maternal smoking status were significant for boys and not girls or for older and not younger children, the authors never actually carried out statistical tests of interaction. Based on the data presented we find that none of the differences between smoking and nonsmoking parents vary significantly by the sex of the child and only for PC_{20} does the difference clearly vary significantly by age. As a result of this, we believe that the authors have rather over-interpreted their data when they concluded that "compared with girls, boys were more sensitive to passive smoking, and that its adverse effect increased with age and with duration of exposure".

An abstract briefly described results of a study in New York (Lilienfeld et al., 1990) of inner city children aged 3-14 years, comparing 72 acute asthmatics in a hospital emergency room and 35 non-acute asthmatics in the asthma clinic. The acute asthmatics had a non-significantly lower frequency of a urinary cotinine/creatinine ratio greater than 30 ng/mg (odds ratio 0.92, p=0.85). The cotinine/creatinine ratio was used as an index of ETS exposure. Household smoking was also determined by questionnaire but results were not presented comparing these two groups. The authors concluded that "recent smoke exposure is not the trigger of the acute attack". This study was more fully reported later, as described below (Ehrlich et al., 1992).

The results of the New York study earlier described in an abstract (Lilienfeld et al., 1990) are described more fully in a paper (Ehrlich et al., 1992). Results for the same two groups of 72 acute asthma patients and 35 non-acute asthma patients are presented. The groups were found to be of similar age (range 3-14 years), sex (62% male) and SES, and all the children were nonsmokers. African-American children were noted to be over-represented in the acute group (37% vs 26%), though this difference was not statistically significant. The acute asthma group were significantly more likely to have had a recent upper respiratory infection (odds ratio 2.5, 95% CI 1.1-5.6), and to have previously used the emergency room (97% vs 86%, p=0.02). Interestingly they were less likely to have had any previous attendance at an asthma clinic (65% vs 100%, p<0.001), or to use daily asthma medication (36% vs 80%, p<0.001). As shown below, there were no differences between the two groups as regards ETS exposure variables.

The authors note that "we were unable to show an effect of passive smoke exposure on the precipitation of acute asthmatic effects". They comment that their numbers were too small to explore the possibility than an effect of ETS might be evident only in patients not on regular medication.

ETS exposure variable	Asthma		Odds ratio (95% CI)
	Acute	Non Acute	
Any smoker at home	53%	57%	0.84 (0.37-1.89)
Cigs/day by all smokers	7.7	10.7	Not significant
Maternal caregiver smokes	40%	51%	0.64 (0.28-1.44)
CCR* $\geq$ 30 ng/mg	38%	39%	0.90 (0.39-2.06)
Mean CCR (ng/mg)	46.2	38.5	Not significant
Number of subjects	72	35	

*CCR = cotinine/creatinine ratio

In an analysis based on 4331 children aged 0-5 years who participated in the 1981 US National Health Interview Survey (Weitzman et al., 1990b), a table of results was presented giving, by maternal smoking status in pregnancy, the number of mothers, the prevalence of asthma and the percentage of children using asthma medications. Based on these data, one can estimate the following for the asthmatic children (though this is subject to some inaccuracy due to the frequencies provided only being given to one decimal place).

	Maternal smoking in pregnancy (cigs/day)				
	0	1-9	10+	Any	Total
With asthma	74	17	26	43	117
Not using asthma medications	58	14	15	29	84
Using asthma medications (%)	16 (21.6)	3 (17.6)	11 (42.3)	14 (32.6)	30 (25.6)
Odds ratio (95% CI)	1.00	0.78 (0.20-3.04)	2.66 (1.02-6.91)	1.75 (0.75-4.07)	

These results, which are unadjusted for any potential confounding factor, show some evidence of an association among asthmatics between maternal smoking in pregnancy and use of asthma medications. This is not statistically significant overall, but is marginally significant ($p<0.05$), subject to the observations made above, for maternal smoking of 10+ cigs/day.

The authors also present a figure showing the mean number of overnight hospitalisations by maternal smoking in pregnancy, separately for non-asthmatic and asthmatic children. For asthmatic children, the numbers (1.1 for no smoking, 1.3 for 1-9/day and 1.0 for 10+/day) show no significant relationship.

In a further paper by the same group (Weitzman et al., 1990a) data on asthma and asthma medication use were presented for children aged 2-5 years on the basis that parents of younger children might mistakenly report respiratory illnesses associated with wheezing as asthma. With the same reservations concerning potential numerical inaccuracy as before, the following table can be constructed:

	Maternal smoking in pregnancy (cigs/day)	
	None or 1-9	10+
With asthma	76	23
Not using asthma medication	62	14
Using asthma medication (%)	14 (18%)	9 (39%)
Odds ratio (95% CI)	1.00	2.85 (1.03-7.88)

These data clearly considerably overlap those presented in the table above.

A fourth paper from the study in Vancouver (Murray & Morrison, 1992) concerned 240 nonsmoking asthmatic children aged 7 to 17. As reported in the previous studies (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989), children whose mothers smoked had significantly more severe asthma. Inasmuch as the children analysed in this paper are a subset of those described in the third paper (Murray & Morrison, 1989), the results add nothing new to the evidence for this relationship. The purpose of the paper was to investigate the effect of maternal smoking on asthma severity separately for those children who did or did not have atopic dermatitis. The analyses led to the conclusion that atopic

dermatitis had no effect on the severity of asthma and that there was no interaction of atopic dermatitis with maternal smoking on severity.

A study conducted in Freiburg, Germany (Frischer et al., 1992) investigated the relationship between maternal smoking and bronchial hyperresponsiveness (as assessed by a decrease of 15% or greater in PEFR following a standardized free running test) in 1461 primary school children of mean age 7.3 years. 171 of the children were asthmatics. Among this group the prevalence of bronchial hyperresponsiveness was non-significantly higher if the mother smoked in pregnancy (22.2% vs 14.5%) or if the mother smoked at age 1 year (24.2% vs 13.5%), but was non-significantly lower if the mother smoked at age 8 years (9.5% vs 17.7%). In a multivariate analysis involving prematurity, pneumonia during the first year of life, atopy, education and sex of the child, the authors reported no significant relationship to maternal smoking in pregnancy (OR 2.20, 95% CI 0.29-16.57), a significant and huge positive relationship to maternal smoking at age 1 year (20.56, 2.5-168.9) and a significant and huge negative relationship to maternal smoking at age 8 years (0.05, 0.005-0.61). It seems to us that these analyses may be unstable due to the strong correlations between maternal smoking at the various time points, and that the association of ETS with bronchial hyperresponsiveness is unclear from these data. However, the authors cite the findings in the abstract, noting the very strong positive odds ratio with maternal smoking in the first year of life, but also noting that "current exposure to maternal smoking was associated with less hyperresponsiveness". They comment that "The effect of current maternal smoking might reflect changes in smoking habits by mothers of children with symptoms, whereas exposure to tobacco smoke in early life might be causally related to bronchial hyperresponsiveness", and conclude by stating that "Our findings support the general hypothesis that early lung injuries have an impact on the later respiratory health of children".

Essentially the same findings were presented two years later (Meinert et al., 1994), though the results presented, with odds ratios of 1.3 for mother smoked before pregnancy, 1.7 for smoking during pregnancy, 2.2 for smoking

in the child's first year and 0.5 for smoking in the child's eighth year, were based on separate analyses. The authors reported a significant (p=0.02) association between bronchial hyperresponsiveness and changes in smoking habits between years 1 and 8.

Percentage of children with and without bronchial hyperresponsiveness (BHR) with defined changes in smoking habit

Change in smoking habit	With BHR	Without BHR
Began smoking after pregnancy	20	8
Began smoking between 1st and 8th year	0	12
Stopped smoking between 1st and 8th year	16	3

Based on the same study, another paper (Frischer et al., 1993) reported the relationship of maternal and paternal smoking to PEFR variability based on 991 of the 7 year old children (48% male), 113 of whom were asthmatic. The PEFR was measured twice daily over a 1 week period, with the log of a week's mean of daily amplitude calculated as an index of variability. In multivariate analysis, only current maternal smoking and atopy were found to have a significant relationship to PEFR variability. For asthmatic children without atopy (n=80), PEFR variability was 54.7% higher (95% CI +5.5% to +226.8%) if the mother smoked, whereas in atopic asthmatic children (n=33), it was 8.5% lower (95% CI –41.2% to +42.3%). In the latter group there was evidence that mothers changed their smoking habits subsequent to the development of disease in their children. The authors conclude that "exposure to maternal smoking can increase the variability of PEFR and thus might contribute to the development of asthma".

A review was published in 1992 (Witorsch, 1992) entitled "Does environmental tobacco smoke (ETS) cause adverse health effects in susceptible individuals?". This paper contained a section describing the results of various experimental chamber studies of ETS exposure, noting that the findings are "inconclusive", though "a small subset of individuals with asthma may react adversely to ETS exposure". It also correctly considered that "the

epidemiological data with respect to long-term effects of ETS exposure on adult asthmatics are inconclusive", but did not mention any of the evidence for children discussed above.

Another review published in 1992 (Shephard, 1992) was entitled "Respiratory irritation from environmental tobacco smoke". Although the author considered that "ETS exposure induces only small immediate changes of respiratory function", he stated that "ETS can … aggravate asthma, particularly in subjects who do not have a family history [of] atopy". The section in the paper on "influence of asthma on sensitivity to ETS" was relatively short, and was mainly concerned with the experimental evidence from chamber studies and evidence relating to allergy.

In a study conducted in Portland, USA reported in the New England Journal of Medicine (Chilmonczyk et al., 1993) and previously in an abstract (Salmun et al., 1992), data for 199 asthmatic children aged up to 13 (72% boys) were collected on smoking by parents and other household members, smoking at day-care, cotinine in urine, number of acute exacerbations of asthma in the past 12 months, lung function (from 145 of the children), serum theophylline (from 63 of the children) and on demographic and other variables. The main finding of the study was that there was a trend towards an increasing number of exacerbations of asthma and decreasing lung function with increasing ETS exposure whether this was based on parental reports (no exposure, mother or others smoke, mother and others smoke) or on urinary cotinine adjusted for creatinine (<10, 10-39, >39 ng/mg). The increased risk of asthma exacerbations was significant after adjustment for maternal age and education level, and the child's age, sex and day-care attendance, with children in the highest exposure group having almost twice the number of exacerbations of the lowest exposure group (change per category of reported exposure 0.83, 95% CI 0.39 to 1.26, and per category of cotinine/creatinine ratio 0.63, 95% CI 0.10 to 1.07). Although the corresponding reductions in FEV_1 were not statistically significant, significant reductions were seen in FEV_1/FVC and $FEF_{25-75\%}$ for both exposure indices. Serum theophylline

levels were found to be similar in children prescribed theophylline and exposed to smoke in the home, and in children prescribed theophylline and not ETS exposed, suggesting that the two groups followed medical advice similarly.

The authors emphasized the value of using urine cotinine levels as a smoker of ETS exposure and concluded that their study "provides further evidence of an association between exposure to environmental tobacco smoke and pulmonary morbidity in children with asthma." It should be noted that although data were collected on severity of the underlying disease, no attempt was made to take this into account in analysis. Did the children in the more ETS exposed group have more attacks because they were exposed more, or because they had more severe disease to start with?

A fifth paper from the Vancouver study (Murray & Morrison, 1993) concerns 807 nonsmoking children with asthma aged 1-17 years referred between 1983 and 1990. Comparisons were made of the 415 children seen before July 1986, and the 392 children seen afterwards. Doctors referring patients to the clinic have, since 1985, been urged to counsel parents of asthmatic children never to smoke when in the home. The main findings of the study were as follows:

(i) Although the total number of cigarettes smoked by parents was similar for the two periods, there was a highly significant drop in the number of cigarettes reported to be smoked in the presence of the child, from 7 to 3 for the mother, and from 5 to 2 for the father.

(ii) Where the mother was a smoker, there was a highly significant ($p<0.001$) decline in the asthma score and increase in FEV_1 and $FEF_{25-75\%}$ between the two periods. In contrast, where the mother was a non-smoker, there was no decline in asthma score, and a smaller increase in lung function. A similar pattern was seen in relation to paternal smoking except that the decline in asthma score was not significant.

(iii) The number of cigarettes reported to be smoked in the presence of the child by the mother was significantly correlated with the child's asthma score (positive) and with the two indices of lung function (negative). Similar correlations with paternal smoking were also significant for lung function but not for asthma score.

(iv) Adjustment for sex, age, and age of onset of asthma confirmed the relationships noted in (ii) above. Further adjustment for number of cigarettes smoked by the parents when in the same room as the child reduced the significance of the association.

The authors conclude that "there is evidence that since 1986 an increasing awareness of the harmful effects of second-hand smoke has caused parents to smoke fewer cigarettes when with their asthmatic children, and that the resulting decrease in exposure has been associated with a marked improvement in the severity of asthma of the smokers' children who have been referred to our clinic".

In considering these results, some important points should be made:

(a) Smoking habits of the parents were usually provided only by the mother and were unvalidated. Is it possible that at least part of the reported reduction in smoking in the presence of the child by the parents may have resulted from increasing denial? After all, there is abundant evidence in the literature that people advised by their doctor to give up smoking frequently falsely admit that they have done so (Lee, 1988). A similar scenario seems likely to exist if, as here, the doctor advised parents not to smoke in the presence of the child.

(b) The study showed no real evidence at all that bronchial hyper-responsiveness, as measured by the PC_{20} test, was associated with smoking by the parents or that it decreased between the two periods.

(c) Inspecting the detailed results presented, a striking fact emerges, namely that though in the first period the mean asthma score was highly significantly ($p<0.001$) higher if the mother smoked (mean 8.2

S.E. 0.3) than if the mother did not smoke (mean 6.4 S.E. 0.2), in the second period the mean asthma score was actually significantly ($p<0.05$) lower if the mother smoked (mean 5.8 S.E. 0.2) than if the mother did not smoke (mean 6.6 S.E. 0.2). The authors completely fail to mention this point, which seems inconsistent with their thesis. It is also true that, while before July 1986 pulmonary function was much lower if the mother smoked, after July 1986 it was very similar in children whose mothers smoked or did not smoke.

(d) Finally, and very importantly, one can compute from the results presented the following differences between the two time periods for children where the parent smokes:

	Difference post- vs pre-July 1986	
	Unadjusted*	Adjusted*
Asthma score	-0.99	- 1.02
$FEV_1\%$	+14.5	+11.4
$FEF_{25-75\%}$	+14.7	+11.95

*For number of cigarettes smoked in same room as child.

It can be seen that only a small proportion of the difference in recorded response between the two time periods (and essentially none of it as regards asthma score) can be explained by the parents smoking less in front of their children. This is in direct contrast to the authors' claims. Although there has been a marked improvement in asthma score and lung function over the period in children of smokers, it appears to be mainly due to reasons other than reduced smoking by the parents in the child's presence. It is also notable from the data presented in the paper that there are quite substantial improvements in lung function (though not in asthma score) over the time period in children whose parents do not smoke.

Generally, the paper must be regarded as unconvincing, with parts of the data inconsistent with the authors' claims not really brought to the reader's attention.

A review was published (Ehrlich et al., 1993) entitled "Is passive smoking a cause of asthma in children?". In the section "Studies of asthmatics" the review notes the distinction between the types of studies attempting to determine "whether asthma occurrence is associated with passive smoking" and those which investigate "whether passive smoking aggravates the asthmatic state". However, studies cited to support the conclusion that "There is also consistent evidence that among children already asthmatic, maternal smoking is associated with more severe asthma, more frequent visits to the emergency room, and greater bronchial hyperresponsiveness" include a number that are not relevant to asthma exacerbation. Of the studies referred to earlier in this document, only the series of studies in Vancouver (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989) and two other studies (Evans et al., 1987; Frischer et al., 1992) are cited. The review, which is really too short for such a complex issue, and does not consider the evidence from experimental chamber studies at all, adds little, although it does refer to a number of important possibilities of confounding that need to be controlled for, including socio-economic status, active smoking and symptom prevalence in parents.

For each of a number of studies relating ETS to asthma published from 1986 to 1992, the US EPA report "Respiratory health effects of passive smoking: lung cancer and other disorders" (National Cancer Institute, 1993) presents a paragraph summarizing the results. The studies reviewed included those providing evidence on asthma induction as well as asthma exacerbation. Four epidemiological studies on asthma exacerbation that were considered have been summarized previously in this document (Evans et al., 1987; O'Connor et al., 1987; Murray & Morrison, 1989; Ehrlich et al., 1992). As regards asthma exacerbation the report concluded: "There is now sufficient evidence to conclude that passive smoking is causally associated with

additional episodes and increased severity of asthma in children who already have the disease. Several studies have found that bronchial responsiveness is more prevalent and more intense among asthmatic children exposed to maternal smoke. Emergency room visits are more frequent in children of smoking mothers, and these children also have been found to need more medication for their asthma than do children of nonsmoking mothers".

A study in Chandigarh, India (Jindal et al., 1994) compared indices of morbidity and control of severity in 100 adult never smoking asthmatics who were not exposed to ETS at home or at work and 100 adult never smoking asthmatics who were exposed. The ETS-exposed group were of mean age 39.5 years and the unexposed group were of mean age 33.8 years. These were stated to be comparable but based on the standard deviations given (9.90 and 10.03) are highly significantly different ($p<0.001$). The sex of the patients is undescribed. Information on asthma control and morbidity was assessed during their follow-up visits in the chest outpatient clinic by inquiring into emergency department visits, hospitalisation, acute episodes, requirement of parenteral drugs at home, corticosteroids and maintenance bronchodilators in the preceding 1-year period. Lung function was recorded by the measurement of forced expiratory flows on the same day as the follow-up visit. Subjects were excluded if they had been hospitalised or had a severe acute attack in the preceding 2 weeks. The authors report a number of statistically significant reductions in the ETS exposed group. For FEV_1 (68.7% vs 80.8%), FEV_1/FVC (63.5% vs 78.4%) and $FEF_{25-75\%}$ (54.3% vs 75.7%) the reductions are stated to be significant at $p<0.05$, but are actually highly statistically significant ($p<0.001$) based on the standard deviations presented. For maintenance bronchodilator requirement daily (66% vs 56%), maintenance bronchodilator requirement intermittent (56% vs 42%) and steroid requirement intermittent (56% vs 42%) the increases in frequency in the ETS exposed group are stated to be significant at $p<0.01$, but are not even significant at $p<0.05$. Also claimed are significant ($p<0.01$) excesses in the ETS-exposed group for emergency department visits (0.82 vs 0.6), acute episodes (1.32 vs 0.6), number of parenteral bronchodilators (8.6 vs 6.0), weeks absent from

work (3.6 vs 3.0) and weeks requiring steroids (11.3 vs 8.6). Here the data presented are not sufficient to check the significance levels.

Though the study claims that "the control of asthma is poor and morbidity greater in adult patients with asthma exposed to ETS at home and/or at work" failure to age adjust and obvious errors in statistical analysis mean that one cannot trust these findings. It should also be noted that the data cited above for frequency of maintenance bronchodilator requirement for the ETS exposed group seems impossible. How can 66% have a daily and 56% an intermittent requirement, as 66% + 56% > 122%?

A study in Baltimore, USA (Ogborn et al., 1994) obtained data on parent-reported ETS exposure and collected urine samples from 56 children aged 3-11 (57% male) on two occasions, first when they had attended at the hospital emergency department during an acute episode of asthma and second 3 to 4 weeks later when they were free of symptoms of asthma and feeling well. No significant difference between the acute and the well visit was seen as regards urinary cotinine (means 81 vs 77 ng/ml), cotinine/creatinine ratio (93 vs 97 ng/ml) or the proportion with a ratio of 30 ng/ml or above (80% vs 82%), using matched-pairs analysis. There was also no significant difference in the reported hours of exposure in the past 48 hours (mean 32 vs 32 hours) or the total number of cigarettes smoked at home in the past 24 hours (31 vs 25). There was, however, a significant (p=0.02) difference in the amount of exposure:

State of patient	None	A little	Some	A lot
Acutely asthmatic	10	12	16	14
Well	17	13	20	4

The authors believe that "this difference may have been due to the parent becoming more sensitised to the issue of passive smoke exposure by the study questionnaire itself and perhaps wanting to minimize the reported

exposure". It also seems possible that knowledge of the asthmatic attack may have affected the answers given to this rather subjective question.

While most previous studies considered have related to infants or children, a study from Denver, USA (Ostro et al., 1994) concerned 164 nonsmoking asthmatic adults aged 18-70 (mean age 45.5 years), with 32.2% male. The study investigated the relationships between various indoor combustion products (including ETS) and daily symptoms. Both symptom and exposure data were recorded by the study participants over a 3-month period. Relative risks (95% CI) for ETS exposure (based on answers to the question "Were you exposed to cigarette smoke at home today?") for the various endpoints studied were as follows. The first relative risk, RR1, taken no account of autocorrelation between the repeated measures while the second, RR2, does.

Endpoint	RR1 (95% CI)	RR2 (95% CI)
Moderate or severe cough	1.21 (1.01-1.48)	1.15 (0.97-1.36)
Moderate or severe shortness of breath	1.85 (1.57-2.18)	1.34 (0.84-2.15)
Nocturnal asthma	1.24 (1.00-1.53)	1.08 (0.72-1.56)
Restricted activity	2.08 (1.63-2.64)	1.61 (1.08-2.46)

It can be seen that only for restricted activity did the association with ETS remain significant after adjustment (as is appropriate) for autocorrelation. Reporting the presence of smokers in the home at the start of the study was also associated with a significantly increased relative risk of 2.05 (95% CI 1.78-2.40) for moderate or severe shortness of breath. The authors note that all the regressions adjusted for outdoor air pollution, the number of the day of the survey, and whether the subject reported a symptom on the previous day. Temperature, humidity and the age of the participants were considered as potential confounding variables, but were excluded from the final model. Relative risks for the four endpoints (RR1s) were presented separately for those with or without respiratory infections on that day. Associations with cough or wheeze seemed to be similar in the two subgroups, but associations

with shortness of breath seemed stronger in those without respiratory infection.

A review published by scientists from IARC (Trédaniel et al., 1994) entitled "Exposure to environmental tobacco smoke and adult non-neoplastic respiratory diseases" concluded that "On the basis of the available data, no definite conclusion (excluding the acute irritating effect of ETS on respiratory mucous membranes) can be drawn. Although biologically plausible, it remains controversial whether ETS exposure is associated with chronic respiratory symptoms and occurrence of chronic obstructive pulmonary disease, including asthma". The section on asthma mainly concerned the experimental chamber studies, with mention of some observational studies where a proportion of asthmatics considered that their asthma was aggravated by ETS. As the review concerned adults, the studies of children summarized in the earlier paragraphs of this documents were not considered.

A study conducted in Seattle, USA, and reported as an abstract (Abulhosn et al., 1995) followed up 22 children aged 2-9 years who had been hospitalised for asthma. Comparisons were made of 11 children who lived in homes where 1 or more parents smoked and 11 children living in nonsmoking homes. The two groups were stated to be "comparable" in age, gender and pre-admission NIH chronic asthma severity score. They were also similar regarding the proportion discharged home on anti-inflammatory and on beta-agonist asthma therapy. Based on data reported by the parents over the four weeks following hospital discharge, the children in smoking homes had more symptomatic days (3.3 vs 1.4, $p<0.05$). The reduction in use of beta-agonist therapy over the period following discharge was also less in these children (18.5 to 14.6 vs 18.5 to 6.3 treatments per week, $p=0.001$). Children in smoking homes also had more symptomatic nights (2.3 vs 1.4) though this was not significant ($p>0.1$). The authors concluded "that children returning to smoking households following hospitalisation for acute asthma remain more symptomatic despite greater beta-agonist therapy within four weeks after hospital discharge and therefore recover less completely when compared with

those children returning to non-smoking homes". As described below, the results summarized in this abstract were later presented more fully (Abulhosn et al., 1997).

In a study of 46 asthmatic children conducted in Taiwan and reported as an abstract (Chan & Chen, 1995) peak expiratory flows (PEFRs) were measured at night and in the morning daily over a 6 month period, a PEFR lower than 80% of predicted being defined as an asthmatic attack. The cotinine/creatinine ratio (CCR) of urine samples collected at different PEFR levels was used as a biomarker for ETS exposure. The CCR associated with a PEFR ratio <0.8 was stated to be significantly higher than that associated with a PEFR ratio >0.8 (13.95 vs 7.09 ng/mg) for urine samples collected in the night, though the actual significance level was not given. There was also a significant trend in CCR increase as the PEFR ratio decreased. The abstract does not make clear how the multiple data per subject have been dealt with, and whether the analyses have been based on within- or between-subject comparisons. The data clearly have the potential to test whether, within-subject, PEFR varies by CCR, which would be valuable to know.

A study conducted in Davis, USA (LeSon & Gershwin, 1995) included all asthmatics aged 5-12 years admitted to a medical centre over a 10 year period excluding patients with cystic fibrosis. There were 300 children, 55% male, of which 13 required intubation for their asthma. A wide range of factors were studied for their relationship to the odds of intubation. Exposure to secondhand smoking (from parents, family members or room-mates) was reported by 85% of the children who required intubation and by 20% of those who did not, a highly significant ($p<0.001$) odds ratio of 22.4 (95% CI 7.4-68.0). [From the data presented we estimate a similar odds ratio of 22.2 but a much wider confidence interval of 4.8-102.9. However the relationship is still highly significant.] It should be noted that their analysis identified 11 other factors with a significant odds ratio for intubation, 8 with an odds ratio above 6 and highly significant ($p<0.001$), though none with an odds ratio as high as for secondhand smoke. Despite this, all the analyses were conducted on a one-factor at a time basis, with no attempt to determine which of the factors were

independent. As with the Portland study (Chilmonczyk et al., 1993), data were available on severity but not used in analysis.

In a case-control study carried out in Sheffield, England (Strachan & Carey, 1995), 486 secondary-school children who, in an earlier study two years before, had reported that over the previous 12 months they had suffered either 12 or more wheezing attacks or a speech limiting attack of wheeze (over 90% of whom had doctor-diagnosed asthma) were compared to a further 475 children with no history of asthma or wheeze, frequency matched for age and school class. While comparison of cases and controls is not relevant to exacerbation of asthma, tables are presented which allow comparison of parental smoking habits among 113 children with frequent and speech limiting wheeze ("severe cases") and children with frequent or speech limiting wheeze but not both ("less severe cases"). As shown in the table below, there was a significant tendency for severity of asthma to be greater if either the mother or the father smoked. However no dose-relationship was evident. The authors reported that results were similar for maternal smoking around the time of the child's birth, but did not present any details.

		Smoking habits (cigs/day)			
Parent	Asthma	0	1-10	≥10	Any
Mother	Less severe	289	57	27	84
	Severe	75	25	13	38
	Odds ratio	1.00	1.69	1.86	1.74
	(95% CI)		(0.99-2.88)	(0.91-3.77)	(1.10-2.76)
Father	Less severe	313	39	20	59
	Severe	85	18	9	27
	Odds ratio	1.00	1.70	1.66	1.69
	(95% CI)		(0.93-3.12)	(0.73-3.77)	(1.01-2.82)

A four page review of "passive smoking in childhood" (Di Benedetto, 1995) included a section on "asthma and bronchial responsiveness". The author stated that "it is well known that maternal cigarette smoking aggravates asthma symptoms and bronchial responsiveness in children with an established

diagnosis of the disease", citing associations with increased use of health services, asthma medications and asthma symptoms. However, no references are cited and it is clear that the review is very far from comprehensive. The author notes that "the mechanisms by which passive smoking might increase bronchial responsiveness is still unclear" and it is possible that "children exposed to passive smoking might exhibit an increased risk of acquiring severe viral infections, which might cause bronchial hyperresponsiveness".

In a second study in Chandigarh, India, reported in an abstract (Jindal et al., 1996), exposure to ETS in the preceding 24 hours was compared in 100 nonsmoking patients with acute exacerbation of asthma and another 100 with stable non-acute asthma. The authors reported that "There was a significant higher ($p<0.01$) prevalence of exposure to ETS in patients with acute exacerbations. Quantitatively, measured in 'man-hours', there was a higher exposure in this group. Sixty percent asthmatics had one or other symptom on acute exposure to ETS" and concluded that "Exposure to ETS causes acute worsening in non-smoker asthmatics". No further details of the findings were presented.

A study conducted in Toronto, Canada (MacArthur et al., 1996) concerned 68 children of median age 3 years, 71% male, who had their first ever admission for treatment of asthma in a defined 19 month period and who had been readmitted to the same hospital because of asthma within 12 months of the first admission. This cohort was followed forward, and their probability of readmission within 12 months of the second discharge related to a variety of risk factors. 17 of the 30 (57%) subjects with one or more smokers in the home qualified in this respect, as against 15 of the 38 (39%) with no smokers in the home. This represented a non-significant relative risk of 1.44 (95% CI 0.87-2.37).

A study conducted in Zwolle, the Netherlands (Meijer et al., 1996) involved 55 children of mean age 9.3 years, 60% boys, with symptoms of asthma, increased total IgE, an allergy to house dust mite but not to dog, cat,

tree, grass or milk, an $FEV_1 \geq 70\%$ of the predicted value and increased bronchial responsiveness to histamine. The children all had asthma symptoms well controlled by daily inhaled corticosteroids (ICS) and β_2-adrenergic drugs if needed. PEFR amplitude ((maximum-minimum) mean as % over a 24 hour period) were obtained during and 6 days after withdrawal of ICS. 26 of the 55 children had a parent who smoked. PEFR amplitude in relation to ETS (from parental smoking) and ICS withdrawal was as follows:

		Median (Minimum-Maximum) PEFR amplitude	
Exposure	n	During ICS	After ICS withdrawal
No ETS	29	20.6 (5.7-63.4)	19.4 (0.0-56.5)
ETS	26	28.7 (10.7-99.0)	29.7 (3.9-56.6)
Significance of difference*		Not significant ($p>0.05$)	$p<0.05$

*From Mann-Whitney U test.

The authors note that "children exposed to ETS … had significantly higher PEFR amplitudes after withdrawal of ICS than did nonexposed children" and that "This was not found during ICS" and conclude that "exogenous stimuli such as exposure to ETS … contribute to an increased circadian PEFR amplitude after withdrawal of ICS and therefore to nocturnal worsening of asthma in HDM-allergic asthmatic children". But the difference in medians between ETS and non-ETS exposed children is in fact very similar during ICS (28.7-20.6 = 8.1) and after ICS withdrawal (29.7-19.4 = 10.3) and is clearly not significantly different.

The authors also report the results of an analysis investigating simultaneously factors associated with PEFR amplitude after withdrawal of ICS. Although the difference associated with ETS increases only slightly, from 10.3 to 11.2, the p value now becomes highly significant ($p<0.001$). The authors also note an interaction between the effects of ETS and of bronchial responsiveness on PEFR amplitude after ICS withdrawal, finding a significant association between ETS and PEFR amplitude only in those with an above

average bronchial responsiveness (p=0.008). Given that the difference in amplitude associated with ETS exposure is only significant at p=0.05 for those with above average responsiveness, and that the difference is in the same direction for those with below average responsiveness, it is difficult to see how the interaction is in fact significant at all, let alone significant at p=0.008.

Apart from these doubts about the validity of the statistical analysis, one must also wonder how the endpoint of the study, PEFR amplitude, actually relates to exacerbation of asthma. It should be noted that their own data showed no relationship of FEV_1 to PEFR amplitude.

Two years after the abstract describing the study in Seattle was published (Abulhosn et al., 1995), a paper appeared (Abulhosn et al., 1997). Little extra relevant material was presented. It was noted that the 22 children were aged 2-13 (not 2-9 as previously stated), the mean age being 5.2 in both the 11 living in a house where one or more parents smoked and in the 11 where neither did. 9 of the children (41%) were boys. The difference in symptomatic days in the 4 week follow-up period resulted from a distribution in which 8 (73%) of the children in smoking homes had 2 or more symptomatic days as against 2 (18%) of the children in nonsmoking homes. The data for change in use of beta-agonist therapy between weeks 1 and 4 differed from that given in 1995, now being from 20.8 to 8.9 doses per week in the group with non-smoking parents and from 15.3 to 18.0 where the parents smoked ($p<0.001$).

A study carried out in San Sebastian, Spain (Callén Blecua et al., 1997) of 312 asthmatic children aged 3-19 years (mean 9.01) compared 187 cases with at least one of the following criteria: FVC < 85%, FEV_1 < 85%, PEFR < 85% or $FEF_{25-75\%}$ < 60%, and 125 controls satisfying none of these. One or more parents smoked in 70.1% of the cases and 56.0% of the controls, giving an odds ratio of 1.84 (95% CI 1.12-3.03). The authors also presented a table comparing pulmonary function variables according to at home ETS exposure, presumably based on all 312 children. For all four variables, values were lower in the exposed group (FVC 96.9% vs 97.4%, FEV_1 91.9% vs 93.7%,

PEFR 87.2% vs 92.6%, $FEF_{25-75\%}$ 72.2% vs 76.7%) but none of the differences were statistically significant, with the p values >0.2 for each comparison. Despite this lack of association, one of the conclusions given is that "pulmonary function in asthmatic children is influenced by parental smoking habits". The basis for this conclusion is not apparent. COHb was measured in both children and parents. Though results were presented which found that smoking parents have higher COHb, it seems somewhat surprising that the child's COHb was not compared in the two groups of asthmatic children.

A study conducted in Chicago, USA (Hu et al., 1997) involved 705 fifth-graders, mainly blacks aged 10 to 11 years. 5% had ever smoked. 167 (51% male) reported having been diagnosed with asthma. Self-reported prevalence of symptoms and medical treatments were related to maternal smoking habits in pregnancy and in the past week. Based on these results comparisons can be made of the proportion of those with physician diagnosed asthma who took asthma or wheezing medication in the past 2 weeks or who attended the emergency room for treatment of asthma in the past 12 months (assuming that those who took medication or who attended the emergency room was restricted to those with physician diagnosed asthma). As can be seen, the proportion of asthmatics taking medication or attending the emergency room was non significantly lower if the mother smoked.

Smoking	Nonsmoker	Nonsmoker	Smoker	Smoker	Odds ratio
Treatment type	No treatment	Treatment	No treatment	Treatment	(95% CI)
Maternal smoking in pregnancy					
Took medication in past 2 weeks	25	52	15	21	0.67 (0.30-1.52)
Emergency room in past 12 months	31	46	16	20	0.84 (0.38-1.87)
Maternal smoking in past week					
Took medication in past 2 weeks	18	44	17	28	0.67 (0.30-1.52)
Emergency room in past 12 months	24	38	19	26	0.86 (0.40-1.89)

3. Summary of the studies

Section 2 summarizes relevant material from 41 papers or abstracts. Seven are review papers (Canadian Paediatric Society, 1986; Witorsch, 1992; Shephard, 1992; Ehrlich et al., 1993; National Cancer Institute, 1993; Trédaniel et al., 1994; Di Benedetto, 1995) and three are abstracts (Lilienfeld et al., 1990; Salmun et al., 1992; Abulhosn et al., 1995) describing studies reported in more detail later (Ehrlich et al., 1992; Chilmonczyk et al., 1993; Abulhosn et al., 1997). Of the remaining 29, five (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989; Murray & Morrison, 1992; Murray & Morrison, 1993) are non-independent reports from an accumulating database of asthmatic children in Vancouver, three (Frischer et al., 1992; Frischer et al., 1993; Meinert et al., 1994) report results from the same cohort of children in Freiburg, and two (Weitzman et al., 1990a; Weitzman et al., 1990b) report analyses based on the 1981 US National Health Interview Survey. The other 21 (O'Connell & Logan, 1974; Aderele, 1982; Gortmaker et al., 1982; Fergusson & Horwood, 1985; Evans et al., 1987; O'Connor et al., 1987; Martinez et al., 1988; Ehrlich et al., 1992; Chilmonczyk et al., 1993; Jindal et al., 1994; Ogborn et al., 1994; Ostro et al., 1994; Chan & Chen, 1995; LeSon & Gershwin, 1995; Strachan & Carey, 1995; Jindal et al., 1996; MacArthur et al., 1996; Meijer et al., 1996; Abulhosn et al., 1997; Callén Blecua et al., 1997; Hu et al., 1997) appear to describe distinct studies. The 41 papers or abstracts therefore relate to 24 separate studies.

Some characteristics of the 24 studies considered are summarized below:

Publication date As shown below, studies were rarely published until the mid 1980's. The majority of the papers were published towards the end of the period considered.

Date	Studies first published
1973-77	1
1978-82	2
1983-87	4
1988-92	4
1993-97	13

Two of the studies (Chan & Chen, 1995; Jindal et al., 1996) are described only in abstracts.

Location Twelve studies were conducted in the USA, with two each in Canada and India, and one each in England, Germany, Italy, New Zealand, Nigeria, Taiwan, the Netherlands and Spain.

Number of asthmatic subjects The last report of the Vancouver study (Murray & Morrison, 1993) included the largest number of subjects studied, 807. The other 22 studies where this was known ranged from 21 to 486 subjects.

Age of subjects Three of the studies, including the two in India, were conducted in adults (Jindal et al., 1994; Ostro et al., 1994; Jindal et al., 1996). Of the 21 studies in children, many covered a reasonably wide age range, though some were of children in a given class (or grade).

Sex of subjects The sex of the subjects was not reported in two of the three studies of adults. In the 13 studies of children where the sex of the subjects was reported, the distribution clearly demonstrated the preponderance of boys among asthmatics. The mean percentage of boys was around 60%.

<38	38-42	43-47	48-52	53-57	58-62	63-67	68-72	73+
0	1	0	1	2	6	0	3	0

Smoking habits Of the three studies in adults, one (Jindal et al., 1994) was stated to be in never smokers, while the other two (Ostro et al., 1994; Jindal et al., 1996) stated to be in nonsmokers. Some authors use the term

nonsmokers to imply lifelong nonsmokers, while some use it to include former smokers as well as never smokers. In neither of the two studies of "nonsmokers" is the definition clear.

Most of the papers describing studies in children did not mention smoking by the child, though some were based on children so young that smoking could effectively be ruled out (Fergusson & Horwood, 1985; Martinez et al., 1988; Weitzman et al., 1990b; Weitzman et al., 1990a; Frischer et al., 1992; Frischer et al., 1993; Meinert et al., 1994; MacArthur et al., 1996). In the study in Ibadan (Aderele, 1982) it was stated that "as far as could be ascertained, none of the asthmatic children smoked". In the study in New York (Evans et al., 1987) smokers were excluded and in the studies in Boston (O'Connor et al., 1987) and New York (Ehrlich et al., 1992) there were no smokers among the asthmatic sample. The first report of the Vancouver study (Murray & Morrison, 1986) included two children who admitted smoking in their analyses, but later reports (Murray & Morrison, 1988; Murray & Morrison, 1989; Murray & Morrison, 1992; Murray & Morrison, 1993) excluded smokers. The study in San Sebastian (Callén Blecua et al., 1997) included one child who smoked. In the study in Chicago (Hu et al., 1997) 5% of all children had ever smoked a cigarette, but this was not reported for the asthmatics.

Selection of sample In a number of studies the children were cases of asthma attending asthma clinics. Other sample selections are summarized below:

The study in Baltimore (Ogborn et al., 1994) identified children who attended the hospital emergency department during an acute episode of asthma, following them up for 3 or 4 weeks when they were now well.

The study in Toronto (MacArthur et al., 1996) identified children who had had a first ever admission for asthma in a defined 19 month period and who had been readmitted to the same hospital for asthma within 12 months,

following the cohort to investigate the probability of a further readmission in the 12 months after the first readmission.

The studies in Davis (LeSon & Gershwin, 1995) and Seattle (Abulhosn et al., 1997) included children admitted as inpatients, while the New York study (Ehrlich et al., 1992) included both acute cases presenting at ER and non-acute clinic attendees.

The study in Zwolle (Meijer et al., 1996) restricted attention to a defined subset of asthmatic children with increased total IgE, an allergy to house dust mite but not to other specified allergens, an FEV $\geq$ 70% of predicted, and increased bronchial responsiveness to histamine. As the children were stated to be "visiting primary school" it is unclear how these subjects were identified.

The studies in Michigan and Massachusetts (Gortmaker et al., 1982), Christchurch (Fergusson & Horwood, 1985), Viterbo (Martinez et al., 1988), Freiburg (Frischer et al., 1992; Frischer et al., 1993; Meinert et al., 1994) and Chicago (Hu et al., 1997) were based on unselected samples of children and refer to whether the child had ever had asthma. The studies in Boston (O'Connor et al., 1987), and that based on the National Health Interview Survey (Weitzman et al., 1990b; Weitzman et al., 1990a), were also based on unselected samples but refer to whether the child currently had asthma.

The study in Sheffield (Strachan & Carey, 1995) was a case-control study in which the cases (which provided the relevant data) were identified from a population-based cross-sectional study carried out 18 months earlier, as those asthmatic children with at least 12 or more wheezing attacks or a speech limiting attack of wheeze in the past year.

It is clear that the characteristics of the populations are quite variable, and that the average severity of asthma will vary from study to study.

Study design The studies were of various designs:

There was one experimental study. This was the study in Zwolle (Meijer et al., 1996), which related lung function to ETS exposure before and 6 days after withdrawal of inhaled corticosteroids.

There were five studies with a prospective element. The study in Minnesota (O'Connell & Logan, 1974) related improvement of asthma over a period of up to 2 years to whether the parents had stopped smoking. The study in Christchurch (Fergusson & Horwood, 1985) followed children from birth to age 6, collecting information on asthma and ETS exposure on eight occasions. The study in Baltimore (Ogborn et al., 1994) compared ETS exposure in children at the time they had an acute attack of asthma and 3 to 4 weeks later when they were well. The study in Toronto (MacArthur et al., 1996) concerned children who had had a first ever admission for asthma and who had been readmitted within 12 months of this. It related ETS exposure to the probability of further readmission within the next 12 months. The study in Seattle (Abulhosn et al., 1997) compared indices of asthma severity over the next four weeks in groups of children hospitalised for asthma, subdivided by their ETS exposure.

The remaining studies were more of a cross-sectional or case-control design. In two studies ETS exposure and indices of asthma severity were collected over a period, of either 3 months (Ostro et al., 1994) or 6 months (Chan & Chen, 1995). The Vancouver study analyses were all cross-sectional in nature, with indices of asthma severity compared in subjects subdivided by ETS exposure – the various papers presenting results investigating for interactions of this association by time of year (Murray & Morrison, 1988), sex and age (Murray & Morrison, 1989), presence of atopic dermatitis (Murray & Morrison, 1992) or year of admission (Murray & Morrison, 1993). The analyses based on the National Health Interview Survey (Weitzman et al., 1990b; Weitzman et al., 1990a) were also cross-sectional, as were the studies in Viterbo (Martinez et al., 1988) and Freiburg (Frischer et al., 1992; Frischer et al., 1993; Meinert et al., 1994). A further eight studies were essentially cross-sectional in nature (Aderele, 1982; Gortmaker et al., 1982; Evans et al.,

1987; O'Connor et al., 1987; Chilmonczyk et al., 1993; Jindal et al., 1994; Strachan & Carey, 1995; Hu et al., 1997), though in five of these (Evans et al., 1987; Chilmonczyk et al., 1993; Jindal et al., 1994; Strachan & Carey, 1995; Hu et al., 1997) the asthma data collected included events in the previous year. Other studies could be considered to have more of a case-control design, with comparisons of acute and non-acute asthmatics (Ehrlich et al., 1992; Jindal et al., 1996) intubated and non-intubated asthmatics (LeSon & Gershwin, 1995), and asthmatics satisfying or not satisfying defined conditions for severity (Callén Blecua et al., 1997).

ETS exposure Most of the studies recorded data on parental smoking or smoking by household members. Exceptions were the first study in India (Jindal et al., 1994), which recorded ETS exposure at home and at work, the second study (Jindal et al., 1996) which did not define ETS exposure, the study in Portland (Chilmonczyk et al., 1993), which considered household and day-care exposure, and the study in Davis (LeSon & Gershwin, 1995) which recorded data on exposure from parents, family or room-mates. The study in Taiwan (Chan & Chen, 1995) only reported analyses using the urinary cotinine/creatinine ratio (CCR) as the index of exposure. Other studies using CCR as an index (Ehrlich et al., 1992; Chilmonczyk et al., 1993; Ogborn et al., 1994) also reported results relating to questionnaire-assessed ETS exposure.

Some studies provided information relating to the effect of changes in ETS exposure. In the study in Minnesota (O'Connell & Logan, 1974), improvement in asthma was linked to whether the parents had stopped smoking, while in the study in Baltimore (Ogborn et al., 1994), CCR was measured at the time the children had an asthmatic attack and 3 to 4 weeks later when they were well. The Baltimore study is the only one that reported a within-child analysis, all other analyses being between-child. The two studies that recorded ETS exposure over a period of 3 to 6 months (Ostro et al., 1994; Chan & Chen, 1995) had the potential to study the effect of within-person changes in ETS exposure but did not report relevant results.

Smoking in pregnancy The studies in Chicago (Hu et al., 1997) and Freiburg (Frischer et al., 1992; Meinert et al., 1994) presented results for maternal smoking in pregnancy as well as for ETS exposure. The nationwide study in the US (Weitzman et al., 1990a; Weitzman et al., 1990b) presented results for maternal smoking in pregnancy, but not for ETS.

Asthma endpoints studied Table 1 summarizes the asthma endpoints used in the various studies. Of the 24 studies, all but five included at least one index based on asthma severity. Eight reported data on lung function, while five reported data on bronchial responsiveness, though one of these (Meijer et al., 1996) related bronchial responsiveness only to lung function and not to ETS exposure.

It should be pointed out that the endpoints listed in Table 1 under "asthma severity" are quite numerous, and that a number of them may be regarded as rather indirect or poor indices of severity. Thus one should note:

(i) a number of studies (Evans et al., 1987; Weitzman et al., 1990b; Weitzman et al., 1990a; Jindal et al., 1994; LeSon & Gershwin, 1995; MacArthur et al., 1996) are based on hospital admission, which may depend not only on the severity of the attack, but also on the use and availability of medication, as well as on the decision to admit, given severity, factors which may depend upon poverty and parental education;

(ii) in some studies (e.g. O'Connell & Logan, 1974; Aderele, 1982) the definition of asthma severity or worsening is not clear and may have been subjective;

(iii) some studies (e.g. Ehrlich et al., 1992; Jindal et al., 1996) are based on the distinction between acute and non-acute cases, which is not necessarily the same as comparisons based on severity; and

(iv) one study (Strachan & Carey, 1995) compared children with both frequent (12 or more) and speech limiting wheezing attacks in the last 12 months with children who had either frequent or speech limiting

attacks, but not both. The relationship of this comparison to other indices of severity is unclear.

Control of potentially confounding variables Control of potential confounding was generally quite poor. For 14 of the 23 studies which involve between-subject analysis (O'Connell & Logan, 1974; Aderele, 1982; Fergusson & Horwood, 1985; Weitzman et al., 1990a; Weitzman et al., 1990b; Ehrlich et al., 1992; Jindal et al., 1994; Chan & Chen, 1995; LeSon & Gershwin, 1995; Strachan & Carey, 1995; Jindal et al., 1996; MacArthur et al., 1996; Meijer et al., 1996; Callén Blecua et al., 1997; Hu et al., 1997) no relevant analyses were adjusted for any variable at all, not even the age and sex of the child. However, two of these studies (Ehrlich et al., 1992; Abulhosn et al., 1997) noted that the groups being compared were similar in a limited number of variables. Table 2 lists the variables taken account of in the other nine studies. Not all of those listed were considered in all the analyses presented. It should be noted that the age of the subject was only considered in four studies (though in four more the children were all of essentially the same age) and the sex in five. A social class related variable (maternal education) was only considered in two studies. Only the Vancouver studies took into account an extensive list. A recent history of infections or colds was only considered by two studies, none taking into account respiratory symptoms in the parents.

TABLE 1

Asthma endpoints studied

Study	Asthma severity	Lung function	Bronchial Responsiveness
O'Connell & Logan, 1974	Asthma improved	-	-
Aderele, 1982	Severity	-	-
Fergusson & Horwood, 1985	Medical consultations, asthmatic attacks	-	-
Gortmaker et al., 1982	Functional impairment	-	-
Vancouver*	Symptoms, use of therapy	FEV_1, FVC, $FEF_{25-75\%}$	To histamine
Evans et al., 1987	Symptoms, hospitalisation, ER** visits	FEV_1, PEFR, $FEF_{25-75\%}$	-
O'Connor et al., 1987	-	FEV_1, FVC, $FEF_{25-75\%}$	To cold air
Martinez et al., 1988	-	-	To carbachol
Weitzman et al., 1990b; Weitzman et al., 1990a	Hospitalisation, use of therapy	-	-
Ehrlich et al., 1992	Acute/non-acute	-	-
Freiburg†	-	PEFR variability	To exercise
Chilmonczyk et al., 1993	Acute exacerbations	FEV_1, FEV_1/FVC, $FEF_{25-75\%}$	-
Jindal et al., 1994	Hospitalisation, ER** visits, acute episodes, days off work, use of therapy	FEV_1, FEV_1/FVC, $FEF_{25-75\%}$	-
Ogborn et al., 1994	Acute/well	-	-
Ostro et al., 1994	Symptoms, restricted activity	-	-
Chan & Chen, 1995	-	PEFR	-
LeSon & Gershwin, 1995	Intubation	-	-
Strachan & Carey, 1995	Severity	-	-
Jindal et al., 1996	Acute/non-acute	-	-
MacArthur et al., 1996	Readmission	-	-

TABLE 1 (continued)

Study	Asthma severity	Lung function	Bronchial Responsiveness
Meijer et al., 1996	-	PEFR amplitude	To histamine
Abulhosn et al., 1997	Symptoms, use of therapy	-	-
Callén Blecua et al., 1997	Severity	FEV_1, FVC, PEFR, $FEF_{25-75\%}$	-
Hu et al., 1997	Use of therapy, ER** visits	-	-

* Applies to the five papers from the Vancouver study taken together (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989; Murray & Morrison, 1992; Murray & Morrison, 1993), though not all presented results for each endpoint.

** ER = Emergency room.

† Applies to the three papers from the Freiburg study taken together (Frischer et al., 1992; Frischer et al., 1993; Meinert et al., 1994), though not all presented results for each endpoint.

TABLE 2

Potential confounding variables taken account of

Study	Age	Sex	Others
Gortmaker et al., 1982	No	No	Sample (= urban/rural)
Martinez et al., 1988	All 9	Yes	Atopy
Vancouver*	Yes	Yes	Recent respiratory infection, recent medication, positive skin test, family history of asthma, hot air heating, wood stove, gas range, pets, duration of asthma, age of onset of asthma, number of siblings, atopic dermatitis
Evans et al., 1987	No	No	Days with asthma symptoms per month (in analysis of emergency room visit data only)
O'Connor et al., 1987**	(Yes)	(Yes)	History of cold in last two weeks, (height, atopy)
Freiburg†	All 7-8	Yes	Prematurity, pneumonia in first year, atopy, education
Chilmonczyk et al., 1993	Yes	Yes	Day-care attendance, mother's age and education
Ostro et al., 1994††	(Yes)	No	Outdoor air pollution, survey day, previous symptoms, (temperature, humidity)
Meijer et al., 1996	Yes	No	Pets, house dust mite exposure

* The analyses in the five papers (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989; Murray & Morrison, 1992; Murray & Morrison, 1993) adjust for varying numbers of the variables considered – none take them all into account.

** Age, sex, height and atopy were found not to have any material effect so were not considered in the final analyses.

† The analyses in the three papers (Frischer et al., 1992; Frischer et al., 1993; Meinert et al., 1994) adjust for varying numbers of the variables considered – none take them all into account.

†† Age, temperature and humidity were found not to have any material effect so were not considered in the final analyses.

4. Results

4.1 Studies in adults

Only three studies of non-smoking asthmatics have reported relevant results.

In one study (Jindal et al., 1994), ETS exposure was reported to be associated with a significantly reduced lung function, increased use of bronchodilators and steroids, and increased number of emergency department visits, acute episodes of asthma and weeks absent from work. As noted in section 2, the groups being compared (100 exposed and 100 unexposed) were of significantly different age and there are a number of obvious errors in the statistical analyses presented.

The second study in India, (Jindal et al., 1996) reported in an abstract that there was a significantly ($p<0.01$) higher prevalence of ETS exposure in 100 patients with acute exacerbation of asthma than in 100 with stable non-acute asthma. No further details of the findings were presented.

In the study in Denver (Ostro et al., 1994), exposure to cigarette smoking at home today was associated with an increased incidence of moderate or severe cough, moderate or severe shortness of breath, nocturnal asthma and restricted activity. However, only for restricted activity did the excess remain significant after taking account of the repeated measures design. Presence of smokers in the home at the start of the study was also increased with a significantly increased risk for moderate or severe shortness of breath.

While the overall evidence for adults suggests a relationship, it is too limited and poorly reported to allow a confident conclusion.

4.2 Studies in children

There are 21 studies of asthmatic children. It is convenient to consider separately results for asthma exacerbation/severity, lung function and bronchial responsiveness.

4.2.1 Asthma exacerbation and severity

Table 3 summarizes the results relating ETS exposure to asthma exacerbation and severity from 15 studies. The results relate to a wide variety of endpoints (see section 3). The majority of the associations are in the direction of increased ETS exposure being linked to a greater severity of asthma. Exceptions include a study in New York (Ehrlich et al., 1992) which found that acute asthma cases had nonsignificantly lower ETS exposure than did non-acute asthma cases, the post-July 1986 results from the Vancouver study (Murray & Morrison, 1993) which found that maternal smoking was associated with a significantly lower asthma symptom score, one of the matched-pair analyses of the Baltimore study (Ogborn et al., 1994) which found that CCR was nonsignificantly lower around the time the child had an acute attack than when the child was well, and the study in Chicago (Hu et al., 1997) which found that maternal smoking was associated with nonsignificantly lower use of medication or ER visit.

A number of the studies report a significant association in the direction more generally seen for one or more endpoints. The clearest was:

- the very strong relationship of ETS exposure to intubation in the Davis study (LeSon & Gershwin, 1995).

Other significant associations included:

- the improvement in asthma associated with parents quitting smoking in the Minnesota study (O'Connell & Logan, 1974);
- the increase in emergency room visits in households with a smoker in the first New York study (Evans et al., 1987);
- the association of household smoking and CCR with acute exacerbations in the previous year in the Portland study (Chilmonczyk et al., 1993);

- the association of maternal smoking with asthma severity score in the pre-July 1986 results from the Vancouver study (Murray & Morrison, 1993);
- the greater parent-reported ETS exposure when ill than when well in the Baltimore study (Ogborn et al., 1994);
- the association of maternal and of paternal smoking with asthma severity in the Sheffield study (Strachan & Carey, 1995);
- the greater symptomatic days and smaller reduction in beta-agonist therapy in the four weeks after an acute attack where the parent smokes in the Seattle study (Abulhosn et al., 1997); and
- the association of parental smoking with asthma severity in the San Sebastian study (Callén Blecua et al., 1997).

In total, this represents 9 of the 15 studies.

Additionally, a further study (Weitzman et al., 1990a; Weitzman et al., 1990b) reported that maternal smoking in pregnancy was associated with greater use of asthma medication where the mother smoked 10+ cigarettes a day. This is the only study reporting results for maternal smoking in pregnancy and not postnatal ETS exposure, but has been included as the authors considered that the measure of maternal smoking they used "reflects both prenatal and postnatal exposure".

Overall, though there are unexplained exceptions, these data, taken together, show considerable evidence of an association.

4.2.2 Lung function

Table 4 summarizes the main results related to lung function based on data from eight studies.

For FEV_1 the general tendency, except in the first study (Evans et al., 1987) and for children seen after July 1986 in the Vancouver study (Murray & Morrison, 1993), is for ETS exposure to be associated with a decrease.

However, this association is only significant in one case, for mother smoking in the Vancouver study (Murray & Morrison, 1993) and then only for children seen before July 1986.

For $FEF_{25-75\%}$ significant reductions are again seen for mother smoking in the Vancouver study for children seen before July 1986 and they are also seen in the Portland study (Chilmonczyk et al., 1993). However no significant effect was seen in the later Vancouver data or in the three other studies reporting findings.

The limited evidence for FVC does not really suggest an effect of ETS.

The evidence on PEFR or its variability does not show a very consistent association.

Overall the data do not conclusively demonstrate an association between ETS exposure and lung function in asthmatics.

4.2.3 Bronchial responsiveness

Only four studies related ETS exposure to bronchial responsiveness.

In the Boston study (O'Connor et al., 1987) the response to cold air challenge (fall in FEV_1 as a percentage of predicted FEV_1) was higher if the mother smoked, but not if the father smoked. The association with maternal smoking was significant ($p=0.02$) using one statistical technique, but not ($p=0.07$) using another.

In the Viterbo study (Martinez et al., 1988) the response to carbachol was significantly ($p=0.036$) greater if the parents smoked when the whole population (asthmatics and non-asthmatics) was considered, with the relationship noted to be stronger ($p=0.02$) in asthmatic subjects. Among the asthmatics, the odds ratio was estimated as 18.7, but had a very wide confidence interval of 1.5 to 232.3.

In the Vancouver study, bronchial responsiveness to histamine was found to be significantly related to maternal but not to paternal smoking in the first four papers reporting results (Murray & Morrison, 1986; Murray & Morrison, 1988; Murray & Morrison, 1989; Murray & Morrison, 1992). Interestingly, in the final paper (Murray & Morrison, 1993) the increase in bronchial responsiveness (reduction in log PC_{20}) in relation to maternal smoking was evident only in children examined before July 1986. In children examined after July 1986 bronchial responsiveness was found to be somewhat lower if the mother smoked, though not statistically significantly. This was also true if the father smoked, the difference here being close to statistical significance (log PC_{20} 0.74, SE 0.26 for father smoker; 0.10, SE 0.20 for father nonsmoker, $p<0.1$).

In the Freiburg study (Frischer et al., 1992; Meinert et al., 1994) bronchial responsiveness, as determined by a 15% decrease in PEFR following an exercise test, was higher if the mother had smoked in pregnancy or had smoked when the child was 1 year old, but was lower if the mother smoked when the test was done at age 8. These differences were non-significant in univariate analyses, but significant differences were seen in multivariate analyses that are open to question (see section 2).

Clearly more data are needed to reach a firm opinion regarding the relationship of ETS exposure to bronchial responsiveness in asthmatic children.

4.2.4 Comment

The studies of asthmatic children that have been identified as providing relevant data do not conclusively demonstrate an association between ETS exposure and lung function, and do not allow any firm conclusion to be reached regarding bronchial responsiveness.

Although there is strong evidence of an association of ETS exposure with asthma exacerbation/severity, statistically significant for at least one endpoint in 9 of the 15 studies with such data available, there are a number of

weaknesses of the evidence that hinder interpretation of the association in terms of a causal relationship. These include:

(i) Lack of clear evidence of an association between asthma severity and ETS exposure in the only within-child analysis carried out (Ogborn et al., 1994), though it should be noted that this was a relatively small study;

(ii) Limited reporting of many of the study details, with one of the studies in children reporting findings only in an abstract (Chan & Chen, 1995) and, for example, many of the studies providing no information on the active smoking habits of the children;

(iii) Failure generally to present results separately for boys and girls, and for infants, young children and older children – the one study giving such details (Murray & Morrison, 1989) failing properly to test for variation in associations by age and sex;

(iv) Failure properly to control for potential confounding variables. Of the 14 studies in children which reported the results of between-child analyses, 10 did not adjust for any variables at all, with the age and sex of the child each only considered in two studies. Only one study took account of any social class related variable. It may be particularly important that none of the studies adjusted for smoking in pregnancy, only one considered a recent history of infections or colds in the child and none considered such a history in the parent. The Vancouver series of studies, which took the widest range of potential confounding variables into account, reported associations of maternal but not paternal smoking with severity, but only in the children studied before July 1986 and not in those studied afterwards.

Overall, the data on asthma exacerbation/severity seem highly suggestive of a causal relationship, but not completely conclusive, with evidence from more studies being required to clarify the issue.

TABLE 3

Summary of results relating asthma exacerbation and severity in children to ETS exposure

Study	Endpoint	Results by ETS exposure		
		Parent continued to smoke	Parent stopped smoking	RR (95% CI)
O'Connell & Logan, 1974	Asthma improved over 2 years	4/15 (27%)	18/20 (90%)	3.38 (1.44-7.91)
		Household member does not smoke	Household member smokes	OR (95% CI)
Aderele, 1982	Asthma moderate or severe	138/281 (49%)	56/99 (57%)	1.35 (0.85-2.14)
		Mother nonsmoker	Mother 1-10/day	Mother 11+/day
Fergusson & Horwood, 1985	Medical consultations (n/year)	0.80	0.53	0.96
	Asthmatic attacks (maternal report) (n/year)	1.59	0.96	2.03
		Father nonsmoker	Father 1-10/day	Father 11+/day
	Medical consultations (n/year)	0.82	0.64	0.85
	Asthmatic attacks (maternal report) (n/year)	1.55	1.60	1.46
		Mother nonsmoker	Mother smoker	OR (95% CI)
Gortmaker et al., 1982	Functionally impaired	23/105 (22%)	32/112 (29%)	1.43 (0.79-2.65) (adjusted for sample)
		Household member does not smoke	Household member smokes	p
Evans et al., 1987	Emergency room visits in previous year (n)	2.12	3.46	0.008 (adjusted for symptoms)
	Hospitalisation, symptoms	Data not shown	Data not shown	Not significant
		Mother nonsmoker	Mother smoker	OR (95% CI)
Murray & Morrison, 1988	Recent bronchodilator medication:			
	October to May	34/136 (25%)	19/44 (43%)	2.28 (1.12-4.65)
	June to September	16/40 (40%)	3/10 (30%)	0.64 (0.14-2.86)
	Combined			1.75 (0.93-3.30) (adjusted for season)

TABLE 3 (continued 1)

Study	Endpoint	Results by ETS exposure			
		No smoker at home	Smoker at home		OR (95% CI)
Ehrlich et al., 1992	Asthma acute	34/49 (69%)	38/58 (66%)		0.84 (0.37-1.89)
		Maternal caregiver does not smoke	Maternal caregiver smokes		
	Asthma acute	43/60 (72%)	29/47 (62%)		0.64 (0.28-1.44)
		CCR<30ng/mg	CCR 30+ ng/mg		
	Asthma acute	45/66 (68%)	27/41 (66%)		0.90 (0.39-2.06)
		No exposure	Mother or others smoke	Mother and others smoke	Change per category (95% CI)
Chilmonczyk et al., 1993	Acute exacerbations in previous year	2.2	2.5	3.9	0.83 (0.39-1.26) (Adjusted for mother's age and education, and child's age, sex, day-care attendance)
		CCR<10 ng/mg	CCR 10-39 ng/mg	CCR 40+ ng/mg	
	Acute exacerbations in previous year	2.1	2.8	3.6	0.63 (0.10-1.07) (Adjusted for mother's age and education, and child's age, sex, day-care attendance)
		Mother nonsmoker	Mother smoker		p
Murray & Morrison, 1993	Asthma severity score Before July 1986	6.4	8.2		<0.001
		Father nonsmoker	Father smoker		
	Asthma severity score Before July 1986	6.7	7.1		NS
		Mother nonsmoker	Mother smoker		
Murray & Morrison, 1993	Asthma severity score After July 1986	6.6	5.8		<0.05
		Father nonsmoker	Father smoker		
	Asthma severity score After July 1986	6.3	6.5		NS
		Cotinine (ng/mg)	CCR (ng/mg)	CCR 30+ ng/ml	
Ogborn et al., 1994	When acutely ill	81	93	80%	
	When well	77	97	82%	
	p	NS	NS	NS	
		Hours exposure in past 48 hrs	N cigs smoked at home	ETS exposure some or a lot	
	When acutely ill	32	31	30/52 (58%)	
	When well	32	25	24/54 (44%)	
	p	NS	NS	0.02 (Based on full distribution of grades)	
		No ETS exposure	ETS exposure		OR (95% CI
LeSon & Gershwin, 1995	Requiring intubation	2/232 (0.9%)	11/68 (16%)		22.4 (7.4-68.0)*

TABLE 3 (continued 2)

Study	Endpoint	Results by ETS exposure		
		Mother nonsmoker	Mother smoker	OR (95% CI)
Strachan & Carey, 1995	Asthma severe	75/364 (21%)	38/122 (31%)	1.74 (1.10-2.76)
		Father nonsmoker	Father smoker	
	Asthma severe	85/398 (21%)	27/86 (31%)	1.69 (1.01-2.82)
		No smokers in home	Smokers in home	RR (95% CI)
MacArthur et al., 1996	Readmission for asthma	15/38 (39%)	17/30 (57%)	1.44 (0.87-2.37)
		Parents do not smoke	Parent smokes	p
Abulhosn et al., 1997	In four weeks after acute admission			
	symptomatic days	1.4	3.3	<0.05
	symptomatic nights	1.4	2.3	NS
	reduction in beta-agonist therapy	20.8 to 8.9	15.3 to 18.0	<0.001
		Parents do not smoke	Parent smokes	OR (95% CI)
Callén Blecua et al., 1997	Asthma severe	56/111 (50%)	131/201 (65%)	1.84 (1.12-3.03)
		Mother nonsmoker in past week	Mother smoked in past week	OR (95% CI)
Hu et al., 1997	Used asthma medication in last 2 weeks	44/62	28/45	0.67 (0.30-1.52)
	Emergency room visit in last year	38/62	26/45	0.86 (0.40-1.89)

* Our own estimates are 22.2 (4.8-102.9) based on the data provided. The reported CI is certainly too narrow.

TABLE 4

Summary of results relating lung function to ETS exposure

Study	Exposure	Lung function variable			
		FEV_1	FVC	$FEF_{25-75\%}$	PEFR
Evans et al., 1987	No household smoker	1.49ℓ		1.42ℓ/sec	2.74ℓ/sec
	Household smoker	1.60ℓ		1.60ℓ/sec	3.19ℓ/sec
	p	NS		NS	NS
O'Connor et al., 1987	Mother nonsmoker	102.9%	104.0%	85.8%	
	Mother smoker	100.8%	107.8%	76.1%	
	p	NS	NS	NS	
Frischer et al., 1993	Effects of mother smoking in non-atopic children				+54.7%† (+5.5% to 226.8%)
	Effect of mother smoking in atopic children				-8.5% (-41.2% to +42.3%)
Chilmonczyk et al., 1993	No household smoker	109.3%		85.4%	
	Mother or others smoke	102.4%		71.8%	
	Mother and others smoke	102.2%		73.6%	
	Trend p	NS		p<0.05	
	Cotinine <10 ng/ml	108.8%		85.4%	
	10-39 ng/ml	105.2%		74.9%	
	40+ ng/ml	98.5%		67.3%	
	Trend p	NS		p<0.05	
Murray & Morrison, 1993*	Before July 1986				
	Mother nonsmoker	84.4%	93.8%	71.7%	
	Mother smoker	77.3%	91.2%	59.5%	
	p	<0.01	NS	p<0.001	
	Father nonsmoker	84.2%	94.5%	70.0%	
	Father smoker	80.2%	90.6%	67.1%	
	p	p<0.05	p=0.05	NS	
Murray & Morrison, 1993	After July 1986				
	Mother nonsmoker	90.8%		79.4%	
	Mother smoker	91.3%		81.0%	
	p	NS		NS	
	Father nonsmoker	90.1%		78.0%	
	Father smoker	93.0%		84.1%	
	p	NS		NS	

TABLE 4 (continued)

Study	Exposure	Lung function variable			
		FEV_1	FVC	$FEF_{25-75\%}$	PEFR
Chan & Chen, 1995	Cotinine/creatinine ratio (CCR)				CCR significantly higher where PEFR<80% of predicted for samples collected at night, not during the day
Meijer et al., 1996	During ICS**				
	Parents nonsmokers				20.6%
	Parent smokes				28.7%
	p				NS
	After ICS withdrawal				
	Parents nonsmokers				19.4%
	Parent smokes				29.7%
	p				<0.05
Callén Blecua et al., 1997	No household smoker	93.7%	97.4%	76.7%	92.6%
	Household smoker	91.9%	96.9%	72.7%	87.2%
	p	NS	NS	NS	NS

* FVC data are from Murray & Morrison, 1989.

** ICS = inhaled corticosteroids. PEFR values are PEFR amplitude = (maximum-minimum)/mean based on 24 hour data.

† Data are percentage increase in PEFR variability in children with a smoking mother.

5. Other reviews of this evidence

5.1 The California EPA report

The report "Health effects of exposure to environmental tobacco smoke" (National Cancer Institute, 1999) contains an 18 page section, 6.1.1, on "asthma (exacerbation)" which is about equally divided into "epidemiologic evidence" (6.1.1.1), pp 187-194) and "evidence from chamber studies" (6.1.1.2, pp 194-203). The latter section, which only considers studies published up to 1993, so excluding one important study (Lehrer et al., 1997), ends with the conclusion that

> "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."

Their review of the epidemiological evidence concludes with the following paragraph:

> "The studies reviewed in this section support the previous finding by the U.S. EPA (1992) that there is 'sufficient evidence … that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease.' There is suggestive evidence that ETS exposure may exacerbate adult asthma. The U.S. EPA (1992) estimated that ETS exposure potentially could exacerbate pre-existing asthma in approximately 20 percent of 2 to 5 million children, i.e., in 0.4 to 1 million children. Assuming that 12 percent of those children reside in California would result in estimates

of 48,000 to 120,000 asthmatic children who could experience a worsening of their condition due to exposure to ETS."

The main body of this section consists of mini-reviews of studies identified by them as relevant. It includes two studies (Bailey et al., 1990; Hong et al., 1994) which we have rejected because they are not restricted to nonsmokers – a deficiency not noticed in the report. They also fail to mention some earlier studies we cite (including O'Connell & Logan, 1974; Aderele, 1982; Gortmaker et al., 1982; Fergusson & Horwood, 1985; Martinez et al., 1988; Weitzman et al., 1990a; Weitzman et al., 1990b; Frischer et al., 1992; Frischer et al., 1993) as well as any study published between 1995 and 1997, with one exception (Strachan & Carey, 1995), so missing a further eight studies we consider (Chan & Chen, 1995; LeSon & Gershwin, 1995; Jindal et al., 1996; MacArthur et al., 1996; Meijer et al., 1996; Abulhosn et al., 1997; Callén Blecua et al., 1997; Hu et al., 1997).

There are a few points that should be noted about the mini-reviews and section 6.1.1 in general:

(i) While they generally summarize the results of the studies accurately enough, they are uncritical in that they fail to detect obvious flaws we have noted in section 2. These include the errors in the analysis of the first study in India (Jindal et al., 1994), the failure to properly investigate interactions with age and sex in the third Vancouver paper (Murray & Morrison, 1989) and the failure to detect the lack of association with ETS exposure in the second half of the Vancouver study (Murray & Morrison, 1993).

(ii) There are also some strange statements. These include the unsound view that in the Denver study (Ostro et al., 1994) "This investigation also had more than 10,000 observations, which afforded substantial power to detect associations with indoor exposures, including ETS". But power depends mainly on the number of subjects, and only 164 asthmatics were studied! Also, having described the Sheffield study (Strachan & Carey, 1995) they conclude that "This study examines risk

factors for having severe asthma versus not having asthma at all; it does not address whether exposure to ETS or other factors influence the severity of asthma among children who already have the disease". If this is true, why include it in the section? In fact, one can extract relevant data (see section 2 of this document), but these are not the data they cite.

(iii) Where associations are not seen, comments are often made about lack of power and of possible underestimation of effects due to misclassification of exposure. The section contains no discussion whatsoever of any potential sources of possible bias. As such the section, which contains no linking paragraphs between the mini-reviews and the conclusion which describe how its conclusion has been reached, is totally one-sided and unscientific, and provides no valid reasons for its conclusions.

5.2 The reviews of the St George's Hospital Medical School group

Of the series of 10 papers on effects of parental smoking on the respiratory health of children published in Thorax by the group from St George's Hospital Medical School, two deal specifically with data relevant to the present document.

The first, paper 6 in the series, is entitled "Parental smoking and childhood asthma: longitudinal and case-control studies" (Strachan & Cook, 1998). It reviews epidemiological studies in healthy children as well as in asthmatics, and concludes that:

> "The excess incidence of wheezing in smoking households appears to be largely non-atopic 'wheezy bronchitis' with a relatively benign prognosis, but among children with established asthma, parental smoking is associated with more severe disease. This apparent paradox may be reconciled if environmental tobacco smoke is considered a co-factor provoking wheezing attacks, rather than a cause of the underlying asthmatic tendency."

Elsewhere in the paper it makes it clear that the mechanism postulated is that ETS is a co-factor "operating with intercurrent infections".

In their Table 4 they summarize data from 13 studies of asthma severity. Based on these data, in a section entitled "Severity", they state that "due to the different approaches employed in each study, no formal meta-analysis is possible" (a view one cannot dissent from), but a "qualitative review … suggests greater disease severity in children exposed to smoking in the household, a pattern which is more consistent among asthmatics attending hospital as outpatients or inpatients than among cases identified through population surveys". They also comment on the lack of adjustment for potential confounding in these studies and consider that "some of the associations of parental smoking with health service utilisation, in particular, may reflect a common association with lower socio-economic status". They also note that the striking association of intubation with ETS exposure seen in the Davis study (LeSon & Gershwin, 1995) "was stronger than that with a range of psychosocial variables, suggesting that it would not be entirely explained by socio-economic confounding".

Also relevant in this review is a section entitled "Effect of reducing tobacco exposure" which notes that the results of the early Minnesota study (O'Connell & Logan, 1974) are difficult to interpret. In this section they also highlight the change in the relationship between maternal smoking and asthma severity before and after July 1986 seen in the Vancouver study (Murray & Morrison, 1993). They are not convinced by the authors' claim that this is due to an alteration in parental smoking habits following advice from clinicians to avoid smoking in the home or in the presence of the child, noting that this claim is based only on anecdotal reports and not on objective evidence.

The second relevant paper from St George's Hospital Medical School Group, paper 7 in the series, is entitled "Parental smoking, bronchial reactivity and peak flow variability in children" (Cook & Strachan, 1998). This paper

concluded that "A clear effect of exposure to environmental tobacco smoke on BHR in the general population has not been established. While the meta-analysis suggests a small but real increase in BHR in school aged children, it seems likely that this estimate is biased upwards due to publication bias. In contrast, limited evidence suggests greater variation in peak expiratory flow in children of smoking parents."

These conclusions are mainly based on data for healthy children. Though some studies concerning asthmatics are referred to, these are not clearly separated out in the tables summarizing the results. In a section entitled "Susceptibility of children with asthma or a parental history of atopy" the authors note that of five studies that had commented on the effect of exposure to ETS on bronchial hyperresponsiveness in asthmatic or wheezing subjects compared with normal subjects, two reported a stronger effect in asthmatics (O'Connor et al., 1987; Martinez et al., 1988), two reported a stronger effect in non-asthmatics (Strachan et al., 1990; Frischer et al., 1992) and one reported a similar association (Agudo et al., 1994). Only three of these five studies (Martinez et al., 1988; Frischer et al., 1992; O'Connor et al., 1987) were considered in section 2 of this review, the other two (Strachan et al., 1990; Agudo et al., 1994) being rejected for reasons discussed in Appendix 1. A lack of significant association in asthmatic children with ETS exposure was also noted in this review for peak flow variability in another study considered in section 2 (Frischer et al., 1993).

Overall, the St George's Hospital Medical School reviews seem far more thorough than the review of the California EPA. However, it should be noted that the reviews give little attention to the problem of confounding. The fact that their mechanism hinges around ETS acting as a co-factor operating with intercurrent infection makes it all the more surprising that the authors have apparently not investigated at all the possibility of bias if exposure to infections is greater in households with smokers, given the increased proneness of smokers to infections of various types. There is also no emphasis

on the absence of data to distinguish potential effects of smoking in pregnancy and of ETS exposure.

5.3 Reviews of effects in adults

As described in section 4.1, the epidemiological evidence published up to 1997 relating ETS exposure to severity of asthma in adults is extremely limited. This was also the view of two reviews published in the next two years.

The first of these was a review entitled "Effects of environmental tobacco smoke exposure on pulmonary function and respiratory health in adults: update 1997" (Witorsch, 1998). This contained quite a detailed analysis of the experimental evidence on ETS exposure in asthmatics which concluded that "…acute exposure to ETS does not consistently evoke adverse pulmonary effects in most asthmatics. Several studies from a single research group suggest that a small sub-set of asthmatics may respond to acute ETS exposure with a $\geq$20% decrement in FEV_1 as well as an increased responsiveness to bronchoconstrictors. The mechanism for this responsiveness does not appear to be allergic in nature and is subject to speculation". As regards epidemiology, no actual attempt is made to separate out effects on asthmatics and the normal population and of the 18 studies cited "of asthma incidence, exacerbation or symptoms", only one of the three studies in adults we identified (Ostro et al., 1994) is referred to. The rest are mainly studies of normal individuals, though one or two (e.g. Hong et al., 1994) are ones rejected by us, for reasons described in Appendix A. Witorsch regards the evidence from the 18 studies as inconsistent.

The other is a review entitled "Environmental tobacco smoke exposure and asthma in adults" (Weiss et al., 1999). Again this review gives greater attention to the more extensive experimental evidence. As regards the epidemiological evidence, it cites the earlier two of the three studies we identified (Jindal et al., 1994; Ostro et al., 1994). It regards the data from the study in India as providing "positive findings" which "need cautious

interpretation" because of potential bias in selection, recall and exposure assessment, failing to note the statistical errors described in section 2 of this report. For the Denver study (Ostro et al., 1994) the authors surprisingly cite only the results of the analyses not taking into account the repeated measures design, so giving a false impression of significant associations that may not be present. The authors note the self-reported nature of the ETS exposure data collected and note the failure to assess workplace exposures. Overall, taking the experimental and epidemiological evidence into account (which also includes studies of asthma induction) they conclude that "It appears that there are only scant data assessing the role for ETS exposure in adult asthma" and that "ETS exposure has not yet been confirmed as a hazard for adults with asthma".

6. Summary and conclusions

This document reviews epidemiological evidence published up to 1997 relating exacerbation of asthma to ETS exposure.

Only three relevant studies of nonsmoking adult asthmatics were identified. One study in India reported a significant association of ETS exposure with various indices of asthma severity but did not control for differences in age and other potential confounding variables that differed between ETS-exposed and ETS-unexposed individuals, and included a number of obvious errors in its statistical analyses. A later study in India reported a significantly higher ETS exposure in patients with acute than non-acute asthma, but only in an abstract with little detail. A study in the USA also reported associations of ETS exposure with various indices of asthma severity, but for only one (restricted activity) was the association significant when the repeated measures design was taken into account in analysis.

While the overall evidence for adults suggests a possible relationship, it is too limited and poorly reported to allow a confidence conclusion.

There is far more evidence on exacerbation and ETS exposure in studies in children.

Fifteen studies related ETS exposure to various indices of asthma severity. These included emergency room visits, hospitalisations requiring intubation, hospital admissions for asthma in general, acute episodes or exacerbations, symptom scores, severity grades, or use of therapy. One of these studies compared ETS exposure within-child at times when the child was acutely ill or was well, finding no significant difference in urine cotinine (or cotinine/creatinine ratio) but some evidence of a higher reported ETS exposure when ill.

The other 14 studies based their conclusions on between-child comparisons. Of these, eight reported significant associations of increased ETS exposure with increased asthma severity, the strongest being the very

much higher frequency of intubation with ETS exposure in the study in Davis. In another one of these studies (conducted in Vancouver) a significant positive association was noted in children admitted in the first period of the study, and a significant negative association in children admitted in the second period.

Overall, the data relating to asthma severity in children show considerable evidence of an association. However interpretation of this association is not straightforward for a number of reasons. These include the lack of clear evidence that increases in ETS exposure within child are associated with exacerbations of asthma, limited reporting of relevant study details by many authors (including information on active smoking by the child) and failure to separate out results by sex and by age. Most importantly, failure to control for potential confounding variables is a feature of the studies. No studies adjusted for maternal smoking in pregnancy, only one for any social class related variables, only one for infections in the child (and none for infections in the parent) and very few even take the sex or age of the child into account. Furthermore, some of the various endpoints used may not be very direct or reliable measures of asthma severity.

Eight studies relate ETS exposure to lung function in asthmatic children. Although there are occasional reports of statistically significant decreases in FEV_1, FVC and $FEF_{25-75\%}$ or increases in PEFR amplitude associated with ETS exposure, most analyses show no significant effect, with associations weak and sometimes in the opposite direction. Overall the data do not conclusively demonstrate an association of lung function with ETS exposure.

Data relating ETS exposure to bronchial responsiveness in asthmatic children are limited and no clear conclusions can be reached.

This document also considers other reviews of this evidence. The California EPA report, which concludes that ETS exposure exacerbates asthma in children, is limited by failing to detect obvious flaws in some of the evidence, not discussing any sources of potential bias at all and not even

describing how its conclusion had been reached from the data available. The review by the group from the St George's Hospital Medical School are far more thorough but also contain deficiencies. Notably a mechanism is postulated by which ETS is considered a co-factor, operating with intercurrent infection, to exacerbate asthma, but no consideration is given to the possibility of bias resulting if exposure to infections is greater in households with smokers. There is also no emphasis on the absence of data to distinguish effects of ETS exposure and of smoking in pregnancy. Two reviews of the evidence in asthmatic adults agree that the data available are very limited and inconclusive.

Overall the epidemiological data published in 1997 must be considered as quite highly suggestive that ETS exposure exacerbates asthma in children, but not conclusive.

APPENDIX A

Some papers not considered in this review with a brief description and reasons for rejecting them

Study/population	Description	Reasons for rejection
Speer, 1968 Children and adults	Self-reported incidence of reactions to tobacco smoke compared in 191 allergic nonsmokers and 250 non-allergic nonsmokers.	Allergic group included patients with diseases other than asthma. No data on ETS exposure.
Lebowitz, 1984a; Lebowitz, 1984b	In a study of 117 families, there was reported to be no association of ETS exposure with PEFR, VMAX or symptoms in children or adults, asthmatics or others.	No detailed results reported, results for adults not apparently restricted to asthmatic nonsmokers. Results for children not given for asthmatics.
Toyoshima et al., 1987 Children	Smoking in the family compared in 48 infants who were wheezy but had no dyspnoea, subdivided according to whether they were later diagnosed as asthmatic, wheezy or non-wheezy.	Group not asthmatic at the start. Does not relate to exacerbation.
Connolly et al., 1989 Adults	Peak expiratory flow rate related to smoking, ETS exposure and other factors in 630 asthmatics.	Analyses not restricted to nonsmokers.

Study/population	Description	Reasons for rejection
Bailey et al., 1990 Adults	Asthma severity, symptoms and pulmonary function related to smoking, ETS exposure and other factors in 263 asthma patients aged 17+.	Analyses not restricted to nonsmokers.
Strachan et al., 1990 Children	Salivary cotinine related to symptoms, spirometry and exercise-induced bronchospasm in 770 7 year old children.	Results relating cotinine to bronchospasm given separately for children with a history of wheeze but not for asthmatic children.
Bener et al., 1991 Children	Numbers of frequent and infrequent asthma attacks given in relation to parental smoking habits in 3043 children aged 7-12 years.	Data presented totally implausible as imply that at least 85% of the children had asthma and that among these the odds of having a frequent attack was 34 times higher if one or more parents smoked. There are other clear errors in the paper.

Study/population	Description	Reasons for rejection
Dales et al., 1992 Adults	111 asthmatics (mean age 33.7) presenting to an emergency department with an acute attack asked whether cigarette smoke aggravated their asthma and how many were exposed at home.	Results relating aggravation of asthma to ETS exposure not presented. Smoking habits not mentioned.
Wood et al., 1993 Children	78 Hispanic children aged 6-16 with at least two acute-care visits or one hospitalisation for asthma were asked about at home exposure.	Results relating severity of asthma to ETS exposure not presented.
Agudo et al., 1994 Children	ETS exposure compared in 121 children with exercise induced airways narrowing and 217 controls without it. Of these children (aged 9-14), 35 cases and 5 controls had diagnosed asthma.	Relationship of ETS to airways narrowing given for all 338 children and for the 298 excluding the asthmatics, but not for the asthmatics only. The results for the asthmatics cannot be inferred.
Hong et al., 1994 Adults	Index of clinical severity of asthma relates to active and passive smoking and a range of other factors in 787 asthmatics attending outpatient clinics.	Analyses not restricted to nonsmokers.

Study/population	Description	Reasons for rejection
Huss et al., 1994 Children	Data collected from 392 asthmatic children on asthma severity, environmental exposures (including parental smoking) and on factors thought to trigger wheezing (including cigarette smoke).	Parents of severe asthmatics were significantly more likely to believe that cigarette smoke was an asthma trigger for their children than parents of mildly asthmatic children. However, no analyses were presented linking asthma severity to parental smoking.
Abramson et al., 1995 Adults	Comparison of 159 diagnosed asthmatics and 430 with symptoms of asthma but undiagnosed. Subjects asked what factors (including cigarette smoke) triggered wheezing.	No data collected on ETS exposure. Cigarette smoking not mentioned.
Henderson et al., 1995 Children	Case-control study of children without recurrent wheezing or with 2-4 or 5+ episodes, of whom 0%, 23% and 72% respectively had a current asthma diagnosis, with data collected on cotinine and on smoking by household members.	No results presented restricted to asthmatic children.

Study/population	Description	Reasons for rejection
Chadwick, 1996 Children	Data collected from 32 asthmatic children included household smoking and whether smoke aggravated their asthma.	Severity of asthma not actually linked to ETS exposure.

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