

Chapter 8.1 Environmental tobacco smoke

General description

Environmental tobacco smoke (ETS) is generated by the combustion of tobacco products. It is composed of sidestream smoke (SS), emitted from the smouldering tobacco between puffs, and exhaled mainstream smoke (MS) from the smoker. When a cigarette is smoked, roughly half of the smoke generated is SS and the other half MS.

ETS, SS and MS are complex mixtures of over 4000 compounds. These include more than 40 known or suspected human carcinogens, such as 4-aminobiphenyl, 2-naphthylamine, benzene, nickel, and a variety of polycyclic aromatic hydrocarbons (PAHs) and *N*-nitrosamines. A number of irritants, such as ammonia, nitrogen oxides, sulfur dioxide and various aldehydes, and cardiovascular toxicants, such as carbon monoxide, nicotine and some PAHs, are also present.

While ETS, SS and MS are qualitatively similar with respect to chemical composition, the absolute and relative quantities of the constituents can differ substantially (1,2). A major quantitative difference is that ETS is a diluted mixture of SS and exhaled MS. In addition, because SS is produced at lower temperatures and under more reducing conditions than MS, many carcinogens and other toxicants are generated in greater amounts in SS than in MS. For example, *N*-nitrosodimethylamine, a potent animal carcinogen, is emitted in quantities 20–100 times greater in SS than in MS (3), and SS:MS ratios of about 7–30 for the known human carcinogens 4-aminobiphenyl and 2-naphthylamine have been measured (4). These quantitative differences are consistent with animal and genotoxicity studies, suggesting that SS is more potent than MS per unit of tobacco smoked (5,6).

There are also differences between MS and ETS in the physical state of various constituents. For example, nicotine is present primarily in the particulate phase in MS and in the vapour phase in ETS. Also, as ETS “ages” over time, constituents of the particle phase shift to the vapour phase (2,7). Furthermore, particle sizes are smaller in ETS (0.01–1.0 µm) than in MS (0.1–1.0 µm).

The differences between ETS and MS in relative quantities of toxic agents, physical states of constituents and particle sizes, coupled with differences in breathing patterns between passive and active smokers, imply that the regional distribution and deposition of smoke constituents in the respiratory tracts of passive and active smokers will also differ. Therefore, while the toxic potential of ETS can be qualitatively inferred from the effects of active smoking based on chemical similarities, the quantitative potency of ETS to elicit health effects cannot be directly extrapolated from the potency of MS (1,8).

Concerns about the health effects of ETS generally focus on the unsolicited exposures of nonsmokers. Although active smokers are likely to be the most heavily exposed to ETS, and a portion of their smoking-attributable excess health risks may actually result from heavy ETS

exposures, the added risk to smokers from passive smoking is expected to be relatively insignificant compared to their voluntary risk from active smoking.

Sources and occurrence in indoor air

The sole source of ETS is the combustion of tobacco products. ETS is nearly ubiquitous in most societies. Exposure occurs in indoor air wherever there is smoking of tobacco products – in homes, workplaces, vehicles and public places. The degree of exposure depends on the number of smokers and the amount of tobacco smoked, as well as size and ventilation characteristics of the indoor space and the duration of exposure.

Since ETS is a complex mixture of thousands of compounds, in particulate and vapour phases, it cannot be directly measured as a whole. Instead, various environmental and biological marker compounds are used to determine and quantify exposure. Questionnaires and population surveys are also used to elicit surrogate exposure data, for example smoking by household members or co-workers. Time–activity surveys can be used to determine the amount of time spent in different exposure environments.

While various ETS-related compounds can be measured above background levels in indoor environments (e.g. PAHs and carbon monoxide), most are not practical markers of ETS either because they have many sources in addition to tobacco smoke and/or because they are difficult or expensive to measure. The most widely used marker compounds for assessing the presence and concentration of ETS in indoor air are vapour-phase nicotine and respirable suspended particle (RSP) mass.

Nicotine has the advantages of being specific to tobacco smoke and of being present in large quantities in ETS. A potential drawback is that it has a high affinity for interior surfaces and, under certain circumstances, measurements could lead to an underestimate of the levels of other ETS constituents. Similarly, nicotine can be later re-emitted from surfaces, after other ETS constituents have been removed. None the less, many studies have demonstrated that nicotine is a reliable marker of ETS levels (Fig. 1) and that it correlates well with other exposure indices, such as RSPs and reported number of smokers (9).

RSPs are also present in large quantities in ETS, and levels in indoor air are a useful marker for the particulate phase of ETS. However, RSPs in indoor air are not unique to ETS, and background levels from other sources must be accounted for when using RSPs as a marker for ETS.

In the United States, nicotine concentrations in homes where smoking occurs typically range from less than $1 \mu\text{g}/\text{m}^3$ to over $10 \mu\text{g}/\text{m}^3$ (1). Concentrations in offices where smoking occurs typically range from near zero to over $30 \mu\text{g}/\text{m}^3$. Levels in restaurants, and especially bars, tend to be even higher, and concentrations in confined spaces like automobiles can be higher still. Measurements of ETS-associated RSPs in homes where smoking occurs range from a few $\mu\text{g}/\text{m}^3$ to over $500 \mu\text{g}/\text{m}^3$, levels in offices are generally less than $100 \mu\text{g}/\text{m}^3$, and those in restaurants can exceed $1 \text{mg}/\text{m}^3$. ETS levels are directly related to smoker density; in countries with a higher smoking prevalence, average ETS levels could be higher than those given here.

Biological markers of ETS exposure provide evidence of uptake of appreciable quantities of ETS constituents by nonsmokers. The most widely used biomarker of ETS exposure is cotinine, the major metabolite of nicotine. Cotinine is specific to tobacco, can be measured in saliva, blood, or urine, and has an elimination half-life of about a day, or longer in children (1).

Many population studies have demonstrated the association of cotinine levels in saliva, serum and urine with reported exposure to ETS, including a number of European studies (10–12). A10-country study conducted by the International Agency for Research on Cancer (IARC) collected data for nonsmoking women from 13 cities, including 5 in Europe (13,14). For all 13 centres combined, regression analyses generated mean urinary cotinine/creatinine levels of 6.2 ng/mg for ETS exposure from husband's smoking, 2.4 from workplace exposure, 9.0 ng/mg from husband and workplace, and 3.1 ng/mg from public places and other sources. A study of salivary cotinine levels in over 4000 children aged 5–7 years in England and Wales reported geometric mean levels of 0.29 ng/ml in children with no reported exposure, 4.05 ng/ml in households where both parents smoked, and 9.03 ng/ml if both parents smoked over 20 cigarettes per day (15).

Surveys and other studies can provide data on the prevalence of ETS exposure in various environments. In the United States, where an estimated 28% of men and 23% of women were current smokers in 1990 (16), two national surveys in 1988 revealed that roughly 40% of employed adults worked in locations where smoking was allowed (17), and about 42% of children aged 5 years and under lived in households with current smokers (18). Countries with higher smoking prevalences and fewer smoking restrictions are likely to have a greater proportion of the population exposed and higher levels of ETS exposure. In the early 1990s, reported smoking prevalences in Europe ranged from about 26% (Sweden) to 77% (Latvia) in men and from 1% (Uzbekistan) to 47% (Denmark) in women (19). A German analysis based on a 1987 national survey in the Federal Republic of Germany estimated that about 59% of children under 2 years of age, 50% of children aged 2–5 years and 68% of children aged 6–13 years lived in households with at least one smoker (20). Other European data suggest that about 60% of households in the Netherlands and Romania, and 65% in Poland have at least one smoker (19). Cook et al. (15) reported that 53% of the children they studied in England and Wales were exposed to ETS, while Forastiere et al. (21) reported that 70–73% of children aged 7–11 were exposed to parental smoking in their Italian study. In a large Swiss study, Leuenberger et al. (22) observed that 70% of nonsmoking males and 52% of nonsmoking females were exposed to ETS at work.

Routes of exposure

The only route of exposure of concern for ETS is inhalation.

Toxicokinetics

The many compounds in ETS will have different toxicokinetic and metabolic pathways. Vapour and particulate phases of constituents will also have different patterns of absorption and retention. Highly soluble gases, such as formaldehyde, will be almost completely absorbed in the upper respiratory tract, especially during nasal breathing, while those with low solubility, such as carbon monoxide, will be slowly absorbed from the alveoli (23). Diffusion in the alveolar region of the lung is the major deposition mechanism for small particles in the size range of those in ETS; the deposition efficiency is estimated to be about 10% for ETS particles (24).

Some compounds may elicit health effects without metabolic activation, while others may require activation. Carbon monoxide, for example, can directly bind to haemoglobin and decrease the oxygen-carrying capacity of the blood. Nicotine can also directly affect the cardiovascular system. Carcinogenic tobacco-specific *N*-nitrosamines, on the other hand, require metabolic activation (25).

The uptake and metabolism by ETS-exposed nonsmokers of three major classes of carcinogens found in tobacco smoke, aromatic amines, nitrosamines and PAHs, has been elucidated in recent publications. Hammond et al. (26) reported that levels of haemoglobin adducts of the aromatic amine 4-aminobiphenyl in nonsmokers increased significantly with increasing ETS exposure and that nonsmokers in the highest exposure quartile had adduct levels that were about 18% of those in smokers. Such high relative levels are consistent with observations that 4-aminobiphenyl concentrations are up to 30 times greater in SS than in MS (4).

Hecht et al. (27) examined levels of metabolites of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in the urine of nonsmokers exposed to sidestream smoke. They demonstrated that mean levels of specific metabolites in the urine of nonsmokers were significantly higher after ETS exposure than at baseline.

Crawford et al. (28) observed that PAH-albumin adducts were significantly higher in young children of smoking mothers than in those of nonsmoking mothers. Children whose mothers smoked had roughly 40% of the excess adduct levels (i.e. above the levels in subjects with no smokers in the household) of their smoking mothers. PAHs are not specific to tobacco smoke; however, Crawford et al. also found, using limited measures of dietary, residential and occupational sources of PAHs, that ETS was the most important contributor to PAH-albumin adduct levels in nonsmokers.

Excretion of tobacco smoke components is predominantly through ventilation and urinary and fecal excretion. Some studies have shown that the mutagenic potential of urine is increased by ETS exposure (29).

Health effects

Effects on experimental animals and *in vitro* test systems

Carcinogenic effects

The carcinogenicity of tobacco smoke has been demonstrated in a number of lifetime animal bioassays: inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin-painting in the mouse (24,30).

The Syrian golden hamster has been the most useful animal inhalation model for studying smoking-induced carcinogenesis. The hamster is refractory to the induction of lung tumours by known carcinogens; however, inhalation of MS induces carcinomas of the larynx in a dose-related manner (31). There are no lifetime animal inhalation studies of ETS or SS.

Mutagenic effects

Tobacco smoke is genotoxic in virtually every *in vitro* system tested (30,32), providing strong supportive evidence for its carcinogenic potential. IARC (30) concluded that there was “sufficient” evidence in short-term tests for genetic activity (mutation and chromosomal effects) for both cigarette smoke and cigarette smoke condensate. Whole SS (33) and extracts of ETS collected from indoor air (34) have also been shown to be mutagenic in *Salmonella typhimurium*. Claxton et al. (6) found that SS accounted for approximately 60% of the total *S. typhimurium* mutagenicity per cigarette, 40% from particulates and 20% from semivolatiles.

Cardiovascular effects

Subchronic and acute exposures to tobacco smoke and various tobacco smoke constituents have been shown to elicit a wide variety of cardiovascular effects in several animal species. These effects have been comprehensively reviewed by Glantz & Parmley (35,36), and include promotion of atherosclerosis, activation of platelets and leukocytes, exacerbation of ischaemia/reperfusion injury, and reduction of respiration by myocardial mitochondria.

The development of atherosclerosis in response to exposure to tobacco smoke, as well as to some individual constituents of tobacco smoke (e.g. PAHs), has been demonstrated in a number of animal models (35). Penn et al. (37) exposed young cockerels intermittently for 16 weeks to SS levels equivalent to ETS exposures under heavy smoking conditions. The number (not statistically significant) and size (statistically significant) of plaque-containing abdominal aorta segments in the exposed animals was increased over control levels, suggesting that short-term ETS exposures are sufficient to enhance plaque development. Furthermore, the increase in plaque size was not as great as that observed under higher exposure conditions (38), suggesting the existence of an exposure–response relationship.

Zhu et al. (39) also demonstrated that ETS increases atherosclerosis in the lipid- and cholesterol-fed rabbit model. The percentage of arterial surface area that was covered by atherosclerotic plaques was increased by ETS in an exposure-related manner in the aorta and pulmonary artery; the increase was independent of serum triglyceride, cholesterol and high-density lipoprotein (HDL) cholesterol levels.

Animal studies also indicate that exposure to tobacco smoke increases platelet activation, which can contribute to the development of atherosclerosis and thrombosis (40). Sun et al. (41) and Zhu et al. (39) reported significantly shorter bleeding times in rabbits exposed to tobacco smoke compared with control rabbits. Both groups also reported that bleeding times were reduced by a similar magnitude for all exposure groups, suggesting a saturation of the effect of tobacco smoke on platelets.

Tobacco smoke has also been shown to increase leukocyte activation, which can also contribute to the development of atherosclerosis. Lehr et al. (42) exposed hamsters to the smoke of one cigarette and observed leukocyte adhesion to the endothelium and promotion of the formation of aggregates of leukocytes and platelets in exposed animals.

Other animal studies suggest that ETS causes exacerbation of ischaemia/reperfusion injury. Increased myocardial infarct size has been observed in rats in an ischaemia/reperfusion model (43)

and dogs (44). Zhu et al. (43) also demonstrated that infarct size increased significantly with increasing duration of SS exposure, and that more of the SS-exposed rats died from ventricular fibrillation during the procedure than control animals, although the difference was not statistically significant.

There is also evidence that tobacco smoke causes a reduction in the myocardium's ability to process oxygen to adenosine triphosphate for cellular energy (45,46).

Other toxicological effects

Other toxicological effects observed in experimental animals include reproductive and immune system effects. For example, Rajini et al. (47) exposed pregnant rats intermittently to SS and observed small but significant reductions in mean pup weight in the resulting litters. A study of immune system effects (48) revealed both a reduction in the number of alveolar macrophages with phagocytic activity and a decrease in the phagocytic efficiency of these activated macrophages in mice after acute exposure to the smoke of just one cigarette.

Effects on humans

Epidemiological studies of ETS and chronic diseases such as lung cancer and heart disease are faced with the difficulties of discriminating between exposed and unexposed subjects and estimating past exposures. Never-smoking women are the most common subjects of these studies, because the prevalence of smoking in women has historically been less than that of men. Furthermore, most researchers consider the smoking status of the husband to be the best single surrogate of past ETS exposure for adult female never-smokers. In general, home exposure has been found to be the greatest single source of exposure contributing to total ETS exposure (13). Other exposure surrogates used, such as exposure at work or during childhood, tend to be less reliable because workplace exposure is less stable and the exposure sources are more difficult to recall over time, especially when proxy interviews are the source of exposure information (49,50).

Two forms of exposure misclassification exert a downward bias on relative risk estimates in ETS epidemiology studies and make ETS-related health effects difficult to detect. In the first, an individual classified as "exposed" based on spousal smoking status may actually receive little exposure; in the second, an "unexposed" person may receive considerable exposure from sources other than the spouse (e.g. workplace or social exposures). In most Western societies, ETS is so ubiquitous that recruitment of a truly "unexposed" group is impossible. Spousal or home exposure is generally a better surrogate of total ETS exposure in more traditional societies such as Greece and Japan, with historically high male and low female smoking prevalences. Such countries may offer the best opportunities for studying the effects of long-term exposure to ETS.

A potential source of upward bias, known as smoker (status) misclassification bias, arises because some current or former smokers will be misclassified as people who have never smoked (never-smokers). Smokers thus misclassified would be more likely to develop lung cancer and to be married to smokers (i.e. classified as "exposed" in ETS studies) than true never-smokers. Smoker misclassification rates reported from population survey studies suggest that this bias, if it exists in the lung cancer studies, could explain an increase in risk of 10–15% in some studies. This bias, however, is not sufficient to explain the observed increases in the high-quality United States study of Fontham et al. (51), the larger risks observed in studies in countries with historically low female

smoking prevalence, the average increase of 70–100% observed in the highest exposure groups in the individual studies after adjustment for smoker misclassification, or the consistent exposure–response trends (1,52).

For some ETS-associated health effects, lifestyle differences (e.g. diet) and other factors that correlate with socioeconomic status must be considered potential confounders. However, positive exposure–response trends for health effects from ETS exposure provide evidence against confounding. Also, the consistently observed increases in risk for lung cancer, for example, in studies from a number of different countries, with very different diets and other lifestyle factors, provide further evidence against confounding as an explanation for observed associations.

Despite the known difficulties of studying the chronic health effects related to ETS, the epidemiological database is quite extensive for lung cancer and, to a lesser extent, heart disease. Information on other cancers, however, is very limited. There is also a substantial database on a variety of non-cancer respiratory effects and reduced birth weight, and there are a few recent studies on sudden infant death syndrome. Each of these health effects is discussed below.

Lung cancer

The evidence on ETS and lung cancer has been assessed by many health organizations, all of which concluded that exposure to ETS increases the risk of lung cancer (1,23,24,30,53). The US Environmental protection Agency (EPA) declared ETS to be a known human lung carcinogen based on the total weight of evidence: (a) similarities in chemical composition between ETS and MS, including over 40 known or suspected human carcinogens; (b) the known lung carcinogenicity of MS, with clear exposure–response relationships down to low levels and no evidence of a threshold; (c) supporting evidence from animal bioassays and genotoxicity tests; (d) measured exposure to, and bodily uptake of, ETS constituents; and (e) the consistent exposure-related increases in risk seen in so many epidemiological studies from different countries using different designs.

The 30 epidemiological studies analysed by EPA examined the lung cancer risks of never-smoking women with smoking and nonsmoking husbands. Other studies examining lung cancer risks from ETS exposure at work or during childhood, and/or in never-smoking men were also available, but these databases are smaller and the studies generally less reliable (see above). The statistically significant pooled average relative risk (RR) estimates due to ETS from smoking by spouses in such varied countries as Greece (RR = 2.0, two studies), Japan (RR = 1.4, five studies) and Hong Kong (RR = 1.5, four studies), where smoking by spouses is considered to provide a larger proportion of total adult exposure, are higher than the 20% increases observed in western Europe and the United States. Generally, the increases were not large – about 30% overall, and about 70–100% for women whose spouses smoked the most – but they were consistent across studies of different design from several different countries and, despite most studies being of small size, several increases were statistically significant. Furthermore, the consistency seen in risks in the highest exposure groups and in the positive exposure–response trends is highly persuasive.

The largest and best designed case–control study (51), with 665 cases and a large percentage of direct case interviews, found statistically significant overall increases and exposure–response trends for never-smoking United States women exposed to spousal (30% excess risk), workplace (40% excess risk) and social (50% excess risk) ETS. Current nonsmoking status was confirmed in a

subsample of the study population using cotinine measures. An index of total adulthood ETS exposure produced exposure–response trends with the highest level of statistical significance.

Another study, the Dutch nested case–control study of de Waard et al. (54) is noteworthy because, although it consisted of only 212 nonsmoking females (23 cases and 191 controls), past nonsmoking status and ETS exposure were determined by biomarker measurement (cotinine level in a 12-hour urine sample taken up to 15 years prior to case ascertainment) rather than on the basis of questionnaire responses as in the other ETS-lung cancer epidemiology studies. The results, although not statistically significant, yield an odds ratio (OR) of about 2.6 for lung cancer from ETS exposure.

A recent meta-analysis (55) looked at 37 published epidemiological studies of nonsmokers who did and did not live with smokers. The excess risk of lung cancer was 24% (95% confidence interval (CI) 13–38%, $P < 0.001$) in nonsmokers who lived with a smoker. The excess risk, adjusted for the effects of bias and dietary confounding, was 26% (7–47%). The dose–response relationship for the risk of lung cancer with the number of cigarettes smoked by the spouse and with the duration of exposure were significant.

Other cancers

A recent review by Tredaniel et al. (56) evaluated the limited epidemiological evidence from studies of ETS and sinonasal, bladder, breast and uterine cervix cancers in adults, and a few other sites for which the evidence is very sparse. They concluded that there was suggestive evidence of an association with sinonasal cancer, no evidence of an association with bladder cancer, and equivocal evidence of associations with breast and cervical cancer.

The conclusion with respect to sinonasal cancer was based on two positive studies of Japanese female never-smokers with strong exposure–response relationships but only about 60 cases in total. More recently, a third studying the United States has also reported a statistically significant increased risk for never-smoking men with wives who smoked (OR = 3.0, 95% CI = 1.0, 8.9), based on 28 cases (57). Considering these consistent exposure–related responses and the strong supportive evidence, including the known causal association of active smoking and sinonasal cancer, the known causal association of ETS and lung cancer, and the fact that the nasal sinuses are generally the site of first contact of ETS; there is strong suggestive evidence that ETS is causally associated with sinonasal cancer.

It has been suggested that bladder cancer may be associated with ETS exposure. However, the epidemiological evidence from the two studies reviewed by Tredaniel et al. (56) and a third study by Hirayama (58) is equivocal. An association between ETS and cervical cancer has also been suggested, but the few existing studies provide contradictory findings. The two studies of never-smokers reviewed by Tredaniel et al. are generally positive, a third study found no consistent increases (59), while a Japanese cohort study reported a RR estimate of about 1.3 for nonsmoking wives of heavily smoking husbands (58).

Wells (60) reviewed data from two epidemiological studies suggesting that there may be an association between ETS exposure and breast cancer in nonsmokers. Two other studies have also found evidence of an association (61,62), with RR estimates ranging from about 1.3 to 2.4, but no consistent association between active smoking and breast cancer has been established.

Non-cancer respiratory health effects

Children. Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and childhood. They may also weaken the lung and predispose it to asthma and other chronic respiratory diseases and lower levels of respiratory function later in life (1). Considering the known adverse acute and chronic effects of active smoking on the respiratory system, it is plausible that exposure to ETS could similarly adversely affect the immature system of infants, and that continued exposure could be a major risk factor in disease development throughout life.

Nearly all studies of ETS in children focus on the level of parental, and especially maternal, smoking. Parental smoking is generally a very good surrogate for total ETS exposure in young children, although exposure misclassification could be an important source of downward bias in studies of older children (63).

In many Western countries, overall cigarette smoking prevalence has declined. However, the proportion of smokers of lower educational status, and especially of young, poor women has increased. Lower socioeconomic status is already associated with a higher prevalence of childhood respiratory diseases; poorer children are often at still higher risk from parental smoking (after adjusting for this). The effect can start prenatally if the mother smokes during pregnancy (1). As most studies do not distinguish pre- from post-natal smoking, however, maternal smoking during pregnancy should be considered a potential effect modifier for ETS effects in children.

At least 150 epidemiological studies on ETS and non-cancer respiratory health effects in children have been published in the last 25 years. Several reviews (1,23,24,64) have already assessed the database, and there is strong consensus that ETS affects the developing respiratory system and causes an increased risk of the following health effects:

- lower respiratory tract infections (e.g. bronchitis, bronchiolitis and pneumonia) in infants and young children;
- chronic middle-ear effusion in young children;
- increased frequency and severity of asthma attacks in asthmatic children;
- irritation of the upper respiratory tract; and
- reduced lung function.

Several recent studies on respiratory effects in children are especially noteworthy because they ascertain biomarker evidence of ETS exposure, in addition to questionnaire data such as asthma (65), middle ear effusions (66), bronchitis (67) and reduced lung function (68). The biomarker data correlate well with the questionnaire data and the various respiratory effects, validating the use of questionnaire data and also supporting the direct association between recent ETS exposure and non-cancer respiratory health effects.

Adults. A number of reviews (1,22,64) have concluded that adult nonsmokers exposed to ETS may experience small reductions in lung function and an increased frequency of respiratory symptoms. A review by Tredaniel et al. (69) found no consistent evidence for an association between ETS and

chronic respiratory symptoms or chronic obstructive pulmonary disease, including asthma, although decreased lung function from ETS exposure was noted

Other studies have reported symptoms of acute irritation of the eyes and respiratory tract associated with ETS exposure (23,24,70). More recently, Bascom et al. (71) observed symptoms of eye and nose irritation, odour perception and headache in subjects exposed to SS under controlled conditions. They also reported increased nasal congestion in the highest exposure group. Most of the field and laboratory studies of annoyance and acute irritation effects of ETS have focused on adults; however, these effects are likely to occur in children as well, since they are even more sensitive than adults to other non-cancer respiratory effects of ETS (see above).

Decreased birth weight

It is well established that maternal smoking during pregnancy is causally associated with low birth weight, in an exposure-related manner (40). Maternal smoking has been reported to cause an average decrease in birth weight of 150–200 g (72). This is supported by evidence from animal studies (47).

The most widely accepted hypothesis for this effect on fetal development is that smoking induces fetal hypoxia, probably mediated, at least in part, by carbon monoxide and/or nicotine (73). Carbon monoxide is known to decrease the oxygen-carrying capacity of haemoglobin. Fetal haemoglobin has a higher affinity for carbon monoxide than adult haemoglobin, and the impact on the fetus is more severe than on the mother as fetal tissues receive even less oxygen. Nicotine is a vasoconstrictor and is believed to decrease placental perfusion, which could also lead to low fetal tissue oxygenation.

A number of studies have shown that pregnant nonsmokers exposed to ETS also have an increased risk of delivering babies with lower birth weights. While most of the decreases in birth weight are of small magnitude and do not achieve statistical significance, the studies demonstrate a consistent pattern, even after adjusting for major potential confounders and considering potential smoker misclassification bias. The decrease in mean birth weight associated with ETS exposure generally ranges from 10 g to 110 g, with an average decrease of about 35 g. Increased cotinine levels have been measured in the amniotic fluid of pregnant nonsmokers exposed to ETS, as well as in the urine of their newborn infants on the first day of life (74), confirming that the fetus is exposed to ETS constituents.

Some noteworthy studies include the large prospective studies of Haddow et al. (75), Eskenazi et al. (76) and Rebagliato et al. (77). These studies of pregnant nonsmokers used biomarker measurements to categorize ETS exposure and validate smoking status, and all three studies adjusted for a variety of potential confounders. Haddow et al. (N = 1231) observed a significant 108-g deficit in mean birth weight associated with a serum cotinine level of 1.0–9.9 ng/ml compared to <0.5 ng/ml; Eskenazi et al. (N = 2243) reported a mean birth weight reduction of 45 g for a serum cotinine level of 2–10 ng/ml compared to <2 ng/ml; and Rebagliato et al. (N = 710) observed a significant decrease in mean birth weight of 87 g for the highest salivary cotinine quintile (>1.7 ng/ml) compared to the lowest quintile (<0.5 ng/ml).

In summary, the weight of evidence provided by the consistent results of numerous studies of ETS and birth weight from a variety of countries, the finding of ETS constituents in the urine of newborn infants of nonsmoking mothers, and the established causal association between active maternal smoking and reduced birth weight leads to the conclusion that ETS exposure in nonsmoking women during pregnancy causes a small reduction in birth weight. Because most of the ETS studies were designed to gauge the effects of exposure to maternal smoking, one possibility that cannot be ruled out is that paternal smoking has reproductive effects on the father that are responsible for the observed reductions in birth weight. The health implications of a small reduction in birth weight are uncertain; however, if the entire birth weight distribution is shifted downwards, a large number of infants already at risk are placed at greater risk.

Sudden infant death syndrome (SIDS)

Sudden infant death syndrome (SIDS) is the sudden, unexpected and inexplicable death, usually during sleep, of infants aged 1 month to 1 year. In developed countries, this is the most common cause of post-neonatal death. Maternal smoking has been consistently shown to be a major risk factor, independent of low birth weight and other potential confounders (78). The etiology is, by definition, unknown; however, one of the proposed mechanisms by which tobacco smoke may contribute to SIDS involves the reduction of infants' hypoxia tolerance (79,80). Milerad et al. (81) observed that nicotine administration decreased the hyperventilatory response to hypoxia in young lambs.

Early studies did not adequately distinguish between postnatal ETS exposure and maternal smoking during pregnancy, so that the direct effects of infant exposure to ETS on the risk of SIDS could not be assessed. More recent studies, however, examine the effects of ETS exposure. One reported a crude OR of 1.39 for paternal smoking for infants born to mothers who did not smoke during pregnancy (82), while another found no effect of paternal smoking when the mother did not smoke (131 cases, 1081 controls) (83). The latter did, however, report an OR of 1.65 (95% CI, 1.20–2.28) for maternal smoking adjusted for maternal smoking during pregnancy, breast-feeding, and other potential confounders, although few smoking mothers did not smoke during pregnancy. In a further study, a statistically significant OR of about 2, adjusted for various potential confounders, was reported for infants born to mothers who stopped smoking during pregnancy but resumed after the birth versus those born to mothers who did not smoke at all (84). Finally, significant increases were observed in the risk of SIDS for maternal smoking after pregnancy (OR = 2.3), paternal smoking (OR = 3.5) and smoking by other household members (OR = 2.2), all adjusted for maternal smoking during pregnancy, breast-feeding and various other potential confounders (85). These authors also reported exposure–response relationships for ETS exposure of the infant, similarly adjusted for maternal smoking during pregnancy and other factors. In other studies, infant bed-sharing was reported to be associated with an increased risk of SIDS when the mother was a smoker (86) and 70% of 24 consecutive cases were found to have high levels of cotinine in pericardial fluid (87). Overall, the evidence suggests that ETS exposure is a risk factor for SIDS.

Cardiovascular effects

A number of recent reviews have assessed the evidence on ETS exposure and cardiovascular disease and concluded that ETS causes such disease in nonsmokers (35,36,53,88–91). One (89) also derived quantitative risk estimates of 35 000 to 40 000 ETS-attributable heart disease deaths per year for never-smokers and long-term former smokers in the United States.

Mechanistic studies have shown that there is evidence of cardiovascular effects in humans of acute ETS exposures. The major effects include decreased oxygen-carrying capacity resulting in decreased exercise ability and, potentially ischaemia, as well as increased platelet activation, endothelial damage, altered lipoprotein levels and increased arterial wall thickness, which can promote atherosclerosis and, in the case of platelet activation, thrombosis. Ischaemia, atherosclerosis and thrombosis increase the risk of myocardial infarction and other serious cardiovascular effects.

A number of studies report evidence of decreased oxygen-carrying capacity and decreased exercise ability in both healthy subjects and people with existing heart disease, resulting from ETS exposure. Carbon monoxide and nicotine may be important in causing these effects. Aronow (92) demonstrated that ETS exposure significantly increased resting heart rate and blood pressure in angina patients, and significantly decreased the duration of exercise until the onset of angina in an exposure-related manner. Aronow also observed premature ventricular beats in 3 of the 10 patients after ETS exposure at the highest ETS exposure level. Leone et al. (93) similarly demonstrated decreased exercise ability in men with previous myocardial infarction, while Pimm et al. (94) and McMurray et al. (95) observed evidence of effects, both resting and during exercise, in healthy subjects exposed to ETS. McMurray et al. also reported that exposure significantly increased blood lactate levels, indicating a greater reliance on anaerobic metabolism as a result of decreased oxygen-carrying capacity. Similar changes have been reported following exposure of men with pre-existing cardiovascular disease to carbon monoxide alone, although levels were higher than in passive smoking conditions (96). Overall, these exercise studies suggest that ETS affects cardiac performance, especially in people with a history of heart disease.

Other evidence that ETS causes significant decrements in oxygen-carrying capacity comes from observations by Moskowitz et al. (97) that blood 2,3-diphosphoglycerate, which increases the oxygen affinity of haemoglobin, was significantly higher in pre-adolescent twins with smoking parent(s) and was correlated with the number of cigarettes smoked daily by the parent(s).

Increased platelet activation, which could increase the risk of atherosclerosis and thrombosis, has also been observed in humans. Decreases in platelet aggregate ratio (98,99), sensitivity to anti-aggregatory prostaglandins (e.g. PGE1, PGI2, PGD2) (100,101) have been reported. Greater effects were noted in nonsmokers compared to smokers. Ozdemir et al. (102) found that platelets of nonsmokers were more sensitive to acute tobacco smoke exposures than those of chronic smokers, which appeared to be "exhausted". These results are consistent with the results of studies of ETS exposures in animals, which demonstrate that ETS increases platelet activity and that the effect of tobacco smoke on platelets appears to saturate at low doses (See the animal section above).

Some of these studies also investigated endothelial damage which is thought to be a preliminary step in the development of atherosclerosis. Increased counts of anuclear endothelial cells (99) and increased plasma levels of factors released by activated endothelial cells (102) have been reported. Further evidence of ETS-associated endothelial damage comes from Celermajer et al. (103), who reported significantly impaired endothelial-dependent dilatation in both active and passive smokers, while endothelial-independent dilatation was similar in all groups. The impairment was not significantly different between passive and active smokers, although there was an exposure–

response relationship for passive smokers based on duration of daily ETS exposure. The investigators concluded that these results suggest early arterial damage from ETS exposure in healthy young nonsmokers. Other effects observed in humans exposed to ETS that might result in increased endothelial damage include sensitization of circulating neutrophils, increasing the risk of oxidant-mediated tissue damage (104), and reduced levels of plasma ascorbic acid (105).

Other indications that ETS can increase the risk of cardiovascular disease comes from evidence of altered lipoprotein levels in ETS-exposed children and adults. Significantly lower HDL cholesterol levels have been reported in children exposed to ETS (97,106) and adults exposed to ETS at work (107). It should be noted that if ETS is affecting HDL or other cholesterol levels, adjusting for cholesterol in the epidemiological studies may not be appropriate. In addition, ETS exposure found to be associated with arterial wall thickening (108,109) provided further evidence that ETS contributes to atherosclerosis.

Epidemiological studies have clearly established that active smoking is causally associated with cardiovascular disease (110). Studies of ETS and cardiovascular disease morbidity and mortality in nonsmokers vary with respect to the disease outcome (e.g. fatal and/or nonfatal events), sex and surrogate measures for ETS exposure (e.g. spousal smoking, cohabitant smoking, work exposure). They also vary substantially in size and in potential confounders examined.

As with other epidemiological studies, exposure misclassification and publication bias are potential sources of downward bias. Consultants for the tobacco industry have suggested that because of publication bias, published studies overestimate the association of ETS and cardiovascular disease, and have conducted their own analyses of three large, publicly available databases for which results on ETS and cardiovascular disease were previously unavailable (111,112). They conclude that there is no evidence of an association between ETS and cardiovascular disease from any of the three databases. A more sophisticated assessment of two of the databases conducted by Steenland and the American Cancer Society (113) contradicts this conclusion, reporting RR estimates of 1.22 (95% CI, 1.07–1.40) in never-smoking men and 1.10 (0.96–1.27) in never-smoking women married to current smokers compared to those married to never-smokers, adjusted for many cardiovascular disease risk factors for one database and inadequate quality of the data on smoking status and ETS exposure for the second. The third database is by far the largest, but was not specifically designed to study ETS or cardiovascular disease. A careful and cautious reassessment of this database is warranted.

A large cohort study (114) reported RR estimates for death from arteriosclerotic disease from household ETS exposure of 1.31 for men and 1.24 for women, adjusted for a range of confounding factors. A significant exposure–response relationship was seen for women but not for men. This study did not adjust for important cardiovascular disease risk factors such as hypertension, diet, and serum cholesterol. A second large study (115,116) observed a small increased risk of coronary heart disease death and a significant exposure–response trend from spousal smoking in women. Both studies suggest that the increased relative risks may be greater in younger age groups, as observed for active smoking. Smaller cohort studies (117–120) reported overall increased risks for a number of fatal and nonfatal cardiovascular disease endpoints, from marriage or cohabitation with a smoker after adjusting for a variety of confounders. Svendsen et al. (118) reported adjusted RR estimates of 2.23 (95% CI, 0.72–6.92) for death from coronary heart disease and 1.61 (95% CI,

0.96–2.71) for fatal or nonfatal coronary heart disease events from wife's smoking and positive exposure–response trends for both deaths ($P < 0.05$) and events.

Case–control studies (121–123) have also examined a large number of cardiovascular disease risk factors. Odds ratios of 1.21 (95% CI, 0.57–2.52) for acute myocardial infarction from marriage to a current smoker for both sexes combined; 1.50 (95% CI, 1.28–1.77) for coronary heart disease in women, and 1.85 (95% CI, 0.86–4.00) for nonfatal incident cases of the disease in women from exposure at work and 1.24 (95% CI, 0.56–2.72) from husband's smoking have been reported. Furthermore, positive exposure trends were also reported.

In addition to the cohort and case–control studies, there is a cross-sectional study examining cardiovascular disease morbidity and ETS (124). Statistically significant exposure–response relationships were observed for self-reported exposure and all coronary heart disease groupings. Serum cotinine showed a strong relationship only with diagnosed coronary heart disease.

In summary, overall increased risks and increasing exposure–response trends are consistent across the different studies from different countries. These increased risks for both fatal and nonfatal cardiovascular disease events were observed from actual environmental levels of ETS, despite the likelihood that exposure misclassification resulting from other sources of ETS exposure obscures some of the effect. Although most of these results did not individually achieve statistical significance, the increased risks persist when the risk estimates are adjusted for other major cardiovascular disease risk factors. Finally, the consistency of results across countries with different lifestyles and diets and the positive exposure–response relationships suggest that the observed increases are not due to confounding.

These findings are confirmed in a recent meta-analysis (125) of 19 epidemiological studies of lifelong nonsmokers living with a smoker, which reported a relative risk of ischaemic heart disease associated with exposure to ETS of 1.30 (95% CI, 1.22–1.38) at 65 years of age. Detailed analyses indicated that dietary confounding could account for an excess risk of 6%, revising the excess risk due to ETS from 30% to 23%.

Evaluation of human health risks

Exposure evaluation

ETS is a dynamic complex mixture of thousands of compounds in particulate and vapour phases, and cannot be measured directly as a whole. Instead, various marker compounds, such as nicotine and respirable suspended particulates (RSPs), are used to quantify environmental exposure. In the United States, nicotine concentrations in homes where smoking occurs typically range from less than $1 \mu\text{g}/\text{m}^3$ to over $10 \mu\text{g}/\text{m}^3$ (1). Concentrations in offices where people smoke typically range from near zero to over $30 \mu\text{g}/\text{m}^3$. Levels in restaurants, and especially bars, tend to be even higher, and concentrations in confined spaces such as cars can be higher still. Measurements of ETS-associated RSPs in homes where people smoke range from a few $\mu\text{g}/\text{m}^3$ to over $500 \mu\text{g}/\text{m}^3$, while levels in offices are generally less than $100 \mu\text{g}/\text{m}^3$ and those in restaurants can exceed $1 \text{mg}/\text{m}^3$. ETS levels are directly related to smoker density; in countries with a higher smoking prevalence, average ETS levels could be higher.

In Western societies, with adult smoking prevalences of 30–50%, it is estimated that over 50% of homes are occupied by at least one smoker, resulting in a high prevalence of ETS exposure in children and other nonsmokers. A large percentage of nonsmokers are similarly exposed at work.

Health risk evaluation

ETS has been shown to increase the risks for a variety of health effects in nonsmokers exposed at typical environmental levels. The pattern of health effects from ETS exposure produced in adult nonsmokers is consistent with the effects known to be associated with active cigarette smoking. Chronic exposures to ETS increase lung cancer mortality. In addition, the combined evidence from epidemiology and studies of mechanisms leads to the conclusion that ETS increases the risk of morbidity and mortality from cardiovascular disease in nonsmokers, especially those with chronic exposure. ETS also irritates the eyes and respiratory tract. In infants and young children, ETS increases the risk of pneumonia, bronchitis, bronchiolitis and fluid in the middle ear. In asthmatic children, ETS increases the severity and frequency of asthma attacks. Furthermore, as with active smoking, ETS reduces birth weight in the offspring of nonsmoking mothers.

Other health effects have also been associated with ETS exposure, but the evidence is not as conclusive. In adults, there is strong suggestive evidence that ETS increases mortality from sinonasal cancer. In infants, recent evidence suggests that ETS is a risk factor for sudden infant death syndrome.

Populations at special risk for the adverse health effects of ETS are young children and infants, asthmatics, and adults with other risk factors for cardiovascular disease. Levels of exposure where these effects have been observed are indicated by nicotine levels of 1–10 $\mu\text{g}/\text{m}^3$ (nicotine has been demonstrated to be a reliable marker of ETS levels).

Because of the extensive prevalence of ETS exposure and the high incidence of some of the health effects associated with ETS exposure, such as cardiovascular disease in adults and lower respiratory tract infections in children, even small increases in relative risks can translate into substantial mortality and morbidity on a population basis.

Based on the combined evidence from several studies, WHO has estimated that some 9–13% of all cancer cases can be attributed to ETS in a nonsmoking population of which 50% are exposed to ETS. The proportion of lower respiratory illness in infants attributed to ETS exposure can be estimated at 15–26%, assuming that 35% of the mothers smoke at home. Those estimates, when applied to the European population, will result in approximately 3000–4500 cases of cancer in adults per year, and between 300 000 and 550 000 episodes of lower respiratory illness in infants per year, which are expected to be related to ETS exposure (19).

Comparable results were calculated for nonsmokers in the United States (1). The EPA recently estimated that ETS causes 3000 lung cancer deaths in adult nonsmokers (roughly 100 million never-smokers and long-term former smokers) in the United States each year. The EPA also estimated that ETS is responsible for between 150 000 and 300 000 lower respiratory tract infections annually in the roughly 5.5 million children under 18 months of age, and that it exacerbates asthma in about 20% of asthmatic children. These estimates are based on a large quantity of human data from actual

exposure levels, and involve no high-to-low-dose or animal-to-human extrapolations; thus confidence in these estimates is considered high.

Quantitative population estimates for cardiovascular disease mortality are less certain than those for lung cancer. The main reasons for greater quantitative uncertainty in estimates for cardiovascular disease are that (a) there are fewer epidemiological data available (in particular, there are few data for males, which is especially critical because males have a very different baseline risk of cardiovascular disease than females), and (b) there are more risk factors for cardiovascular disease that need to be adjusted for to obtain a reliable risk estimate. In general, the relative risk estimates for cardiovascular disease from ETS exposure are similar to those for lung cancer; however, the baseline risk of death from cardiovascular disease in nonsmokers is at least 10 times higher than the risk of lung cancer. Therefore, the population risks could be roughly 10 times higher as well. Thus, while there is more confidence in the presented estimates for lung cancer, the public health impact of ETS is expected to be substantially greater for cardiovascular disease.

Guidelines

ETS has been found to be carcinogenic in humans and to produce a substantial amount of morbidity and mortality from other serious health effects at levels of 1–10 $\mu\text{g}/\text{m}^3$ nicotine (taken as an indicator of ETS). Acute and chronic respiratory health effects on children have been demonstrated in homes with smokers (nicotine 1–10 $\mu\text{g}/\text{m}^3$) and even in homes with occasional smoking (0.1–1 $\mu\text{g}/\text{m}^3$). There is no evidence for a safe exposure level. The unit risk of cancer associated with lifetime ETS exposure in a home where one person smokes is approximately 1×10^{-3} .

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Fig. 1. Week-long nicotine concentrations measured in the main living area of 96 residences compared with the number of questionnaire-reported cigarettes smoked during the air-sampling period

Source: Leaderer & Hammond (9).