

# Risk Assessment for Heart Disease and Workplace ETS Exposure among Nonsmokers

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In 1994 the U.S. Occupational Health and Safety Administration (OSHA) published a study of risk assessment for heart disease and lung cancer resulting from workplace exposure to environmental tobacco smoke (ETS) among nonsmokers. This assessment is currently being revised. The present article considers different possible approaches to a risk assessment for heart disease among nonsmokers resulting from workplace ETS exposure, reviews the approach taken by OSHA in 1994, and suggests some modifications to that approach. Since 1994 the literature supporting an association between ETS exposure and heart disease among never smokers (sometimes including long-term former smokers) has been strengthened by new studies, including some studies that have specifically considered workplace exposure. A number of these studies are appropriate for inclusion in a meta-analysis, whereas a few may not be due to methodological problems or problems in exposure definition. A meta-analysis of eight relative risks (either rate ratios or odds ratios) for heart disease resulting from workplace ETS exposure, based on one reasonable selection of appropriate studies, yields a combined relative risk of 1.21 (95% confidence interval [CI], 1.04–1.41). This relative risk, which is similar to that used by OSHA in 1994, yields an excess risk of death from heart disease by age 70 of 7 per 1000 (95% CI 0.001–0.013) resulting from ETS exposure in the workplace. This excess risk exceeds OSHA's usual threshold for regulation of 1 per 1000. Approximately 1,710 excess ischemic heart disease deaths per year would be expected among nonsmoking U.S. workers 35–69 years of age exposed to workplace ETS. *Key words:* environmental tobacco smoke, heart disease, risk assessment. — *Environ Health Perspect* 107(suppl 6):859–863 (1999).

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Environmental tobacco smoke (ETS) has been shown consistently to cause heart disease among never smokers in a large number of studies, and the association can be reasonably assumed to be causal, especially for a public health agency charged with protecting employees from involuntary risks. In 1994 the U.S. Occupational Safety and Health Administration (OSHA) published a preliminary risk assessment for ETS, attempting to quantify the excess risk from lung cancer and heart disease attributable to ETS. Here I review different possible approaches to risk assessment for ETS, consider the most recent literature, suggest some changes to the original OSHA approach in the light of more recent literature, and calculate one reasonable estimate of excess risk for heart disease among nonsmokers exposed to ETS

## Two General Approaches to ETS Risk Assessment

As there are many ways to do risk assessment, the subject can be divided between two general approaches: *a*) a unit risk or continuous approach, and *b*) exposed/nonexposed or categorical approaches. In approach *a*, one determines excess lifetime risk by level of exposure, usually in terms of a unit risk, i.e., the lifetime excess risk per unit of exposure. For this approach exposure must be measured quantitatively (e.g.,  $\mu\text{g}/\text{m}^3$  of air nicotine for ETS). This approach relies on quantitative

dose–response analyses of animal or epidemiologic data (usually via modeling) from a single study or a variety of studies.

In approach *b*, one determines the excess lifetime risk due to exposure compared with nonexposure; this determination is usually based on epidemiologic studies that consider relative risks for exposed compared to nonexposed populations (relative risk is hereafter taken generically to mean either rate ratios or odds ratios). Again, one can rely on a single study or a meta-analysis of numerous studies in determining the relative risk. Modeling exposure–response relationships is not required.

Both types of risk assessment must ultimately convert a relative risk for a population to an individual lifetime excess risk as of a certain age. OSHA generally seeks to limit exposure to a level (over a 45-year working lifetime) that entails an excess risk of death or serious disease less than 1 in a 1000.

## Applicability of the Two Approaches to ETS Epidemiology

In the case of ETS and heart disease, no epidemiology study provides quantitative dose–response analyses by some measurable exposure such as nicotine in the air. Tunstall-Pedoe et al. (1) relate urinary cotinine to heart disease in Scotland, but the cross-sectional design makes causal inference difficult [the situation is not much better for lung cancer;

there is only a single study with small numbers, which uses baseline levels of urinary cotinine to measure exposure (2)]. To use approach *a*, one must convert the qualitative ETS measures used in epidemiology (exposed as work, smelled smoke at work, occasional exposure at work, regular exposure at work) to estimated quantitative levels of an agent, with air nicotine as the most likely candidate.

One method for this approach is to use some existing industrial hygiene measurements of workplace exposures to crudely estimate the average exposure for someone reporting exposure to ETS at work. Most epidemiologic studies date from the era prior to the establishment of workplace policies restricting smoking, so the data from workplaces without smoking restrictions would be most relevant. Hammond et al. (3) measured air nicotine in area samples in worksites without smoking restrictions and found a median of  $8 \mu\text{g}/\text{m}^3$  in 1992. Similar exposure levels to air nicotine were found in some areas of hospitals in 1987 (4) and more recently among casino workers using personal sample (5). Exposure levels may have been somewhat higher in workplaces in the 1980s when subjects in epidemiologic studies were exposed, as the prevalence of smoking was higher in the 1980s. Hammond (6) has provided the most thorough summary to date of workplace ETS exposure.

One could then try to apply these exposure data more or less directly to the relevant epidemiologic studies, simply assuming measured levels in a variety of workplaces could be averaged and applied to subjects in the epidemiologic studies. In one case there are some measured workplace exposures (4) for a specific occupational group that has been studied epidemiologically [nurses in Boston (7)], although not for the specific subjects studied.

A second method for applying approach *a* is to use assumptions about the average workplace setting to derive estimated workplace concentrations of nicotine; to use this method, one must make assumptions about

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the amount smoked in the presence of the index subject, the number of smokers in the room, the duration of the smoking exposure, the size of the room where the smoking took place, and the ventilation rate in the room, etc. Hammond (6) and Repace and Lowrey (8) developed models to make such estimations. Because of the lack of data on the parameters required, this method seems less attractive than simply applying an average of measured workplace exposures.

Because of the limitations to the dose-response approach (approach *a*) outlined above, the more feasible approach to risk assessment may be *b*, based on rate ratios (or relative risks) comparing exposed to non-exposed. In this approach, one would obtain the best estimate of the rate ratio or relative risk of heart disease resulting from workplace ETS exposure compared to no such exposure. This might involve picking one large well-designed and representative study to obtain the relative risk, or conducting a meta-analysis of epidemiologic studies (see next section). This estimated relative risk would then be used along with a known background rate of heart disease among never smokers (or possibly never smokers and long-term ex-smokers) to determine a lifetime excess risk of death. This approach was adopted by OSHA in its 1994 risk assessment (9).

### OSHA's 1994 Risk Assessment

In 1994 OSHA issued a risk assessment for ETS and two end points—lung cancer and heart disease (9). OSHA's original methodology for heart disease was to rely on a single relative risk based on the Helsing et al. cohort study (10) of never smokers exposed to ETS at baseline in 1963 and followed for 12 years. Exposure was determined by living with a smoker or ex-smoker. The relative risks were 1.31 for men and 1.24 for women, adjusted for several confounders. These relative risks due to exposure at home were assumed to apply to the workplace, under the reasonable assumption that exposures in different settings are likely to have similar effects, and under the assumption that exposure levels in the workplace were comparable in intensity to exposure levels at home (3).

At this point OSHA could have proceeded to estimate excess lifetime risk for an exposed individual on the basis of a known background rate of heart disease (or mortality) among non-smokers, as well as standard formulas for converting rates to risk. However, OSHA chose to use an alternative but similar procedure, i.e., to estimate the number of heart disease deaths attributable annually to ETS exposure, then divide this estimate by the population at risk.

OSHA estimated the percentage of non-smokers at 73%, based on a 1991 Health Interview Survey (HIS) (9). OSHA then

determined the percentage of nonsmoking workers exposed to ETS in the workplace, which was taken either as 18.8% from HIS data or as 49% from a survey of 339 subjects by Cummings et al. (11). Both these numbers were used to calculate two different estimates of annual deaths attributable to ETS.

Background levels of expected heart disease among never smokers were taken from the study in Framingham, Massachusetts, and averaged for men and women as 3 per 1000 during age 35–64. Using the relative risks for ETS exposure from Helsing et al. (10) and conventional formulas for attributable risk, OSHA determined the number of excess heart disease deaths expected annually due to workplace ETS exposure. This differed depending on whether the prevalence of exposure among nonsmoking workers was judged to be 19 or 49%.

OSHA then divided the number of annual excess deaths resulting from ETS exposure by the population at risk to derive an annual risk, then converted this annual risk to a lifetime risk, assuming continuous exposure over a 45-year working lifetime through age 65. The excess lifetime risk was 7 or 16 per 1000, depending again on which estimated number of excess deaths was used to derive the annual and lifetime risk. Both estimated excess risks exceeded the excess risk level (1 per 1000) that OSHA usually considers acceptable and justified OSHA's call for eliminating smoking from the workplace.

### Issues for a Revised Risk Assessment of ETS and Heart Disease

#### Causality, Mechanisms, and Epidemiology of ETS Exposure at Home

The case for a causal relation between ETS and heart disease has been strengthened since the publication of OSHA's 1994 risk assessment (9). There are now 19 studies of heart disease among never smokers exposed to ETS from spousal smoking. Law et al. (12) have reviewed these studies and found them relatively homogeneous, with a common relative risk estimated to be 1.30 (1.22–1.38) in a meta-analysis. This excess risk is at the lower limit of what can be reasonably detected with some certainty by epidemiologists and the possibility that it could be due to confounding needs to be considered. However, there exist reasonable data indicating that the observed excess risk is unlikely to result from confounding by traditional cardiovascular risk factors. Most studies controlled for many cardiovascular risk factors; furthermore, in many studies (some with relatively homogeneous populations) control over cardiovascular risk factors often had no or little effect on

the relative risks, indicating confounding was not important.

The size of this relative risk (1.30) seems high when compared to that of mainstream smoking of 20 cigarettes a day [relative risk of 1.78, as estimated by Law et al. (12)] if one assumes that ETS exposure corresponds to smoking only a small amount, on the order of 1 cigarette a day. There are two counter arguments to this point. First, mainstream smoke and ETS are qualitatively different, and it is not clear how to derive a "cigarette equivalent" for ETS exposure. Usually the calculation of cigarette equivalency has been based on cotinine in the urine of mainstream smokers and nonsmokers exposed to ETS. However, it is not known which components of mainstream tobacco smoke cause increased heart disease, and hence it is not known which component would best be compared between sidestream and mainstream smoke to derive a cigarette equivalent (for example, carbon monoxide, relatively more prevalent in sidestream smoke, might be a better marker than urinary cotinine). However, even if one accepts that ETS exposure is approximately equivalent to 1 cigarette per day, the predicted cardiovascular effects may be not much different from what has been observed. Law et al. (12) argue that the epidemiology for mainstream smoke suggests that smoking one cigarette a day would yield a relative risk on the order of 1.30. Furthermore, there are experimental data, principally on platelet aggregation, that also suggest that smoking only one cigarette a day would result in an excess risk as high as 30%. These issues have been discussed previously in the literature (13), and one can conclude that there are reasonable arguments, based on both experimental and ancillary epidemiologic evidence, for the biologic plausibility of an excess risk of 30% for ETS exposure.

It appears from most of the data that the principal risk of heart disease is from an acute effect, e.g., on platelet aggregation. However, there is also some evidence of chronic effects, e.g., an increase in endothelial thickness of the carotid artery with ETS exposure (14). Some of the epidemiologists who have considered the question suggest that only those exposed to current smokers at baseline (in cohort studies) show an excess risk but not those exposed in the past to former smokers, an observation consistent with an acute effect.

#### Relative Risk for Workplace Exposure

At the time of the original 1994 OSHA risk assessment, there were very few studies reporting the relative risk for never smokers exposed to ETS in the workplace, which forced OSHA to rely on a study of heart disease among non-smokers exposed at home. Since that time there are a number of new studies reporting

relative risks for the workplace. The eight studies reporting relative risk for ETS in the workplace have recently been reviewed by Wells (15), who reports a relative risk of 1.50 for the three best studies, and of 1.18 when all eight studies are considered. The range of 13 relative risks (men and women are reported separately in studies in which both were studied) in these studies goes from 0.66 to 1.85. The highest and lowest relative risks are somewhat outliers with wide confidence intervals; excluding the results in a range of relative risks from 0.95 to 1.68.

It is preferable to consider studies of ETS exposure in the workplace because the excess risk that one seeks to measure is that which results from workplace exposure. However, it is worth noting that it is much more difficult to measure workplace ETS exposure than home exposure by a single question on a questionnaire. While "do you live with a smoker" is reasonably precise, "are you exposed at work" is quite imprecise, with exposure possibly varying from 5 min a day at a distance of 100 ft from a smoker, to 8 hr a day at a distance of 5 ft. This imprecision is likely to lead to random misclassification of workplace exposure that will usually cause a bias to the null for workplace relative risks.

One issue in considering ETS workplace exposure is what to do about ETS home exposure. Some studies have reported a relative risk for ETS workplace exposure after adjusting or stratifying on home ETS exposure but most have not. Kawachi et al. (7) estimated the relative risk for those exposed at the workplace only compared to those with no exposure at home or work. This is a relevant odds ratio for OSHA's purposes, although the universe at risk from workplace ETS also includes workers exposed both at home and work. Therefore, one might wish to estimate the relative risk due to workplace exposure (vs no workplace exposure), as a weighted average across those exposed at home or those not exposed at home (e.g., stratifying on or adjusting for home ETS exposure). Absent such adjustment over home exposure, one would hope that home ETS exposure is approximately the same for the workplace exposed and the workplace nonexposed. A priori this might be unlikely given that home and work exposures may be correlated. However, some empirical data suggest that home and work exposures might not be strongly correlated. In a large representative sample of the U.S. population [Third National Health and Nutrition Examination Survey (NHANES III) (16)], 80% of nonsmokers reporting workplace exposure reported no home exposure. In my own analyses below, given the lack of data in most studies, I have used relative risks for workplace exposure without considering home exposure.

Another issue is that it is probably preferable to include only the employed in these analyses of workplace exposures, as the exposed-at-work are by definition employed, whereas the nonexposed may not be employed. Employment or the "healthy worker effect" may act as a confounder here. Those not actively employed tend to have higher background heart disease rates, potentially biasing relative risks downward. In addition, the population of interest to OSHA is the employed. However, most studies have not restricted the nonexposed to the employed.

It would not appear appropriate to conduct a simple meta-analysis of the eight studies of ETS workplace exposure to estimate a common relative risk, regardless of whether formal tests of heterogeneity indicate that they might be combined. Some qualitative consideration of which studies to include would appear necessary, and several different selection criteria and meta-analyses might be conducted using a sensitivity analysis. In some studies the methods are either sketchy or suggest problems and/or the exposure definition is absent or imprecise (17,18). One study is restricted to a high-risk population and the definition of exposure is indirect ("Did most of your co-workers smoke?") (19). One study was conducted in China where exposure conditions may be somewhat different (possibly higher prevalence and intensity of workplace exposure), but the study is well designed and would seem to be a candidate for inclusion, as the effects of ETS on the heart should be similar in different countries (20). Two studies are unpublished PhD dissertations (18,21), but this should not exclude them if they are valid and well-conducted studies.

Excluding three studies for the reasons stated above (17–19), one reasonable set of studies to include would be the four studies from the U.S. and one from China without

any apparent major design or exposure definition problems (7,20–23). Three are cohort studies (7,21,23), whereas two are case-control (20,22); three are based on incidence (7,20,22), whereas two are based on mortality (21,23). The workplace exposures occurred generally in the early 1980s, although the time frame for exposure in the study of Muscat and Wynder (22) is not given. Some of these studies include morbidity and mortality data as well as different definitions of heart disease, but these issues can probably be reasonably ignored. These five studies show eight relative risks (some include men and women separately) ranging from 1.0 to 1.85 (Figure 1). Two studies (7,20) provide dose-response data. Both these studies suggest a positive trend, which tends to strengthen the case for a true workplace effect. Although it appears in these eight studies that women have higher relative risks than men, the differences between the male and female relative risks are not statistically significant. More important, the more abundant data from studies of spousal ETS indicate that the relative risks for men and women are very similar, and the apparent differences between men and women in workplace ETS exposure studies could well be attributed to statistical variation. Therefore we consider here all eight studies together, without stratifying on gender. The combined relative risk from these eight studies weighting each study's log relative risk by the inverse of its variance (24) and using a fixed effects model (the heterogeneity test is not significant) is 1.21 (95% confidence interval [CI], 1.04–1.41). This relative risk is insensitive to the inclusion or exclusion of specific studies, so that most reasonable selections of studies to include will yield a similar result. For example, exclusion of the study with the highest relative risk [the Chinese study (20)]

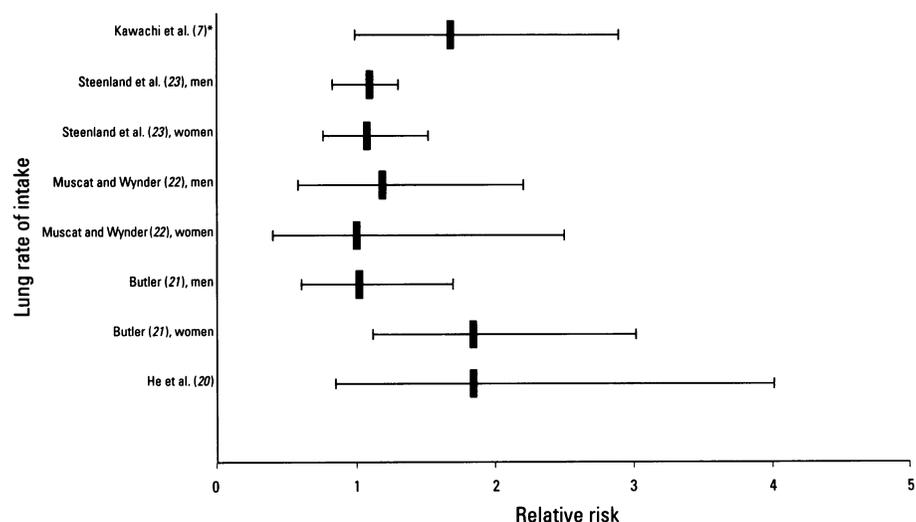


Figure 1. Studies of heart disease and workplace ETS.

yields a combined relative risk of 1.19 (95% CI, 1.02–1.39).

The above relative risk (1.21) is probably a conservative estimate, underestimating the true relative risk. As mentioned earlier, the exposed group is restricted to workers whereas the referent is not, so that the healthy worker effect may cause a bias towards the null.

### Conversion of Relative Risk to Lifetime Individual Risk

It seems reasonable that lifetime excess risk should be calculated through age 69, as most workers retire around that age and the heart disease risk from ETS exposure might be expected to wear off within a short time of ceasing exposure (assuming a primarily acute effect). To calculate lifetime excess risk, one uses conventional formulas for converting rates to risks. For a common cause such as heart disease, it is preferable to consider competing causes of death in calculating lifetime risks, via an adjustment proposed by Gail (25). Gail's formula is as follows:

$$\text{Excess risk} = \sum_{i=35}^{69} (rr - 1) * q_i(i) \exp\left[-\sum_{j=35}^i (rr - 1)q_l(j) + q_a(j)\right]$$

where excess risk refers to cumulative excess risk of ischemic heart disease death by age 69,  $rr$  is the rate ratio for ischemic heart disease for ETS-exposed nonsmokers versus nonsmokers not exposed to ETS,  $q_l$  is the ischemic heart disease mortality rate for nonsmokers,  $q_a$  is the overall all-causes mortality rate for nonsmokers. Here we assume no increased rates of heart disease for nonsmokers until after age 35, based on a background rate close to 0 at these early ages.

Using the results of the meta-analysis above (rate ratio = 1.21), the lifetime excess risk of heart disease death due to ETS workplace exposure among never smokers is 0.004 (95% CI, 0.001–0.008) by age 65, increasing to 0.007 (95% CI, 0.001–0.013) by age 70. An assumption of an ETS risk persisting until age 70 is reasonable either because people continue to work and be exposed or because the risk is assumed to persist 5 years after exposure. This excess risk exceeds the level of risk usually acceptable to OSHA (0.001). In this calculation I have assumed an ischemic heart disease death rate for never smokers of 6/100,000 (men and women combined) between age 35–44, a rate 89/100,000 from age 45–64, and a rate of 307/100,000 for age 65–69, as estimated from four large cohorts of never smokers (26). No heart disease death risk was assumed prior to age 35, and U.S. age-specific mortality rates from 1996

were used for the correction for competing causes of death.

### Attributable Risk

An estimation of attributable risk is not required for calculating excess lifetime risk but can be a useful exercise from the point of view of public health. Some modifications might be made to OSHA's previous methods. The population at risk should probably be employed men and women who are never-smokers or former smokers who have quit at least 5 years earlier, rather than all nonsmokers. Estimates of these numbers are available from the 1991 HIS survey. Former smokers who quit more than 5 years ago have a similar background risk as never-smokers.

The number of ETS-exposed among the population at risk is a more difficult question. It would seem best to estimate this number of large national representative surveys. The HIS survey in 1991 estimated 18% of nonsmokers were exposed to ETS at work. The NHANES III survey (16) estimated in 1988–1991 that 25% of nonsmokers were exposed at work (could smell tobacco smoke). These percentages would have to be adjusted downward to exclude recent former smokers. Furthermore, as workplace smoking policies are more common, the most recent data should be used and would also presumably show somewhat lower percent ages.

Gerlach et al. (27) found in a 1991–1992 survey of 100,000 workers in indoor environments, excluding the self-employed, that 33% of nonsmokers reported working in workplaces without smoking restrictions. These numbers would seem to correspond roughly to the percentages of nonsmokers reporting exposure in HIS and NHANES III. It is likely the numbers have decreased since the early 1990s because of increased numbers of worksites with smoking restrictions.

For the purposes of my estimates here, I will assume that roughly 20% of nonsmokers are exposed to ETS as work. I will also assume (following OSHA's 1994 calculations) that there are approximately 74,000,000 nonsmokers, age 18 to 65, in U.S. workplaces. From demographic data I estimate that approximately 52,000,000 (70%) of these workers are age 35–65 (28) and that there are an additional 5 million ex-workers age 65–69 still at risk from the effects of ETS, so that the population of nonsmokers at risk totals approximately 57,000,000. Using a weighted average across four cohort studies on nonsmokers (26) and assuming equal numbers of men and women, I estimate an annual ischemic heart disease mortality rate of approximately 75/100,000 in nonsmoking workers age 35–69. Using the standard formula for

attributable fraction ( $AF = p(rr - 1) / \{p(rr - 1) + 1\}$ , here  $p = 0.2$ ,  $rr = 1.21$ ), one obtains an approximate attributable fraction of 4%. This attributable fraction in turn leads to an approximate estimate of 1,710 ischemic heart disease deaths a year expected among nonsmoking workers age 35–69 resulting from ETS exposure ( $57,000,000 \times 75/100,000 \times 0.04$ ). This number increases dramatically if one assumes that ETS has a chronic effect that extends beyond age 70, because the background rate for heart disease shows a large increase at older ages (the rate among nonsmokers more than 70 years of age is approximately 1200/100,000, an additional approximately 24 million ex-workers would be at risk, and approximately 11,500 excess deaths from ETS exposure would be expected in this group).

These estimated numbers of excess deaths would also change if the proportion exposed were lower or higher. For example, if in the future fewer people smoke and the proportion exposed to ETS at work decreases to 10%, the attributable fraction would decrease to 2%, and the number of excess deaths among nonsmokers age 35–69 drops by half, to 855 deaths. If, on the other hand, smoking were to increase, and the proportion exposed increased to 30%, the attributable fraction would increase to 6%, and we would expect 2565 excess deaths by age 69.

### Conclusion

ETS has been shown consistently to cause heart disease among never smokers in a large number of studies; the association can be reasonably assumed to be causal, especially for a public health agency charged with protecting employees from involuntary risks. The approach to calculating excess lifetime risk suggested here follows OSHA's earlier risk assessment, but with some modifications. These modifications include using newer epidemiologic studies with relative risks specific to workplace ETS exposure. There are a number of uncertainties involved in this risk assessment; perhaps the most important is knowledge of the true relative risk for workplace ETS exposure.

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