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Environmental Tobacco Smoke and Coronary Heart Syndromes: Absence of an Association

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Concerns about possible cardiovascular and especially coronary effects of environmental tobacco smoke (ETS) derive from the reported effects of active smoking. Despite similarities, however, ETS has composition and physical characteristics different from the mainstream smoke (MS) that active smokers inhale and appears relatively more chemically inert and less biologically active. ETS doses to nonsmokers are small and often below the sensitivity of detection technologies. They are several orders of magnitude less than MS doses in active smokers. Numerous epidemiologic studies report that the active smoking of less than 10 cigarettes/day is not associated with measurable risk of coronary heart disease (CHD). Thus, even assuming that ETS and MS have equivalent biologic activities, conceivable ETS doses to nonsmokers are far below apparent no-effect thresholds for active smoking. Hence, it is no surprise that epidemiologic reports are inconclusive about a possible association of ETS exposure and CHD, some suggesting a slight elevation, others a reduction of risk. Often, the elevations reported are higher than the CHD risk values associated with active smoking. Such equivocations likely result from the presence of contrasting protective or aggravating confounders, of which more than 200 have been reported in the literature—confounders that were not and could not be adequately controlled by any epidemiologic study. By scientific standards, the weight of evidence continues to falsify the hypothesis that ETS exposure might be a CHD risk factor.

INTRODUCTION

Several reviews have attempted to appraise the literature on environmental tobacco smoke (ETS) and coronary heart disease (CHD) (Glanz and Parmley, 1991; Taylor and Johnson, 1992; Steenland, 1992; Wells, 1994). In general these reviews have been selective and conjectural and have failed to account for the many pertinent considerations that a scientific evaluation requires. Although written by a long-time consultant to the tobacco industry, this present review strives for a comprehensive evaluation of available knowledge by avoiding assumptions and standing by the evidence.

In considering ETS as a possible CHD risk factor it will be useful to address what is known of the chemical, physical, and biological comparability of ETS and the smoke that smokers inhale. Exposures and doses will then be compared in light of the no-observable adverse effect levels for active smoking and CHD, as reported in the literature. Finally, the epidemiologic studies of ETS exposure and possible CHD risk are evaluated against the background of numerous confounders, difficulties in establishing and measuring exposures, classification and other logistic biases, statistical criteria of significance, and inferential conjectures from *in vitro* and *in vivo* experiments and clinical effects in humans.

In a public health context this review should be seen as purely a risk assessment exercise. The National Academy of Sciences determined that risk assessment should be an objective scientific analysis distinct from the judgmental risk management policies that may follow (NAS, 1983). Accordingly, this review follows standard principles of the scientific method.

Most epidemiologic studies of chronic multifactorial diseases are not adaptable to the scientific method. Observational studies—the basis of ETS epidemiologic studies—encounter especially vexing logical difficulties in their interpretation, fully recognized by epidemiologic theory. For instance, in his authoritative analysis Rothman writes:

> Despite philosophic injunctions concerning inductive inference, criteria have commonly been used to make such inferences. The justification offered has been that the exigencies of public health problems demand action and that despite imperfect knowledge causal inferences must be made. (Rothman, 1986, p. 17).

Clearly, the exigencies of public health represent imperatives other than scientific, raising the question of what rules of evidence to adopt if the scientific method does not apply. The question has been resolved in a set of judgmental guidelines—the criteria mentioned by Rothman—initially proposed in the first Surgeon Gen-

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eral's report on smoking and expanded shortly after by Sir A. Bradford Hill (USSG, 1964; Hill, 1965). They are now familiar considerations used to extend judgmental inferences of causal associations in a metascience context: strength, consistency, specificity, temporality, response gradient, plausibility, coherence, analogy, and experimental evidence.

On this basis, judgmental inferences of causality have been advanced in situations that substantially met these qualifiers. However, other difficulties in the epidemiology of multifactorial diseases have identified additional obstacles to causal inferences, also described by Rothman and well known to epidemiologists. These are structural problems deriving from the inevitable biases in data collection and the logistic impossibility of controlling for multiple confounding in multifactorial diseases.

The resulting uncertainties in many studies often prevent even the application of the "causality criteria" and, therefore, of causality inferences. Thus, even more elastic ways of appraisal have been sought in what is known as the "weight of evidence" approach (NAS, 1983). In principle, this approach entails a lose qualitative integration of what evidence may be available, sometimes sufficient to justify holding onto a research hypothesis but clearly inadequate for its verification. On the other hand, contrary weight of evidence may be sufficient to falsify and discard a research hypothesis on the basis of reliable indirect evidence. The latter is precisely the situation in the matter of ETS and cardiovascular diseases.

ETS AND ACTIVE SMOKING

ETS comes from the dilution of sidestream smoke produced by smoldering cigarettes and from the small residues of mainstream smoke (MS) exhaled by active smokers. Generated and existing under much different conditions, these different smokes have some similarities but marked differences in chemical and physical composition and behavior. All comprise a gas phase and small respirable suspended particles (RSP). These particles in turn may contain at various times different amounts of water and other volatile components that may exchange with the gas phase.

Mainstream smoke—inhaled directly by smokers—is concentrated and confined to the moist environment of mouth, throat, and lung. Its higher gas-phase concentrations favor larger respirable particles that condense and retain more water and volatiles. By contrast, ordinary ETS is over 100,000 times more diluted, with much lower humidity and extremely low concentrations of volatiles. Evaporation is faster from ETS particles, which—within fractions of a second from their generation—attain sizes 50 to 100 times smaller in mass and volume than their mainstream counterparts. As ETS ages, it undergoes oxidative and photochemical transformations, polymerizations from loss of water and volatiles, reactions with other environmental components, differential absorptions to environmental surfaces, and other changes (NAS, 1986; USSG, 1986; USEPA, 1992c; Guerin *et al.*, 1987; Baker and Proctor, 1990). The reducing capacity and free radicals of MS are lost within minutes (Schmeltz *et al.*, 1977, Tanigawa *et al.*, 1994), and ETS is considerably less cytotoxic than inhaled MS (Sonnenfeld and Wilson, 1987).

Of the several thousand components identified in mainstream smoke, only 100 or so have been detected in sidestream smoke under field conditions, due to extreme dilutions. Because of even greater dilution, only about 20 ETS components have been identified directly under field conditions. In natural settings, most ETS components are below the sensitivity of current analytical capabilities (Guerin *et al.*, 1987; Baker and Proctor, 1990). Compilers of ETS reports from the National Academy of Sciences (NAS, 1986), the U.S. Surgeon General (USSG, 1986), and the Environmental Protection Agency (USEPA, 1992c) have been forced to infer the presence of ETS components by proxy, based on the composition of the sidestream smoke from which ETS primarily derives.

Nominally, then, ETS and mainstream smoke may share some components, but their chemical and physical differences are substantial. Moreover, the presence of most ETS components can only be postulated because they are beyond material detection. Also, the chemical and biologic reactivity of ETS is less than that for the MS that active smokers inhale, because of the loss of free radicals, other quenchings, and absorption losses during dilution and aging.

ESTIMATING ETS EXPOSURE

A major limitation of epidemiologic studies on ETS has been the unreliable estimates of dose, which compound the uncertainties of personal or proxy recall of the intensity, frequency, and duration of exposures over individual lifetimes. Even the simple dichotomous classification of exposed and nonexposed subjects presents recognized uncertainties, such as those deriving from the self-classification of some smokers as nonsmokers or the propensity to exaggerate exposure estimates by publicity-sensitized patients (USEPA, 1992c; Lee, 1992, 1993). On comparatively more solid grounds, a range of probable momentary exposures to ETS can be inferred from physical and chemical derivations. These inferences are also insufficient to determine cumulative exposures, but raise compelling doubts about the reliability and meaning of epidemiologic estimates.

On the basis of extrapolations from sidestream and mainstream smoke data, the National Academy of Sciences calculated that for nicotine alone the difference in peak inhalation concentrations between smokers and ETS-exposed nonsmokers varies between 57,000- and 7,000,000-fold (NAS, 1986). Dose estimates based on body fluid concentrations of nicotine or cotinine yield

higher values, but depend on environmental and pharmacokinetic assumptions of unlikely validity (USEPA, 1992c; USOSHA, 1994). They also depend on a set of equally dubious systematic assumptions as listed by the National Research Council: "Current smoking patterns reflect past patterns. Cotinine or nicotine concentrations . . . are linearly correlated to recent exposures to ETS and to the carcinogens in ETS among nonsmokers. All subjects in the various studies began to be exposed to ETS at the same time and have continued to be exposed at the same rate throughout the follow-up period. . . ." (NAS, 1986, p. 290).

Estimates of exposure to other ETS components are even more problematic because of numerous sources external to ETS. For instance, plasma concentrations of volatile organics in nonsmokers appear to be as much as two-thirds of the corresponding levels in active smokers (Angerer *et al.*, 1992; Brugnone *et al.*, 1992; Perbellini *et al.*, 1988)—an indication of significant sources other than tobacco combustion (Richter *et al.*, 1994; Ong *et al.*, 1994).

By utilizing surrogate sidestream smoke values, conceivable ETS exposure has been compared with current federal standards of permissible occupational exposure to several smoke components. Considering an unventilated room of 100 m^3 (3533 cubic feet), the number of cigarettes that would have to be burned before reaching official threshold limit values varies among 1170 for methylchloride to 13,300 for benzene to 222,000 for benzo(*a*)pyrene to 1,000,000 for toluene (Gori and Mantel, 1991).

In any event, the measurement of ETS-respirable particles (ETS-RSP) has been more fruitful than the measurement of single chemical species. Methods have been devised that separate particles that may derive from ETS and other sources. Use of these methods yields the current consensus—supported by EPA's reports on ETS—that prevailing concentrations of ETS-RSP are below 50 $\mu g/m^3$ in households with smokers, the environments studied in most epidemiologic studies that have suggested elevated risks (USEPA, 1992c; Gori and Mantel, 1991; Samet, 1992; Steenland, 1992).

Because of aerodynamic size and other differences, EPA recognizes that only about 10% of inhaled ETS-RSP may be retained by nonsmokers, compared to nearly 90% for mainstream smoke RSP in active smokers (USEPA, 1992c). Furthermore, lung clearance is faster and more efficient in nonsmokers than in smokers (Kennedy *et al.*, 1984; Vastag *et al.*, 1985; Foster *et al.*, 1985; Zayas *et al.*, 1990; Gerde *et al.*, 1991), and target cell doses are far smaller because of greater lung surface at the greater depths reached by ETS-RSP (Mercer and Crapo, 1993). Recent studies (Emmons *et al.*, 1992) endorsed by the Occupational Safety and Health Administration indicate that the average duration of daily exposure to ETS is around 1.5 hr, with an upper confidence interval of 2 hr (USOSHA, 1994).

TABLE 1
Relative Dose Estimate of Respirable Suspended Particulates (RSP) in Typical Active Smokers and ETS-Exposed Nonsmokers

Active smoker	30 cigarettes per day 15 mg RSP inhaled per cigarette 90% lung retention efficiency Daily dose about 400 mg
ETS-Exposed Nonsmoker	0.05 mg RSP/cubic meter of air 1.5 hr per day exposure[a] 0.7 cubic meters per hour inhaled 10% lung retention efficiency Daily dose about 0.00525 mg
Crude dose ratio 0.00525:400 about 1:75,000	
Lung surface permeability some three times greater in smokers Lung clearance some three times more efficient in nonsmokers ETS dose distributed over greater surface deeper in lungs Net dose ratio at target tissue <1:500,000	

[a] USOSHA, 1994; Emmons *et al.*, 1992.

Overall, these considerations lead to the conclusion that the prevalent ETS-RSP dose is minuscule. Although difficult to define, Table 1 shows that it is likely at least 100,000 times smaller than the mainstream smoke dose in active smokers, as official EPA reports acknowledge (USEPA, 1992a). For the average ETS-exposed individual, this estimate translates into an annual dose equivalent to far less than the mainstream RSP of 1 cigarette evenly dispersed over a 12-month period (Gori and Mantel, 1991).

Documented observations—also plainly perceived in everyone's life and experience—indicate that people have innate capacities to cope with multiple low-level exposures. The question, then, is whether very small doses of ETS pose plausible risks to nonsmokers.

COULD MINUTE ETS EXPOSURES POSE A HEALTH RISK?

Because direct measurements of the biologic activities, exposures, and doses of ETS are so problematic, initial attempts have inferred ETS-linked health risks by arithmetic derivation from the apparent risks associated with active smoking. However, this approach has been controversial (USEPA, 1992b). A review by the EPA (USEPA, 1992b) dedicates a chapter to the proposition that: ". . . due to the similarity in chemical composition between [mainstream smoke] and ETS and the known human exposure to ETS. . . , ETS would also be classified as a . . . human carcinogen" (pp. 4–10). Elsewhere, the review lists the many differences of MS and ETS, suggesting that risk extrapolation from active smoking may not be feasible (pp. 2–7). A direct comparison also has been questioned in a review of the association of ETS exposure and CHDs, citing the obvious contrasts (Steenland, 1992). In reality, the only reasonable infer-

ences would come from the foregoing estimates. Accordingly, the health risks of ETS—if any—would have to be so much smaller as to be unmeasurable, when compared to MS-associated risks.

Moreover, epidemiologic studies of active smoking give evidence of no-observable-adverse-effect-levels (NOAELs), namely that at low daily consumption of cigarettes the epidemiologic risks associated with certain diseases become nonsignificant (Gori, 1976; Gori and Mantel, 1991). No-effect observations at comparatively high doses are also routinely reported in experimental animal exposure to whole smoke or its fractions. In a recent evaluation of smoking and health issues, the Congressional Research Service of the Library of Congress stated:

> The existence of an exposure threshold for disease onset below which many passive smokers fall is not implausible. Most organisms have the capacity to cleanse themselves of some level of contaminants. It is for this reason that public policy usually does not insist that every unit of air or water pollution be removed from the environment. . . . In fact, strongly nonlinear relationships in which health effects rise with the square of exposure, and more, have been found with respect to active smoking (see Surgeon General's Report, 1989, p. 44). Were these relationships projected backwards to construct the lower (unknown) portion of the health effect/physical damage function, the observed relationship might lead researchers *a priori* to expect no empirical relationship. Thus, the issue raised by this potential break in the causative chain is whether researchers should expect to find a significant relationship between passive smoking and health effects. (Gravelle and Zimmermann, 1994, p. 45).

The presence of NOAELs for active smoking would have a disposing relevance in the evaluation of claimed CHD risks of ETS exposure. A compendium of 34-year follow-up data was recently published for the prospective Framingham study, the longest and most closely monitored epidemiologic study of its kind in the United States (Freund *et al.*, 1993). The report states: "For all CHD a clear relationship exists only for younger men. Women may have a slightly increased risk below age 65, while no relationship is seen for men or women past age 65." However, for any smokers of 1–10 cigarettes/day the age-adjusted rates are generally below the rates of nonsmokers. Age-adjusted rates are also unchanged for lung cancer in any smokers of 1–10 cigarettes/day below age 65. These reports are consonant with previous reports from the Framingham trial (Kannel *et al.*, 1987).

A large Swedish study also reported no correlation between smoking and cardiovascular illness (Lapidus, 1985). The British Doctors study in England is widely regarded as the best continuing study outside the United States and perhaps the best in the world. A 1980 paper reported on mortality rates in female British doctors after 22 years of observation (Doll *et al.*, 1980). There was no increase in mortality rates at any level of daily cigarette consumption for pulmonary heart disease. For ischemic heart disease and lung cancer, mortality rates were the same in nonsmokers and in smokers of 1–14 cigarettes/day. Mortality for all diseases was actually slightly lower in smokers of 1–14 cigarettes/day than in nonsmokers.

For male British doctors, mortality rates in the group smoking 1–14 cigarettes/day were slightly elevated after 20 years of observation (Doll and Peto, 1976). However, extrapolation from dose/response functions indicates that mortality for cardiovascular diseases would not be elevated for smokers inhaling an evenly dispersed daily dose equivalent to 4–5 pre-1960 cigarettes (Gori, 1976; Gori-Mantel, 1991).

A large cohort study of white women in Maryland reported threshold effects (Bush and Comstock, 1983). The Western Collaborative Group Study also reported clear threshold values, especially after adjustment for type A personality confounding (Jenkins *et al.*, 1968). Moreover, many studies would have likely reported threshold values if their lowest exposure category had been 10 or less cigarettes/day (Oliver, 1974; PPRG, 1978; Rosenberg *et al.*, 1985).

In a more circumstantial context, a study by the National Center for Health Statistics found that patterns of heart diseases and ischemic heart diseases did not parallel patterns of smoking habits in different U.S. regions (Gillum, 1994). Another recent study reports that cigarette smoking fails to explain international differences in mortality for chronic obstructive pulmonary diseases (Brown *et al.*, 1994). The worldwide and massive WHO-MONICA study recently concluded that cigarette smoking, hypertension, and total cholesterol "measured cross-sectionally at the population level do not reflect well the variation in mortality between populations" (MONICA, 1994). Much earlier, the large Seven Countries study determined in the '60s that smoking was not associated with excess CHD mortality (Keys, 1980). In the Finnish North Karelia–Kuopio study, female CHD mortality declined 68% despite an 80% increase in smoking prevalence between 1972 and 1992 (Vartiainen *et al.*, 1994).

To these reports one should add the generally accepted evidence that moderate pipe and cigar smoking are not associated with increased risks of lung cancer and cardiovascular and respiratory illnesses. On this basis, the first Surgeon General's report on smoking and health, and others, concluded that nicotine and carbon monoxide are unlikely to have adverse cardiovascular effects, since their blood levels are quite similar in cigarette, pipe, and cigar smokers (USSG, 1964; Wald *et al.*, 1981). In regard to nicotine, this conclusion was also echoed officially by the Independent Scientific Committee on Smoking and Health of the United Kingdom (Froggatt, 1988). Such considerations directly oppose the conjecture that ETS is a CHD risk factor, given that pipe and cigar smokers must be among the subjects most substantially exposed to ETS.

The combined evidence of epidemiologically derived

NOAEL thresholds for active smoking and CHD supports the *a priori* inference that typical ETS exposures could not represent a CHD risk.

EPIDEMIOLOGIC STUDIES

Of the published studies on the possible association of ETS exposure and CHD risk, most are not statistically significant. As could be expected, Fig. 1 shows that the instability of results is more pronounced in studies of small sample size. On the other hand, the larger studies—derived from the databases of the American Cancer Society and of the National Center for Health Statistics—have massive power and do not sustain an association of ETS exposure and CHD risk.

In the smaller studies, the sample deficiencies amplify the effects of biases and confounders and thus the variance of the results. CHDs are of multifactorial origin and unless all significant factors can be accurately controlled, the noise-to-signal ratio would be large and results suggesting slightly increased or decreased risk would be uninterpretable. In fact, the weakness of the risk signals precludes not only causal conclusions, but even the formulation of reasonable research hypotheses.

Taking clues from the first Surgeon General's report (USSG, 1964), several studies have shown that smokers in general display lifestyles that include peculiar risk factors other than smoking; for instance, they may exercise less, consume more alcohol, have less healthy diets, and so on (Margetts and Jackson, 1993; Cress *et al.*, 1994). Also, the literature shows that these less healthy habits and risks eventually extend to nonsmoking members of a household (Gori and Mantel, 1991). The relatively low elevation of CHD risk for active smokers belittles the impact of smoker/nonsmoker misclassification, but the instability of results is still enhanced by interview, exposure assessment, publication, and other biases present in virtually all of the epidemiologic reports cited. For all such and other reasons, epidemiologic studies—especially small ones—suggesting an association of ETS exposure and CHDs are doomed to produce the equivocal results reported in Fig. 1.

Published metaanalysis estimates of the combined excess risk from selected ETS-CHD studies have produced typical estimates of risk around 1.3. Authoritative textbooks and commentators have warned that relative risk values less than 2 or 3 may not be interpretable, especially when studies are affected by multiple uncertainties, and depend on simplistic working hypotheses (Wynder, 1987; Rothman, 1982; Breslow and Day, 1980). In fact, some individual ETS-CHD studies report no change in risk or reduced risk, inverse dose/response gradients, or relative risks for ETS exposures that are of the same or higher magnitude as risks for active smoking. The apparent risk of cardiovascular diseases for active smokers is only 1.7 (Steenland, 1992), and even for active smokers there are solid reports of negative cardiovascular risks and threshold levels, as reviewed above. The paradox has not gone unnoticed, the reported risk in active smokers being only slightly higher than the apparent risk from ETS studies, despite vastly smaller ETS doses (Steenland, 1992).

The closeness of the reported risk values for ETS and active smoking indicates either the unlikely hypothesis of extreme differences in the specific biologic potencies of ETS and mainstream smoke or the more plausible likelihood of interferences from biases and confounding risk factors other than ETS (Steenland, 1992). In fact, the role of confounders is certain, given that only a few of the nine studies of ETS and cardiovascular diseases have controlled for at most 2 or 3 of the over 250 CHD risk factors reported in the literature (Hopkins and Williams, 1991).

A defensible metaanalysis exercise requires a reasonable degree of homogeneity in study design, subject entry criteria, interview questionnaire and procedures, bias and confounder controls, disease and mortality diagnostic certification criteria, statistical methods and rules of interpretation, and other variables. Without some reasonable homogeneity, metaanalysis estimates impose too many conjectural assumptions and become questionable exercises in numerology devoid of scientific content and justification. In fact, even a cursory analysis shows that it is virtually impossible to certify minimal standards of homogeneity for the available ETS-CHD studies.

Hirayama (1981, 1984, 1990). This cohort study of nonsmoking Japanese women suffers from critical flaws. It did not control for classical CHD risk factors and determined smoking status only at enrollment time in 1965 but not during the 15-year follow-up. The author admitted having incorrectly calculated relative risk values in different papers (Hirayama, 1990), leaving unresolved discrepancies between the 1981 and subsequent reports. The overall results did not achieve statistical significance. Follow-up losses are likely to have been excessive (Layard and Viren, 1989).

Garland et al. (1985). This study of a middle-class white cohort from Rancho Bernardo, California, determined smoking status, plasma cholesterol, obesity index, and systolic blood pressure only at enrollment time but not during the 10-year follow-up. The reported age-adjusted mortality rate for never-smoking wives of currently smoking husbands was based on 2 deaths only and was smaller than the corresponding rate for wives of former smoking husbands (2.7 vs 3.6).

Lee et al. (1986). A case–control study from England generally reporting no association of CHD and ETS exposure is described. The study suffers from exposure characterization imprecision and does not control for CHD confounders.

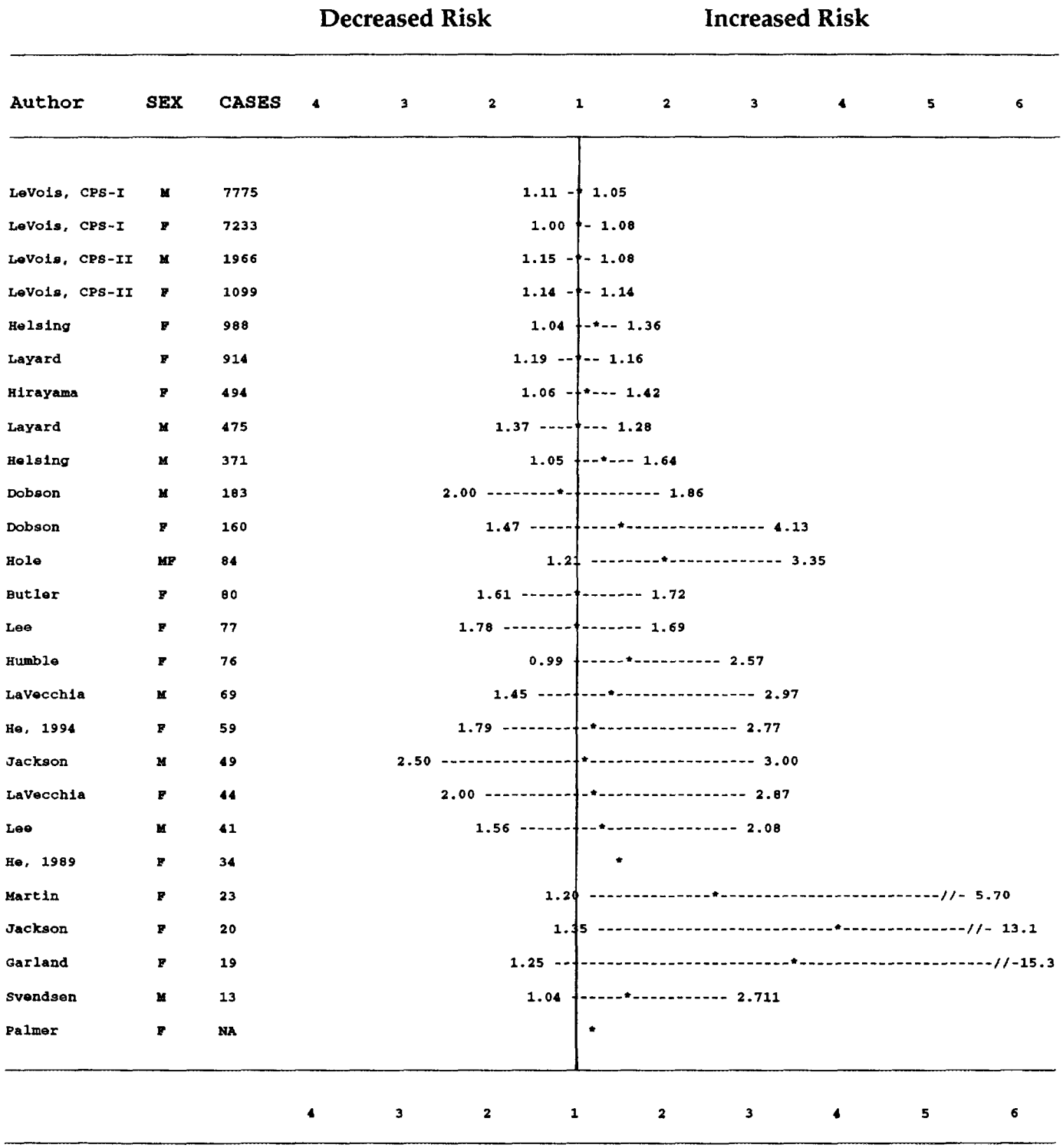

FIG. 1. Reported increased and decreased risks of heart diseases in nonsmokers exposed to environmental tobacco smoke listed in order of decreasing sample size. Cases are exposed and unexposed combined. The logarithmic analysis leading to relative risks (RR) or odd ratios (OR) confines reduced risk values to the interval from 0 to 1, while increased risk values span the interval from 1 to infinity. The correct visual representation requires that reduced and increased risk values be displayed on equivalent scales. The symmetry is achieved by giving reduced risk values as the reciprocals of the less than 1 values obtained logarithmically and as such reported in published studies. The central vertical line represents the null risk value (value 1). Decreased risk values are to its left, increased risk values to its right. For each study cited, the asterisk marks the midpoint estimate and the dotted lines span the domain of the 95% confidence interval, if reported in the cited publications.

Martin et al. (1986) (abstract). An abstract of a small case–control study reported at the 114th meeting of the American Public Health Association. Based on 23 cases, it reported a CHD relative risk (RR) of 2.6. No information was given about data collection and analysis methodologies, and no confounding adjustments were made.

Svendsen et al. (1987). This cohort study followed for about 7 years a subsample of nonsmoking husbands of smoking wives from the MRFIT intervention trial. Its results are of questionable relevance because the MRFIT trial recruited only men encumbered with known CHD risks and therefore a sample not representative of an open population. The nonsmoker category included exsmokers. Nonsmoking husbands of smoking wives were heavier and consumed more alcohol than nonsmoking husbands of nonsmoking wives. Moreover, none of the reported relative risk values are statistically significant, and the sample size is one of the smallest.

Helsing et al. (1988); Sandler et al. (1989). These two studies reported on one cohort of never-smoking men and one of never-smoking women from the Washington County of Maryland, followed from 1963 to 1975. The study did not control for many known CHD risk factors and did not report on follow-up losses. Only deaths occurring inside but not outside Washington County were reported. Dose–effect gradients were not apparent. Relative risks for females differ in the two papers (1.24 vs 1.19), although the same database and adjustment were apparently used. Despite an elaborate scoring procedure for estimating ETS exposure, no data were reported relating to smoking spouses alone, thus precluding a reasonable comparison of this with other studies. Smoking data were collected only for 1963 at entry, but not for the follow-up period. The authors admitted inadequate control of confounders, among other things because "[t]he general increase in mortality [during the study] leaves open the possibility that the lifestyles of people who live with smokers differ from those who do not live with smokers. Factors such as alcohol consumption and dietary habits which are correlated with both smoking and risks for some diseases [and which were not collected in the 1963 census] seem especially likely to be alternative explanations for our findings, to the extent that diets and alcohol use are similar among household members." These studies were considered inadequate by the ETS reviews of the National Academy of Sciences, the U.S. Surgeon General, and EPA (NAS, 1986; USSG, 1986; USEPA, 1992c).

Butler (1988). This study concerns a cohort of California Seven Day Adventists. The sample may be inconsistent, as only 58% of registered Adventist households responded to questionnaires. Two cohorts were extracted from the responses: One spouse-pair cohort and the other a cohort of subjects participating in an air pollution survey (the AHSMOG cohort). The spouse-pair cohort showed a nonsignificant CHD relative risk of 1.4 for nonsmoking wives of smokers, although the value derived from only four recorded CHD deaths. For the AHSMOG cohort, CHD relative risks for those married to smokers were decreased in nonsmoking men and increased in nonsmoking women. The same inverse association held for nonsmoking men and women working with smokers. There were significant discrepancies in exposure classification regarding many individuals listed in both cohorts.

Gillis et al. (1984); Hole et al. (1989). These two studies refer to an urban Scottish cohort of men and women combined. The latter is a 11.5-year follow-up report, giving CHD mortality relative risks of 2.01 and 2.27 for passive and active smoking, respectively. The authors commented that the RR value for passive smoking "seems large in comparison with that found for active smoking, and the possibility that chance has inflated the risk cannot be excluded. . . ." They also noted that such a small difference precluded the inference that the passive smoking association was biologically plausible. A decisive flaw of this study is that the nonsmoker category included exsmokers, with no indication of their prevalence in the cohort nor of the length of time of their abstinence.

Humble et al. (1990). This study concerns a small rural cohort of nonsmoking women from Evans County, Georgia. None of the reported relative risk values attained statistical significance. For white women, ETS exposure was inversely associated with socioeconomic status, showing reduced risk values for the less affluent group. Smoking status was determined at entry only but not during the 20 years follow-up. The authors also noted that no information was available of exposure changes due to remarriage.

Jackson (1989). This unpublished dissertation is difficult to interpret because of unclear determination of exposures, lack of control for confounders and biases, and the discrepancy between male and female reports.

He et al. (1989). A case–control study from China based on 34 cases and 68 controls reported a CHD risk of 1.5 for nonsmoking women married to smokers. Contrary to the authors' claim, this value cannot be statistically significant on account of its small value, the small number of cases, and the wide variance reported for the unadjusted estimate. The study is questionable in that no details of data collection and subject selection procedures are given. Apparently no corrections for confounders were introduced, even though the study states that "[w]omen exposed to passive smoke also showed abnormal levels of serum LDL-C, HDL-C, apoA1, and apoB."

Dobson et al. (1991). An Australian case–control study reports a decreased risk for nonsmoking men, but an increased CHD risk (RR = 2.46) for nonsmoking

women married to smokers. Based on a small sample, no excess myocardial infarction (MI) risk was reported for workplace exposure in men or women. The study states that no results were statistically significant. No controls for CHD risk factors were provided. Serious methodological problems are apparent, as information for cases and controls was obtained by different procedures.

La Vecchia et al. (1993). A small case–control study from northern Italy reported an overall male/female adjusted CHD RR of 1.21. Responsibly, the authors concluded: "The interpretation of this study remains inconclusive because of the lack of statistical significance, limited exposure assessment, and potential misclassification of smoking status of subjects interviewed and their spouses."

He et al. (1994). A study of nonsmoking Chinese women exposed to ETS both at home and at the workplace is described. There is no control for workplace confounders and the sample size is very small.

Layard (1995). A case–control study extracted from the massive database of the National Mortality Followback Survey (NMSF), a national probability sample of U.S. adult deaths in 1986, produced by the National Center for Health Statistics. From a total of 18,733 deaths, the sample provided 475 male and 914 female deaths for ischemic heart disease (IHD). It also provided 988 male and 1930 female controls from death causes unrelated to smoking. Users of less than 100 cigarettes/lifetime were classified as nonsmokers. Multiple regression over several variables of interest yielded IHD odds ratios of 0.97 (0.73–1.28 95% CI) for nonsmoking males and 0.99 (0.84–1.16 95% CI) for nonsmoking females married to smokers. No dose/response gradient was observed in relation to spouse's smoking habits.

LeVois and Layard (1995). An analysis of data from the two large Cancer Prevention Studys I and II (CPS-I, CPS-II), two national surveys conducted by the American Cancer Society (ACS). These two surveys provide a total of 18,073 CHD deaths, a number that far outstrips all combined cases ever published on the subject. These and the data from the National Mortality Followback Survey provide a record of over 19,462 CHD deaths, compared with less than 2400 from all reports published to date. The CPS-I and CPS-II studies report risks of CHD for ETS exposure ranging from 0.97 to 1.03. Pooled data from CPS-I, CPS-II, and the NMFS give a CHD risk estimate of 1.00 (0.97–1.04 95% CI).

The absence of homogeneous characteristics among ETS-CHD studies precludes a metaanalysis numerical summation that could be credible and scientifically justified. Especially the data from the stronger studies show that epidemiologic studies are unable to conclude that ETS exposures represent a CHD risk. Together, all studies highlight the futility of further studies to measure what appears to be an absent effect, in light of the vast MS/ETS dose differentials and the CHD-NOAELs for active smoking.

With this in mind, conjectures of possible causal pathogenic mechanisms become a superfluous exercise. However, investigations about mechanistic hypotheses have produced additional evidence of no-effect thresholds for active smoking and CHD and further contribute to negate the hypothesis of CHD risks from ETS.

ETS AND POSSIBLE CHD RISK FACTORS IN HUMANS

The evidence of NOAEL thresholds for active smoking and ETS is not confined to epidemiologic studies: it is also generally apparent in studies of the biomarkers and risk factors that are thought to have a pathognomonic role. Thresholds should also be viewed in the context of the obvious resistance and defenses that humans must develop against xenobiotics from a variety of sources and against the inevitable background of DNA damage from natural metabolic functions that cause an average of 10,000 measurable DNA modification events per hour in each mammalian cell (Billen, 1990; Ames and Gold, 1991).

ETS and xenobiotics. It has been suggested that mutagens and carcinogens may have a role in the initiation and pathogenesis of CHDs. In this context, the meaning of the mutagenicity associated with smoking remains speculative. Extensive studies by the National Toxicology Program and other researchers have failed to validate mutagenicity as a predictor of carcinogenicity in animal bioassays or in man (Ashby and Tennant, 1991; Zeiger *et al.*, 1990; Tennant, 1988; IARC, 1987; USEPA, 1986; OECD, 1984). Studies have also shown that the mutagenicity of smokers' urine is elevated only in smokers of over 10 cigarettes/day, offering other evidence of a threshold effect (van Doorn *et al.*, 1979; Mohtashamipur *et al.*, 1985). More recent studies report that—although mutagenic—cigarette smoking may actually protect against additional genotoxic insults (Oesch *et al.*, 1994).

A review by the International Agency for Research on Cancer listed 10 studies that could not find differences in sister chromatid exchange (SCE) frequencies in peripheral lymphocytes of smokers and nonsmokers, while studies reporting a dose/response gradient were consistent with a NOAEL threshold for smoking less than 10 cigarettes/day (IARC, 1986, pp. 191–192). The situation has been confirmed by more recent studies of SCE frequencies in ETS-exposed subjects (Sorsa *et al.*, 1989; Gorgels *et al.*, 1992).

Significantly, studies report that aborted fetuses from smoking mothers have 40% less chromosomal abnormalities than fetuses from nonsmoking mothers (Kline *et al.*, 1993), while other studies report that maternal

smoking is associated with a much decreased risk of mongoloid retardation or Down syndrome (Kline *et al.*, 1993; Cuckle *et al.*, 1990).

In general, no association was found between 4-aminobiphenyl-hemoglobin adducts, pack years of smoking, and cancer diagnosis (Weston *et al.*, 1991). Following nuclease P1 enrichment techniques, DNA adducts were detected in oral tissues, but the adduct burden in smokers of 1–10 cigarettes/day was not different from the burden in nonsmokers, giving another confirmation of threshold (Jones *et al.*, 1993). Studies of human lung cancer tissues found that serum cotinine levels and adduct levels were not correlated and could detect adducts only in 7 of 38 individual tumor samples (Shields *et al.*, 1993). DNA adducts of aromatic hydrocarbons in lymphocytes were not found to correlate with smoking habits (van Schooten *et al.*, 1992; Grzybowska *et al.*, 1993). DNA adducts were at similar levels in sperm cells of smokers and nonsmokers, a finding of interest given the intense DNA replication in spermatogenesis (Gallagher *et al.*, 1993). Equal similarities were reported for DNA adducts of cervix tissues (King *et al.*, 1994).

ETS, thrombus formation. Hypotheses have proposed that increased blood-clotting capacity may explain the association of heavy smoking and cardiovascular events. However, the Framingham study reports an absence of cardiovascular risks for smokers of 1–10 cigarettes/day, consonant with an immaterial change in mean fibrinogen (about 1%) in smokers of less than one pack of cigarettes/day (Kannel *et al.*, 1987). It has been suggested that two eicosanoids, prostacyclin and thromboxane A_2, are altered in smokers, but studies indicate no change in smokers of less than 10–15 cigarettes/day (Wennmalm *et al.*, 1991). The large Kuopio prospective study in Finland found a correlation of plasma fibrinogen levels with several psychosocial and socioeconomic variables, but not with smoking (Wilson *et al.*, 1993). Thrombomodulin levels were not found to be elevated after smoking (Kubisz *et al.*, 1994). Vicari *et al.* (1988) measured several thrombotic factors and found no differences due to active smoking. Haire *et al.* (1988) found no changes in fibrinolytic activity after active smoking. Yamashita *et al.* (1988) found no effect of smoking on platelet aggregation. Handley and Teather (1974) and Barbash *et al.* (1993, 1994) give indication that smoking may protect against thromboembolic complications after myocardial infarction and surgery. Similar results were reported by Pollack and Evans (1978). The Atherosclerosis Risk in Communities Study of 15,800 men and women in the United States found that smoking was positively associated with levels of Antithrombin III, a major anticoagulant factor (Conlan *et al.*, 1994).

Some studies that suggest differently have been flawed or misinterpreted. A study by Burghuber *et al.* (1986) may be irrelevant because the exposure and ADP level used to induce platelet aggregation were 10- to 20-fold higher than under normal physiologic conditions. The study also found implausible changes in platelet sensitivity in nonsmokers but not in active smokers. Equally, studies by Davis *et al.* (1989) used a nonstandard platelet aggregation assay, which is influenced by the procedure to draw blood, the presence and kind of anticoagulant, centrifugation parameters, and other variables. Also, the meaning of endothelial cell carcasses in circulation is not apparent. In any event the study reports that "After passive smoking, the percentage carboxyhemoglobin level did not correlate significantly ($P > 0.60$) with the platelet aggregate ratio or the endothelial cell count. . . . Neither the plasma nicotine concentration after passive smoking nor its change from before to after passive smoking was significantly ($P > 0.20$) correlated with the corresponding values of the platelet aggregate ratio or the endothelial cell count." Further, the paper states that "The significance of the platelet aggregate formation and an increased concentration of anuclear carcasses of endothelial cells in blood after passive smoking is not known."

ETS, cholesterol, lipidemias, and hypertension. The Framingham Offspring Study and a Kaiser Permanente study report that cigarette smoking was not correlated with Lipoprotein(a) levels (Jenner *et al.*, 1993; Selby *et al.*, 1994). Between 1981 and 1990, an evaluation of 11,199 randomly selected subjects in New England found no association of smoking and dyslipidemic hypertension (Eaton *et al.*, 1994). The British Regional Heart Study, a large prospective study of 7735 men aged 40–59, reported on alcohol drinking, smoking, and cholesterol levels, concluding that "current smokers who were heavy drinkers or nondrinkers had the lowest mean cholesterol levels" (Wannamethee and Shaper, 1992). A Japanese study also found no difference in plasma cholesterol between smokers and nonsmokers (Imaizumi *et al.*, 1991). A study of 51,723 participants of community-based cholesterol screening clinics in 10 U.S. cities found no association between active smoking and plasma cholesterol levels in men and women over age 60 and no elevation of plasma cholesterol for younger subjects smoking less than 10 cigarettes/day (Muscat *et al.*, 1991).

The Cardiovascular Health Study Collaborative Research Group reports that in a cohort of 5201 men and women over 65 years of age, cigarette smoking was a negative predictor of blood pressure, confirming a number of prior reports (Tell *et al.*, 1994). A recent collaborative study of the Center for Disease Control of the U.S. Department of Health and Human Services found that coronary occlusion was inversely correlated with levels of high-density lipoproteins (HDL), but unrelated to smoking (Freedman *et al.*, 1994).

The massive WHO-MONICA study actually "showed a strong negative association between regular smoking and high cholesterol in the male populations and a

strong negative association between regular smoking and high blood pressure in female populations" (MONICA, 1994). Well known is the so called "French paradox," whereby the French population shows 55% less CHDs that the rest of the populations surveyed in the MONICA project, despite experiencing high levels of cigarette smoking, hypertension, and total cholesterol (Renaud and de Longeril, 1993). The Helsinki Ageing Study reports a slight inverse association of active smoking and aortic valve degeneration in the elderly (Lindroos *et al.*, 1994). In China, coronary mortality is some 10 times less frequent than in Germany, although the prevalence of smoking is 70% in China versus 37% in Germany. Total cholesterol, however, is much higher in German than Chinese subjects (Stehle *et al.*, 1991). Yet, also in Germany, the prevalence of most CVD risk factors increased considerably during a period of substantial mortality declines (Hoffmeister *et al.*, 1994). Anomalies such as these have led prominent clinicians to conclude that total and low-density lipoprotein (LDL) cholesterol may be the only demonstrable CVD risk factor (Roberts, 1989).

These considerations tell that the active smoking of less than 10 cigarettes/day or ETS exposures are unlikely to adversely influence lipidemic CHD risk factors. As such, they support the notion of NOAELs for active smoking and cardiovascular diseases. In fact, the National Cholesterol Education Program only lists smoking of over 10 cigarettes/day as a possible CHD risk factor (NCEP, 1988).

ETS and ventilatory function. Compromised ventilatory function has been suggested as a possible risk factor for CHDs; however, there is evidence for respiratory NOAELs in the reported associations with active smoking. Early reports of forced respiratory volume (FEV_1) and forced vital capacity (FVC) deficits in smokers are still compatible with NOAEL thresholds below 10 cigarettes/day (Dockery *et al.*, 1988; Sorlie *et al.*, 1987). The Multiple Risk Factor Intervention Trial (MRFIT) tested 6347 males randomly distributed in a usual care group (control) and a special intervention group that included an intensive and substantially successful smoking cessation program. During a 6- to 7-year follow-up, FEV_1 measures were similar in the two groups, a finding that confirms reports from previous studies (Browner *et al.*, 1992).

A threshold effect at some 10 cigarettes/day was also reported for emphysema in asthmatic patients (Kondoh *et al.*, 1990). Elastin peptide concentration in circulation has been suggested as a marker of lung elastin degradation and thus of emphysematous changes. A recent study found no correlation between elastin peptide concentration and smoking (Frette *et al.*, 1992). Another study found that severity of microscopic emphysema did not increase with daily cigarette consumption (Gillooly and Lamb, 1993). More recently, a high-resolution computed tomography study of patients with interstitial lung disease reported no correlation of smoking with either the disease or emphysema (McDonagh *et al.*, 1994).

ETS and carbon monoxide. The possible effects of carbon monoxide (CO) on the cardiovascular system are largely based on inferences from dated claims (Aronow, 1978). In general, such claims hold that 1–2% CO concentrations trigger angina episodes, even though they are close to typical background ambient concentrations. Such claims are difficult to accept because most epidemiologic studies of active smoking report no-effect thresholds for angina at well over 10 cigarettes smoked per day, as noted above. Over the years these claims have been criticized even by the U.S. EPA as suffering from a number of technical and design problems (Sheps *et al.*, 1987). The National Research Council had this to say of these claims:

> There were some subjective elements in the evaluation of these patients, and the physician conducting these tests was aware of the test conditions, i.e., smoking or not and ventilated or not. Consequently, the findings of this study, in the absence of a true double-blind approach, require verification by other research workers (NRC, 1986).

In regard to the possible aggravation of angina by CO, the National Academy report on ETS as well as EPA regulations consider that such effects may occur at carboxyhemoglobin (COHb) blood concentrations above 3% (NAS, 1986, p. 261; USEPA, 1984). Because this is a risk management figure with an ample safety margin, the true threshold would obviously be substantially higher. In any event, a 3% COHb level is not reached even at high ETS exposure (NAS, 1986; IARC, 1986; Jarvis *et al.*, 1983). Moreover, the first Surgeon General's report found no adverse cardiovascular effects in moderate pipe and cigar smokers despite CO exposures far exceeding typical ETS exposures (USSG, 1964).

EXPERIMENTAL STUDIES IN ANIMALS

Animal studies mostly refer to MS exposures, are generally set up for maximum effect, and hence push dosages to the extremes compatible with survival. Some studies, for instance, cause COHb blood levels as high as 40% in treated animals, a condition that finds no close parallel in human smokers. Also, experimental studies have utilized animals whose reactions to high doses of MS, ETS, or their components are ostensibly of unknown relevance to human responses, given profound differences in smoke generation and exposure conditions, and in anatomy, physiology, and metabolism. In the end, there is no doubt about potential pathogenic effects of cigarette smoke administered at extremely high doses to animals. At the same time, it is equally clear that the interpretation of such effects in equivalent human terms requires inferences that are unwarranted

by the profoundly different conditions under which they are obtained.

Olson (1985) reported increased ornithine decarboxylase activity in tracheas of rats exposed to sidestream cigarette smoke. However, this study failed to show increased activity in the lungs, and no effect whatsoever was noted at the 10% sidestream smoke dose, despite considerable exposure documented by COHb levels around 6%.

Because they could both inactivate and activate xenobiotic to electrophiles of concern, a possible pathognomonic meaning is still a matter of conjecture in regard to the active-smoking induction of such polymorphic enzymatic systems as cytosolic glutthione S-transferase, P450 cytochromes for aromatic hydrocarbons and debrisoquine—aryl hydrocarbon hydroxylases (AHH) or microsomal monooxygenases (MMO)—and the arylamine acetylators. The interpretation of their significance is further complicated by a multitude of genetic controls and determinants in specific phenotypes (Ketterer *et al.*, 1992; Anttila *et al.*, 1992; Bartsch *et al.*, 1992; Caporaso *et al.*, 1992; Vineis and Ronco, 1992). For instance, Gairola (1987) found that such induction happened in mice and rats but not in guinea pigs, the latter actually experiencing a small reduction of activity, a finding confirmed by other studies and in other animal species (Bilimoria *et al.*, 1977; Lubawy and Isaac, 1980). In any event, HHA-MMO activity may be necessary to both activate and deactivate xenobiotics, and therefore the significance of such changes remains moot.

The studies by Zhu *et al.* (1993, 1994) are equally remarkable for their lack of adverse findings. The rabbits of the first study were exposed to extreme concentrations of what amounts to freshly diluted sidestream smoke, with particulate concentrations 100 times and 1000 times higher than for typical ETS at the low and high doses, respectively, when considering that typical ETS particulate concentrations listed by the EPA are in the order of 30 $\mu g/m^3$ (USEPA, 1992c). There were conflicting effects on serum triglycerides, cholesterol, and high-density lipoprotein cholesterol. Bleeding time decreased in the treated groups, but paradoxically platelet aggregation and platelet count also decreased in control animals. The atherosclerotic changes mentioned in the paper actually amounted to somewhat increased lipid deposits in the arterial walls, although the study does not provide the micrographs necessary for an independent evaluation. The pathognomonic significance of such changes is unknown, given that they were similar in unexposed control animals and that no report is given of the likely effects of the stress induced by smoke exposure. Also, the results presented and the presence of lesions in control animals must be interpreted in the context of the natural predisposition of New Zealand rabbits to atherosclerosis, especially when fed a high-cholesterol diet as in this study. The second Zhu *et al.* study also entailed exposures to sidestream smoke at concentrations two to three orders of magnitude higher that for typical ETS exposures, reaching COHb levels near 9% in plasma and plasma nicotine levels two to three times higher than in average active smokers. Baseline hematologic values were substantially different among different groups. Paradoxically, the exposure significantly reduced total plasma cholesterol. The animals were also implanted with a snare occluder to the left anterior descending coronary artery, which was eventually activated to cause left ventricle infarction. No controls were provided to account for the obviously severe general and cardiac stress. Studies in cockerels produced weaker results and are even less interpretable in relative human terms (Penn and Snyder, 1993; Penn *et al.*, 1994).

One of the largest, best-planned, and rigorously conducted inhalation studies of cigarette smoke ever performed was a 2-year massive inhalation study sponsored and directed by the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI). It was performed between February 1978 and March 1980 on 220 purebred beagles fed a 5% cholesterol diet and exposed by tracheostomy to mainstream cigarette smoke variously spiked to provide excesses of nicotine or CO or of both (Hazleton Laboratories America Inc., 1980). The study was designed and monitored by a group of top experts specifically assembled by NCI-NHLBI. After 2 years of exposure, the unexpected results gave unequivocal indication that increasing levels of cigarette smoke, CO, and nicotine reduced the severity of atherosclerotic lesions. The final report concluded that "[t]hese results appear more indicative of a possible protective effect from cigarette smoking and/or CO inhalation than of an atherogenic effect." The study could not find incidental lesions of the respiratory system nor significant changes in blood lipids among the exposed groups.

Thus, the data from laboratory and animal experiments offer no plausible argument to classify ETS as a human CHD risk, they do not contradict or rather support the evidence of NOAELs for active smoking and CHD, and therefore contribute to falsify the hypothesis of CHD risks from ETS.

CONCLUSION

Plausible ETS doses are thousands of time less than MS doses that appear to have no adverse CHD effects in active smokers. Such determination precludes the inference that ETS is a CHD risk, unless we are prepared to forgo all we have learned since Paracelsus about pharmacodynamic and kinetic discontinuities at low doses. By far the majority of experimental reports in man or animals either do not contradict or support this conclusion and together indicate that epidemiologic studies have been chasing an absent CHD effect—a conclusion sustained by the generally equivocal or null reports from epidemiologic studies of ETS. The instability of data

from most epidemiologic studies, the heterogeneity in study design, data collection, and evaluation methods, precludes a metaanalysis numerical summation that is scientifically justifiable. The evidence favoring the ETS-CHD association remains conjectural, while the evidence against the association is suitably documented. According to the scientific method, the only justifiable conclusion is that available data continue to falsify the hypothesis that ETS is a CHD risk factor.

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