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DR. R. T. GOTTESMAN

Gerrie Bjornson

February 19, 1985

EPA STUDY

Please note the attached UPI story concerning a study of indoor air pollutants by an EPA scientist.

It alleges that vinyl chloride fumes account for 27 cancer deaths annually -- second only to cigarette smoke.

Could you please (a) obtain a copy of the report, and (b) advise the best means of beating up on the EPA?

Thanks.

G. R. Snider, Jr.

GRS/gfs/VS0729M

Attachment

cc: N. C. Jacobs
A. J. Olson
J. D. Tanzilli
R. T. Gottesman (VI)

2ND-HAND SMOKE A KILLER, STUDY SAYS

WASHINGTON (UPI)—Tobacco smoke has become one of the most deadly indoor air pollutants and can be expected to kill between 00 and 5,000 non-smokers a year, government scientist said yesterday.

"We believe it's 5,000. The lower ound is 500, and it's certainly not ss than 500," said James Repace, n analyst for the Environmental rotection Agency's office of air nd radiation.

The report singled out second-hand or "passive" tobacco smoke from cigarettes, cigars and pipes as the major cause of death due to cancer caused by airborne carcinogens.

"We don't have anything else that causes even 500 deaths a year," Repace said.

Repace and Alfred Lowrey, a chemist at the Naval Research Laboratory, based their conclusion on several years of research on non-smokers who are exposed to tobacco smoke.

The two conducted their study independently, not for the government.

EPA spokesman Dave Cohen said the agency's Carcinogen Assessment Group questions the conclusion that second-hand smoke could kill as many as 5,000 non-smokers a year.

"The EPA review of the report tends to adhere to the part of it that supports the possibility of 500 deaths per year," Cohen said.

Vinyl chloride, a chemical used in manufacturing plastics, is in second place, blamed for 27 cancer deaths annually, according to Repace's study.

William Toohey of the Tobacco Institute criticized the report, saying Repace, a physicist, was "out of his area of expertise here."

"Even the surgeon general has not asserted that ambient tobacco smoke causes cancer in non-smokers," he said.

In the study, Repace and Lowr said their statistics should be considered "preliminary and subject change as improved research becomes available."

The report likened the heavie exposure to that encountered by non-smoking musician who pe forms regularly in a smoky nigl club and who resides in a sm apartment with a chain smoker.

SPI-00173

SUBJECT: Repace and Lowrey's Estimate of the Lung Cancer Risk From Passive Smoking

FROM: Elizabeth L. Anderson
Director
Office of Health and Environmental Assessment (RD-689)

TO: Joseph Cannon
Assistant Administrator
for Air and Radiation (ANR-443)

THRU: Bernard D. Goldstein
Assistant Administrator
for Research and Development (RD-672)

This memo is in response to your request that the Carcinogen Assessment Group (CAG) review the paper by Repace and Lowrey on the risk of lung cancer due to passive smoking. Herman Gibb of the CAG has prepared a review of the Repace and Lowrey paper, and a copy of his review is attached. His conclusion is that of the two annual lung cancer risk estimates for passive smoking generated by the authors, the lower risk of 0.87×10^{-5} is better supported. It should be noted that even this risk would, given the size of the population exposed to passive smoking, translate into a significant population risk in comparison to other environmental carcinogens.

Attachment

cc: Vicki Vaughan-Dellarco (RD-689)

SUBJECT: Repace and Lowrey's Estimate of the Nonsmokers' Lung Cancer Risk From Passive Smoking

FROM: Herman J. Gibb
Epidemiologist
Carcinogen Assessment Group (RD-689)

TO: Elizabeth L. Anderson
Director
Office of Health and Environmental Assessment (RD-689)

THRU: Robert E. McGaughy
Acting Technical Director
Carcinogen Assessment Group (RD-689)

As requested, I have reviewed the report by Repace and Lowrey entitled "Estimate of the Nonsmokers' Lung Cancer Risk from Passive Smoking". The authors have derived two estimates of the annual lung cancer risk to passive smokers. One estimate is 0.87×10^{-5} per year and is based on a one-hit model ($P = 1-e^{-Bd}$ where B is the response in smokers and d is the dose from passive smoking). The second estimate of 8.0×10^{-5}, an order of magnitude higher than the estimate from the one-hit model, is a so-called "phenomenological" estimate and is based on the excess lung cancer incidence rate for nonsmoking non-Seventh Day Adventists over that of nonsmoking Seventh Day Adventists (SDAs). Since SDAs do not smoke, Repace and Lowrey assumed that they would not be exposed to passive smoking from spouses. Moreover, a substantial portion of SDAs were reported to "work for an organization owned and operated by the SDA church" and thus would probably not be exosed to smoking at their place of employment. Differences in susceptibility, dose-rate, and dose to the target tissue between smokers and nonsmokers would, the authors theorized, make the higher "phenomenological" estimate more valid than the one-hit model which utilized a dose-response in smokers.

The lung cancer risk estimate for nonsmokers derived by the authors with a one-hit model is a rather crude approach that utilized a slope derived by dividing a lung cancer excess risk of all smokers as a group by the average amount of tar smoked by a smoker. In an independent anaylsis, however, Thorslund (1982) of the Carcinogen Assessment Group (CAG), using a more sopnisticated model, achieved a result similar to that of Repace and Lowrey's. Thorslund (1982) used Doll's (1978) model of the lung cancer risk to British physicians due to smoking cigarettes and a 1982 estimate by Repace and Lowrey of the tar intake for a passive smoker to calculate the lung cancer risk to a

passive smoker.

The major problem with the "phenomenological" estimate is the authors' assumption that the difference in the lung cancer rate between non-SDA and SDA nonsmokers is due to passive smoking. SDAs are a very unique group and may differ from the general population with regard to lung cancer risk by more than just their lack of exposure to passive smoking. In addition to not smoking, SDAs do not drink, and they maintain rather strict diets. As indicated above, they tend to work in SDA businesses. Repace and Lowrey, by their discussion, attempted to mimimize the possibility that lifestyle differences other than smoking may be partially accountable for the difference in lung cancer risk, but the issue has not been resolved.

A separate problem with the "phenomenological" estimate is Repace and Lowrey's calculation of the age-adjusted lung cancer rates for SDAs and non-SDAs. They have multiplied an age-adjusted lung cancer mortality ratio of SDA non-smokers to non-SDA non-smokers, provided by the author of the SDA study, by the crude lung cancer mortality rate for non-SDA nonsmokers to arrive at an age-adjusted lung cancer mortality rate for SDA non-smokers. This approach will not provide the age-adjusted rate. The calculation of the age-adjusted rate for both SDA non-smokers and non-SDA non-smokers would require information not provided by the authors of the SDA study in the original report.

Lastly, the authors indicate that the age-adjusted lung cancer rate attributable to passive smoking from the SDA study is similar to that of the Hirayama study of non-smoking females married to smokers. The Hirayama study has been severely criticized in letters to the British Medical Journal where the study was published. Two of the issues which raise considerable concern to this reviewer are: 1) it is unclear from the Hirayama study and from his replies to the criticism whether the rates are age-adjusted for the females or not; 2) there does not appear to have been any analysis by length of exposure. The many issues raised by other reviewers of the Hirayama study are too lengthy to go into here, but further discussion can be provided if necessary.

In summary, the estimate of the annual lung cancer risk to passive smokers derived by the authors using a one-hit model (0.87×10^{-5}) is more reasonable than their "phenomenological" estimate (8.0×10^{-5}). The assumption of the "phenomenological" estimate that the entire difference between the lung cancer rate in non-SDA nonsmokers and SDA nonsmokers is due to passive smoking is questionable. The use of data from the Hirayama study in an attempt to verify this absolute difference is also questionable because of the shortcomings in the Hirayama study. As a final note, it would be interesting to attempt to validate the authors' theories with regard to susceptibility, dose rate, and dose-to-the-target tissue in nonsmokers. Information derived from such studies might then be used to improve the risk model for passive smokers.

cc: Charles Ris (RD-689)
Todd Thorslund (RD-689)
James Repace (ANR-445)

SPI-00176

REFERENCES

Doll, Richard and Richard Peto. 1978. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. Journal of Epidemiology and Community Health. 32:303-313.

Thorslund, Todd. 1984. Estimation of the effects of exposure to a carcinogen that fluctuate over time on the lifetime risk of cancer death. Presented at the Pacific Division of the American Association for the Advancement of Science Annual Meeting, Santa Barbara, California, August 1982.

Dr Bonnell
Schwartz
Georgetown U.

SUMMARY OF CONCLUSIONS

In a recent report, Repace and Lowrey attempted to quantify the relationship between exposure to environmental tobacco smoke (ETS) and lung cancer in the non-smoker. The analysis relies on two distinct risk assessment methodologies. The first method uses a "phenomenological" model that focuses primarily on data purportedly derived from a study of Seventh Day Adventists. The second method uses a "one-hit" model applied to excess mortality estimates from case-control studies.

This report reviews the conclusions drawn by Repace and Lowrey as well as the methodologies they employed. Stated briefly, qualitative and quantitative analyses of risk leading to the conclusion that ETS exposure results in excess cancer death are based on assumptions and derivations which are supported neither by the data nor appropriate risk analysis technique.

The phenomenological model estimates are based on presumptions inconsistent with the data and the conclusions of the investigators who published the data. Specifically, Repace and Lowrey have recalculated and reinterpreted the data from the Seventh Day Adventists (SDA) study by Phillips et al (1980, a;b) in a way which has not been validated. The problem is compounded by an attempt to support the analysis with data from several recent studies of cancer incidence among non-smokers. The report also contains no evaluation or consideration of those studies that have failed to demonstrate a lack of excess risk.

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Risk estimates based on a purely mathematical (one-hit) model are inadequately validated and essentially unsupported. There are two basic reasons for this. First, the exposure estimates are based on clearly speculative assumptions. Second, the exclusive use of the one-hit model is both biologically and statistically unsound.

During the past several years, a number of scientific bodies have convened to share views and information regarding the health consequences, if any, of exposure to ETS. The conclusion consistently reached has been that the relationship between exposure to ETS and lung cancer in non-smokers is equivocal at best. For reasons which are unclear, the authors have not considered this information in their report. It is worthwhile to review what the authors did not address in their report.

HISTORICAL PERSPECTIVE

Three times in little more than a year, groups of scientists have gathered in the United States and in Europe to discuss environmental tobacco smoke. Among the 65 participants at the three meetings were many scientists whose contributions to knowledge about ETS, its measurement and possible health consequences, have been significant internationally. The three workshops to which specific reference is made are the:

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Second Workshop on Environmental Tobacco Smoke: "A Workshop on Effects and Exposure Levels," March 15-17, 1983, University of Geneva, Switzerland; organized by Ragnar Rylander, M.D., University of Gothenburg, Sweden, and the University of Geneva.

"Workshop on Respiratory Effects of Involuntary Smoke Exposure: Epidemiologic Studies," May 1-3, 1983, Bethesda, Maryland; convened by Division of Lung Diseases, National Heart, Lung and Blood Institute, U.S. Public Health Service, Department of Health and Human Services.

Symposium on "Passive Smoking from a Medical Point of View," April 9-12, 1984, Vienna, Austria; organized by American Health Foundation, Austrian Society for Occupational Medicine, Bavarian Academy for Occupational and Social Medicine, German Society for Occupational Medicine, under the patronage of the Austrian Federal Ministry of Health and Environmental Protection and the Bavarian Ministry for Labor and Social Order, in cooperation with the World Health Organization and International Green Cross.

In all three workshops, participants have expressed the view that current data do not allow for reaching conclusions about whether ETS has any chronic health effects on the non-smoker. Conclusions from these workshops, released separately between December 1983 and April 1984, continue to support the determination made five years ago by the Surgeon General of the USPHS that "healthy non-smokers exposed to cigarette smoke have little or no physiologic response to the smoke." They support as well conclusions in reports released in 1983 by the British Royal College of Physicians and the World Health Organization:

> "[T]he extent to which passive smoke exposure can damage the health of otherwise healthy individuals is by no means clear."
>
> "Health or Smoking?"
> Royal College of Physicians,
> 1983

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"[A]lthough epidemiological studies have been undertaken to investigate the possible carcinogenicity of passive smoking and its relationship to respiratory diseases, further work is clearly required."

WHO, "Indoor Air Pollutants: Exposure and Health Effects: Report on a WHO meeting," EURO Reports and Studies 78, 1983

Two of the ETS workshops also called for further research into possible health effects of ETS exposure. The third, meeting specifically to examine available studies on any ETS effect on the respiratory system, urged that existing data sets be thoroughly evaluated before any new large-scale population studies be undertaken. The NHLBI workshop concluded that "a review of the data from the studies which have been carried out or are in progress which address the effect of ETS on the respiratory system suggests that the effect varies from negligible to quite small."

The Vienna workshop concluded that available studies on lung function are conflicting and that metabolic lung changes have not been demonstrated to be caused by ETS. The conference summary (written by Dr. Ernst Wynder, president of the American Health Foundation, and Dr. H. Valentin, who heads the Bavarian Academy for Occupational and Social Medicine) concluded that a health hazard from ETS has not been demonstrated.

The Geneva workshop in March 1983 was a follow-up to a similar conference in 1974, the first international conference on

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the subject. Rylander concluded from the workshop that "Irritation and annoyance must still be considered to be the most prevalent effects ascertained from exposure to ETS." So far as lung cancer is concerned, which is the focus of the Repace/Lowrey analysis, he concluded that:

> "In view of the uncertainty of the ETS exposure in the general population, calculations cannot be made regarding the presence of disease such as lung cancer in the non-smoking population due to exposure to ETS by making reference to the data reported in epidemiological studies on the association between smoking and lung cancer."

All three workshops concluded that ETS exposure and effect have not been adequately quantified. No dose-response relationships can be ascertained if actual exposure has not been measured:

> "Most information on dose response relationships is derived from laboratory experiments and the application to normal conditions is as yet uncertain * * *. For future work, a major research priority is to determine exposure levels of ETS in different segments of the non-smoking population under normal everyday conditions * * *. Not until such data are available can the possible effects related to ETS exposure be further evaluated." -- Geneva workshop, 3/83
>
> "Lack of proper attention to the estimation or measurement of exposure is a major weakness of all the studies carried out so far." -- Bethesda workshop, 5/83
>
> "A drawback in all epidemiological studies up to now consists in the fact that they have been conducted without sufficient quantification of ETS." -- Vienna workshop, 4/84

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Among the confounding factors in ETS studies listed by the Bethesda workshop are unvented combustion products from stoves used for both heating and cooking; other indoor pollutants; indoor environmental characteristics such as temperature, humidity and frequency of air changes; socioeconomic status, culture and crowding; demographic and medical characteristics; parental symptoms; and the possible reporting biases of annoyance and other psychological or social responses to tobacco smoking.

"Extensive as this list of potentially confounding variables may be, the importance of taking them into consideration in the study design and analysis cannot be overemphasized," as stated in the Bethesda report.

Given the obvious concern about the lack of a consistent and coherent body of scientific data demonstrating a relationship between ETS exposure and adverse health effects among non-smokers, the risk estimates generated by Repace and Lowrey are, at the very least, premature. In fact, those estimates suffer from a host of other fundamental deficiencies even if the prematurity of the estimates are overlooked.

SPI-00183

INTRODUCTION

A document entitled "An Estimate of Non-Smokers' Lung Cancer Risk From Passive Smoking" has recently received lay media attention. The report was written by James L. Repace, who is identified as a physicist and policy analyst in the Office of Air and Radiation, U.S. Environmental Protection Agency, and Alfred H. Lowrey, who is identified as a research chemist in the Laboratory for the Structure of Matter, Naval Research Laboratory. I have been asked to comment on the Repace/Lowrey report -- in particular, to review its scientific reliability and credibility.

The report contains a discussion of literature relating to environmental tobacco smoke (ETS) in the home and workplace. In addition, the authors present an interpretation of the data, which they believe demonstrates a casual relationship between ETS and lung cancer. Based on this interpretation, they suggest alternative approaches for quantifying the purported lung cancer risk from exposure to ETS.

The two methods the authors used for quantifying risk are:

(i) A "Phenomenological" model of lung cancer incidence based primarily on a comparative study of a Seventh Day Adventist (SDA) population and a non-Seventh Day Adventist (Non-SDA) population.

(ii) A "linear one-hit" mathematical model based on modeled exposure of the non-smoking population to ETS.

SPI-00184

From the outset it should be stated that, in my view, the scientific quality of the work of Repace and Lowrey is critically undermined by frequent highly derivative and circular reasoning.

The Introduction section of the Repace/Lowrey report sets the tone by presenting a flow of reasoning not directed at evaluating the health consequences of ETS but rather at providing a basis for its regulation in the workplace. For example, the authors state that the "existence of a threshold for carcinogenesis is doubtful * * *." But no attempt is made to temper this broad conclusion by distinguishing among types of carcinogens. Neither do the authors consider the multi-stage concept of carcinogenesis, which in one version or another is generally accepted.

EXPOSURE

The Repace/Lowrey analysis is based largely upon a presumed measure of exposure to environmental tobacco smoke. The authors rely upon their earlier work that predicts the exposure of non-smokers to up to 14 mg of cigarette "tar" per day, with the average population smoke exposure for adults of working age being 1.5 mg/day "tar."

The conclusions the authors reach regarding ETS exposure depend upon several oversimplified or unjustified assumptions. The most obvious of these assumptions is the conflation of room exposures to environmental tobacco smoke, personal exposures, and personal dose. Such an assumption fails to recognize the

complexities associated with attempting to characterize complex airborne mixtures such as ETS.

In their earlier papers, Repace and Lowrey attempted to demonstrate that particulates are an adequate surrogate for the presence of environmental tobacco smoke, and that the presence of such particulates puts the population exposed to them at risk (Repace and Lowrey, 1980; 1982). The pitfalls of this approach have been discussed by others (Sterling, 1982; First, 1984; Jenkins and Guerin, 1984). For example, the particulate levels reported by Repace and Lowrey may have been better correlated with population density than with smoker density. In other words, the data are also consistent with dust raised by the indoor activity of people.

Repace and Lowrey claimed that their field survey data were verified by studies undertaken in a smog chamber. But the ideal mixing conditions found in smog chambers do not replicate the behavior of tobacco smoke in an ordinary or realistic setting. Sidestream smoke, or smoke from the burning cone of a cigarette, is quickly diluted within a room's air and is not distributed evenly, as Repace and Lowrey assume, throughout the volume of a room. Such phenomena have been appreciated by inhalation toxicologists for years. Because of this behavior of environmental tobcco smoke in a realistic setting, and because particulates are not a suitable surrogate for tobacco smoke, the assumption that room measurements can yield knowledge of overall

personal exposures is unfounded.

A further problem with the Repace/Lowrey exposure analysis is the assumption that personal dose can be inferred from data on personal exposure. Personal exposure can be effectively determined only through the use of personal dosimetry, and dose can be effectively determined only through the use of dosimetry and analysis of bodily fluids (e.g., saliva, urine, blood concentrations of nicotine and/or cotinine). Neither personal exposure nor dose was directly determined in the Repace/Lowrey analysis.

Both overall and personal exposures have been determined using nicotine, a substance that, unlike particulates, appears to be unique to tobacco smoke (Hinds and First, 1984; Murumatu et al, 1984). The results of such studies on nicotine show that ordinary exposures are likely to be significantly less than those reported by Repace and Lowrey. Cotinine, a metabolite of nicotine, recently has been used to assess dose in certain circumstances but its variability across individuals is yet to be assessed.

Thus, it is apparent that (1) the exposure estimates, insofar as they are based upon their field survey data and other assumptions, are unfounded and (2) the inference from room exposure to personal dose estimates has not been validated. Therefore, even if Repace and Lowrey were able to develop models for predicting carcinogenic risk, they do not have exposure data of acceptable confidence level that could be used in the model.

BASIS OF CAUSAL INFERENCE

Repace and Lowrey cite a total of nine epidemiologic studies which they consider relevant to passive smoking and the potential relationships that this may have to the incidence of lung cancer or other health disturbances. In addition to these studies, there is the Seventh Day Adventist study which was utilized in the development of phenomenologic risk model. This latter study will be discussed separately.

For one or more reasons, four of the nine studies cannot be used in the evaluation of causal relationship between environmental or lifestyle state and disease. They are either unpublished, poorly described or poorly done. These four studies are of Knoth et al (1983), Miller (1984), Chan and Fung (1983), and Gillis, et al (1983).

Knoth et al (1983) did not have a comparison group as controls. The data from these studies cannot be used since it cannot be determined that a comparable, control gruop did, indeed, act differently than the test group. Miller attempted to ascertain the causes of death in his studies from surviving relatives. No effort was made to verify the cause of death in the majority of cases. It is necessary in epidemiologic study to use objective data from reliable scientific or medical sources. Without some qualified verification of disease, the study must be considered unreliable. Chan and Fung (1983) used an unreliable

questionnaire to obtain passive smoking histories. The differentiation between exposed and non-exposed is blurred and no conclusion as to the effects of one or the other conditions, i.e., exposure or non-exposure can be reached. Furthermore, the citation used by Repace and Lowrey is incorrect. The correct citation is to a German abstract of the paper. The complete paper with data to back this up is not, to my knowledge, available. Similarly Gillis et al (1983) have not yet published a report of their studies. Without a full disclosure of the methods and results obtained therefrom analysis cannot be made.

Some valid information is available from the remaining five epidemiologic studies quoted by the authors. These studies are not, however, as consistent in findings in the report portrays them.

Two of the studies, Hirayama (1981, a;b) and Garfinkel (1981) are cohort studies, i.e., these studies investigated the population from the point of view of exposure rather than of lung cancer. The remaining three studies, Trichopolous et al (1981), Correa et al (1983) and Kabat and Wynder (1984) were case control studies which indicates that they were initiated with groups of individuals having lung cancer and then distribution was made according to exposed and non-exposed to environmental tobacco smoke. All dealt with relatively small populations and there are some indications that some problems exist with all five studies.

They all vary with methods used to classify individuals as to disease state and/or as to exposed and non-exposed.

Repace and Lowrey also failed to mention two other published studies, one from Hong Kong (Koo et al, 1984) and the other from the Netherlands (Vanderbroucke et al, 1984), which report no effect from tobacco smoke exposure among women married to smokers. Thus, close examination reveals that the "evidence proffered by Repace and Lowrey for their claim that non-smoking spouses married to smokers run a higher risk of lung cancer shows that of the eleven available studies, six show no effect on non-smoking wives of smokers.

The studies of Hirayama and Garfinkel amply demonstrate the impossibility, using currently available data, of calculating a lung cancer risk ratio among non-smoking populations exposed to ETS. The sample populations in both studies were extremely large. One of the studies (Hirayama) reported a positive relationship between ETS and lung cancer among non-smokers, while the other (Garfinkel) found no significant relationship. Specifically, Hirayama examined the incidence of lung cancer deaths among non-smoking women whose spouses were smokers versus women whose spouses were not smokers. A risk ratio of 2.5 to 3 was reported. But Hirayama's conclusions have been widely criticized, in part, because the investigators conducted very limited verifications of

actual disease state (the lung cancer diagnosis was confirmed in only about one-third of the subjects). Garfinkel, by contrast, reported the results of a large cohort study in the United States. These authors concluded that the associations between ETS exposure and lung cancer did not reach statistical significance.*

Taken as a whole, these studies do not provide reliable data upon which to base a mathematical prediction of risk. The largest problem with the data reported in most of the studies is the poor quality of data on exposure to ETS.

Remarkably, Repace and Lowrey claim that the results of the pertinent studies are sufficiently consistent and reliable to justify their using a phenomenological model to measure the risk of lung cancer from ETS exposure. They then focus on Phillips' Seventh Day Adventists study, from which they actually derived the data used in their phenomenological risk analysis.

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* Repace and Lowrey claim that recalculation of the negative data from the Garfinkel study supports their conclusion that the association between ETS exposure and lung cancer is significant. The authors offer as support a letter to the editor by Repace. In fact, the Garfinkel study is grossly misrepresented in that letter. The authors have not recalculated the Garfinkel data. Rather they performed a hypothetical rearrangement of a subset of the data based on an assumed misclassification by Garfinkel. This hypothetical rearrangement was made without access to Garfinkel's data and without the support of Garfinkel or his co-workers. The Garfinkel study did not report exposure and/or non-exposure in the workplace. Thus, it is impossible to determine from the Garfinkel study which people were exposed to ETS and which were not. Repace and Lowrey simply estimated workplace exposure and then treated the hypothetically constructed classes statistically. This is clearly invalid.

THE PHENOMENOLOGICAL RISK ESTIMATE

The phenomenological estimate provided by Repace and Lowrey is based primarily on data from a study by Phillips et al (1980, a;b) of Seventh Day Adventists and other similar individuals in California. The study presented the incidence of many health states in Seventh Day Adventists as compared to the population as a whole. Since the incidence of most diseases is far lower in this group than in the population at large and since this group differs from the population at large in many respects including smoking, diet, exercise and various other aspects of lifestyle, the authors of the study, Phillips et al, specifically declined to speculate on causation. In essence, Phillips and his co-workers specifically declined to use the data from the study in exactly the way Repace and Lowrey have done.

Phillips and colleagues reported that some adjusted mortality risks for non-smoking Seventh Day Adventists were different from those for the non-smoking U.S. population as a whole. Part of the difference was explained by selection -- that is, the self-selection of those who chose to convert to that religion. Converts tend to be better educated and of a higher socioeconomic status than the U.S. population as a whole as well as more disciplined in matters of eating, drinking and exercise. These attributes are generally associated with lowered mortality rates. In addition to the effects of selection, the investigators

suggested that the low lung cancer incidence among the Seventh Day Adventists may be related, at least in part, to lack of exposure to smoking. The authors were careful to point out that various differences in lifestyle, the issue of selection, and differences in exposure were all operating in this comparison. They pointed out that they could not say how much of the observed difference in lung cancer rates, if any, was attributable to exposure to ETS.

Repace and Lowrey proceeded to do what the authors of the Seventh Day Adventist study refused to do -- they restricted the data to simulate a cohort study complete with risk ratios.* Phillips and co-workers reported on health habits and defined a health habit index. From these data Repace and Lowrey reconstructed theoretical risk ratios. Phillis et al., were careful to point out that this health habit index was constructed after the fact and that its validity is unmeasured. Repace and Lowrey ignore this caveat and, as a result, this line of reasoning in their report is not only uninterpretable but also based on unproved hypothesis.

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* Repace and Lowrey refer to, but do not otherwise disclose or discuss, unpublished data that they attribute to Phillips. If Repace and Lowrey possessed unpublished data that mitigated or explained their manipulation of the reported Phillips data, they should have presented that data for evaluation.

The the phenomenological risk calculations made by Repace and Lowrey cannot be reconciled with the Phillips data. The authors invoke concordance among the nine epidemiologic studies previously discussed to support their use of the SDA study. In my view, these epidemiological studies do not provide the consistent support that Repace and Lowrey claim. In fact, when viewed as a whole, the available data has not yet established any relationship between ETS and the development of lung cancer. As noted, this is the conclusion that has been reached during the past two years by all of the major reviewing bodies that have examined the issue.

REPACE/LOWREY ESTIMATE OF AGGREGATE RISK BASED ON RISKS IN SMOKERS

In their estimate of aggregate risk, the authors used a linear one-hit risk estimation model. The linear one-hit model is based on the presumption that there is no threshold for the carcinogenic substance in question. It relies not on a compelling hypothesis based on detailed study of the real system but on a worst case presumption. By using a linear one-hit model, the analyst is saying that he or she does not know what the dose-response curve for the carcinogen looks like but that it is clearly no worse than a straight line limited to a 100 percent response at advanced doses, with zero probability of response occurring only at zero dose. One thing that should be immediately

obvious is that the method does not accurately predict the likely number of cancers associated with exposure to a low dose of any carcinogenic substance.

Indeed, use of the linear one-hit is tantamount to our saying that if we wish to set a standard such that the population is exposed to no greater than, for example, a $1x10^{-6}$ excess cancer risk, we can derive an estimate that we are certain is below the exposure concentration for that risk. That does not mean that going above that exposure concentration results in a risk greater than $1x10^{-6}$ but, rather, means that we do not know the upper limit. This result is far different from stating reliably that if the population is exposed to a particular concentration of a carcinogen some known excess of cancer deaths can be expected. In my view, the exclusive use of the one-hit model by Repace and Lowrey cannot be justified in this context. To understand why requires a brief discussion of the current status of risk modeling.

Currently a number of mathematical models are employed to estimate the human cancer risk following exposure to typically low levels of carcinogens. In general, these models fall into two broad categories: (1) tolerance distribution models and (2) stochastic models.

Tolerance distribution models are based on the assumption that every person in the population has his or her own individual

tolerance to the carcinogen in question. Exposure to this carcinogen at any level below this tolerance is assumed to have no effect on the person. However, exposure to the agent at a level greater than the tolerance results in a carcinogenic effect. The tolerances are assumed to vary among individuals in the population. In essence, while each person has a threshold, there may be no population threshold with the minimum tolerance being zero. Assumptions about tolerance determine the dose-response curve. Examples of the most commonly employed tolerance distributions are the (a) log-normal, which gives rise to the probit model; (b) the log-logistic, which gives rise to the logistic model; (c) the Weibull model and (d) the Gamma-multi-hit model.

By contrast, stochastic models are founded on the premise that a carcinogenic response results as a consequence of a random occurrence of one or more biological events and, further, that each individual in the population has an equal probability of these events occurring at a particular dose. The one-hit model that was used by Repace and Lowrey assumes that a cancer may occur after the critical site has been hit by a single biologically effective dose. The multi-hit model follows directly from the one-hit model but assumes that more than one hit is needed to cause the cancer. The multi-stage model assumes that the initiation of the process of carcinogenesis is caused by a number of different stages or biological events, the time rate of occurrence being linearly related to the dose.

Data from high-dose animal experiments yield nearly identical estimated models yet their low-dose behavior is quite different. The shape of the dose-response relationship at low doses has a critical effect on the estimation of risk at such levels of exposure. For example, the one-hit model is linear at low doses, whereas the logit, Weibull, multi-hit and multi-stage models may be either linear or sublinear at low doses. The probit model is always sublinear at low doses and always results in lower risk estimations than other models.

When different models have been applied to the same set of data they typically yield markedly varying estimates of risk. Krewski and Vay Ryzin (1981) described risk assessments for twenty individual chemicals. The calculations unequivocally revealed considerable differences in the estimation of risk among the six models. Figure 1 depicts the results reported by Krewski and Van Ryzin for four carcinogens. In general, for a fixed dose the linear or one-hit model consistently resulted in the highest estimate of risk followed by the multi-stage. The risk estimates for the multi-hit and the logit models are in reasonable accord with each other but are noticeably less conservative than the previously mentioned models. As noted earlier, the probit model provides the lowest estimate of risk.

If the estimates provided by these dose response models vary so widely at low doses, how can they be used for risk estimation and thus guidance? It is natural to ask if it is possible that

one or two of the models may be more biologically plausible than the others. If so, which one and what should be the criteria for deciding on which model to use?

In deciding upon which model to use to predict dose-response relationships at low levels (levels of carcinogen exposure), it is critical that insofar as possible the model be consistent with the present understanding of the process of carcinogenesis in the affected system. This line of reasoning has been a major argument by EPA in justifying the adoption of the multi-stage model since it incorporates several important insights into chemical carcinogenesis, including the premise that carcinogenesis may originate within a single cell and may involve a number of stages. However, even this model has limitations that affect the credibility of its risk estimates. For example, the multi-stage model is limited by the fact that no one knows how many stages there are in the process of carcinogenesis. Consequently, specifying the number of stages in the multi-stage model estimates is in fact not based on a knowledge of the complete process of carcinogenesis. Far worse are models, such as the one-hit model, that incorrectly assume that the quantity of a carcinogen finding its way to the critical cellular sites is proportional to the total exposure. In this overly simple model, the important biological mechanisms of activation and detoxification are ignored.

A lack of biological plausibility on the individual level, stemming from knowledge of the process of carcinogenesis, has been a major criticism of tolerance distribution models such as the probit and logit models. While it is true that these models do not specifically address the nature of the carcinogenesis process on the individual level, they do use the well established fact that differential susceptibility to carcinogenic agents within any population. As noted earlier, the stochastic models assume incorrectly that each individual has an equal likelihood of developing cancer from a fixed dose. Present understandings of the process of carcinogenesis acknowledge that suceptibility to developing cancer is markedly affected by a number of factors such as heredity, diet and age. The tolerance distribution models at least indirectly recognize this while the stochastic models do not.

Given the foregoing, it can be concluded that each model has limitations and is difficult to justify solely on its own merits. For this reason, when regulatory bodies such as EPA, FDA and OSHA have been required to provide estimates of risk, they consider the range of risk estimates these models provide. Then, to limit uncertainty, a goodness of fit analysis is routinely used to place the disparate risk estimates in perspective.

The use of the one-hit model for any serious risk analysis is inappropriate and technically without merit. If the results provided by the one-hit model are desired for completeness and comparison to other more valid approaches, it must be bounded by goodness of fit considerations.

In summary, there are currently two classes of risk models -- (1) stochastic and (2) tolerance distribution. Neither of these classes is satisfactory in inteself inasmuch as ach explains only part of the process of carcinogenesis. Thus, while tumor induction is to a certain extent probabilistic, the susceptibility is known to vary between individuals. This means that none of the available models, used in isolation, has sufficient biological plausibility for widespread scientific acceptance. The one-hit model is generally considered to provide the least plausible and appropriate approach to risk assessment.

The Repace/Lowrey analysis relies exclusively on the one-hit model. Their analysis thus demonstrates a lack of insight into the discipline of risk assessment and a disregard for the minimum requirements for rigor in such analyses.

FINAL NOTE

Based on the foregoing, a number of conclusions can be drawn regarding the Repace/Lowrey analysis of ETS and lung cancer. As to estimates provided by the phenomenological model, I conclude that:

- They are at irrelevant, and probably incorrect.
- They rely on data from studies that have been widely criticized and involve calculations fabricated from data of uncertain origin. This view is not unique to ourselves inasmuch as when reviewed by EPA itself, similar conclusions were reached.

An evaluation of the Repace and Lowrey analysis was made by an epidemiologist from the Carcinogen Assessment Group (CAG) of the Enrivonmental Protection Agency. This evaluation discounted the conclusions of Repace and Lowrey that were based on the SDA study (the phenomenological risk estimate). The EPA reviewer stated that the authors "attempted to minimize the possibility that lifestyle differences other than smoking may be partially accountable for the difference in lung cancer risk, but the issue has not been resolved." The CAG epidemiologist expressed serious reservations regarding Repace and Lowrey's use of data from the Hirayama study to support the findings of the phenomenologic risk model.

As regards the one-hit model,

- The analysis lacks a discussion of the results obtained with other mathematical models.
- Exclusive reliance on the one-hit model is not justified either statistically or biologically.
- The risk estimate thus derived lacks even minimal basis or justification.

Although the CAG reviewer fell short of totally discounting the one-hit estimates of Repace and Lowrey, the reviewer did characterize the one-hit estimates as "crude." Given the current status of risk modeling, we conclude that the estimates provided by the one-hit model are of no relevance to the issue of the relationship between ETS and lung cancer in non-smokers.

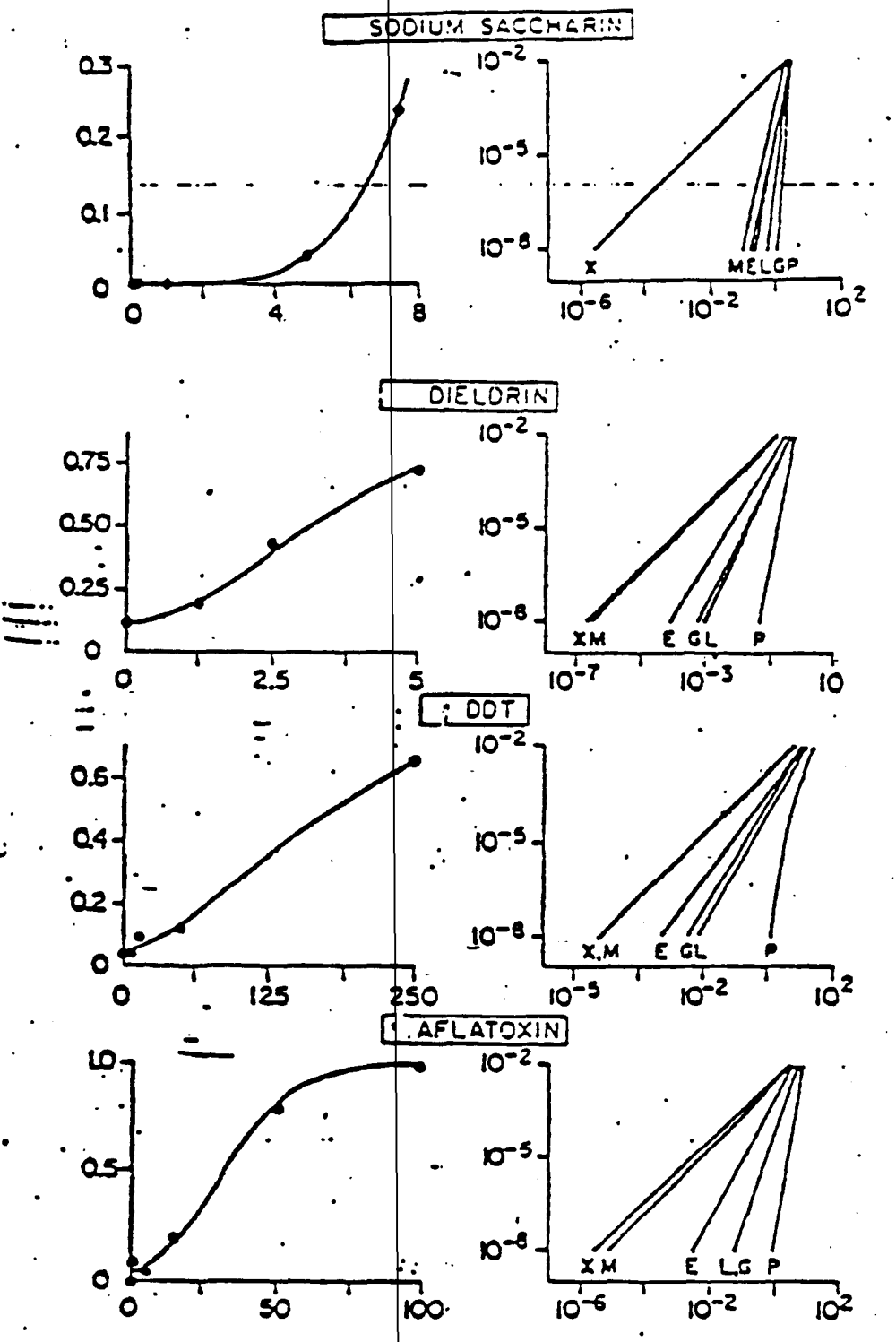

Figure 1

Fitted Extreme Value Dose Response Curves and Estimates of Excess Risk Based on Six Extrapolation Procedures

X - Linear Extrapolation
K - Multi-Stage
E - Extreme Value
L - Logit
G - Gamma Multi-Hit
P - Probit

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Source: Krewski and Van Ryzin (1981).