THE SIRC REVIEW

RESEARCH • TECHNOLOGY • PUBLIC POLICY

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Spotlight on Risk Assessment: More Art than Science?

Comment and Overview

There are many signs of growing interest in improving current risk assessment practices. In the previous issue of *The SIRC Review*, we printed an overview and analysis by the Office of Management and Budget on current regulatory issues and concerns of risk assessment and risk management (Vol. 1, No. 2: 9–21). This critique claimed that the government's approach to risk assessment was heavily biased, exaggerated the actual risks by many orders of magnitude, and led to serious distortions in the risk process and ultimately to public policy. These distortions were most severe, it indicated, in the area of cancer-risk assessment. This process was taken a stage further in March, when the Center for Risk Analysis at Harvard's School of Public Health sponsored a two-day invitational workshop to subject the OMB report to rigorous scrutiny by experts in the field of risk assessment and management. With the permission of Dr. John Graham, the Center's Director, this issue carries a summary of those discussions and the recommendations that emerged from them. We believe they provide a valuable contribution to a better understanding of the issues involved and the difficulties in reforming the process.

The EPA's Administrator, William K. Reilly, also recently addressed the problems embedded in the risk assessment process. In a letter to the Heritage Foundation publication, *Policy Review*, he wrote

> "Environmental risk assessment remains an inexact science at best, one that must incorporate a great deal of uncertainty. Rarely do we have enough information to make unequivocal, unambiguous decisions about risk. Most of our conclusions about human health risks, for example, are based on debatable assumptions about projections, which may or may not accurately predict human health effects."

Mr. Reilly emphasized the agency's desire to base risk assessments increasingly on science and to subject its risk decisions to "rigorous internal and external peer review."

He concluded:

> "Rigorous science remains our most reliable compass in a turbulent sea of environmental policy. Science can lend much needed coherence, order and integrity to the often costly and controversial decisions that must be made."

Dr. Bernard Goldstein is chairing the Committee on Risk Assessment Methodology of the National Academy of Sciences (NAS). Another NAS committee on risk assessment has been formed in response to the mandates of the Clean Air Act Amendments of 1990. The President's Science Advisor, Dr. D. Allan Bromley, and EPA Deputy Administrator F. Henry Habicht both head interagency working groups to establish common scientific principles and consistency in federal risk assessment procedures. The Office of Technology Assessment is undertaking a study of the assumptions underlying current risk assessment methodologies. Former EPA Administrator Lee Thomas has formed a Risk Assessment/Management Dialogue Group to seek a greater degree of consensus among scientists from government, industry and the academic world. And EPA itself is in the throes of a major re-examination of its risk assessment guidelines. Together, these efforts provide a welcome new focus on a field of vital importance to the health and economies of all industrialized nations. It is to be hoped that the new studies will succeed in rescuing risk assessment from its present turmoil and establishing it firmly as an objective scientific process.

The first issue of *The SIRC Review* contained a summary of the human epidemiology and long-term animal studies on styrene and their use in assessing the carcinogenic potential of styrene (Boyd *et al., SIRC Review* 1:9–23). In this issue, we present the full text of the most recently published

epidemiology study by Dr. Otto Wong, referred to in the Boyd *et al.* articles as the EHA Study. Dr. Wong's study of 15,908 workers in the reinforced plastics industry found no association between styrene exposure and cancer. Drs. Bond, Bodner and Cook follow this with an overview of all the recent epidemiology studies. This is an expansion of their comments in the Boyd *et al.* article. They conclude that "Studies completed to date allow for the most thorough evaluation of relatively modest latency periods and varying levels of styrene exposure, some of which were substantial. Under these circumstances, no overall risk of lymphatic or hematopoietic cancer or its various subtypes has been shown to be associated with styrene exposure."

A number of environmental groups have asserted that low levels of styrene, such as those that might migrate from polystyrene food packaging, cause adverse health effects. This issue of *The SIRC Review* contains three articles which deal with this issue Elizabeth Williams analyzes the Foundation for Advancements in Science and Education (FASE) article which alleges that very low levels of styrene could cause health effects. The presence of very low levels of styrene in human adipose tissue found in the EPA National Human Adipose Tissue Survey (NHATS) has been cited by some activist groups as evidence that styrene from polystyrene packaging is poisoning mankind. We have included a summary of the National Research Council's evaluation of the NHATS program and its recommendation for drastic changes; we also have an article by Drs. Miller, Poole and Nolan which addresses specific deficiencies in the adipose tis sue survey with regard to styrene analysis and interpretation of the data.

There is substantial controversy regarding the carcinogenic potential of styrene. At the present time, there is no clear evidence that styrene is carcinogenic in laboratory animals or man, but the available data are inadequate to reach definitive conclusions. The last article in this issue sets forth the styrene research program to provide a more thorough understanding of the carcinogenic potential of styrene and allow a definitive regulatory assessment.

Finally, on behalf of myself and my colleagues, I would like to pay a brief tribute to my predecessor as chairman of the SIRC Science and Technology Task Group, Geoff Granville of Shell Canada, who laid the foundation for the current research program and established *The SIRC Review* as a means of keeping interested parties informed on relevant new research and reviews. He is currently on leave for two years of public service with the Canadian Government in Ottawa as Associate Director of the Bureau of Chemical Hazards in the department of National Health and Welfare. He carries with him our gratitude as well as our very good wishes.

George Cruzan, Ph.D., DABT
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He has a graduate degree in public health (biostatistics) from the University of North Carolina, Chapel Hill, where he also minored in epidemiology and gained research experience as a trainee in the Occupational Health Studies Group. He has done additional work in physiology at Columbia University and neurobiology at the University of North Carolina.

As Group Leader of the Epidemiology Department of the Dow Chemical Company, **Dr. Gregory G. Bond** is responsible for managing the epidemiology research program for Dow Chemical USA. He obtained a Ph.D. in epidemiologic science from the University of Michigan after receiving a B.S. degree in cellular and molecular biology and a masters degree in public health. He has published more than 30 epidemiology research papers in peer-reviewed literature, including case-control studies of cancers in brain, kidney, lung and connective and soft-tissues, as well as cohort studies of workers exposed to arsenic, acrylamide, benzene, chlorinated dioxins and herbicide 2,4-D.

Dr. Bond has served as an adviser to a number of government agencies, including the National Center for Health Statistics and the Agency for Toxic Substances and Disease Registries. He is board certified and has been elected a Fellow in the American College of Epidemiology.

Dr. Ralph R. Cook is a physician and Corporate Director of Epidemiology at the Dow Chemical Company, where he is also responsible for the Health and Environmental Sciences Computer Research Systems group. Board certified in both occupational medicine and epidemiology, he is a Fellow of the American College of Epidemiology, the American College of Preventive Medicine, and the American College of Occupational Medicine. He has been a consultant to the National Research Council/National Academy of Science, the World Health Organization and the California Department of Health Services. In addition, he is the author or co-author of over 60 scientific publications on epidemiology, occupational health, medical surveillance and risk assessment.

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Dr. John D. Graham is an associate professor of policy and decision sciences at the Harvard School of Public Health. He formerly served as staff associate to the Committee on Risk and Decision Making at the National Academy of Sciences (1980–81) and as visiting scholar on regulation at the Brookings Institution (1983–84). After graduating in economics from Wake Forest University and in public policy from Duke University, he received his Ph.D. in public policy from Carnegie Mellon University. He became a post-doctoral fellow in environmental health and public policy at Harvard in 1985 and founded the Center for Risk Analysis in 1989. He is the author of three recent books: In Search of Safety: Chemicals and Cancer Risks (with Laura Green and Marc Roberts); Auto Safety: Assessing America's Performance; and Harnessing Science for Environmnetal Regulation.

Dr. Roland R. Miller is with the Toxicology Research Laboratory at Dow Chemical U.S.A. in Midland, where he is project manager, Styrene Health, Safety and Environmental Issues. Much of his research focuses on animal inhalation toxicology studies and metabolism studies. He re-

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Dr. Miller holds a Ph.D. in toxicology from the University of Michigan and is the author of more than 20 publications. He serves on the Science and Technology Task Group of the Styrene Information and Research Center.

A former instructor in pharmacology and toxicology at the University of Kansas, **Dr. Richarch J. Nolan** is a toxicologist in the Health and Environmental Sciences division of Dow Chemical USA working in the Biotransformation Group and in Biomedical Research. An author of numerous publications, his primary areas of interest lie in the analytical use of pharmacokinetics/metabolism in dose response and species sensitivity.

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Dr. Alan Poole is a scientist specializing in toxicology issues with the Health and Environmental Sciences Division of Dow Europe in Switzerland. He was previously with the Toxicology Research Laboratory of Dow Chemical in the United States, following several years in research work on toxicological and health issues with the pharmaceutical industry and with the British Medical Research Council, where he was responsibe for pioneering research on the pathogenesis of pulmonary fibrosis and carcinogenesis.

An honors graduate from the universities of Wales and Surrey, Dr. Poole earned his Ph.D. in hepatotoxicology at Surrey and is a member of the Royal College of Pathologists. In addition to co-authoring A Practical Approach to Toxicological Investigations, he has contributed chapters to many other scientific textbooks and published over 50 papers in peer reviewed journals.

Elizabeth J. Williams is a senior toxicologist in the Health, Safety and Environment Department of Shell Canada, Ltd, where she provides toxicological support and advice to business units throughout the company. Her primary area of interest is health risk assessment. She serves on the Toxicology and Benzene Issues committees of the American Petroleum Institute and the Canadian Petroleum Products Institute Benzene Committee as well as the SIRC Science and Technology Task Group.

Ms. Williams joined Shell Canada in 1988 after earning her graduate degree in biomedical toxicology at the University of Surrey in England. She is also an honors graduate from the University of Alberta (Zoology) and has completed a two year diploma program in analytical chemistry.

Dr. Otto Wong is chief epidemiologist at Applied Health Sciences, Inc., specializing in occupational and environmental epidemiology and quantitative human risk assessment and risk apportionment. He has conducted over 60 occupational mortality studies in various industries and has also conducted research in reproductive epidemiology, cancer incidence, neurological effects, birth defects, diet and hypertension, occupational health information systems and cancer registries. Dr. Wong has served as a consultant to the National Cancer Institute, the National Institute for Occupational Safety and Health, the Occupational Safety and Health Administration, the National Institutes for Health and various corporations and industrial associations. He has published over 70 articles on epidemiology in professional journals and is a Fellow of both the American College of Epidemiology and the Human Biology Council.

After receiving his Ph.D in occupational epidemiology and biostatistics at the University of Pittsburgh Graduate School of Public Health in 1975, Dr. Wong was appointed Assistant Professor of Epidemiology and Community Medicine at Georgetown University School of Medicine. Prior to his current position with Applied Health Sciences, he was a principal in charge of the epidemiology program at Environmental Health Associates.

Tyranny of the Single Number: Harvard Looks at Risk Assessment Reform

*John D. Graham, Ph.D., et al.**

Risk managers at federal regulatory agencies are seeking to achieve multiple objectives. They include:

- protection of public health from widespread exposure to toxic agents;
- protection of highly exposed and/or sensitive groups from toxic agents on the basis of equity or fairness, even when exposure is not widespread;
- protection of the natural environment and ecosystems from the adverse effects of toxic agents on behalf of both current and future generations;
- responsiveness to public concerns about human health and environmental risks, even when risk assessors are skeptical about the magnitude of the risks posed by toxic agents; and
- economic efficiency by adopting protective regulations when the marginal social benefits of risk management exceed the marginal social costs of risk management (at least where an agency's legislative mandate does not prohibit consideration of economics).

Last fall, the White House Office of Management and Budget issued a detailed critique of the risk assessment process used by EPA and other federal agencies, stating that they vastly overstated actual risks and led to serious distortions of public policy and priorities. In March of this year, the Center for Risk Analysis of the Harvard School of Public Health held a two-day invitational workshop on the OMB report for experts in the fields of risk assessment and management. This summary of their discussion points to perceived strengths and weaknesses in the OMB report and recommends several areas for improvement in current risk assessment techniques.

An adversarial relationship between the Office of Management and Budget (OMB) and the federal regulatory agencies has developed over the years, in part because it is usually impossible to achieve all of these objectives simultaneously. The parties in this adversarial relationship appear to assign differing degrees of important to the achievement of the varios regulatory objectives. Given the different objectives, it should be expected that OMB and the agencies might have different ideas about what is a good risk assessment and what is a good risk management decision.

Several types of risk management decisions are made by the government. At the broadest level, the federal government decides, through a political process involving Congress, the executive branch, and interest groups, how much money and staff will be available at each federal agency to engage in risk management activities. Within each federal agency, decisions are also made about how much money and staff will be allocated to specific risk management programs. Although these resource allocation decisions are of critical national importance, they are not always recognized explicitly as risk management decisions.

Within a particular agency, decisions are made about what rules should be issued and how they should be written. Federal rules address diverse matters

* *This summary was prepared by Dr. Graham and others associated with the Center for Risk Analysis, including John S. Evans and Barry Ryan, Associate Professors of Environmental Health; George M. Gray, Adrienne Hollis and Mark Smith, Postdoctoral Fellows in Environmental Science and Public Policy; and Andrew Smith and Alison Taylor, doctoral candidates in Environmental Health. Dr. Paul Dreisler, a member of the Executive Committee of the EPA Science Advisory Board and former president of the Society for Risk Analysis, was moderator of the workshop.*

such as exposure limits for toxic chemicals in the workplace, tolerance levels for food additives, permissible levels of contaminants in drinking water, and cleanup standards for hazardous waste sites. In addition to national rules, critical decisions are made by regional, state, and local regulatory officials. Cleanup decisions at hazardous waste sites, for example, are made site by site on the basis of feasibility studies, risk assessments, and guidelines established by EPA headquarters and regional offices.

Federal rules are adopted based on legislative mandates that provide risk managers with varying degrees of discretion. When discretion is restricted, it may reflect congressional determination to achieve specific regulatory objectives. Some statutes *(e.g.,* the Toxic Substances Control Act) authorized risk managers to weigh the risks, costs, and benefits of alternative courses of action — even though such factors are not always considered. Other statutes *(e.g.,* the famous Delaney Clause covering carcinogenic food additives and the National Primary Ambient Air Quality Standards under the Clean Air Act) compel the federal government to base decisions solely on health considerations. Still other statutes order risk managers to reduce human health risk to the maximum extent that is technically and economically feasible *(e.g.,* the permissible exposure limits designed to protect worker health under the Occupational Safety and Health Act).

Although regulatory statutes differ markedly, they rarely specify how agencies are to perform risk assessments of human exposures to potentially harmful agents. Risk assessment practice has therefore evolved at federal agencies and become routinized through informal and formal agency guidelines. While statutory mandates and risk assessment practices differ among agencies, the various regulatory cultures share a common policy viewpoint: namely, that risk managers should err on the side of safety when making regulatory decisions in the face of scientific uncertainty.

Within this complex administrative process, OMB requires each federal agency to prepare regulatory impact analyses. Working as an agent of the President, OMB sees the regulatory review process as a device to assure some degree of analytic rigor and economic efficiency in the rulemaking activities of federal agencies. OMB has taken an increasing interest in the technical and policy aspects of risk assessment because risk assessment plays a critical role in rulemaking activities.

White House review of regulatory proposals has been a significant function of the Executive Office of the President since the Ford Administration. Both Democratic and Republican Presidents have seen value in OMB regulatory review, even though such reviews inevitably create an adversarial relationship between regulatory agencies and the Executive Office of the President. While some observers see OMB's regulatory review function as critical to a President's ability to carry out his Constitutional responsibilities and achieve economic and social objectives, others see OMB review as a pernicious barrier to the achievement of the human health and environmental objectives established by the U.S. Congress. Hence, disputes about OMB's role reflect the tensions between Congressional and Presidential authority.

RISK ASSESSMENT AS A REGULATORY TOOL

Risk assessment is an analytic tool rather than an end in itself. Since the tool is used for a wide variety of risk management decisions, it is critical that risk assessors and managers forge a constructive collaboration. Risk assessments should address the needs of risk managers in a rigorous, objective, and timely fashion. Some assessments need to be more refined than others, depending on the importance of the decision.

For chemicals that are known or suspected to cause cancer, federal agencies have adopted standard risk assessment procedures. Specific "default" assumptions are considered appropriate when data are insufficient to complete an assessment. The default assumptions are designed to err on the side of safety in the absence of scientific knowledge. In contrast to more refined risk assessments, these standard assessments do not require extensive case-specific data.

Despite their scientific limitations, standard risk assessments of carcinogens are a useful screening tool *(i.e.,* they help identify potential problems and indicate exposures that are not worthy of further concern). They may also provide a basis for regulatory decisions in cases where risks are potentially significant and the estimated costs of risk reduction are too small to justify a more refined risk assessment.

Refined risk assessments should be tailored to the needs of risk managers as the stakes in risk management decisions increase. Federal agencies are striving to develop refined health risk estimates for human exposures to those chemicals *(e.g.,* benzene, dioxin, and formaldehyde) that cannot be eliminated without imposing substantial economic burdens. Refined risk assessments can be especially helpful when pertinent data are available to replace some of the default assumptions used in standard risk assessments.

Risk managers are often faced with the difficult question of whether to regulate carcinogens on the basis of a standard risk assessment or await a more refined risk assessment. One of the dangers of excessive reliance on refined risk assessments is that regulatory paralysis can result as regulators await additional data. Interestingly, EPA has recently decided to refine its risk assessment of dioxin. In the interim, EPA has decided to continue its current regulatory programs that are designed to reduce human exposure to dioxin.

The three major observations in the OMB Report are quoted below:

> "The continued reliance on conservative (worst-cast) assumptions (by federal agencies) distorts risk assessment, yielding estimates that may overstate likely risks by several orders of magnitude."
>
> "Conservative biases embedded in risk assessment impart a substantial 'margin of safety.' The choice of an appropriate margin of safety should remain the province of responsible risk-management officials, and should not be preempted through biased risk assessments."
>
> "Conservatism in risk assessment distorts the regulatory priorities of the Federal Government, directing societal resources to reduce what are often trivial carcinogenic risks while failing to address more substantial threats to life and health."

STRENGTHS AND WEAKNESSES

The workshop discussion indicated that the OMB Report correctly identified some important deficiencies in the risk assessment practices of federal regulatory agencies.

> Federal agencies do not adequately communicate the scientific uncertainties in the cancer risk estimates that are used to justify regulatory decisions. While many actors in the regulatory process recognize the uncertainties in cancer risk assessment, others are not aware of these uncertainties. By neglecting to characterize these uncertainties, federal agencies provide a misleading picture *(i.e.*, false precision) of what is known about cancer risk to regulators, journalists, Congress, and the American people. Key policy judgements about the treatment of uncertainty are often embedded in the risk assessment itself rather than being presented for resolution to the accountable regulatory officials.
>
> The cancer risk estimates reported by federal agencies, while often based on uniform assumptions and procedures, contain hidden and nonuniform margins of safety. For example, the use of the linearized multistage model for low-dose extrapolation may generate risk estimates which are more protective for some chemicals than others. These inconsistencies arise because the default procedures are scientifically more appropriate for some chemical carcinogens than for others. While in some cases scientists have clues about these inconsistencies, in other cases scientists do not know which chemicals are the best candidates for departing from standard procedures.
>
> Deficiencies in cancer risk assessment may distort the regulatory priorities of the federal government. For example, if standard risk assessments for carcinogens are more protective than those for various noncancer health and safety effects, then they induce the nation to devote too many resources to the control of exposures to selected chemical carcinogens and too few resources to other health problems. Priorities among chemical carcinogens may also be misordered since standard cancer risk estimates are less protective for some carcinogens than for others.

In light of these observations, the OMB Report has raised a red flag about whether America's scarce resources for public health and safety protection are being allocated in the best way.

The Workshop also discussed deficiencies in the OMB Report that it felt were important and should be acknowledged.

> The OMB Report neglected to mention a variety of factors that may cause cancer risks to be underestimated and underregulated. By neglecting to mention these factors, the OMB Report provides an incomplete and imbalanced account of the biases and scientific uncertainties in risk assessment. The regula-

tion of carcinogens is severely limited by the amount of laboratory animal data and epidemiology. Numerous compounds in widespread use have not been adequately tested for carcinogenicity, even though short-term tests and other data may suggest cause of concern. OMB neglected to note that some carcinogenic agents are underregulated simply because they have not been adequately tested.

In its discussion of the biological and statistical issues in risk assessment, the OMB Report makes several misleading and incorrect statements. While these problems are not always highly significant, their cumulative impact is to lessen the scientific quality of the report. Such errors may have been avoided if the document had been peer reviewed prior to publication. Readers should consult more authoritative references on the key issues in risk assessment.

The major findings of the OMB Report are not based on a systematic review of a random sample of agency risk assessments and regulations. Instead, the Report cites selected examples of agency practice in an *ad hoc* fashion to buttress its main points. Workshop participants noted several examples where agency practice was different from the impression given in the OMB Report. Some federal agencies and programs appear to have done a better job than others at the difficult tasks of expressing scientific uncertainty and incorporating new scientific information into risk estimates. Workshop participants noted that the federal government has several efforts underway to improve the risk assessment process.

The OMB Report would have been stronger if it had contained a comprehensive set of recommendations to correct the deficiencies that were identified. Although OMB does urge more quantification of uncertainty and greater use of expected values in cancer risk management. The Report does not, however, recommend specific scientific research programs to reduce uncertainties. Nor does OMB recommend programs to develop credible methods for quantifying uncertainty and calculating expected values of risk. More importantly, the OMB Report does not highlight the specific public health and safety risks that have been neglected due to the alleged distortion of priorities in favor of cancer risk management.

FUTURE DIRECTIONS

In the process of peer reviewing the OMB Report, workshop participants proposed a variety of steps that might be taken in the future to improve risk assessment and management. Although the Workshop did not attempt to achieve consensus on appropriate steps, they are summarized here for consideration by readers.

When risk management decisions are important enough to justify refined risk assessments, analysts should avoid the "tyranny of the single number" by reporting more complete "risk distributions." In some cases numerical distributions may simply reflect scientific uncertainty while in other cases they may reflect known variability in human exposures or sensitivity to toxic agents. These two kinds of distributions should be distinguished and reported separately.

When scientists are unsure about the extent of human exposure or the shape of dose-response curves at low doses, probability distributions should be employed to indicate the extent of uncertainty, thereby taking into account sources of possible conservatism and nonconservatism. The reporting of probability distributions over risk would minimize the hidden policy judgments in risk assessment while forcing risk managers to make explicit policy judgments about what margins of safety are appropriate in risk management. Distributions that highlight uncertainty can also build the case for more scientific research and data collection to reduce uncertainty.

Numerical risk distributions can also be used to elucidate variability in human exposure and sensitivity to toxic agents. Historically, many cancer risk assessments have focused solely on a hypothetical maximally exposed individual. Risk managers should be informed about the full range of human exposures and sensitivities unless there is a compelling policy reason to do otherwise.

In the short run, reporting risk distributions may complicate the tasks of risk managers because it is easier to base decisions on protective point estimates — especially when

the manager's political mandate calls for conservatism in regulatory choice. In the long run, however, numerical risk distributions will better inform everyone about what is at stake in these decisions and thus facilitate more informed political deliberations.

An important limitation of risk distributions is that subjective scientific judgements will be required to quantify at least some of the critical input values and uncertainties *(e.g.,* the shape of the distributions of uncertain biological quantities). Often data will not exist to verify or refute these subjective judgements. There may be situations where subjective judgements are too speculative or polarized to report credible risk distributions. In cases where risk distributions are reported, risk managers and journalists will require training to interpret these distributions properly. Federal agencies have already made some important steps forward in this direction.

The United States should consider implementing an expanded, strategic program of research and data collection to identify and, where possible, reduce uncertainties in risk assessment. A strategic program would focus research resources on the assumptions in risk assessment that have the biggest impact on uncertainty and are resolvable through research and data collection. In the short run, significant payoffs may result from increased application of modern techniques of exposure assessment. In the longer run, an expanded research program on the biological underpinnings of cancer risk assessment is promising. In order to multiply resources and improve the credibility of research, both government and industry should consider making expanded research investments.

Federal agencies should consider adopting a more explicit process for the acceptance of new types of data in risk assessment because some new data are more relevant and valid than others. While current agency guidelines permit departure from default assumptions when warranted by improved science, criteria have not been developed to assess when new information is reliable enough to replace standard assumptions.

It may be easier for agencies to utilize the best science if risk estimates are reported as probability distributions, since probability distributions can be adjusted by scientists to reflect degrees of confidence in new scientific findings. The process of departing from default assumptions should allow for extensive public and scientific comment.

NONCANCER RISK ASSESSMENT

The development of risk assessment methods for noncancer endpoints *(e.g.,* neurological effects and aquatic effects) is critical to making sound regulatory decisions. Reporting noncancer risk estimates may also make it easier for certain cancer risk estimates to be revised downward when new scientific evidence is reassuring. As long as risk managers are presented only cancer risk estimates, there may be a tendency for risk assessors—consciously or subconsciously—to retain certain conservative assumptions in cancer risk assessment in order to capture concerns about other environmental damages and human health effects.

In conjunction with efforts to improve estimates of regulatory benefits due to reduced cancer risk, OMB and federal agencies should also consider uncertainty in the estimated costs of risk management decisions. Although some attempts have been made to quantify the total costs of environmental regulation, less information is available on the specific costs of regulations designed to reduce cancer risk from chemical exposure. More serious consideration of the indirect economic benefits of environmental regulation is also required.

Risk managers also need to know whether the projected costs of regulatory compliance, made at the point of a regulatory decision, are unbiased estimates of the actual costs of compliance incurred several years after the implementation of a rule. Legitimate concerns have been raised about deliberate overestimation and underestimation of regulatory costs. The scrutiny of regulatory costs should extend beyond simple compliance costs and include indirect consequences (both positive and negative) for the productivity, degree of innovation, and competitiveness of American industry.

Efforts to improve risk assessment and management should be undertaken with recognition of the daunting challenge of effective risk communication. More refined risk assessments may make it more difficult for risk assessors and managers to communicate risk estimates to nontechnical audiences. At the same time, more effort needs to be made to understand the concerns of communities that may be at risk because of their proximity to hazardous facilities and to make sure that they are addressed by risk assessors and managers. These communities are often populated by poor and minority groups.

The OMB Report and Workshop discussion identified significant flaws in the federal government's approach to risk assessment and management. Although such flaws were apparent, solutions are not so easy to identify. It is time to move beyond criticisms and begin to propose solu-

tions. The various groups working on improvement of the risk assessment process may want to consider and further develop the future directions that were discussed at the workshop.

The full text of this report may be obtained by contacting Anne T. Jardine, Coordinator, Center for Risk Analysis, Harvard School of Public Health, 677 Huntington Ave., Boston, MA, 02115.

POOR REVIEWS FOR EPA'S ADIPOSE TISSUE SURVEY–I

National Research Council Finds "Fundamental Flaws"

From the NRC Report, "Monitoring Human Tissues for Toxic Substances," May, 1991

The National Human Adipose Tissue Survey (NHATS) was established by the EPA in 1967 to study certain toxicants, e.g., PCB's and organochlorine pesticides, in fat samples from cadavers and surgical patients. A report by Stanley et al. (1986), involving analyses of 1982 NHATS samples, has frequently been cited and often misinterpreted with regard to the human health significance of styrene in fat tissue.

At the request of Congress in 1987, EPA sponsored a special review of the NHATS program by the National Research Council (NRC). After a thorough review, a special committee of the NRC concluded that the program is "fundamentally flawed in concept and execution, and should be replaced in toto". The committee recommended that an improved program be developed that monitors blood samples instead of fat.

With specific regard to the "one time" effort to analyze volatile organic compounds (e.g., styrene) in the 1982 tissue samples, the committee noted that the rationale for analyses was unclear and the methods for sample collection and storage had not been validated. Therefore the integrity of the samples for analyses of volatile organic compounds was questioned.

While collection and analysis of human tissues is "critically necessary" for determining the potential health risk from exposure to toxicants, the program as it now exists "is out of date and only partially fulfills its objectives," the committee reported.

EPA's National Human Adipose Tissue Survey, launched in 1967 to study the prevalence of certain toxic substances in human fat, has been frequently cited and often misinterpreted with regard to the human health significance of traces of styrene found in composite fat samples. In 1987, Congress ordered a review of the program by the National Research Council. The Council appointed a nine member Committee on National Monitoring of Human Tissues, chaired by John C. Bailar III, professor of biostatistics at McGill University School of Medicine, Montreal. The committee's final report was published in May of this year. The committee found the Adipose Tissue Survey to be "fundamentally flawed" and urged that it be replaced by an improved program that would examine blood samples instead of fat.

"A program based on blood samples instead of fat would allow for a broader cross-section of the population to be represented, for a wide variety of chemicals to be studied, and could be carried out using present-day technology at a relatively small cost," the report stated. It pointed out that when NHATS was designed, PCBs and certain organochlorine pesticides—which tend to collect in fat tissue—were targeted for study. But because of new trends in environmental exposure, advances in analytical chemistry, improved equipment, and the discontinuation of such pesticides as DDT and other similar chemicals, blood has become the tissue of choice for monitoring human exposure to toxic substances.

Blood samples are easier to obtain and "less invasive" than collecting fat tissue, the committee noted. Moreover, blood samples reflect more recent exposures, and blood studies could focus more on volatile organic chemicals as well as lead, cadmium and arsenic.

In addition, such a program could be tailored to encompass a more representative sample of the U.S. population. One of the primary deficiencies of the present program, the committee said, is that donors of fat tissue comprise a very selective, not representative, portion of the U.S. population. Fat tissue principally has

been collected from autopsied cadavers at urban hospitals because of the relative availability of specimens. Consequently, the rural population and the healthy population have been greatly underrepresented.

A program based on blood collection would also permit interviews with donors. While some fat tissue samples are taken from surgery patients, the vast majority—nearly 90 percent—is collected from cadavers.

The new program also should incorporate collection of other tissues and specimens, including lean tissue, hair, urine, and other biologic fluids. Regardless of the types of tissues used, all samples should be accompanied by information on demographics, illness, known occupational exposure or other major exposure to chemicals, the committee said.

It recommended that the new program be modeled after the National Health and Nutritional Examination Survey (NHANES) run by the National Center for Health Statistics. NHANES analyzes blood collected from a diverse cross-section of the U.S. population—taking about 16,000 samples a year—to develop statistical information on a wide range of health issues. However, the committee recommended against combining the two programs, citing significant differences in objectives.

The committee stressed the importance of quality control, urging the use of state-of-the-art protocols. Under the existing program, many of the specimens had deteriorated extensively, it found. Specimens improperly stored in plastic bags and glass bottles had dried out. Others were found to be discolored or contaminated with fungus. The committee questioned the worth of this existing archive, explaining that the samples "are likely to have little or no value to a successor program or to other parties inside or outside the government."

Funding for the program had eroded to such an extent, the committee said, that the current level of support—less

NATIONAL RESEARCH COUNCIL BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

Committee on National Monitoring of Human Tissues

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than $1 million per year—"has simply not been enough to sustain it." The program should be funded at a minimum of $3 million per year, "which would be barely adequate to sustain the minimal activity needed to keep the program in long-term existence."

While financial support is crucial, other kinds of resources also are important for the success of the future program, the committee said. Technical staff with expertise in statistics and toxicology is crucial, as well as support at high administrative levels in the agency. "Administrative support informs both the agency and the public that the agency has a firm commitment to the program."

Furthermore, an outside scientific advisory body should be established to advise and provide program oversight. The present program "has suffered seriously from lack of long-term attention from an outside advisory panel; it might otherwise now be in a far stronger position," the committee concluded.

POOR REVIEWS FOR EPA'S ADIPOSE TISSUE SURVEY–II

A Commentary on the Styrene Measurements

By R.R. Miller, Ph.D., A Poole, Ph.D. and R.J. Nolan, Ph.D.

The Environmental Protection Agency (EPA) National Human Adipose Tissue Survey (NHATS) is an annual program to collect a nationwide sample of adipose (fat) tissue specimens and to analyze them for the presence of a variety of organic chemicals. The purpose of the NHATS is to identify and quantify the prevalence and levels of selected chemicals in human adipose tissue. The NHATS samples are collected from autopsied cadavers and surgical patients according to a statistical survey design. The results are used by the EPA to establish an exposure-based chemicals list and to estimate baseline levels and trends of the selected chemicals.

The most recent NHATS results, including data on samples collected between October, 1981, and September, 1982, were reported by Stanley (1986). This report involved a total of 763 individual human adipose tissue samples (subcutaneous, perirenal or mesenteric), which were coalesced into two sets of 46 composite tissue samples. One of the sets was utilized for broad scan analysis of volatile organic compounds, and the other was utilized for analysis of semivolatile compounds. The composite samples were separated by geographical locations *(i.e.* Pacific, Mountain, West North Central, West South Central, East North Central, East South Central, South Atlantic, Middle Atlantic and New England) and then stratified into three age groups (0–14, 15–44 and 45+ years), prior to analysis by high resolution gas chromatography/mass spectrometry. The cooperating physicians and pathologists were requested to take precautions to avoid direct contamination from solvents, plastics, etc., but no specific procedures were required. Also there were no specific instructions to avoid potential contamination that might arise from background contribution of airborne levels of solvents or metals. A wide variety of semivolatile and volatile organic compounds were detected in the composite adipose tissue samples, including dioxins, halogenated solvents, pesticides and miscellaneous other substances including styrene monomer. Styrene monomer was reported to be present in all of the 46 composite samples, with wet tissue concentrations ranging from 8 to 353 ng/g. The highest average styrene concentrations were found in the youngest age group (122.4 ng/g), followed by the intermediate age group with 89.1 ng/g, and the oldest age group with 65.4 ng/g (combining all age groups, the average concentration of styrene in human adipose tissue was 92.3 ng of styrene/g). Since individual tissue samples were not

According to the National Adipose Tissue Survey, styrene was found in 100 percent of the composite samples of human fat reported. This fact has frequently been cited—and misinterpreted—as an indication that the health of the American population may be affected from an overex- posure to styrene. It has even been suggested that this may be the result of the widespread use of polystyrene food packaging. Prior to the recent publication of the National Research Council study pointing to "fundamental flaws" in the adipose tissue survey (see preceding article), the authors of this article examined the specific data relating to styrene and came to similar conclusions, finding the results of the adipose tissue survey "biologically implausible".

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analyzed, the actual percentage of individuals with detectable concentrations of styrene in adipose tissue was not determined. A summary of the composite tissue data is shown in table 1.

TABLE 1

Concentration of Styrene (ng/g) in Human Adipose Tissue Obtained From Different Age Groups
ie 0–14 Years, 15–44 Years on, 45+ years

	0–14 Years	15–44 Years	45+ Years
	38	79	46
	353	28	46
	250	96	76
	250	63	136
	37	41	115
	41	131	61
	44	81	61
	16	46	45
	100	39	42
	180	39	8
	50	28	30
	110	72	78
		70	65
		323	120
		73	9.5
		140	50
		165	124
Range (ng/g) Tissue	16–353	28–323	9.5–136
Average Concentration (ng/g) Tissue	122.4	89.1	65.4

Data obtained from Stanley, J.S. Broad Scan Analysis of Human Adipose Tissue Volume II—Volatile Organic Compounds, EPA MRI Project No. 8821-A01, (1986).

The reliability and utility of the Stanley (1986) NHATS survey for assessing exposure of the general public to styrene is questionable for several reasons, including the possibility of contamination of the samples prior to analysis, and the unknown history of the subjects. Since exposure history was unknown, there is the possibility that the composite samples contained specimens from occupationally exposed individuals which would give results that are not representative of the general public. Nevertheless, the Stanley (1986) report has recently been a focus of concern for some environmental groups. The following evaluation is intended to clarify some of the misconceptions which have arisen regarding the human health implications of the results reported for styrene.

TOXICOLOGICAL SIGNIFICANCE

It is important to note that the Stanley (1986) survey did not establish a relationship between styrene and any type of adverse human health effects. In general, the body fat serves as a temporary storage depot for substances like styrene which have high fat solubility. While stored, there is little potential for harm to the organism (Klaassen, 1986). A substance in the fat is in equilibrium with the free material in the blood, and it is released from the storage site as the substance is metabolized or excreted from the body. Since styrene is rapidly metabolized and excreted (Ramsey and Young, 1978), it has a relatively short biological half-life, even in fat.

In addition to the fact that the Stanley (1986) report did not establish any link between the human adipose tissue styrene concentrations and adverse health effects, other studies provide evidence that even much higher styrene adipose tissue concentrations than those reported in the NHATS samples are not associated with any type of harmful effects in humans. For example, exposure of human volunteers to 50 ppm styrene vapors for 2 hours has been shown to result in average styrene adipose tissue concentrations of 2,420 ng/g when measured during the first 21 hours post-exposure (Engstrom *et al.*, 1978). In this study, the styrene concentration in adipose tissue decreased exponentially, with an estimated half-life in adipose tissue of two to four days. These styrene exposures and adipose tissue concentrations were not associated with any type of adverse effects in the human subjects involved in the study. Moreover, the Occupational Safety & Health Administration (OSHA) recently adopted the current American Conference of Governmental Industrial Hygienists Threshold Limit Value (TLV) of 50 ppm (213 mg/m^3) as the permissible exposure limit (PEL) for workers exposed occupationally to styrene.

Since both the TLV and the PEL refer to airborne concentrations of substances which workers can be repeatedly exposed day after day for a working lifetime without

adverse health effects, it must be concluded that the adipose tissue concentrations associated with airborne exposures up to 50 ppm are not indicative of harmful effects. The average adipose concentrations (2420 ng/g) reported by Engstrom *et al.* (1978) were measured following only two hours of exposure to 50 ppm, and even higher adipose tissue concentrations would occur following an eight hour occupational exposure to 50 ppm. Indeed, Leung & Paustenbach (1988), using physiologically-based pharmacokinetics (PB-PK), estimated that after an eight hour exposure at 50 ppm (213 mg/m^3) the concentration of styrene in adipose tissue would be 9.880 ng/g, approximately 28 times higher than the highest level of 353 ng/g reported by Stanley (1986). Therefore, existing human data clearly indicate that much higher adipose tissue concentrations of styrene at least 7- to 28-fold higher than those reported by Stanley (1986) are not indicative of any type of adverse effects.

It is also important to realize that, while styrene is highly lipophilic, it does not concentrate in tissues of the nervous system to the same extent as it does in adipose tissue. An examination of the composition of various tissues in the human body (Report on the Task Group on Reference Man, 1975) shows that the fat content of adipose tissue can be as high as 91%, while the fat content of human brain is only estimated to be in the range of 9 to 17%, and the fat content of the spinal cord and peripheral nerves is 2.3 to 18.5%. Thus, the fat content of nervous tissue is far lower than for adipose tissue. Since fat content is a primary determinant in the localization of fat soluble substances like styrene, it is not surprising that the concentration of styrene in adipose tissue was found to be 30- to 50-fold higher than in the brain of experimental animals (Savolainen and Pfaffli, 1978).

PHARMACOKINETIC ASSESSMENT

Despite the fact that the levels of styrene in human adipose tissue quoted by Stanley (1986) are not associated with toxicological effects, the reported concentrations were somewhat surprising for non-occupationally exposed individuals. Unfortunately, there are no other published measurements of styrene in adipose tissue from non-occupationally exposed individuals, so direct comparison of these results is not possible. Therefore we evaluated the results from the Stanley (1986) survey by indirect methods, based on pharmacokinetic principles.

Reported styrene levels in breath of non-exposed populations were used together with the styrene air: fat partition coefficient to estimate fat styrene concentrations in the general population. This approach takes advantage of the fact that the relationship between the level of styrene excreted in alveolar air and the level of monomer in the fat can be regarded as a function of the partitioning of styrene between fat and air. Gargas *et al.* (1989) measured the distribution of styrene between fat and air and found a distribution coefficient of 3,500, *i.e.*, at equilibrium there was 3,500 ng of styrene per gram of fat for each ng of styrene per ml of air. This value of 3,500, representing the maximum ratio of concentrations that will exist between styrene in fat and air, can thus be used to estimate concentrations of styrene occurring in fat based on measurements of the monomer in expired air.

TABLE 2

Estimates of Styrene Levels in *Breath Samples (1.1μg/m^3) Seasonal and Geographical Variation

	Mean of Day and Night Samples		
Geographical Location	Summer	Fall	Winter
Elizabeth and Bayonne (NEW JERSEY)	.75	.79	.24
Greensboro (NORTH CAROLINA)	0.4		
Los Angeles (CALIFORNIA)			0.9
Contra Costa County (CALIFORNIA)	0.7		

* Breath samples were collected by a specially-designed spirometer with the subjects inhaling humidified ultrapure air. (For more information see Wallace et al., 1985).

Data obtained from the Total Exposure Assessment Methodology (TEAM) Study (Wallace 1987, Wallace et al., 1987 and Wallace et a1.,1988). The average of all the above measurements is 0.63 μg/m^3.

Using data obtained from the Total Exposure Assessment Methodology (TEAM) Study, [carried out under the auspices of the U.S. Environmental Protection Agency (EPA) between 1979 and 1985 (see Wallace 1987, Wallace *et al.* 1987 and Wallace *et al.* 1988], the average concentrations

of styrene in expired air, collected from U.S. citizens in various geographical locations at different seasons of the year, was estimated (table 2) at 0.63 μg/m³ (0.00063 ng/ml). By combining the average styrene breath measurement from the TEAM study with the fat:air partition coefficient measured by Gargas *et al.,* (1989) the average level of styrene in fat tissue occurring in the general population can be calculated as follows:

BREATH LEVEL (ng/ml)
x FAT:AIR PARTITION COEFFICIENT = FAT CONCENTRATION (ng/g)

0.00063 ng/ml x 3,500 = 2.21 ng/g

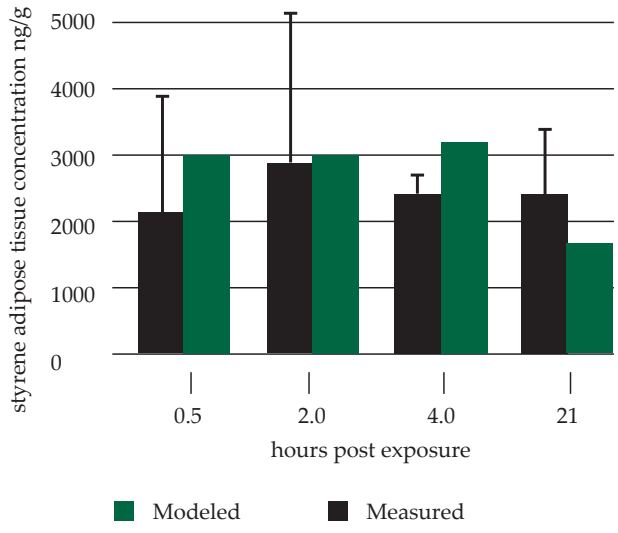
The average concentrations of styrene in adipose tissue reported by Stanley (1986) are therefore approximately 42 times higher than expected, based on expired air measurements for the general public.

The estimates of styrene fat concentrations in non-occupationally exposed individuals described above are based solely on styrene breath measurements together with the reported styrene fat:air partition coefficient, and do not include metabolic considerations. More accurate predictions of the behaviour of chemicals such as styrene, in humans by using a physiologically-based pharmacokinetic (PB-PK) model which incorporates the absorption, distribution, metabolism and elimination of a chemical substance in a biological system such as the human body.

Using the PB-PK model described by Ramsey & Andersen (1984), it is possible to estimate the concentrations of styrene in adipose tissue of humans exposed to 50 ppm of the monomer via inhalation (figure 1). The predicted amount of styrene in adipose tissue following two hours of exposure to 50 ppm styrene vapors (figure 1) is in close agreement with actual adipose tissue measurements by Engstrom *et al.,* (1978) in human volunteers following experimental exposure to 50 ppm styrene for two hours. Using PB-PK modelling, the predicted concentration in adipose tissue is approximately 3,000 ng/g after two hours of exposure to 50 ppm, while the actual measurements averaged 2,850 ng/g after exposure to 50 ppm for two hours. The close agreement between the predicted values and actual measured values verifies that the PB-PK model can accurately estimate adipose tissue concentrations in humans exposed to styrene. It is quite perplexing to note that the actual and predicted concentration of styrene in adipose tissue of humans exposed to 50 ppm is only approximately 30-fold higher than the average tissue concentrations for members of the general public reported by Stanley (1986), since the exposures of the general public are many orders of magnitude lower than 50 ppm.

FIGURE 1

Actual & Predicted Styrene Adipose Tissue Concentrations in Humans Exposed to 50 ppm Styrene



The PB-PK model can also be used to predict styrene adipose tissue concentrations in the general public resulting from dietary intake and low levels in ambient air. In these calculations, estimates of exposure to styrene via the atmosphere are based on measurements of personal air samples obtained from the Total Exposure Assessment Methodology (TEAM) Study conducted under the auspices of the EPA. The data in Table 3 show that the levels of styrene in personal air samples measured at various geographical locations within the U.S. at different seasons (Wallace, (1987), Wallace *et al.,* (1987) and Wallace *et al.,* (1988)). There were no obvious seasonal differences or geographical variations, and the overall average styrene concentration for all of the measurements was 1.79 lig/m³(0.42 ppb). This number is consistent with other data that suggests the average level of styrene in ambient air is approximately 1 ppb (Alexander, 1990).

Assuming a steady state airborne exposure of 0.42 ppb, the maximum predicted styrene adipose tissue concentration of 0.3 ng/g is achieved within five days of continuous exposure (figure 2). Similarly, maximum adipose tissue concentrations of approximately 0.8 ng /g are attained within five days of continuous exposure to 1 ppb. Hence, the styrene adipose tissue concentrations reported by

Stanley (1986) are far higher than shouldoccur in the general public as a result of airborne environmental exposures.

As also shown in figure 2, the predicted adipose tissue concentrations resulting from dietary intake are extremely low. The adipose tissue concentrations resulting from ingestion were predicted using a daily oral intake of 4 μg styrene per day via the food; this intake value is based on a detailed comprehensive assessment of styrene in food packaged in polymers or copolymers of styrene (Ministry of Agriculture, Fisheries, and Food, 1983). Assuming an oral intake of 4 μg per day, the maximum predicted adipose tissue concentration of 0.03 ng/g is 10-fold lower than was predicted from airborne environmental exposures, and several orders of magnitude lower than the adipose tissue concentrations reported by Stanley (1986).

The predicted human adipose tissue concentrations resulting from inhalation or ingestion of styrene are summarized in table 4. It is important to note that the PB-PK model used to estimate styrene adipose tissue concentra tions accurately described the actual styrene adipose tissue levels reported by both Wolff *et al.,* (1977) and Engstrom *et al.,* (1978). Additionally the adipose tissue and breath levels reported by Engstrom *et al.,* (1978), were reasonably consistent with calculations based on the air:fat partition coefficient of about 3,500 as reported by Gargas *et al.,* (1989). In view of these facts, the PB-PK model used in this review appears to provide a reliable method to predict adipose tissue concentrations in individuals exposed to styrene.

The levels of styrene in fat tissue collected from occupationally and experimentally exposed individuals have been measured by Wolff *et al.,* (1977) and Engstrom *et al.,* (1978) respectively. In the first of these studies fat tissue samples were collected from workers in a styrene polymerization plant where exposures were estimated to range from 1 to >5 ppm (4.26 to >21.3 mg/m^3). Analysis of the samples, collected at various periods up to eight hours post-exposure, showed that concentrations of styrene in the fat varied from 100 to 1,200 ng styrene/ g fat (average concentration 430 ng/g). In the study previously discussed by Engstrom *et al.,* (1978) human volunteers were exposed experimentally to 50 ppm styrene (213 mg/m^3) for two hours. The concentrations of styrene in fat tissue, collected during the first 21 hours post-exposure, averaged 2,420 ng/g, while expired air concentrations measured two to four hours after exposure averaged approximately 1. mg/m^3 *(i.e.,* 1 ng/ml).

In view of this data, the results reported by Stanley (1986) appear to be biologically implausible since the re-

TABLE 3

Estimates of Styrene Levels in *Personal Air (μg/m3) Seasonal and Geographical Variation

	Mean of Day and Night Samples		
Geographical Location	Summer	Fall	Winter
Elizabeth and Bayonne (NEW JERSEY)	1.3	1.9	1.5
Greensboro (NORTH CAROLINA)	1.4		
Los Angeles (CALIFORNIA)	1.8		3.6
Contra Costa County (CALIFORNIA)	1.0		

* Personal air was measured by drawing air (approx. 30 ml/min) through glass cartridge samplers containing the solid granular sorbent Tenax-GC. Sampling lasted approximately 12 hours to collect a target volume of 20 litres. The average of all measurements is 1.79μg/m^3.

Data obtained from the Total Exposure Assessment Methodology (TEAM) Study (Wallace 1987, Wallace et al., 1987 and Wallace et al., 1988).

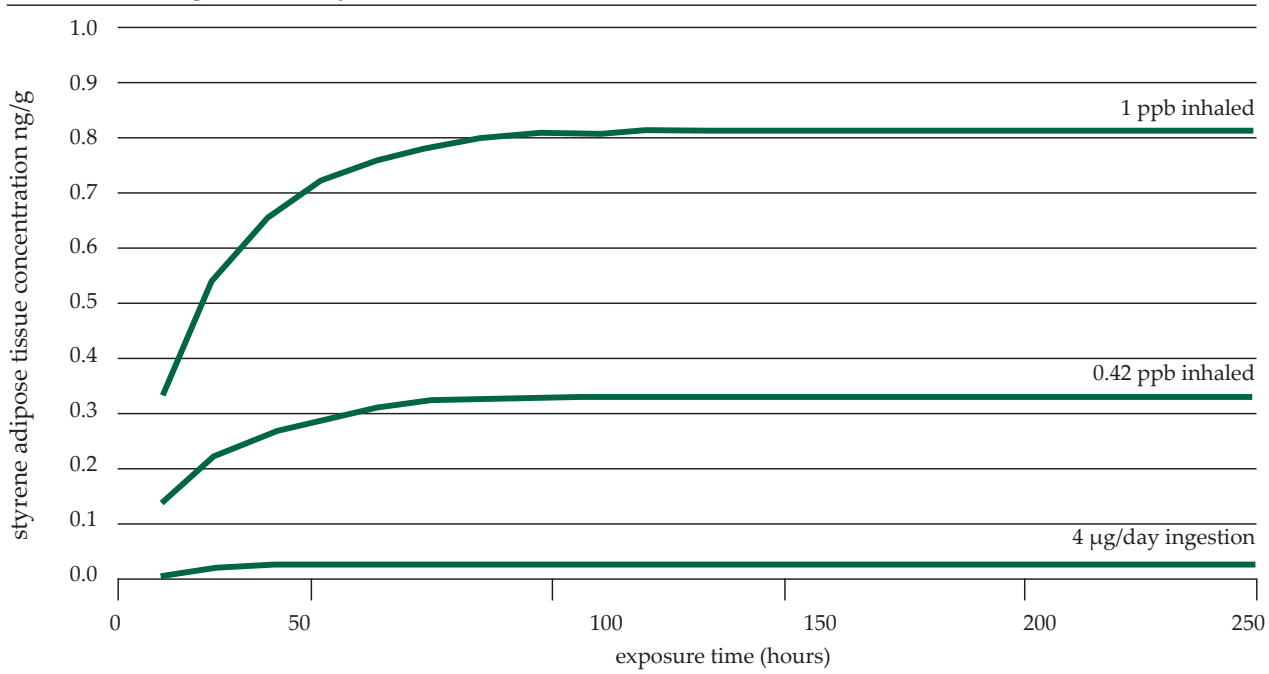
TABLE 4

Styrene Human Adipose Tissue Concentrations from Inhalation or Ingestion of Styrene

Exposure	Fat Level ng/g
50 ppm inhalation (8 hrs)	9880
25 ppm inhalation (8 hrs)	4900
1 ppm inhalation (8 hrs)	220
0.41 ppb inhalation (steady state)	0.33
4 μg/day ingestion (steady state)	0.03

FIGURE 2

Predicted Human Adipose Tissue Concentrations from Inhalation or Ingestion of Styrene



ported average styrene adipose tissue concentrations were only 4 to 25 times lower than were in humans exposed to styrene concentrations several thousand times higher than could be reasonably expected for the general public.

CONCLUSIONS

The primary conclusions to be drawn from this assessment of the NHATS survey reported by Stanley (1986) are as follows:

1. There was no attempt to associate styrene adipose tissue concentrations with human health effects in the study, and the concentrations of styrene reported in adipose tissue are far lower than have been found in asymptomatic, occupationally-exposed individuals.
2. Many substances including dioxins, chlorinated solvents, and pesticides were identified in the adipose tissue samples in addition to styrene. The actual incidence of individuals with measurable concentrations of styrene in adipose tissue was not determined, since composite tissue specimens were prepared from individual specimens. Styrene was however found in all of the composite specimens.
3. While not associated with adverse human effects, the reported styrene adipose tissue concentrations were nevertheless suprisingly high for non-occupationally exposed individuals.
4. The reported styrene adipose tissue concentrations were inconsistent with adipose tissue concentrations found in occupationally- and experimentally-exposed individuals, as well as calculations based on breath measurements and the fat to air partition coefficient.
5. Assessment by pharmacokinetic methods indicates that the reported adipose tissue concentrations are higher than should occur in the general public as a result of dietary intake, or inhalation of low concentrations in indoor and outdoor air.
6. The NHATS sample collection procedures do not preclude the possibility of obtaining samples from occupationally exposed individuals which are not representative of the general public. Moreover, no specific directions were provided to ensure that contamination

with styrene did not occur subsequent to collection of the samples. Therefore, quality control procedures for collection and analysis of NHATS specimens should be carefully reviewed to ensure that the samples are representative of the general public and that contamination of the samples with styrene cannot occur subsequent to collection.

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Low Level Exposures to Styrene: A Discussion of Alleged Health Effects

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Environmental critics of plastics in general and polystyrene in particular frequently cite as their source of health concerns an article published by the Los Angeles-based Foundation for Advancements in Science and Education (FASE), titled "Styrene: Health Effects of Low-level Exposure" (vol. 7. no. 2 winter, 1988). A critical review of this article reveals numerous basic flaws, principally its confusion of high-level and low-level exposures. Health effects attributed to low-level exposures by the general public are either unsupported by any scientific data, or cite effects that would be noticed only at levels exceeding those found in the workplace. The article also relies heavily on the EPA National Human Adipose Tissue Survey recently discredited by the National Research Council and other scientists (see preceding articles).

The concern expressed by the Foundation for Advancements in Science and Education (FASE) about the effects of low level exposure to styrene stems from an EPA document on the National Human Adipose Tissue Survey (EPA, 1989) that reported styrene in 100% of the samples analyzed. In interpreting this information it should first be noted that EPA drew no connection between the presence of styrene in fatty tissues and any type of adverse health effect. Further, although it is sometimes assumed that the only route of exposure to styrene is through the use of polystyrene in food packaging, exposure to styrene occurs from many other sources.

Styrene is a naturally occurring substance as well as being a man-made chemical. The Netherlands Institute for Nutrition and Food Research (TNO-CIVO, 1989) has shown that many foods, including beer, coffee, strawberries, beef, chicken, beans, and milk, all naturally contain styrene. Styrene is also a component of products of combustion sources such as automobile exhaust (Santodonato, 1980) and styrene in cigarette smoke is a major contributor to indoor air pollution (Wallace, 1987). Finding styrene in fatty tissue is therefore not unexpected as we can be exposed to it on a daily basis. Exposure to styrene can occur through the use of polystyrene but as styrene can impart an "off" taste to food and beverages at very low concentrations, polystyrene food packaging is manufactured such that the levels of styrene in the finished packaging materials are less than one tenth of one percent. Polystyrene is also designed to minimize any migration of styrene from packaging into food. Studies have shown that the migration of styrene into food from polystyrene packaging was less than that which is naturally found in a glass of beer or in strawberries (Polystyrene Packaging Council, 1989). Irrespective of the sources, public exposure to styrene is generally thousands of times lower than levels that have been shown to produce any type of adverse effects.

The FASE article states that styrene is distributed throughout the body and deposits in fatty *(i.e.* adipose) tissues. Distribution to body fat is a characteristic of most hydrocarbon substances (which are fat soluble materials) and hence is not a property unique to styrene. A claim was also made that the presence of styrene in maternal and umbilical cord results in the selective concentration of styrene in fetal circulation (Dowty *et al.,* 1976). In a recent review completed on the reproductive and developmental data on styrene (Brown, 1990) a number of deficiencies in the design of this study were identified. These include the observation that no maternal occupations were identified, sampling times were inconsistent *(i.e.* pre delivery or post delivery), sample size was small *(i.e.* 11 paired sam-

ples), and there was no quantitative data presented *(e.g.* no post delivery data, and styrene was never analyzed in umbilical cord samples). Thus the claims made by FASE that styrene is found in cord blood and that styrene is selectively concentrated in fetal circulation are not supported by the data. Further, numerous studies have shown that styrene is not toxic to the fetus (Brown, 1990). Therefore a finding of styrene in maternal circulation does not indicate that any hazard exists.

The FASE article also reported that styrene has been found in the milk of nursing mothers in eight out of eight samples that were analyzed (Peilizzan, *et al.* 1982). This is not an unexpected finding based on the previous discussion of styrene in adipose tissue. Styrene partitions readily into all fatty tissues and as milk contains a high amount of fat, styrene might be found there. Because styrene can be analyzed at levels many thousands of times below levels that would cause an any adverse effect, the mere presence of styrene in milk does not indicate a hazard.

A number of neurotoxic symptoms have been ascribed to styrene exposure (Cherry, 1990). As with any industrial hydrocarbon solvent, high level exposure results in a number of narcotic symptoms and the effects of styrene on the central nervous system are well documented. Short term, high level exposures to levels of 100 parts per million (ppm) or greater styrene in air may result in headache, dizziness, nausea and fatigue. Changes in electroencephalograms and nerve conduction velocities have also been observed at these high levels. These neurotoxic effects, however, are only of significance following either short or long term high level exposure. These symptoms are not uniquely associated with styrene exposure; overexposure to any hydrocarbon solvent or even alcohol will produce these same symptoms. Further, these nervous system effects have not been demonstrated in workers whose exposures have been kept below the Occupational Health and Safety Act permissible exposure limit (PEL) of 50 ppm. In a recent review of the neurotoxicity of organic solvents, it was also concluded that no convincing evidence of chronic irreversible neurotoxic effects to styrene exposure has been documented (Rosenberg and Schaumburg, 1990). Public exposure to styrene in the air is generally at least 100 times less than the PEL considered safe for occupational exposure.

FASE cited a number of publications that have reported chromosomal aberrations and/or sister chromatid exchanges (SCE) in the peripheral lymphocytes of individuals occupationally exposed to styrene. In a recent article Preston (1990) extensively reviewed these studies as well as many others to determine the potential for styrene to alter chromosomes in human and laboratory animals both *in vivo* and *in vitro.* Preston identified a number of study deficiencies that were repeatedly made, including inadequate sample sizes, inadequate or inappropriate control groups, no exposure assessment, inconsistent protocols, lack of a clear dose response, as well as failing to account for confounding factors such as concurrent exposures to other chemicals or smoking. Preston concluded that the data available are inadequate to determine whether or not styrene exposure induces chromosomal aberrations of SCE in peripheral lymphocytes of individuals occupationally exposed to styrene.

FASE further suggested that workers exposed to styrene in the workplace may have an elevated chance of developing cancer. This claim is not supported in a recently completed review of the pooled results of eight cohort studies on workers in the manufacture of styrene and styrene based products (Bodner *et al.,* 1987). Collectively, these eight studies involved nearly 50,000 employees during a 45 year period and overall, the data do not support an association between lymphatic and hematopoietic cancer rates with styrene exposure. The International Agency for Research on Cancer has also concluded that the human data on styrene is inadequate to support classification of styrene as a carcinogen.

The FASE article also claims that chronic industrial exposure to levels less than 10 ppm may affect pituitary function. This statement is based on two papers published by the same group of researchers (Mutti *et al.,* 1984; Arfini *et al.,* 1987). Both of these studies examined the neuroendocrine effects on females occupationally exposed to styrene. Exposures in the initial study were estimated to range from 65–300 ppm as an eight-hour time-weighted concentration based on the urinary excretion of mandelic acid (MA) and phenylglyoxylic acid (PGA). The initial finding observed that serum prolactin and human growth hormone levels were elevated. In the concluding remarks, the authors state that as the effects were observed at levels greater than 50 ppm *(i.e.* the PEL), these effects can not be used for biological monitoring of occupational exposure to styrene. Further, the authors concluded that the styrene-induced neuroendocrine effects were mostly due to acute exposure, with the hormone levels not being influenced by the duration of exposure. The second study referenced also reported elevated levels of prolactin. The study did not cite levels of exposure to styrene but did cite urinary concentrations of MA and PGA. Based on these reported urinary concentrations, the levels of exposure to

styrene would exceed the occupationally acceptable levels. It is not possible to determine the significance of these results and the editors of the *Journal of Occupational Medicine*, in which this article was published, prefaced the paper by indicating that although the data were sound, the results did not necessarily lead to the conclusions stated. Regardless of the debate about the changes, these studies clearly do not support the assertion that exposure to styrene at levels below the occupationally accepted levels have any effect on neuroendocrine function.

CONCLUSION

The FASE article was written to discuss the health effects of low level exposure to styrene. The article cites data from studies that have observed effects associated with styrene at levels generally higher than those accepted in the occupational setting. FASE does not discuss, however, how these effects relate to the concept of dose, a principle that is fundamental to toxicology. All substances may be associated with adverse effects if the dose is high enough. The implication of the article is that the effects that are observed at levels higher than those acceptable in occupational settings will be observed at much lower levels of exposure. The data that FASE presented do not support this assertion. No adverse health effects have been linked to current occupational exposure levels, let alone to low level environmental styrene exposure.

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THE EPIDEMIOLOGY OF STYRENE–I

Studies of Workers in the Reinforced Plastics and Composites Industry

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This report summarizes an epidemiological investigation of mortality experience of workers in the reinforced plastics and composites industry, who were potentially exposed to styrene monomer. The investigation consisted of three separate phases: a feasibility assessment, a historical prospective cohort study, and a case-control study of respiratory cancer.

The cohort consisted of 15,908 men and women who worked for at least six months between 1948 and 1977 in 30 participating manufacturing plants in the reinforced plastics and composites industry. These workers were occupationally exposed to the working environment in the industry, which included exposure to styrene. Cause specific mortality analyses were performed based on the standardized mortality ratio (SMR) with the United States population as a comparison.

No significant excess of cause specific mortality was found for the total cohort. Mortality from cancer was slightly less than expected (SMR = 88.1). For cancer of the respiratory system, a small non-significant excess was detected (SMR = 116.1). For lymphatic and hematopoietic cancer, a non-significant deficit was found (SMR = 73.3). The observed mortality from leukemia was similar to that expected (five observed v. 4.76 expected deaths). The plants with hot processes (injection moulding, centrifugal casting, compression moulding, continuous lamination, and pultrusion) experienced a significantly increased SMR (177.9) for respiratory cancer, which was more than twice that (78.3) for those with cold processes (resin mixing, lay up and spray up, bag moulding, and filament winding). As potential exposure to styrene from hot processes is considerably less than that from the cold processes, this finding could not be attributed to occupational exposures.

A subsequent nested case-control study consisting of 40 cases of deaths from respiratory cancer was conducted. Further information on detailed work history, occupational exposures, and smoking history was collected. The case-control study did not show any significant association between respiratory cancer and direct exposure to styrene (contained in polyester resins), duration of exposure to styrene, the type of process (hot or cold), or whether a resin was used. A statistically significant association (relative risk = 7.33) was found between cigarette smoking and respiratory cancer among the study subjects.

A number of epidemiological studies have been conducted to assess the potential carcinogenicity of styrene (see following review). In this article, first published late last year in the British journal of Industrial Medicine,* the author describes one of the more significant of them: a mortality study of nearly 16,000 workers, including nearly 4,000 women, who were exposed to styrene at manufacturing plants in the reinforced plastics and composites industry between the years 1948 and 1977. Thirty manufacturing plants were involved. The study found no excess of any specific cause of death. The ratio of deaths from cancer was slightly lower among these workers than among the population as a whole. The ratio of deaths from leukemia was similar to those in the general population.

MATERIALS AND METHODS

A feasibility assessment was made to determine whether a mortality study could be done and to provide information for development of protocol. Based on this, 30 reinforced plastics manufacturing plants were selected for the mor-

* *Reprinted from the British Journal of Industrial Medicine 1990;47:753-762.*

tality study. Selection criteria included extent of potential exposure to styrene, number of workers exposed, completeness of employment records, earliest date of record availability, and possible duration of latency.

The cohort consisted of those who worked in an area or areas with potential exposure to styrene for at least six months between 1 January 1948 and 31 December 1977 at any of the 30 selected reinforced plastics manufacturing plants. Those employees who worked in the production areas, the maintenance departments, and the receiving, shipping, and warehousing departments were considered to be potentially exposed to styrene, and were eligible for cohort membership. Office employees, with no previous production experience, were not included.

The cohort was constructed by using employment records available at each plant. The records varied greatly from plant to plant, but generally included the following information: name, social security number, sex, date of birth, date of leaving if appropriate, and summary of work history.

Deaths among active employees and annuitants were identified through company records. Vital state of employees who had left was determined through social security administration records. This was supplemented by local follow up, which included inquiries to plant personnel. For all cohort members who died during the observation period death certificates were requested from appropriate state vital statistics departments. The causes of death were coded according to the 7th revision of the International Classification of Diseases.

It was necessary to develop a method for grouping jobs from different plants with similar potential for exposure to styrene. Because of the lack of reliable data on industrial hygiene in the industry, Arthur D. Little Inc. (ADL), a consulting firm, was contracted independently to collect data on exposure.[1]

A record job title list (RJT) was generated based on personnel records. The initial list was then consolidated to eliminate duplications. The consolidated RJT (by plant) was provided to ADL for the survey of industrial hygiene and classification of exposure. The ADL industrial hygiene survey included current or past time weighted average (TWA) values (ppm) and peak range exposure values (ppm). Similar RJTs were consolidated into study job titles (SJTs), if their TWAs fell within a common 10 ppm increment (0–9, 10–19, 20–29, etc.) and they had identical peak range values' These data were incorporated into a job dictionary with some 4000 RJTs grouped into 173 SJTs. This information was utilized to group cohort members into exposure categories.

The basic unit of statistical computation was the number of years each employee was followed up after six months of employment or 1 January 1948 (whichever was later), to the end of the study period or the date of death (whichever was earlier). For those "lost to follow up," person-years of observation were counted up to the last date of contact, which was usually the termination date. Each year (or fraction thereof) contributed by a particular worker was classified by age, sex, and calendar year, and the person-years of all workers were then summed up by age, sex, and calendar year. The United States national age-cause-race-specific death rates for five year periods from 1948 to 1977 were applied to these person-years to obtain the number of deaths from a particular cause to be expected from an equal number of person-years of the same sex and similar in age and calendar year. Standardized mortality ratios (SMRs) were computed by expressing the observed deaths as percentages of the expected. The actual computation was performed using a standard computer program.[2]

RESULTS OF THE COHORT STUDY

Included in the cohort were 15,908 employees from 30 plants; 12,028 (75.6%) men and 3,880 (24.4%) women. From the employment records, race information was available for 3,658 workers (23.0% of the total cohort). Among these 3,658 workers with known race, only 46 (1.3%) were nonwhite. For the purpose of analysis, the entire cohort was assumed to be white.

Almost half of the cohort (46.0%) had worked for less than two years at the participating plants. About a third (31.9%) had worked for two to five years. Only 22.1% had worked for five years or more.

At the end of the observation period (31 December 1977), 12,843 (80.7%) cohort members were identified as living. The cohort was relatively young, and only 499 (3.1%) were identified as deceased. Death certificates were obtained for 452 (90.6%) of them. For the remaining 47 deaths, the date but not the cause of death was available. These 47 deaths were included in the overall SMR calculation, but not in any cause specific SMR analysis. At the close of the study period, the vital state of 2,567 (16.1%) workers remained unknown. In the subsequent statistical analysis, person-years for these 2,567 subjects lost to follow up were counted up to the date of last contact (for example, date of termination).

The percent of cohort members with unknown vital state was relatively high. An examination of this percent-

TABLE 1

Observed (Obs) deaths by cause and SMRs for workers in reinforced plastics industry

	Total Cohort		Men Workers		Women Workers	
Cause of Death (7th ICD)	Obs	SMR	Obs	SMR	Obs	SMR
All Causes	499	100.0	424	98.1	75	112.7
Infective & parastic diseases (000-138)	5	109.4	4	106.2	1	124.6
All cancers (140-205)	88	88.1	68	87.6	20	90.0
Cancer of buccal cavity and pharynx (140-148)	1	35.1	1	39.2	0	—
Cancer of digestive system (150-159)	20	89.0	14	75.4	6	153.8
Cancer of stomach (151)	3	81.6	2	63.3	1	193.4
Cancer of large intestine (153)	8	102.5	7	115.6	1	57.2
Cancer of rectum (154)	2	82.0	2	98.5	0	—
Cancer of liver (155-156)	2	136.0	0	—	2	650.1
Cancer of pancreas (157)	3	65.4	1	25.5	2	301.9
Cancer of respiratory system (160-164)	34	116.1	29	108.5	5	195.4
Cancer of larynx (161)	4	341.1	4	360.2	0	—
Cancer of lung (162-163)	30	108.1	25	98.8	5	204.0
Cancer of prostate (177)	2	81.9	2	81.9	0	—
Cancer of breast (170)	2	33.1	0	—	2	33.1
Cancer of all uterus (171)	2	95.4	0	—	2	95.4
Cancer of kidney (180)	2	86.3	2	98.6	0	—
Cancer of bladder (181)	3	176.7	3	191.6	0	—
Cancer of skin (190)	3	113.7	3	138.8	0	—
Lymphatic and hematopoietic cancer (200-205)	9	73.3	8	78.7	1	47.4
Lymphosarcoma and reticulosarcoma (200)	0	—	0	—	0	—
Hodgkin's disease (201)	3	124.5	3	147.2	0	—
Leukemia & aleukemia (204)	5	105.1	4	102.2	1	118.5
Diabetes mellitus (260)	4	57.6	2	35.9	2	145.4
Diseases of blood and blood forming organs (290-299)	1	85.8	1	111.5	0	—
Diseases of nervous system and sense organs (330-398)	30	106.9	25	110.1	5	93.1
Diseases of circulatory system (400-468)	154	92.7	137	90.3	17	117.3
Chronic rheumatic heart disease (410-416)	1	17.6*	0	—	1	70.7
Arteriosclerotic heart disease (inc CHD) (420)	118	86.9	107	84.7	11	116.0
Non-malignant respiratory disease (470-527)	11	51.8*	11	59.0	0	—
Pneumonia (490-493)	2	23.8	2	28.0	0	—
Emphysema (527)	6	117.7	6	126.6	0	—
Diseases of digestive system (530-587)	21	75.5	17	72.1	4	94.3
Cirrhosis of liver (581)	9	52.5*	7	48.2*	2	76.6
Diseases of genitourinary system (590-639)	7	129.6	5	116.1	2	182.8
Symptons, senility and ill defined conditions (780-795)	3	39.3	2	30.3	1	95.9
Accidents, poisonings, and violence (E800-999)	121	103.5	108	101.1	13	129.9
Accidents (800-962)	84	107.3	76	104.9	8	138.2
Motor vehicle accidents (810-835)	57	127.3	52	126.0	5	143.1
Suicide (936, 960-979)	21	85.9	19	88.4	2	67.6

*$p < 0.05$

age by plant did not show any concentration at any particular plant. Further investigation showed that the percent was higher in the women (24.1%) than in the men (13.6%).

The total number of deaths, 499, was nearly identical to the expected number of 498.82. The overall SMR for the entire cohort was 100.0. For either the entire cohort or each sex, no significant mortality from any specific cause was seen (table 1).

Mortality from cancer of all sites for the entire cohort was slightly less than the expected (88 observed v. 99.87 expected deaths). A non-significant mortality deficit was found from cancer of the digestive system (SMR = 89.09). There was a slight non-significant mortality excess from cancer of the respiratory system (34 observed v. 29.28 expected deaths). The SMR for respiratory cancer was 116.1 for the entire cohort, 108.5 for the men and 195.4 for the women (non-significant). Four deaths were due to cancer of the larynx among the men, giving an SMR of 360.2, with a p value close to 0.05. The remaining 30 deaths were from lung cancer, which resulted in an SMR of 108.1 for the total cohort.

Although 12.28 deaths were expected from lymphatic and hematopoietic cancer, only nine deaths were seen. The corresponding SMR was 73.3, but the deficit was not statistically significant. The deficit came primarily from lymphosarcoma and reticulosarcoma, for which no death was seen but 2.63 were expected. Mortality from leukemia was as expected (five expected v. 4.76 deaths).

TABLE 2

Observed (Obs) deaths and SMRs by cause and latency for the entire cohort

	Duration of employment							
	<1		1–2		2–5		>5	
Cause of death (7th ICD)	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
All causes	127	128.6	109	117.1	127	101.2	136	74.9**
All cancers (140-205)	22	124.7	19	111.9	24	97.4	23	56.6**
Cancer of digestive system (150-159)	4	107.4	5	136.1	5	91.1	6	62.6
Cancer of stomach (151)	1	164.1	1	162.8	0	—	1	64.8
Cancer of large intestine (153)	1	76.7	2	158.4	2	104.2	3	90.4
Cancer of respiratory system (160-164)	9	189.7	4	83.1	11	161.7	10	77.4
Cancer of larynx (161)	3	1612.1**	1	521.2	0	—	0	—
Cancer of lung (162-163)	6	133.6	3	65.9	11	170.7	10	81.5
Lymphatic and hematopoietic cancer (200-205)	1	38.7	3	126.0	4	127.4	1	24.0
Hodgkin's disease (201)	1	168.5	1	188.3	1	156.0	0	—
Leukemia and aleukemia (204)	0	—	2	213.3	2	163.4	1	63.7
Diseases of nervous system and sense organs (330-398)	7	138.7	6	124.1	6	83.7	11	99.8
Diseases of circulatory system (400-468)	31	112.8	27	97.5	47	116.8	49	69.2**
Arteriosclerotic heart disease (inc CHD) (420)	27	122.4	17	75.9	37	113.7	37	62.9**
Non-malignant respiratory disease (470-527)	3	80.6	4	110.2	2	38.5	2	23.0**
Pneumonia (490-493)	1	62.6	1	65.7	0	—	0	—
Emphysema (527)	1	128.4	3	374.9	1	83.1	1	43.2
Diseases of digestive system (530-587)	6	117.5	4	80.3	3	43.4	8	74.0
Accidents, poisonings, and violence (E800-E999)	31	97.9	36	131.0	28	89.5	26	98.4
Accidents (800-962)	22	100.8	24	128.1	21	100.3	17	101.5
Motor vehicle accidents (810-835)	15	113.4	16	143.7	13	107.9	13	155.5

*p <0.05, **p<0.01.

Mortality from diseases of the circulatory system was slightly less than expected (SMR = 92.7). On the other hand, the deficit in non-malignant respiratory disease was statistically significant (SMR = 51.8). The deficit appeared to come from pneumonia (SMR = 23.8, $p < 0.05$). The deficit for cirrhosis of the liver was also statistically significant (SMR = 52.5, $p < 0.05$).

ANALYSIS OF DURATION OF EMPLOYMENT

Table 2 shows the observed deaths and SMRs by cause and duration of employment for the entire cohort. For total mortality, the SMR decreased with increased duration of employment. For those who worked between six months and a year, the total SMR was 128.6 ($p < 0.05$) and for those with five or more years of employment, the overall SMR was 74.9 ($p < 0. 05$).

For respiratory cancer, the less than one year group showed the highest SMR (189.7). None of the respiratory cancer SMRs by duration of employment was significant, however. Among those who worked between six months and a year, three deaths from cancer of the larynx occurred, giving an SMR of 1612.1 ($p < 0.01$). All three deaths were among the male cohort members.

No trend, either upward or downward, was seen for lymphatic and hematopoietic cancer, or for leukemia. None of the SMRs by any duration of employment was significant for these two categories of diseases for the entire cohort.

TABLE 3

Observed (Obs) deaths and SMRs by cause and latency for the entire cohort

	Latency (y)					
	<10		10-19		20-29	
Cause of death (7th ICDA)	Obs	SMR	Obs	SMR	Obs	SMR
All causes	303	103.7	156	96.9	40	95.9
All cancers (140-205)	48	90.2	29	81.5	11	108.7
Cancer of digestive system (150-159)	12	104.8	5	60.0	3	122.5
Cancer of stomach (151)	2	103.4	0	—	1	267.1
Cancer of large intestine (153)	4	101.8	3	102.6	1	114.3
Cancer of respiratory system (160-164)	12	83.9	14	126.2	8	228.4
Cancer of larynx (161)	2	344.6	1	227.4	1	732.9
Cancer of lung (162-163)	10	74.0	13	123.3	7	209.5
Lymphatic and hematopoietic cancer (200-205)	7	92.5	2	53.6	0	—
Hodkin's disease (201)	3	172.0	0	—	0	—
Leukemia and aleukemia (204)	4	133.9	1	71.1	0	—
Diseases of nervous system and sense organs (330-398)	17	111.7	10	101.4	3	109.1
Diseases of circulatory system (400-468)	88	103.7	52	84.4	14	78.4
Arteriosclerotic heart disease (inc CHD) (420)	66	97.1	42	82.1	10	66.2
Non-malignant respiratory disease (470-527)	4	35.9*	5	65.9	2	87.9
Pneumonia (490-493)	1	21.0	1	35.6	0	—
Emphysema (527)	2	82.1	3	151.4	1	164.8
Diseases of digestive system (530-587)	13	84.3	6	61.3	2	83.4
Accidents, poisionings, and violence (E800-E999)	92	104.1	27	109.5	2	56.1
Accidents (800-962)	64	105.5	19	124.2	1	46.6
Motor vehicle accidents (810-835)	44	121.1	12	160.1	1	111.6

*$p < 0.05$

TABLE 4
Observed and expected deaths, SMRs, and 95% CI for lung cancer among cohort members with at least 20 years latency by sex and duration of employment

	Duration of employment (y)				
Variable	<1	1-2	2-5	>5	Total
Men					
Observed deaths	0	0	3	0	3
Expected deaths	.28	.34	.42	2.01	3.05
SMR	—	—	716.5*	—	98.3
95% CI	—	—	1477-2,095.0	—	20.3-287.4
Women					
Observed deaths	2	0	1	1	4
Expected deaths	0.05	0.03	0.06	0.15	0.29
SMR	4192.7*	—	1693.6	655.2	1382.8**
95% CI	507.6-15,136.0	—	42.8-9,408.9	16.6-3,640.2	376.8-3,536.6

< 0.05; ** p <0.01.

ANALYSIS BY LATENCY

Table 3 represents the observed deaths and SMRs by cause for the entire cohort by latency since hire. An upward trend was detected for cancer of the lung, ranging from an SMR of 74.0 for a latency of less than 10 years, through 123.3 for 10–19 years, to 209.5 for 20–29 years; although none of the SMRs was statistically significant. To further examine the pattern of mortality from lung cancer, analysis by sex and duration of employment among cohort members with at least 20 years of latency was performed (table 4). Statistically significant lung cancer SMRs were found for men with two to five years of employment and at least 20 years of latency (SMR = 716.5, $p < 0.05$), and for women with a latency of at least 20 years (SMR = 1382.8, $p < 0.01$).

The other upward trend shown in table 3 was that for nonmalignant respiratory disease. Although there was an upward trend, none of the three SMRs was more than the expected. In fact, for the group with less than 10 years of latency, the SMR was 35.9 ($p < 0.05$).

ANALYSIS BY DEPARTMENT EXPOSURE

The following were considered departments with high exposure potential: mixing, SMC manufacturing, injection moulding, gel coating, spray up and lay up, winding, casting, centrifugal casting, and pultrusion. The departments with low exposure potential included general non-production, cut, weight, and press, finishing, store and ship, string and fit, foaming, mould preparation, field service, and preform production. According to this classification, 4,754 cohort members were employed in high exposure departments and 9,049 were employed in low exposure departments. It was impossible to classify 2,105 workers by this scheme, because the magnitude of their departmental exposure was unknown.

Table 5 shows the observed deaths and SMRs by cause for departments with high or low exposure. A considerable difference in SMR for lung cancer was seen between the groups. The high exposure group experienced a lung cancer SMR of 69.4 (three observed deaths; non-significant) compared with an SMR of 128.2 (23 observed deaths; non-significant) for the low exposure groups. For leukemia, the SMR in the high exposure group was 199.3 (two observed deaths; non-significant) and that in the low exposure group was 99.3 (three observed deaths; non-significant), indicating a 2–14 fold difference between the two groups. This observation was based on small numbers of observed deaths, however, and the difference was not statistically significant. No death due to Hodgkin's disease was found in the high exposure group, but the SMR for the low exposure group was 197.9 (three observed deaths; nonsignificant).

TABLE 5
Observed (Obs) deaths and SMRs for the cohort by cause and departmental exposure

	Low exposure potential		High exposure potential	
Cause of death (7th ICD)	Obs	SMR	Obs	SMR
All causes	335	106.4	85	88.3
All cancers (140-205)	63	97.4	13	73.3
Cancer of digestive system (150-159)	17	117.1	2	55.7
Cancer of stomach (151)	2	84.3	1	175.9
Cancer of large intestine (153)	7	138.8	0	—
Cancer of respiratory system (160-164)	26	137.4	4	87.8
Cancer of larynx (161)	3	396.0	1	589.5
Cancer of lung (162-163)	23	128.2	3	69.4
Lymphatic and hematopoietic cancer (200-205)	7	89.7	2	79.0
Hodgkin's disease (201)	3	197.9	0	—
Leukemia and aleukemia (204)	3	99.9	2	199.3
Diseases of nervous system (330-398)	23	129.5	2	41.2
Diseases of circulatory system (400-468)	100	93.8	24	94.7
Arteriosclerotic heart disease (420)	82	94.1	16	79.0
Non-malignant respiratory disease (470-529)	6	44.3*	2	57.7
Pneumonia (490-493)	1	18.8	1	65.6
Emphysema (527)	4	122.3	1	149.7
Diseases of digestive system (530-587)	8	44.5*	8	155.0
Accidents, poisionings, and violence (E800-E999)	82	11.6	25	78.6
Accidents (800-962)	52	111.6	19	88.4
Motor vehicle accidents (810-835)	34	128.8	13	101.2

*$p < 0.05$
No of persons = 13,803

ANALYSIS BY TWA

Cohort members were classified according to the maximum (highest) TWA they were ever exposed to throughout their work histories. An arbitrary division of less than 20 ppm (lower) and greater than 20 ppm (higher) was used in the classification, dividing the cohort into two roughly equal groups; 7,373 in the lower maximum and 7,866 in the higher maximum TWA group (the maximum TWA of 669 workers could not be determined).

Table 6 shows the cause specific mortality experience of the cohort by maximum TWA. The SMR in the higher maximum TWA group (SMR = 84.5) was lower than that in the lower maximum TWA group (SMR = 141.5). The difference was even larger when only lung cancer was considered (59.4 v. 143.5). In the higher maximum TWA group, three deaths were due to cancer of the larynx when only 0.41 were expected. The corresponding SMR of 730.5 was statistically significant.

A considerable difference in mortality from leukemia existed between the two groups. The SMR for leukemia in the lower maximum TWA group was 39.9 (one observed death) and that in the higher maximum TWA group was 200.4 (four observed deaths), a fivefold difference between the two groups; but the numbers of deaths were few, and the difference was not statistically significant. For all lymphopoietic cancer, the difference between the two groups was much smaller (SMR = 61.3 in the lower group v. 98.1 in the higher group).

Workers were also classified according to the average TWA (weighted by duration) throughout their work histories. A total of 6,545 workers were classified in the higher average TWA (> 12 ppm) and 8,694 in the lower average TWA (> 12 ppm). The 669 workers with ill defined exposure levels were not included.

As indicated in table 6, whereas the overall SMR for the higher average TWA group (90.2) was lower than that for the lower average TWA group (100.8), the reverse was true for cancer of all sites (97.9 v. 85.4 deaths), and for digestive cancer (126.2 v. 81.9 deaths).

Three deaths in the higher average TWA group were due to cancer of the larynx, giving a statistically signifi cant SMR of 941.1 ($p < 0.01$), whereas only one death in the lower average TWA group was ascribed to cancer of the larynx, with a corresponding SMR of 127.9 (non-significant). For lung cancer, a non-significant deficit was seen in the higher group (SMR = 64.0, five observed deaths), but the SMR in the lower group was increased (SMR = 131.1, 24 observed deaths).

A difference in mortality from leukemia was detected between the two groups. In the lower average TWA group, the leukemia SMR was 33.8 (one observed death) and that in the higher group was 259.6 (four observed deaths), a ratio of more than sevenfold. Both SMRs, however, were based on a small number of observed deaths. On the other hand, mortality from Hodgkin's disease was raised in the lower group (SMR = 204.0, three observed deaths), where-

TABLE 6
Observed (Obs) deaths and SMRs for the cohort by cause and maximum TWA or average TWA

	Maximum TWA				Average TWA			
	Lower max TWA		Higher max TWA		Lower avg TWA		Higher avg TWA	
cause of death (7th ICD)	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
All causes	277	102.3	180	90.5	318	100.8	139	90.2
All cancers (140-205)	49	89.3	35	89.4	55	85.4	29	97.9
Cancer of digestive system (150-159)	10	79.0	10	119.9	12	81.9	8	126.2
Cancer of stomach (151)	1	47.9	2	149.9	2	83.1	1	89.5
Cancer of large intestine (153)	5	115.7	3	100.8	5	99.1	3	133.4
Cancer of respiratory system (160-164)	24	141.9	9	84.5	25	129.4	8	97.1
Cancer of larynx (161)	1	144.9	3	730.5*	1	127.9	3	941.1**
Cancer of lung (162-163)	23	143.5	6	59.4	24	131.1	5	64.0
Lymphatic and hematopoietic cancer (200-205)	4	61.3	5	98.1	5	64.9	4	102.0
Hodgkin's disease (201)	3	244.3	0	—	3	204.0	0	—
Leukemia and aleukemia (204)	1	39.9	1	200.4	1	33.8	4	259.6
Diseases of nervous system (330-398)	17	111.0	9	83.6	20	112.1	6	72.8
Diseases of circulatory system (400-468)	94	98.6	42	70.5*	107	98.2	29	63.1**
Arteriosclerotic heart disease (420)	72	91.7	34	70.6*	84	94.0	22	59.0**
Non-malignant respiratory disease (470-529)	5	41.8*	4	50.4	5	36.4*	4	65.1
Pneumonia (490-493)	0	—	2	61.0	0	—	2	79.1
Emphysema (527)	5	166.3	1	57.3	5	147.4	1	73.6
Diseases of digestive system (530-587)	9	58.9	10	91.3	11	61.5	8	95.9
Accidents, poisionings, and violence (E800-E999)	63	109.5	52	95.5	73	106.7	42	96.4
Accidents (800-962)	39	101.4	39	106.7	45	98.4	33	112.8
Motor vehicle accidents (810-835)	23	106.5	28	130.7	29	112.4	22	127.8

*$p < 0.05$; **$p < 0.01$

as no death due to Hodgkin's disease occurred in the higher group.

ANALYSIS BY HOT AND COLD PROCESS

The reinforced plastics and composites processes were classified by the industrial hygienists in the industry into either "hot" (injection moulding, centrifugal compression moulding, continuous lamination and pultrusion) or "cold" (resin mixing, lay up and spray up, bag moulding, and filament winding). In this analysis, each plant was classified by process, based on information from the

plants; hot process only (seven plants), cold process only (19 plants), and both (four plants). Table 7 compares the cause specific mortality between the "hot only" and "cold only" process plants. A total of 6,558 workers were exposed to the cold process only, and 7,365 to the hot process only.

Overall mortality was lower for the cold process plants (SMR = 89.9) than for the hot process plants (SMR = 160.0). For cancer of all sites, mortality was comparable between the two groups. Mortality from digestive cancer was slightly higher in the cold process group than in the hot process group (SMRs = 111.7 and 73.2).

Mortality from lung cancer was less than expected in the cold process group (SMR = 64.2, seven observed

deaths), whereas a significant excess of lung cancer was found for the hot process group (SMR = 172.1, 22 observed deaths, $p < 0.05$). The ratio between the two SMRs

TABLE 7
Observed (Obs) deaths and SMRs for the cohort by hot and cold process

	Cold		Hot	
	Obs	SMR	Obs	SMR
All causes	162	89.9	260	106.0
All cancers (140-205)	32	93.1	49	97.0
Cancer of digestive system (150-159)	9	111.7	8	73.2
Cancer of stomach (151)	1	75.4	2	111.8
Cancer of large intestine (153)	4	147.8	3	77.6
Cancer of respiratory system (160-164)	9	28.3	24	177.9*
Cancer of larynx (161)	2	423.1	2	378.8
Cancer of lung (162-163)	7	64.2	22	172.1*
Lymphatic and hematopoietic cancer (200-205)	3	71.5	5	19.2
Hodgkin's disease (201)	1	129.1	1	76.6
Leukemia and aleukemia (204)	2	122.8	3	122.7
Diseases of nervous system (330-398)	10	101.9	16	116.0
Diseases of circulatory system (440-468)	47	74.3*	78	100.5
Arteriosclerotic heart disease (420)	36	68.3*	59	94.5
Non-malignant respiratory disease (470-529)	6	74.9	3	30.1*
Pneumonia (490-493)	2	66.8	0	—
Emphysema (527)	3	145.0	1	45.3
Diseases of digestive system (530-587)	10	103.7	10	70.2
Accidents, poisonings, and violence (E800-E999)	35	83.1	67	113.7
Accidents (800-962)	27	95.9	43	109.0
Motor vehicle accidents (810-835)	17	105.7	27	119.6

*$p < 0.05$
No of persons = 13,923

was more than 2.5. Mortality from cancer of the larynx was high in both groups (SMR = 423.1 in the cold process group and 378.8 in the hot process group, neither SMR being significant).

Mortality from lymphopoietic cancer and leukemia was comparable in both groups. On the other hand, mortality from diseases of the circulatory system was lower in the cold process group (SMR = 74.3, $p < 0.05$) than in the hot process group (SMR = 100.5). Finally, mortality from non-malignant respiratory disease in the cold process group (SMR = 74.9, six observed deaths) was higher than in the hot process group (SMR = 30.1, three observed deaths, $p < 0.05$).

CASE-CONTROL STUDY OF RESPIRATORY CANCER

In the cohort study, statistically significant SMRs for respiratory cancer were detected in several subgroups. For example, a twofold difference in SMR for respiratory cancer occurred between hot (SMR = 177, $p < 0.05$) and cold (SMR = 78) process plants. This finding was not consistent with the concept that greater styrene exposure might cause a higher risk of respiratory cancer, as potential exposure to styrene from hot processes was less than that from cold processes. To investigate further the problem of respiratory cancer, a nested case-control study was conducted.

The cases were deaths from respiratory cancer. For each case, a maximum of three controls were selected from deceased members of the cohort, matched with respect to plant, age at death (within five years), year of death (within five years), sex, and race (from death certificates). The decision to use dead controls was based on a consideration of comparability of data to be collected for cases and controls.

The following information on the cases and controls was collected: any additional or more detailed work history, exposure on each job segment regarding hot or cold processes, resins, and other chemicals, exposures from employment outside of the plastics industry, and smoking history. Data sources included employment records, company medical records, health insurance records, and inquiries or interviews with persons who might be able to provide information on the study subjects such as fellow workers or next of kin.

Relative risks (approximated by odds ratios) were computed for each of the factors included for analysis. For dichotomous variables (for example, hot v. cold process), the Mantel-Haenszel X" procedure was used' For polychotomous variables (for example, years of exposure), the extension of the Mantel-Haenszel procedure was used' To examine the data for possible interaction among the variables, the data set was analyzed by the multiple logistic regression technique 5,6

Although 44 deaths (including those after the end of observation but known to us) in the cohort study were attributed to respiratory cancer, only 40 deaths from respiratory cancer were included in the case-control study analysis, because for four cases, no eligible controls could be found. These four cases were all from small plants, for which the number of deaths was small and the availability of potential controls was limited. Some of the 40 cases of respiratory cancer included in the analysis had only one or two, instead of three matched controls, because no more eligible controls could be found. A total of 40 cases and 102 matched controls were included in the analysis.

Although every cohort member in the study had to have had a minimum of six months of employment in an area or areas with potential exposure to styrene to be eligible for the study, not every cohort member actually worked in activities which entailed direct and significant exposure to styrene. Location designations in the work history in employment records might not be specific enough and some sub areas within the production areas might not have any direct and significant exposure to styrene. In the casecontrol study, a detailed review (without knowing the case or control state) of work history regarding direct styrene exposure was done.

The Mantel-Haenszel relative risk between respiratory cancer and direct exposure to styrene was 0.63, with X' of 1.11 (table 8). An analysis by duration of direct styrene exposure based on the Mantel-Haenszel extension X' procedure was also performed. The summary X' was 0.43, indicating a lack of association between duration of styrene exposure and respiratory cancer mortality. Thus the analysis did not demonstrate any association between respiratory cancer and exposure to styrene.

Analysis from the cohort mortality study indicated that plants with hot process jobs experienced a higher rate of respiratory cancer than plants with cold process jobs. Table 8 shows that, adjusting for plant, there was no difference in risk for respiratory cancer between workers exposed to the hot processes and other workers. The type of process was, however, partly confounded by the variable "plant," which was in turn confounded with other concomitant exposures, availability of exposure histories, methods of exposure classification, etc. Few plants had both hot and cold processes, and they did not contribute an adequate number of cases for a separate analysis.

TABLE 8

Mantel-Haenszel relative risk and X' for respiratory cancer, various occupational exposures, and smoking

	Occupational exposure	Cases	Controls	Relative risk	X^2	p-Value
Direct exposure to styrene	Exposed	15	44	0.63	1.11	0.29
	Not exposed	25	58			
Type of styrene process	Hot only	8	23	0.69	0.04	0.52
	Cold only or both	32	79			
Type of styrene process	Hot only or both	8	24	0.65	0.57	0.46
	Cold only	32	78			
Poly resins	Exposed	14	45	0.55	1.33	0.25
	Not exposed	26	57			
Acetone exposure	Exposed	17	50	0.84	0.03	0.87
	Not exposed	23	52			
Smoking	Ever smoked	30	52	7.33	4.27	0.04
	Never smoked	1	11			

A relative risk was also calculated by comparing those exposed to polyester resins with those unexposed (table 8). Although exposure of workers to styrene in the reinforced plastics industry was almost always through polyester resins, two workers directly exposed to styrene were not exposed to these resins. The relative risk for polyester resins was 0.55 (X^2 = 1.86, p = 0.17). Thus no association was found between exposure to polyester resins and respiratory cancer.

A similar analysis was done for exposure to acetone (table 8). The corresponding relative risk was 0.84 (X^2 = 0.18, p = 0.67). Again, no association was found between exposure to acetone and respiratory cancer.

Smoking history was ascertained for 78.2% of the study subjects. A total of 31 matched sets had smoking information for both the case and the controls, and, therefore, could be included in the analysis. The relative risk of respiratory cancer for smokers (cigarettes, pipes, or cigars) was 7.33 when compared with non-smokers (table 8). The corresponding X' was 4.27, and the p value was 0.04. It is reassuring that the study, even with its relatively small sample size, did confirm the well established relation between smoking and respiratory cancer. Thus smoking was the only factor found to be associated with respiratory cancer in this study.

To determine if any interaction existed between the factors, they were examined simultaneously with a multiple logistic regression technique. Smoking, direct exposure to styrene, duration of exposure to styrene, and type of process were included in the multivariate model as main effects, and the effect due to the interaction terms was also examined. The results indicate that, among the factors included, only smoking showed a significant X^2 (X^2 = 4.42, p = 0.04); and the corresponding goodness of fit X^2 was not statistically significant, meaning that the model fits the data reasonably well. Also, none of the interaction terms were significant. The results of this multiple logistic regression analysis were similar to those in table 8.

DISCUSSION AND CONCLUSION

Although the observation period for the cohort study spanned a 31-year interval, the average duration of follow up for cohort members was relatively short (7.7 years). Also, the cohort was young compared with most other occupational studies. Half of the cohort entered the study before age 25.

The vital state of cohort members was determined through the usual source, plant and company records, as well as the Social Security Administration (SSA). The vital state of a relatively large number of workers (16.1%) was undetermined. The reason for this high percentage lost to follow up was unclear. One explanation might be that the cohort included female employees, who might not be actively employed or might have married and changed their names by the end of the study. For these, the SSA follow up would not be productive. It was also noted that the cohort consisted of a high percentage of short term employees. These transient workers may also have contributed to the high percentage lost to follow up.

The overall SMR was 100.0, somewhat higher than that normally expected for an occupational cohort. The healthy worker effect (about 20% deficit in overall mortality) usually seen in occupational groups was not present in this cohort, partly because of the absence of preemployment examinations and the transient nature of the workforce.' The high percentage lost to follow up may have contributed to this finding. As SSA did not have a death record for workers in this group, most likely they were still alive, and the overall SMR presented in this report would be overstated.' Another contributing factor might be that many of the cohort members were transients who were associated with unfavourable mortality experience. Analysis by duration of employment (table 2) supported this explanation; those with employment of less than one year experienced a significantly increased overall SMR of 128.6, whereas those with employment of five years or more had a deficit in overall mortality (SMR = 74.9).

For the entire cohort, mortality from respiratory cancer was slightly, but not significantly raised. For cancer of the larynx, the SMR among the men was 360.2 (four observed deaths), approaching the 0.05 percent significance level. Among the women, the SMR for lung cancer was 204.0 (five observed deaths). This did not reach statistical significance.

When mortality from respiratory cancer was examined by duration of employment, no trend was detected. Close to half of the cohort worked for less than two years, however, and more than three quarters of the cohort worked less than five years. Thus most of the cohort worked for only a short period, and analysis by duration of employment (< 1, 1–2, 2–5, and > 5 years) for respiratory cancer might not be informative.

For cancer of the larynx, statistically significant excess was seen for the group with higher maximum TWA (SMR = 730.5), and for the group with higher average TWA (SMR = 941.1). Both SMRs were based on only three deaths, however, and caution must be exercised in interpreting these figures. Also two of these cases worked for less than one year and the other worked for 17 months at their plants. There was no difference detected when mortality from cancer of the larynx was examined by type of process.

For lung cancer, the groups with less exposure (characterized by either low exposure potential, lower maximum TWA, or lower average TWA) appeared to experience higher SMRs than the groups with higher exposure. No reason is offered for this finding. A twofold difference in mortality from lung cancer was seen between the plants with only cold processes (SMR = 64.2) and those with only hot processes (SMR = 172.1, $p < 0.05$). This finding was not consistent with the concept that greater exposure to styrene might cause a higher risk of respiratory cancer, as potential exposure to styrene from cold processes is generally higher than from hot processes.

To investigate further the problem of respiratory cancer, a nested case-control study was conducted. The case-control study did not show any significant association between respiratory cancer and direct exposure to styrene, duration of styrene exposure, the type of process (hot v. cold), or whether a resin was used. Smoking was the only factor found to be significantly associated with respiratory cancer. No significant interaction existed between the factors examined.

In the entire cohort, only nine deaths were due to lymphatic and hematopoietic cancer, compared with 12.28 expected. For leukemia five deaths were observed and 4.76 were expected. The cohort as a whole did not experience any excess in either lymphopoietic cancers in general, or leukemia in particular. Analysis by duration of employment or latency did not show any trend.

When mortality from leukemia was analyzed by departmental exposure, those in departments with high exposure potential experienced an SMR twice that in departments with low exposure potential (199.3 v. 99.9). Similar differences were also seen when mortality from leukemia was analyzed by maximum TWA and average TWA, but none of the differences was statistically significant. On the other hand mortality from leukemia was identical for

plants with either hot or cold processes.

Because of the small number of deaths from lymphatic and hematopoietic cancer or from leukemia, no definite statement regarding this category of disease could be made. The study did, however, rule out any risk greater than 2.3 fold (an SMR of 230) in lymphopoietic cancer or 3.4 fold (an SMR of 340) in leukemia for the entire cohort (at alpha of 0.05 and 80% power). Because of the small number of deaths, no case control analysis was feasible.

It should be pointed out that there were several limitations in this study. Both the percent lost to follow up and the proportion of outstanding death certificates were higher than we desired, and it was possible that deaths from certain causes were underreported. The cohort was relatively young and the follow up period was short. The numbers of observed deaths from several causes were small, and the corresponding statistical power was limited. Some of these problems can be remedied by extending the observation period in the future. Duration of employment was short for the cohort as a whole, and historical exposure data were very limited. Information on exposure based on records of employment might not be specific. Furthermore, due to the transient nature of the cohort, the members might have been exposed to a variety of different substances and different employment environments. The cohort assembled in this study, however, represents one of the best data sets available to the reinforced plastics and composites industry; many of the limitations mentioned above were not unique to this study, but common to all other occupational epidemiological studies. Given the limitations discussed, no significant cause specific mortality excess for the cohort as a whole was found. The excess in respiratory cancer seen in several subgroups could be explained by differences in smoking habits. Exposure to styrene, as well as to other chemicals used in the reinforced plastics and composites industry, did not increase the risk of respiratory cancer. The data set was too small to offer any definitive conclusion on a modest increase (SMR 200) in risk for leukemia although it suggested that groups with higher exposure to styrene experienced a higher SMR for leukemia than the groups with lower exposure. On the other hand, the study ruled out with reasonable statistical power (alpha = 0.05, power = 80%) any rise in mortality from leukemia greater than 3.4 fold for the cohort as a whole.

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THE EPIDEMIOLOGY OF STYRENE–II

A Critical Review of Eight Studies Involving Nearly 50,000 Workers

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This review examines the eight most recently published epidemiology studies of workers occupationally exposed to styrene. Together, these investigations involved nearly 50,000 employees over a 45-year time period between 1940 and 1986. The studies covered workers in a variety of operations, from boat-building to fiberglass panel construction to styrene monomer and styrene- butadiene rubber manu- facturing. Workplace environments were all characterized by multiple agent exposures, including a number of known or suspected carcinogens, and some of the earlier styrene exposures were substantial. Nevertheless, the studies showed no over- all risk of lymphatic or hematopoietic cancer or the various cancer subtypes to be associated with these workplace exposures to styrene.

Several factors have contributed to a continuing concern over the issue of the carcinogenic potential of styrene. An apparent cluster of two leukemia deaths at two Texas styrene-butadiene rubber facilities in 1976 has been cited as motivation for some research (Meinhardt *et al.,* 1978). However, at the time of these observations, the styrene-butadiene rubber industry had already received much attention by epidemiologists, primarily over concerns for benzene-related health effects. The structural similarity of benzene and styrene, i.e., vinyl benzene, no doubt interested some researchers. Findings of clinical studies on humans (though focused mostly on neurological effects), of toxicology studies on laboratory animals, and of mutagenicity assays are also cited as background reasons for epidemiologic investigations.

Nearly a dozen published reports of epidemiology studies related to styrene or styrene industries have appeared since the rubber workers investigations in the 1970's. Most of this more recent research has been structured similarly enough to allow relatively direct comparisons of results. This review discusses the findings of eight of the more significant of these occupational epidemiology studies. Two earlier reports initially considered for review (Ahlmark, 1978; Frentzel-Beyme *et al.,* 1978) did not provide direct data on cancer rates, and so could not be compared with the other studies.

In all, nearly 50,000 workers were studied, jointly covering the time period between 1940 and 1986. The underlying employee populations represented by study samples were much larger, probably comprising a large fraction of all workers employed in styrene-related industries. The material presented by the eight investigations is extensive, and considered as a whole, provided a sufficient basis for conclusions.

The focus of this review is on the risk of lymphatic and hematopoietic cancer among styrene workers. While a few other causes of mortality as related to styrene exposure have received attention, such reportings have been sparse.

Much can be gained in the joint consideration of multiple investigations of an occupational health issue. Of course, the ideal return on this effort would be a complete resolution of the issue. Even if that is not feasible, the relative strengths, weaknesses, and contributions of the component studies can be weighed from a common perspective, a more balanced and comprehensive analysis of the topic, and a clearer recognition of the factors involved, than any individual study can provide. Furthermore, a direction for future research may become apparent after assessing the joint limitations and patterns of consistencies or inconsistencies in available studies.

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TABLE 1

Average annual age-adjusted incidence rates per 100,000 population, selected neoplasm sites, by race and sex; SEER program 1973-1977

	All races			White			Black		
Site	Total	Male	Female	Total	Male	Female	Total	Male	Female
All neoplasms	331.5	379.3	304.1	325.7	371.6	301.2	359.4	454.3	288.7
All LHC	25.7	31.5	21.3	25.7	31.6	21.4	24.4	31.0	19.3
Leukemia	9.8	12.8	7.7	9.9	13.0	7.7	8.6	11.1	6.8
lymphatic	4.1	5.5	3.0	4.2	5.6	3.1	3.5	5.0	2.5
myelogenous	4.3	5.4	3.6	4.3	5.4	3.6	3.7	4.4	3.2
Lymphoma	12.0	14.0	10.3	12.3	14.3	10.7	7.9	10.3	5.8
Hodgkin's	3.0	3.5	2.4	3.1	3.6	2.5	2.0	3.0	1.1
NHL	9.0	10.4	7.9	9.3	10.7	8.2	5.8	7.2	4.7

Source: Young and Pollack, 1982

DISEASE

Classification

In contrast to other neoplasms, cancers of lymphatic and hematopoietic tissue (LHC) are classified histologically rather than by site. Together, they rank among those neoplasms given the most intensive clinical study, and much attention has been given to cataloging the various morphologically diverse subtypes.

Many advances in the diagnosis of LHC have occurred during the period of time covered by the studies under review. As prime examples, the fifth revision of the International Classification of Diseases, in force from 1940 to 1948, classified Hodgkin's disease among infectious and parasitic diseases, and leukemia as a disease of blood or blood-forming organs, rather than neoplasms. Multiple myeloma was classified as a bone tumor. Since the time frame of follow-up of the eight studies covers the latest five revisions of the International Classification of Diseases, some inaccuracies in attempting to code historical information to modern cause of death rubrics can be expected. This problem would have had more serious implications to the investigation of LHC and styrene had not most of the deaths been observed only during the later years of follow-up.

Specificity

Advances in clinical treatment have demonstrated the importance of specificity in morphologic classification, which will no doubt be further reflected in future cause of mortality coding standards. For the purposes of this review, the major LHC subtypes of lymphoma and leukemia (and "other") will be recognized, as well as the more specific cell type designations of Hodgkin's disease, non-Hodgkin's lymphoma (NHL), lymphatic leukemia, and myelogenous leukemia. While this may not be ideal, it already surpasses the resolution of the data provided in many of the study reports, and no doubt some death certificates available to the investigators.

The specificity of tumor diagnosis is critical to etiologic investigations because of the specificity with which single agents are known to affect biological pathways. This principle is exemplified by many of the definitive causal associations demonstrated by occupational studies, such as that between liver angiosarcoma and vinyl chloride (Berk *et al.,* 1976) and between mesothelioma and asbestos exposure (Selikoff *et al.,* 1965). Equally distinctive biologic activities have been shown in animal models of human carcinogens (Wilbourn *et al.,1986).*

Frequency

A major obstacle to epidemiologic investigations of suspected occupational causes of LHC is the low frequency with which these neoplasms occur. Representative incidence rates for the U.S. are given in table 1. As a unit, LHC accounts for less than 8 percent of all neoplasms in the U.S. and about 2 percent of all deaths.

From an epidemiologic perspective, this means that studies with smaller sample sizes are less likely to detect

potential associations, whereas those risks that are identified will tend to be over-estimated (Beebe, 1984). Also, the few expected observations of deaths from infrequent diseases are apt to fall within the range of effects attributable to procedural errors and biases. For these reasons, the value of jointly considering all available research must be emphasized.

Accuracy of coding

Variations in classification schemes for LHC have made comparisons of the eight study reports difficult in some cases. Few authors specified cell types for leukemia deaths. Ott *et al.* classified LHC deaths as leukemic or non-leukemic, and some authors equated non-Hodgkin's lymphoma with lymphosarcoma and reticulum cell sarcoma. Some variability in classification, and perhaps even in rate calculations is probably attributable to the various computer programs and standard rate tables available to the investigators. To some degree, investigators may have been limited and results affected by the quality and amount of information provided on death certificates. Present day coding of LHC deaths is relatively accurate, but even today, not all certificates are supported by pathologist's reports, nor are they necessarily completed by physicians. Associations between death certificate coding validity and the availability of medical facilities have long been established. Clinicians' awareness of occupational health issues is also suspected of influencing accuracy of death certification (Sackett, 1979).

Since the study cohorts were derived from industrial working class populations, the availability of medical institutions and health professionals may have resulted in death certification that was more accurate than that for the national populations. Consequently, some inflation of LHC risk estimates may be expected. Ideally, local employee cohorts would have been preferable to the national populations as comparison groups, were it not for the inevitable instability of LHC rates due to the small number of deaths. Two of the studies reviewed, however, made limited use of local referents. In the study by Ott *et al.*, expected LHC deaths based on a local cohort were fewer in number than expected deaths based on the U.S. population; however, the former was shown to have significant variability. The unexposed referents in the study by Hodgson and Jones were seen to be at equal or less risk for LHC than the population of England and Wales, but very few LHC deaths were observed. While these two studies did not bear out the possibility of better local LHC diagnosis, it is still a phenomenon worth considering among the other reports.

Regardless of the cause, inaccuracies in death certification such as those noted by Hodgson and Jones *can* reduce the reliability of risk estimates from the eight studies reviewed. In that case, the deviation of one or two observed deaths from expected numbers should be interpreted as possibly being within the margin of error, rather than as a sign of elevated or diminished risk.

Demographic factors

Differences in LHC mortality and incidence rates by race, sex (see table 1), socioeconomic status, and geographic area have long been recognized. While these differences may represent real characteristics of the disease process or of environmental effects, it is also suspected that the accuracy of diagnosis may differ from one group to another. Diagnostic variability due to race and sex differences can be adjusted in analysis by using specific rates from national population rate tables, but the accuracy of this method assumes that no bias exists in disease ascertainment. Race information was not always available to the authors of the studies reviewed. Three authors (Hodgson and Jones, Nicholson *et al.*, Coggon *et al.)* made no mention of the racial or ethnic composition of the workforce, though two of the cohorts were British. Meinhardt *et al.* restricted their cohort to white males, and Okun *et al.* reportedly adjusted for race. The remaining three studies (Ott *et al.*, Matanoski and Schwartz, Environmental Health Associates) assumed cohort members with unknown race to be white. The degree of error introduced by such an assumption is unknown, although the number of non-whites was known to be small.

Standard population mortality rates for socioeconomic categories and for suitable geographic areas are generally not entirely available. The use of local reference groups would have allowed for statistical adjustment of these confounders, but that was not practical due to the small number of LHC deaths. Ott *et al.* found lower risk among professionals within the styrene cohort for all causes of death, all diseases of the circulatory system, and for all neoplasms, compared to a local reference group. On the other hand, non-professionals in the styrene cohort had risks comparable to the reference group. Subsequent comparisons between the styrene cohort and local referents avoided such confounding by considering only non-professional styrene employees. Matanoski and Schwartz found higher risk for LHC among hourly workers than among salaried workers, though styrene exposure was not simultaneously considered.

Therapeutic factors

One of the greatest concerns in the use of mortality rates for determining risk to LHC is the potential for unequal therapeutic treatment of LHC cases. In the general population, the near-term fatality rate for LHC patients, and especially for Hodgkin's disease, has declined dramatically over the course of the styrene study period. The year of death for LHC cases in these studies was usually not mentioned, but in general, higher LHC case fatality would be expected in the earlier years of follow-up of the styrene cohorts, other considerations aside. If therapy is more readily available for the study cohorts than for the general population, as might be expected except for transient styrene workers, the risk estimates derived for LHC on the basis of mortality may be underestimates of true disease incidence, at least for younger workers. If death from LHC was merely delayed through therapy, some study subjects may have died from competing causes. It is more likely, however, that LHC risk would be seen to be elevated among older workers after longer apparent latency.

If the time gap between diagnosis and death from LHC continues to increase, mortality indices will be less useful in epidemiologic research. At the same time, this trend underscores the importance of stratifying study cohorts by the time of first employment, to adjust for changes in diagnosis and treatment.

Latency

All-in-all, not much is known about the environmental etiology of LHC, the greatest amount of information coming from occupational studies of benzene and from investigations of Japanese radiation victims of World War II. These investigations shed little light on any potential disease model for styrene-induced LHC. Moreover, it is very difficult postulating such a disease model without definitive proof of any association to begin with. Lacking such evidence, many exposure and disease models must be considered.

In general, industrial hygiene data have not been adequate even to differentiate between short duration-high concentration exposures and long duration-low concentration exposures to styrene within a single cohort, although in some studies, employment times for some workers were definitely short. Detection of LHC depends on an adequate length of follow-up in relation to an as yet unknown latency period for the disease, if in fact there is any styrene-related cancer to be detected. There is fair agreement on the characteristic 15 year minimal latency for myelogenous leukemia attributed to benzene expo- sure (Bond *et al.,* 1986; Rinsky *et al.,* 1987). There is no *a priori* reason to believe that latencies for the various LHC sub-types should be the same; however, a certain degree of consistency is expected for any particular subtype.

Inconsistencies in disease patterns were seen on occasion among the eight studies. In the study by Hodgson and Jones, for instance, three NHL cases were followed 4, 8, and 17 years until death, and Meinhardt *et al.* found six leukemia cases, three of whom died within four years of first employment. If these cases were taken to be induced by styrene, or at least some occupational exposure, then short latency periods would be expected. Even among younger cohort members, there would have been ample opportunity to observe many more such cases than were seen. On the other hand, if longer LHC latencies are postulated, then these cases are unlikely to be attributable to styrene exposure. It is notable that Coggon *et al.* and Meinhardt *et al.* both failed to find any meaningful patterns between LHC mortality and latency as measured by time since first employment.

STUDY DESIGN

Design structure

As has already been mentioned, the eight studies of this review all had a similar structure, referred to by epidemiologists as a cohort design or follow-up design. Its definitive features include *1) a priori* specifications of exposures to be examined, 2) representative sampling from a relatively healthy population prior to exposure, and 3) the ascertainment of vital status or disease state after a suitable exposure and follow-up period, and comparison of death or disease frequencies with those of an unexposed cohort or population.

In contrast to this design, a case-control study defines two groups, one with the disease under investigation, and one without. The exposures of the two groups are retrospectively determined and compared. Case control studies have certain advantages for etiological investigations, since exposure is not specified *a priori,* and a number of agents or exposure measures can be examined. In this regard, cohort studies are weaker than case-control studies for etiologic research. Because exposure defines the study group in a cohort study, optimally, only one agent per study can be addressed in depth. Whether by plan or by circumstance, a particular cohort may be optimal for studying perhaps only one exposure measure as well; for instance intermittent peak exposures or long duration exposures. The studies reviewed shared this weakness for examining alternate etiologies. They were also noted individually to be limited

by the particular exposure characteristics of their cohorts.

For investigating infrequent causes of death, such as LHC, cohort studies are relatively inefficient, since a large amount of data must be collected on a large number of subjects, only a few of who turn out to be cases. The investigator is usually bound to ask whether a sufficiently large sample was used to allow statistically significant risk determinations, or whether follow-up was sufficiently long for disease or death to occur.

Outcome measures

Also common to the eight studies was the primary outcome of mortality, although some details of LHC incidence were sometimes given as well. Mortality data, primarily death certificates, is generally easier to obtain than disease incidence, even in retrospective examinations. However, as has been discussed, mortality is not always the most direct or accurate measure of the occurrence of disease. In many instances, the presence of disease is noted only after a study subject dies from an alternate cause, and is therefore inadmissible in an investigation which focuses on the underlying cause of death diagnosis. An incidence study would incorporate such a disease case, as well as others among both living and deceased study subjects.

Comparison groups

A third common feature of these studies is that the primary comparison group has been in all cases the general national population. Mortality rate tables for various subsets for the general population by age, race, sex, and calendar year are widely available, and rates are usually precise because of the large number of deaths recorded. Gradually, cancer incidence tables are being constructed and made available for epidemiologic research. One problem with population-based studies is that the general population may be very different than the local cohort with respect to a number of critical risk factors. Socioeconomic status and the availability of medical care have already been mentioned. Background disease rates may also vary considerably from one geographic area to another. There may be a substantial degree of confounding operating in population-based studies, such as the eight studies reviewed, due to known risk factors prevalent in either the cohort or the general population, for which no adjustment can be made.

Since mortality rates for the general population are seldom presented with a suitable degree of demographic detail, it would seem that unexposed local comparison cohorts are a reasonable alternative. The advantages are that the two groups would initially be very similar, and that the influence of a number of heterogeneous personal factors (years employed, job type, age at hire, education, ethnicity, *etc.)* could be adjusted by comparing only similar strata of the two cohorts. However, very large cohorts, not typically available for occupational studies, would be needed to make this approach practical.

Design assumptions

Fundamental to cohort studies is the understanding that cause precedes disease, and that disease status cannot be used to influence cohort selection. Violations of both these assumptions may have occurred within the styrene studies. In the first place, disease initiation and disease onset are two different events for cancers in general, separated by a period of latency. While it is unlikely that individuals in the study cohorts were hired with manifest LHC, some cases may have been initiated by other causes prior to first exposure, or even after having left the workplace. As shorter times of employment are considered, this possibility becomes increasingly more likely. The second violation of design assumptions occurred in the case of at least one study (Meinhardt *et al.)* which was initiated as the result of observing two leukemia deaths which were included in the study cohort. Subsequently, a subset of the cohort containing all five leukemia cases, but otherwise more limited in definition, was reanalyzed statistically. The outcome was inevitable, since knowledge of the disease state was allowed to influence the definition of the cohort.

The follow-up of cohort members in the eight studies was generally close to complete. One study (Nicholson *et al.)* may have achieved complete follow-up by careful definition of the cohort. Another (Environmental Health Associates) achieved only 84 percent follow-up, due to the geographic diversity and the transient nature of the workforce. The success of follow-up is important to cohort studies because subjects lost to follow-up may have had unusual health outcomes or exposures, and their omission could seriously bias the estimate of risk.

WORKPLACE AND WORKFORCE

Industries

Two basic industries are represented by the eight investigations. Coggon *et al.,* Okun *et al.,* and Environmental Health Associates reported on workers in reinforced plastics (RP) manufacturing, of which the earliest operation began in the late 1940's. The remaining five studies dealt with workers involved in various aspects of styrene monomer and polymer production, beginning in the early 1940's. Ott *et al.* and Nicholson *et al.* describe work experi-

ence in all three operations: monomer production, styrene polymerization, and styrene-butadiene latex copolymer (SBR) production. Hodgson and Jones cite only styrene monomer and polymer production, while Matanoski and Schwartz and Meinhardt *et al.* report only exposures in SBR production.

Comparative exposures

In general, exposures in RP industries are much higher than those in styrene polymerization and SBR production. Okun *et al.* cited average ambient styrene concentrations of 72 ppm at one plant, with some jobs receiving mean exposures of over 100 ppm. Most of the workforce in the study by Coggon *et al.* were said to have had recent exposures of from 40-100 ppm styrene. Ahlmark (1978) estimated exposures in Swedish RP industry operations about 1970 to be in the range 250-350 ppm. The greatest contact with styrene is through inhalation of vapors during spray operations and curing, and dermal contact during hand lamination with resin which contained about 40 percent styrene monomer.

Meinhardt *et al.* (1978) cite much lower eight-hour TWA concentrations for styrene in an SBR facility in 1977. The highest level recorded was 12 ppm and most samples were well below 1 ppm. Nicholson *et al.* reported 1974 exposures from less than 1 ppm to 20 ppm styrene. However, considerable changes have taken place in SBR processes, and higher exposures could have occurred historically, especially in batch polymerization processes before about 1950.

Non-styrene exposures

The numbers and kinds of concomitant exposure agents varied considerably between the two industries. Glass fiber, acetone, methyl ethyl ketone, organic peroxides, and asbestos were consistently found in RP operations. Many more materials were used in SBR plants, including several suspected carcinogens. Among the materials cited were benzene and alkylbenzene compounds, butadiene, formaldehyde, antioxidants, extender oils, acrylonitrile, and organic pigments.

Exposure gradients

Few of the investigations had the benefit of historical industrial hygiene data. Ott *et al.* and Environmental

Health Associates used limited past surveys to construct qualitative exposure categories. Coggon *et al.* constructed three graded categories of styrene exposure, plus background, based on recent survey data. A problem common to all these attempts is that recognition of patterns of risk among exposure categories becomes very difficult when only a few cases of LHC are found. In some instances, there are more exposure categories than cases. Meaningful trend analysis requires an abundance of disease cases for a categorical approach, or exact quantitative data on fewer individuals if regression techniques are to be used. Neither requirement was met in the studies reviewed.

Matanoski and Schwartz analyzed four separate job categories: production, maintenance, utilities, and "other". While they did not assign styrene exposure ranks to these categories, Nicholson *et al.* reported that production workers and maintenance staff were exposed to higher levels of styrene. In pooling these two categories in Matanoski and Schwartz' data, however, it is found that production and maintenance workers consistently had lower SMR's for Hodgkin's disease, leukemia, and other lymphomas.

Length of exposure

Length of exposure to styrene was often used as a surrogate measure of dose, and sometimes taken to be length of employment in styrene operations. Ott *et al.* and Nicholson *et al.* looked for associations between length of employment and mortality, but only for broad categories of causes of death. Coggon *et al.* found that the only three cases of LHC (one Hodgkin's disease, one myeloma, one leukemia) with sufficient work history data occurred in the middle time category, one to nine years of employment, thus not displaying any dose-response pattern. Meinhardt *et al.* also reported not to have seen any pattern of LHC with length of employment.

Hodgson and Jones performed a creditable nested case-control analysis within their cohort. They matched four LHC cases with 116 referents having similar ages at the start of employment, and then compared length of employment of the LHC cases with that of the non-cases. Although only a few cases were available for study, this approach is more sensitive than any of the analyses in the other studies. The lack of any meaningful association between LHC disease state and length of employment in styrene operations is therefore in itself an informative finding.

At the same time, these authors noted that length of employment is a poor surrogate for quantitative exposure data, an argument that may have some merit. It might not be expected that all operations at an industrial site would provide the same intensity of exposure, nor that styrene levels at any single job would remain constant, nor that employees would remain at a single job throughout their careers. It is therefore possible that a single length of em-

TABLE 3

Observed and expected deaths from LHC and its subtypes, from the results of eight studies of styrene workers

		Lymphoma			
Study	All Leukemia	HD	NHL	all	All LHC
Ott *et al.*	6 / 3.40			7 / 5.30	13 / 8.70
Matanoski & Schwartz	17 / 18.70	8/ 6.67	5/10.20	13/16.87	40/47.10
Hodgson & Jones	0/0.30			3/0.56	3/0.86
Meinhardt *et al.*	6/3.46	1/1.38	4/2.24	5/3.80	11/8.34
Nicholson *et al.*	1/0.79			1/1.25	2/2.04
Coggon *et al.*	3/6.00	1/2.40	1/4.22	2/6.62	6/14.90
Okun *et al.*	0/1.70			0/2.10	0/4.20
EHA	5/4.76	3/2.41	0/2.63	3/5.04	9/12.28
Pooled	38/39.11	13/12.86	10/19.47	34/41.54	84/98.42
SMR	97	101	51	82	85
95% CL	69-133	54-173	25-94	51-106	68-106

ployment category would represent a wide range of cumulative styrene doses or peak concentrations. On the other hand, job transition patterns are more orderly than one might imagine, and given enough data, secular trends and job-to-job differences should be expected to "average out". Meinhardt *et al.* (1978) have shown that styrene exposures, at least during recent times in SBR production, are very low and fairly uniform, making duration of exposure perhaps the only exposure measure with meaning.

General exposure

The default treatment of styrene exposure classification is, of course, having ever or never worked in operations or plants using styrene. All eight studies had data analyzed from this basis, the findings of which are presented in table 3 and discussed in the Study Results section of this review. It is the only common numerical treatment of LHC risk from styrene. In many respects, this approach is unsatisfactory, since it allows the possibility of exposure misclassification. Clearly, not all employees of a given

plant had substantial styrene exposure, measured either by concentration or duration. In the extreme case, all the LHC deaths might have occurred among workers with either no styrene exposure or those with the greatest exposures. However, examination of the individual studies with regard to exposure gradients does not give the impression of a net trend, either negative or positive in direction, with styrene exposure. Hence serious exposure misclassification is not a concern.

The same problem as that seen for latency analysis is obviated by examining the treatment of exposure measures in these eight studies: it is difficult, if not impossible, to test hypotheses of various exposure models without first having definitive proof of an elevation of LHC risk associates with any styrene exposure.

Value of exposure data

If styrene is related to LHC mortality, the responsible exposures will most likely have occurred in the past, when little useful quantitative exposure data was recorded. Industrial hygiene surveys are perhaps now more frequent and record-keeping more systematic but at the same time, process changes and improved workplace conditions have reduced potential contact with styrene. Both limitations of exposure data and limitations of exposure opportunities present difficulties for etiological investigations.

Cohort characteristics

Just as characteristics of the workplace determine the potential for exposure to styrene, so do characteristics of the workforce. Different amounts and different types of descriptions of the study cohorts are provided by the various investigators. The ability of an investigation to detect an association between LHC and styrene depends on the interrelated workforce characteristics of 1) length of employment, 2) age, 3) cohort size available for study, and 4) length of follow-up. These factors are summarized in table 2 for the eight studies reviewed.

Length of employment

Length of employment was already discussed as a surrogate for duration of exposure. It may be true that the opportunity for exposure to peak concentrations of styrene is greater for employees with greater seniority. Length of employment is also related to age and length of follow-up. An employee with minimal length of employment may have been only recently hired into his first job, or may have joined the styrene cohort at a near-retirement age, or may simply be a transient worker.

The eight investigations specified varying minimum length of employment times, from no minimum requirement for Coggon *et al.* and Okun *et al.*, to a five year minimum for Nicholson *et al.* In the study by Ott *et al.*, 31 percent of cohort members had lengths of exposure of less than one year, while an additional 41 percent had one to four years exposure. Matanoski and Schwartz do not cite employment times. Hiring was generally more recent

TABLE 2

Comparison of cohort characteristics favorable for the detection of an association between styrene and cancers of lymphatic and hematopoietic tissues under two exposure-disease models; from eight epidemiologic investigations of workers employed in styrene industries

	Study Period (Years)	Cohort Size	Expected Deaths (%)	Age	Length of Follow-up (Years)	Minimum Service (Months)	Length of Service (Exposure)	Expected LHC Deaths	Strength Model 1	Model 2
Monomer, Polymer, SBR Production										
Ott *et al.*	36	2,904	15	older	moderate (20)	12	moderate (1-4 yr.)	8.7	+	-
Matanoski and Schwartz	36	13,920	18	older	moderate (20)	12	moderate	47.10	++	+
Hodgson and Jones	30	622	7	young	short (13)	12	?	0.86	-	-
Meinhardt *et al.*	44	2,756	19	older	moderate (18-20)	6	long	8.34	+	-
Nicholson *et al.*	>20	560	19	older	short (+10)	60	long	2.04	-	-
Reinforced Plastics Manufacturing										
Coggon *et al.*	38	7,949	10	young	short (10)	0	short-moderate	49.90	+	++
Okun *et al.*	22	5,201	4	young	v. short (8)	0	short < (1 yr.)	4.20	-	++
EHA	30	15,908	3	young	v. short (8)	6	moderate (1-4 yr.)	12.26	-	++

Model 1: Long-term low-intensity exposure, short latency
Model 2: Short-term high-intensity exposure, very short latency

than that in Ott *et al.,* but the study periods spanned the same number of years. Hodgson and Jones also do not cite length of employment, but it must certainly be less than the average 13 years of follow-up per person. Meinhardt *et al.* report an average of about 10 years employment in their cohort. Nicholson *et al.* do not mention employment time, but the minimum service requirement for the cohort was five years. Coggon *et al.* cite short

exposure times above background levels. Fifty-one percent of this cohort had less than one year exposure, and 41 percent had from one to nine years. Okun *et al.* report very short styrene exposures for high exposure jobs. Only six percent of this group had more than five years exposure, and 26 percent more than one year. Environmental Health Associates report that about 54 percent of their cohort had one to four years employment, with about equal numbers having more or less experience than this group.

AGE

Age is important as an indicator of follow-up and duration of exposure. More importantly, most cancers, perhaps even those induced by chemical exposures, display marked patterns of incidence with age. Ages of the cohorts were seldom described, but in some cases can be estimated from descriptions of hiring practices, and also by comparing the number of expected deaths to the cohort size. For the study by Ott *et al.,* the largest operations started in 1940 or before. Thirty-one percent of the cohort were first exposed before 1950. These observations are indicative of an older workforce. Matanoski and Schwartz described steady hiring throughout the follow-up period, with older workers being hired in the earlier years. The workforce can thus be described as relatively old by the end of the follow-up. Hodgson and Jones note that 67 percent of person-years were accumulated in a relatively young age band of 15-44 years. The long average period of follow-up in the study by Meinhardt *et al.* is in itself indicative of an older cohort. The cohort of Nicholson *et al.* had worked at least five years prior to 1960. Also at that time, the average age can be estimated to be about 42. While it is not clear when follow-up was complete, this workforce can be considered relatively old. Coggon *et al.* described many operations as starting only after 1960. This, as well as a short average follow-up time, indicates a relatively young cohort. Okun *et al.* tabulate the age distribution of person-years, showing most were contributed by workers under 35 years of age. Finally the report by Environmental Health Associates describes about 45 percent of the cohort as being hired after 1970, and nearly half hired at less than 25 years of age.

Cohort size

Cohort sizes were explicitly cited by all authors. The size is highly dependent on the cohort definition, especially on the minimum length of service requirement. All other factors being equal, a large cohort has a greater likelihood of demonstrating a potential association between styrene and LHC.

Length of follow-up

Length of follow-up is important in the consideration of potential latency periods for cancers. The best indicator of length of follow-up, when given, is the average person-years at risk per cohort members. Meinhardt *et al.* cited a long average follow-up of 18-21 years per person. Hodgson and Jones reported about 13 years per person in the exposed group, and Okun *et al.* reported a short follow-up of 8.2 years per individual. The follow-up cited by Environmental Health Associates, 7.7 years was equally short. Matanoski and Schwartz do not mention length of follow-up, but describe early hiring during the 36 years study protocol. Fifty-nine percent of that cohort were hired more than 20 years from the end of follow-up. Nicholson *et al.* defined a minimum ten year follow-up, but it is not known if that term was exceeded by cohort members. A moderately long follow-up can be estimated for the study of Ott *et al.,* based on the hiring practices and the age of the operations. Coggon *et al.* do not mention length of follow-up, but the description of their cohort includes the number of individuals recruited into the study and the time period of recruitment from each of eight companies. These figures impose absolute limits of between 5 and 20 years of potential follow-up, without considering deaths or loss of data. The average follow-up time would be expected to be closer to the lower limit, . perhaps about 10 years.

Expected deaths

Table 2 also presents the number of expected deaths from all causes in the eight cohorts as percentages of cohort size. This index reflects the combined effects of length of follow-up and age. In addition, the number of expected LHC deaths is tabulated.

Some patterns among the studies are clear. Length of follow-up and length of employment, as well as minimum service time required by the cohort definition were short for cohorts in the RP industry. These cohorts were also relatively young. It may seem to be a contradiction that the number of expected LHC deaths for two RP cohorts were large, but this was a result of the unusually large cohort size, which, under stricter cohort definitions, would have

been smaller. For instance, a one year minimum length of employment requirement would have eliminated 24 percent of the study sample.

Exposure-disease models

Workplace styrene concentrations, duration of exposure, age, cohort size, and length of follow-up can be combined to assess the effective power of each of the eight studies to detect a postulated LHC-styrene association, using either of two proposed exposure-disease models.

The two models chosen are extreme cases. The first requires chronic low-level exposures while the second specifies only short but high-level styrene contact. If an especially long latency period were required, few of the eight studies would have the ability to detect any but the most extreme risk. Rather, short (5-15 years) and very short (less than five years) latency periods were considered for models 1 and 2, respectively. It is important to keep in mind, however, that duration of exposure is still non-specific; it may at the same time be a measure of many different agents found in the workplace.

Not surprisingly, the two industries seem divided according to which model they are best suited to test at this time. The few exceptions are also understandable. The cohort of Coggon *et al.* was followed longer than those of Okun *et al.* or Environmental Health Associates, which, considering also its size, makes it moderately suitable for testing the first model. Also, the size of Matanoski and Schwartz's cohort, with some allowance for the possibility of high historical styrene exposures, makes that study moderately well suited for testing the second model.

On the basis of size, neither the Hodgson and Jones study nor the Nicholson *et al.* study would be expected to have much effective power for testing either model. This would be especially true for the Hodgson and Jones study, in light of the paucity of expected deaths compared to the cohort size. The limitations of size of individual studies emphasizes the importance of examining them in aggregate.

STUDY RESULTS

Summary of individual findings

None of the eight investigations claimed to have shown definitive results, or in considering existing literature, to have tipped the balance of evidence one way or another towards the assessment of the carcinogenic potential of styrene. Most have instead acknowledged the problems associated with few expected deaths and with limited follow-up of the workforce.

Three studies (Meinhardt *et al.*, Ott *et al.*, Hodgson and Jones) have reported a positive association between workplace exposure and lymphatic and hematopoietic cancer (LHC).

Meinhardt *et al.* found elevated but not statistically significant leukemia mortality in a reinforced plastics cohort which he interpreted as suggestive of an association with the workplace (6 observed, 3.46 expected; SMR=173, 95% CL=64-377). Five of the six cases were myelogenous.

Ott *et al.* found a statistically significant excess in incidence (living and dead cases) of lymphatic leukemia among workers involved with colorant blending, roll compounding or extrusion of plastics (5 observed, 0.26 expected; Standard Incidence Ratio = 1923, 95% CL=625-4487). This operation was characterized by multi-chemical exposures, but the authors allowed the possibility of a single etiological agent in early operations. However, the implication of styrene as such a cause is inconsistent with the absence of any lymphatic leukemia among the groups with highest exposure to that material. In the overall cohort, leukemia mortality was found in excess, though not statistically significant (6 observed, 3.4 expected; SMR=176, 95% CL=65-384).

Hodgson and Jones found a statistically significant excess in lymphoma mortality among workers producing styrene monomer and polymers, (3 observed, 0.56 expected; SMR=536, 95% CL=110-1565). All three of the lymphomas were non-Hodgkin's (NHL), though one was entered as Hodgkin's disease (HD) on the death certificate. The authors claimed their results to be consistent with previous reports, including that of Ott *et al.*, that they believed suggested an association with styrene.

Two of the most recent studies (Coggon *et al.*, Matanoski and Schwartz), both published in 1987, demonstrated deficits for almost all sub-types of LHC, including some that were markedly diminished.

Coggon *et al.* reported only six cases of LHC among reinforced plastics workers, where 14.9 were expected (SMR=40, 95% CL=15-88). Diverse tumor subtypes were represented: one HD, one NHL, three leukemia, one multiple myeloma (MM). The overall deficit was statistically significant. The authors stated that their *a priori* suspicions of styrene were not borne out.

A large study of styrene-butadiene rubber workers by Matanoski and Schwartz reported 40 deaths from LHC. A mild excess for HD was not significant (8 observed, 6.67 expected; SMR=120, 95% CL=52-236) nor was a larger deficit for NHL (5 observed, 10.2 expected; SMR=49, 95% CL=16-114). All other LHC subtypes occurred at below-expected frequencies. The authors indicated merely that no excesses were detected. Three other studies (Okun *et al.*, Envi-

ronmental Health Associates, Nicholson *et al.)* showed no marked departures from expected LHC frequencies.

Okun *et al.* found no LHC deaths at all in a large but young cohort of reinforced plastics boatbuilders with limited follow-up (0 observed, 4.2 expected; upper 95% CL=88). The authors preferred to interpret the results as inconclusive rather than negative.

The Environmental Health Associates report claimed a very slight elevation in leukemia mortality (5 observed, 4.76 expected; SMR=105 95% CL=34-245) which was not significant. Referring to 80 percent power calculations, the authors concluded that no more than a 3.4-fold risk, if any, could exist for this cause of death.

Nicholson *et al.* found one lymphoma and one leukemia case (2 observed, 2.04 expected; 95% CL=12- 354), and concluded that such information was not definitive except to indicate that an environmental risk could not be extraordinary.

Two other reports reviewed were not useful for assessing potential styrene carcinogenicity, and therefore, not summarized. A report by Ahlmark (1978) gave demographic descriptions of a cohort targeted for future investigation, and a survey by Frentzel-Beyme *et al.* (1978) provided comparisons only on relative proportions of causes of death rather than on rates (a proportional mortality study).

Patterns in results

Unless one is willing to entertain a theory of general lymphatic/hematopoietic carcinogenicity with varying manifestations from group to group, there appear to be no unifying features among the results of these studies relative to LHC. Those reports with positive findings have each pointed to a different tumor type. It is unlikely that all resulted from a single environmental factor. Add to these the two reports of disease deficits plus the three that failed to detect any sizeable deviation from expected mortality and it becomes more apparent that the neoplasms seen are diverse and unrelated events.

A risk estimate, such as the SMR, is the usual summary statistic for epidemiologic research. Such an estimate, however, can be very unreliable when it is used to describe associations of rare diseases with small expected frequencies. A large risk estimate may depend on very few observed events, and it is important to consider just how many such events are involved, since statistics cannot distinguish between observed events caused by exposure and observed events caused by other non-random mechanisms. In examining the positive studies, it will be seen that for each of the three findings, fewer than three deaths separate observed and expected figures. Thus, any determination of styrene carcinogenicity would rest upon the reliability and interpretation of no more than seven to eight total cases of mixed neoplasms observed among three of the eight studies.

The differences among the results do not seem to be clearly attributable to known dissimilarities among the cohorts or work environments. While some of the cohorts were not followed long enough to expect cancers with long latency times to become manifest, Matanoski and Schwartz provided reasonable follow-up time without observing any unusual outcomes. All three positive studies examined the styrene polymer manufacturers (Hodgson and Jones do not cite the use of butadiene copolymer, as do the others), but Matanoski and Schwartz, as well as Nicholson *et al.* studied that industry also, without finding excess risk. Ott *et al.* examined a moderately old workforce, and the cohort of Hodgson and Jones was relatively young, yet both studies reported elevated overall LHC mortality (albeit of different cell types). Benzene was probably present as a potential exposure agent in the positive studies as well as some showing no excesses or deficits in mortality. The multiplicity of outcomes are either chance occurrences or, if real, could be a result of as many as three separate environmental agents operating at different sites, which were only investigated as a unit because of the coincidental common presence of styrene.

Combined results

Keeping in mind the heterogeneity of results in the studies being reviewed, their combined weight of evidence is still the ultimate basis for evaluating the hypothesized association of styrene and LHC. A statistical summary is as helpful for pooled studies as it is for any single study. Table 3 presents observed and expected mortality figures extracted or derived from these eight studies with comparable designs.

Some assumptions have been made in order to condense the data into a common form, but any errors in so doing should be minor. For example, Ott *et al.* classified LHC deaths as leukemia or non-leukemia, whereas in the table, non-leukemia was taken to be primarily lymphoma. Likewise, NHL is used to describe what some authors have presented as lymphosarcoma and reticulosarcoma. Not all reports provided detailed information on LHC cases, so the sub-categories HD and NHL do not reflect all eight studies and should be interpreted cautiously. Only Meinhardt *et al.* and Ott *et al.* gave partial breakdowns of leukemia mortality by cell type, so there is no benefit in tabulating those results.

In the major categories, lymphoma and leukemia, as well as for all LHC, only deficits in mortality are seen. The confidence limits indicate only a slight chance that even a mild risk from styrene could exist. It could be safely stated that, had these overall results, or at least the risk estimates, come from a single early study, little motivation for continued investigation of styrene would have been provided.

One consideration that is not reflected in the statistical treatment of these studies is their individual and net ability to detect cancers that may appear only after a considerable latency period from a critical exposure. It is premature to speculate as to how long such a latency period might be at a time when there is so little evidence of which disease outcome, if any, to expect. The studies reviewed probably have the ability to test for cancer after a latent period of up to 15 years, though in doing so, the effective sample size of many of the cohorts would be diminished. Updated follow-up of these cohorts could extend the range by as much as 10 years, as well as double the number of expected cases. Except for transient workforces, updated investigations would also increase the likelihood of sufficient chronic exposure, if such an exposure model is to be entertained.

Of course, any extraordinary risks of styrene exposure would probably already be evident from these investigations. The prospects for future research is a matter for speculation. There is no basis in the eight study reports to predict that later work will provide more "positive" evidence than what is available now. An objective evaluation of the mass of available epidemiologic data argues against, rather than for a carcinogenic potential of styrene at levels found in industry.

Individual summaries of the eight selected studies are available by *contacting the Styrene Information and Research Center. Also included with the summaries are discussions of design features or study cohort characteristics that were important to the assessment of carcinogenic risk.*

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Clarifying the Carcinogenicity Issue: The Styrene Research Program

The Science and Technology Task Group of the Styrene Information and Research Center

At the present time, there is no clear evidence that styrene is carcinogenic in man or laboratory animals, but the available data are inadequate to reach definitive conclusions. This article summarizes the current international research being conducted by the Styrene Information and Research Center, the European Chemical Industry Ecology and Toxicology Center and the International Agency for Research on Cancer to resolve the outstanding issues. Completion of this research program should allow a more thorough understanding of the carcinogenic potential of styrene, as well as the potential human health significance of styrene oxide as an intermediate metabolite of styrene.

One of the principal purposes of the Styrene Information and Research Center (SIRC) is to clarify any potential health effects to humans from exposures to styrene. While numerous studies have been conducted over the past 50 years, inconsistencies and deficiencies in many of these studies have made definitive conclusions difficult to establish. This is particularly noticeable in the attempts to assess the carcinogenic potential of styrene, which have been subject to many different interpretations. In 1987, the International Agency for Research on Cancer (IARC) changed its classification of styrene from Group 3 (not classifiable) to Group 2B (possible human carcinogen). This decision was not based on new longterm animal or human data, but by the inclusion of other data not previously considered. In 1988, the twelve member European Community reviewed the styrene literature and concluded that styrene should not be regulated as a carcinogen. After reviewing the literature and public comments, the Occupational Safety and Health Administration (OSHA) decided in 1989 that styrene should not be regulated as a carcinogenic hazard in the workplace. In January 1991, the Office of Drinking Water of the Environmental Protection Agency (EPA) chose to regulate levels of styrene in drinking water without making a carcinogen classification; however, the classification of styrene remains a topic of discussion within EPA. The Food and Drug Administration (FDA) regulations pertaining to styrene do not involve a carcinogenicity classification. A number of state agencies are developing regulations which affect styrene, and in a few states there have been proposals to regulate styrene as a carcinogen.

This article summarizes the current research program to assess the carcinogenic potential of styrene (figure 1), including studies sponsored independently by SIRC and the European Chemical Industry Ecology and Toxicology Center (ECETOC) as well as by IARC. They also involve a number of collaborative research efforts. Together they amount to a major international program involving scientists in many countries.

Several factors are important in determining the carcinogenic potential of a substance. The two most important factors are the evidence of carcinogenic potential (or lack thereof) in human epidemiology studies and the results of longterm animal bioassays. Other types of data, such as structure/activity relationships, metabolism, cytogenetics, and marcomolecular binding, may be considered when they are relevant.

EPIDEMIOLOGY STUDIES

Epidemiology studies are either case-control studies or cohort studies. In case-control studies, a group of individuals with a specific disease is identified, and then

attempts are made to identify commonalities in exposures that the group may have experienced in the past. In cohort studies, the health status of a group of individuals known to have had similar exposures is evaluated to determine if there are any specific abnormalities which might be excessive in comparison to an appropriately matched control population. Although epidemiology studies are quite powerful when clear differences exist, there are several difficulties which often limit their utility; for example, the degree of exposure to any given chemical is usually not available; appropriately matched control groups are very difficult to identify; workers are usually exposed to varying concentrations of a variety of substances; and it is difficult to control for related risk factors (e.g., smoking) that have serious effects on health.

Eight cohort mortality studies have been reported on styrene which collectively involved nearly 50,000 employees during the time period between 1940 and 1986. The combined weight of the evident from these studies argue against a carcinogenic role for styrene. Although any extraordinary risks posed by exposure to styrene should already be evident from these investigations, the current epidemiology data base is probably sufficient to test for cancer after a latency period up to 15 years.

In order to extend the latency period by another 10-15 years, SIRC is currently exploring the feasibility of a followup study on a very large cohort of approximately 16,000 employees in the reinforced plastics and composites industry. In addition, the International Agency for Research on Cancer (IARC) initiated an epidemiology study in 1988 which involves a very large cohort of approximately 20,000 employees of the reinforced plastics and composites industry. According to IARC, this study will have a longer latency period than other studies, and it will incorporate many highly exposed workers with good estimates of past exposure which should allow the identification of even low risks, if they exist. These epidemiology studies will be extremely important in making final judgments about the carcinogenic potential of styrene.

LONG-TERM ANIMAL STUDIES

Animal studies are usually conducted based on the long-standing assumption that potential effects in humans can be inferred from effects in animals. This assumption has in fact been shown to be generally correct, and the principle of extrapolation of animal data to humans has been widely accepted in the scientific and regulatory communities. The extrapolation from animals to humans is based on similar anatomical, physiological, and biochemical parameters across species. Although the general principle of extrapolating animal data to humans is well founded, there are known exceptions. Therefore, it is important to carefully evaluate all known interspecies differences before inferring human effects based on animal data. Critical aspects of evaluating long-term animal data include the number of animals, route of exposure, dose, dose-response relationships, frequency of exposure, historical control data, and mortality data.

A total of nine long-term animal studies have been conducted on styrene, and two additional studies have been conducted on a mixture of styrene and 13- nitrostyrene (See Boyd, *et al.*, 1990 for more details). Although there are many deficiencies and limitations in these studies which preclude definitive conclusions, the available long-term animal data provide no clear evidence of a carcinogenic response related to styrene exposure. This conclusion is supported by a weight-of-the-evidence approach: several studies showed no oncogenic response, other studies with increased tumors do not show a dose-response pattern or there was no consistent target organ or effect *(i.e*, no organotropism) in the various studies that have been conducted. In reviewing these studies, the National Toxicology Program (NTP) concluded that the results were "... equivocal because of small numbers of animals, the use of obviously toxic doses of styrene, unusually low spontaneous tumor incidences in control groups, and poor survival of control and test animals due to infections." Because we agree with NTP's assessment of these studies, SIRC is currently planning a new long-term inhalation animal bioassay with rats and mice. This bioassay will be conducted in accordance with currently accepted guidelines and practices, and the information from this study will be critical in reaching definitive conclusions about the carcinogenic potential of styrene.

OTHER RELEVANT DATA

Three other areas provide data which are relevant to judging the carcinogenic potential of styrene: structure/activity relationships, metabolism and pharmacokinetics and genotoxicity.

Structure/Activity Relationships

The effects of chemicals on living organisms are determined by their chemical structure. Materials having similar structures may have similar toxicologic properties. Thus, carcinogenicity data on materials similar to styrene

gives some insight into the carcinogenic potential of styrene. Carcinogenicity studies conducted by NTP using inhalation exposure in rats and mice demonstrated a lack of carcinogenicity by vinyltoluene (32-35% p-methylstyrene, 65-71% m-methylstyrene). In addition, p-methylstyrene (>97% para) was not carcinogenic in rats or mice following oral administration. These closely related homologs of styrene provide additional evidence that styrene is not carcinogenic. SIRC is currently conducting a structure/activity analysis that will help determine what additional chemicals should be compared to styrene, based on structure.

Metabolism/Pharmacokinetic Data

The metabolism (biotransformation) of styrene is known to proceed through styrene-7,8-oxide (SO) to mandelic acid and phenylglyoxlic acid, which are then excreted in the urine. Several studies have confirmed that metabolism of styrene is highly dose- (exposure concentration) dependent. In humans as well as laboratory animals, metabolism becomes disproportionate at styrene exposure concentrations greater than 200 ppm. As a result, toxic effects that occur at high exposure concentrations in excess of 200 ppm cannot be directly extrapolated to low exposure concentrations. This fact is highly important in making human risk estimations based on laboratory animal data.

The toxicological significance of SO as an intermediate metabolite of styrene has become a focus of concern in recent years. Long-term oral studies in which SO was given at high doses by gavage (stomach intubation) have resulted in increased incidences of hyperplasia and neoplasia of the forestomach in rodents (see section on styrene oxide). SIRC is therefore sponsoring metabolism and pharmacokinetic studies which, together with additional ECETOC sponsored studies in Europe, will be extremely important in developing a better understanding of the toxicologic significance of SO as an intermediate metabolite of styrene. The relative rates of information and degradation of SO in various animal and human tissues are being determined. These data will allow the development of a physiologically-based pharmacokinetic model in order to better understand the relative sensitivities of laboratory animals and humans.

Genotoxicity

Genetic toxicology studies focus on the interaction of chemical and physical agents with the process of heredity. Short-term tests for genotoxicity were originally developed to study mechanisms of chemically induced DNA damage, and to assess the potential genetic hazard of chemicals to humans. A series of assays (prokaryotic and eukaryotic) are currently available to assess the various kinds of genetic damage that could potentially be caused by environmental chemicals. The role of these tests has increased, however, because of evidence supporting the somatic cell mutation theory of carcinogenesis . In recent years the predictability of the short-term tests for carcinogenicity potential is being more seriously questioned. Nevertheless, because short-term mutagenicity studies measure genetic endpoints, it is commonly assumed that they are useful in making judgements about the carcinogenic potential of substances that act through genotoxic mechanisms.

Mutagenicity

The potential mutagenicity of styrene and its intermediate metabolite, styrene-7, 8-oxide, has been the subject of many studies in a variety of assay systems, both prokaryotic and eukaryotic. Overall, the studies indicate that styrene itself is not mutagenic in in vitro assays without metabolic activation. The response to styrene is assay systems which incorporate metabolic activation systems is equivocal; it is either very weakly mutagenic or nonmutagenic. Styrene-7,8-oxide is mutagenic in the presence or in the absence of metabolic activation in in vitro prokaryotic and eukaryotic assays. No additional short-term mutagenicity tests are currently planned.

The significance of the styrene-7,8-oxide short-term mutagenicity studies to humans exposed to styrene *in vivo* remains unclear. At present, the *in vitro* studies are difficult to extrapolate to *in vivo* human risk estimations. Additional studies currently in progress *(e.g.,* metabolism/pharmacokinetics, styrene oxide mechanism studies, DNA binding studies) may help clarify the relevance of short-term studies to judgments about the carcinogenic potential of styrene.

Cytogenetics

There are wide variety of assay systems to evaluate potential cytogenetic effects *(i.e.,* effects on chromosome structure and number) of chemical agents. The assays examine chromosomal aberrations (deletions of parts of chromosomes or rearrangements of chromosomes), sister chromatid exchanges (apparent reciprocal exchanges between the two chromatids of a single chromosome) and aneuploidy (gains or losses of one or more chromosomes). The cell

types studies in these assays may be obtained from humans or animals exposed in vivo *(e.g.,* peripheral blood lymphocytes), or the cells from unexposed humans or animals may be exposed to test chemicals *in vitro.*

There is substantial controversy regarding the human health significance of cytogenetic assays. Some experts maintain that results of cytogenetic assays cannot be used directly to estimate adverse health effects that might arise from exposure to a particular agent for one or more of the following reasons:

(a) the unsuitability of the cell type for direct extrapolation,

(b) the end-point does not have known biological consequences *(e.g.,* sister chromatid exchanges), or

(c) specific alterations that might be related to genetic or somatic adverse effects are not measured.

Nevertheless, regulatory officials occasionally interpret cytogenetic effects as supportive evidence for carcinogenicity potential.

There have been a substantial number of cytogenetics, assays involving styrene, including *in vitro* studies using human and animal cells and *in vivo* studies of humans exposed occupationally to styrene. As a result of various technical problems *(e.g.,* inadequate protocol, small sample size, only superficial control matching, uncontrolled sources of variation, poorly characterized exposures to styrene and other chemicals), the available studies involving induction of chromosome aberrations in human peripheral lymphocytes are not adequate to allow risk estimation. SIRC is therefore considering research proposals for additional cytogenetic studies, focusing initially on laboratory animal studies. These studies should help to clarify the inconsistencies and uncertainties in the existing data, and allow more informed judgments about the human health significance of the cytogenetic studies.

Styrene-7,8-Oxide Mechanism Studies

Concern about the carcinogenic potential of styrene is based in large part on the fact that long-term animal studies on styrene oxide indicate that styrene is metabolized to styrene-7,8-oxide (SO). A total of seven long-term animal studies have been conducted on styrene oxide; five of those involved administration of the material at high doses by gavage (stomach intubation), while in the other two studies it was applied to skin as a 5% or 10% solution in either acetone or benzene. The two skin application studies did not result in the development of skin tumors.

The gavage studies consistently showed increased incidences of tumors in the forestomach, but no treatment-related tumors in any other organ or tissue. The tumors in the forestomach of rodents given high gavage doses of SO were associated with substantial irritation, as evidenced by observations of squamous cell hyperplasia and/or hyperkeratosis of the forestomach. The absence of an oncogenic response in the skin studies, together with the fact that humans are certainly not exposed to high oral doses of either styrene or SO, makes it very difficult to assess the human health significance of SO gavage studies. Moreover, the significance of the SO gavage studies are of even greater uncertainty when making risk estimations for individuals in which SO occurs at only low levels as a transient metabolite of styrene.

SIRC is therefore focusing on mechanistic studies to determine if non-genotoxic effects *(e.g.,* chronic cellular injury) are important in the development of forestomach tumors. Cellular proliferation of the forestomach epithelium will be used as an index of cellular injury in animals given high gavage doses of SO. This information will augment ECETOC sponsored DNA-binding studies to assess the extent of DNA damage in the forestomach epithelium resulting from high gavage SO doses. These DNA-binding studies together with the cellular proliferation studies in the rodent forestomach will allow an assessment of the relative importance of genotoxic versus non-genotoxic mechanisms, and will thereby provide important perspective about SO as an intermediate metabolite of styrene.

Macromolecular Binding Studies

Macromolecular binding studies have become increasingly important in the assessment of genotoxicity potential, and as potential biomonitoring tools to estimate the degree of exposure to reactive substances. The somatic cell mutation theory of carcinogenesis suggests that cancer is caused by genetic damage, and that mutations resulting from covalent interactions of chemicals with DNA may be an important initial stage in chemical carcinogenesis. Studies on the binding of chemicals to DNA and the mechanisms of formation of DNA adducts are therefore important considerations in identifying potential carcinogens. In addition, protein adducts found in easily accessible body fluids *(e.g.,* hemoglobin adducts) sometimes may reflect potential DNA adduct formation. They may also be a useful biomonitoring tool to assess cumulative exposure to substances which form adducts.

ECETOC is currently sponsoring studies to assess the potential of styrene and SO to form hemoglobin adducts in laboratory animals. These studies will be important because hemaglobin is easily accessible in large amounts from both experimental animals and man, and therefore the methodology could potentially be extrapolated to humans occupationally exposed to styrene. In addition, SIRC is currently considering research proposals to evaluate DNA-binding potential in peripheral blood lymphocytes of animals exposed to styrene and SO. This DNA-binding methodology may also potentially be adaptable to human population monitoring, and will provide additional perspective about the genotoxic potential of styrene and styrene oxide.

FIGURE 1

Summary of Research for Evaluation of Carcinogenic Potential of Styrene

I.	**Epidemiology**	Ten years additional follow-up of ~16,000 cohort New study of ~20,000 cohort
II.	**Animal Bioassays of Styrene**	State-of-the-art 24-month inhalation studies in rats and mice
III.	**Other Data**	
A.	*Structure/Activity Relationships*	Structure analysis and literature review planned
B.	*Metabolism and PBPK*	*In vitro* and *in vivo* studies in rats and mice *In vitro* human studies; PBPK model
C.	*Mutagenicity*	No further studies on styrene planned
D.	*Cytogenetics*	Research plan being developed
E.	*Styrene Oxide*	Determine role of genotoxicity and tissue irritation in forestomach tumors Styrene oxide *in vivo* mutagenicity under review
F.	*Macromolecular Binding*	Effectiveness of styrene and styrene oxide at forming DNA adducts in target tissue Binding to RBC hemoglobin

Articles Featured in Previous Issues

April 1990, Vol. 1, No. 1

Styrene: Perspectives on the Carcinogen Question by Daniel P. Boyd, Ph.D., *et al.,* Technical Consultant; Former Director of Standards, Occupational Safety and Health Administration.

The authors review and discuss the major studies to date on the possible carcinogenicity of styrene. They begin with the work of the International Agency for Research on Cancer (IARC) which in 1987 changed its classification of styrene from "not classifiable" to "possibly carcinogenic to humans", despite the lack of any new human or animal data. They point out that several major national and international organizations have disagreed with this classification and have determined that the evidence does not support the classification or regulation of styrene as a carcinogen. They believe that significant studies currently in progress will clarify some of the issues and allow the development of improved risk estimations.

The Potential Mutagenicity of Styrene and its Metabolites by R. Julian Preston, Ph.D., Section Head, Biology Division, Oak Ridge National Laboratory.

Dr. Preston discusses the published data on mutagenicity with respect to styrene and its metabolites, the adequacy of the data and their statistical significance. He concludes that styrene is not mutagenic in *in vitro* assays unless there is metabolic activation. Even when there is activation, however, styrene remains non-mutagenic or is only very weakly mutagenic. The metabolite styrene oxide is mutagenic, but the role of styrene oxide as a mutagenic intermediary in the metabolism of styrene *in vivo* cannot be adequately assessed from existing evidence.

The Environmental Fate of Styrene by Martin Alexander, Ph.D., Professor, Cornell University, Department of Agronomy.

Dr. Alexander reviews the research and substantive monitoring data on the fate of styrene in water, soil and the atmosphere. He concludes that the transport of styrene in nature is "very limited" because of its volatility from soils and surface waters, its rapid destruction in air, and its biodegradation in soils and surface and groundwaters. The most probable source for any human exposure is the atmosphere, especially urban air, where values up to 6.0 ppb have occasionally been recorded. However, because styrene is highly reactive and rapidly destroyed by ozone and hydroxyl radicals, it is unlikely to be transported to any significant extent, or to be a source of styrene in waters or soils. There is little possibility of styrene occurring in drinking water or entering the food chain.

Carcinogen Classification Systems: A Time for Change by Robert J. Moolenaar, Ph.D., Project Director, Health and Environmental Sciences, Dow Chemical Company; Chairman, Scientific Committee, American Industrial Health Council, 1982-87.

The identification of a substance as a "possible", "probable" or "reasonably anticipated to be" human carcinogen sounds many alarm bells. It raises the concerns of the public, of regulators and health officials, and of corporate executives whose companies manufacture or use the substance. It can have significant health, economic, financial and legal consequences. Yet the national and international systems used to classify carcinogenicity are confusing, contradictory, unreliable — and often arbitrary. The U.S. Environmental Protection Agency and its Science

Advisory Board have recognized the deficiencies in EPA's own classification process and are seeking ways to improve it. Dr. Moolenaar discusses the problems and recommends ways to make the classifications more accurate and more meaningful to those who depend on them.

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Risk Assessment and Risk Management: Current Regulatory Issues and Concerns, an Overview and Analysis, from the Regulatory Program of the United States Government, published by the Office of Management and Budget.

This excerpt from the recently published Regulatory Program of the United States Government, prepared by the Office of Management and Budget, is a major review of problem areas in the federal government's current risk assessment and management practices. It points out that by continued reliance on worst-case assumptions and by incorporating hidden policy judgments within scientific assessments of risk, the government has departed significantly from the recommendations of the National Academy of Sciences (NAS) and seriously distorted the risk process. The subsequent distortions are often of several orders of magnitude and are probably most severe in the area of cancer-risk assessment.

Styrene and its Metabolites: A Discussion of Results from Cytogenetic Assays, by R. Julian Preston, Ph.D., Section Head, Biology Division, Oak Ridge National Laboratory.

A possible association between styrene exposure and chromosomal damage in humans has been the subject of numerous investigations in recent years, particularly in Europe. While these studies have been largely inconclusive, conclusions have been drawn from them that give rise to considerable confusion and concern outside the scientific community. In this article, Dr. Preston examines the principle assays for chormosomal analysis and discusses their use for genotoxicity assessment in cellular, animal and human studies. He notes that the better conducted human monitoring studies indicate no difference in aberrations between those exposed to styrene and the control groups who were not exposed.

A Critical Review of the Reproductive and Developmental Data on Styrene by Nigel A. Brown, Ph.D., Teratology Section Head, Medical Research Council, St. George's Hospital Medical School, University of London (UK).

Though styrene has sometimes been referred to as teratogenic (causes malformations) or as a potential human developmental toxicant, the only previous comprehensive review of the data, published in 1981, did not reveal any definite specific effects. Dr. Brown re-reviews the data up to the present, including the unusually large number of Soviet studies. He finds no evidence for teratogenicity in any of the studies and little indication that styrene can exert any specific developmental or reproductive toxicity. He notes that while initial human studies linked styrene exposure with congenital malformation and spontaneous abortion, these findings were later disproved by subsequent more extensive investigations by the same researchers.

Too Many Rodent Carcinogens: Mitogenesis Increases Mutagenesis by Bruce N. Ames, Ph.D. and Lois Swirsky Gold, Ph.D., Division-of Biochemistry and Molecular Biology, University of California, Berkeley.

These two distinguished researchers, in this most recent paper published in *Science,* Vol. 249, point out that if current progress continues we should understand the causes of the major human cancers by the close of this decade. They anticipate that these discoveries will invalidate many of the assumptions underlying current regulatory policies, particularly the utility and meaning of routine animal cancer tests. They emphasize that too little attention has been paid to the enormous background of natural carcinogens, which have led to the development of layers of natural defenses against toxic chemicals. This means that humans are "well buffered" against toxicity at low doses from both man-made and natural chemicals.