Assessment of the Health Hazards of 1,3-Butadiene and Styrene

Meeting Report

Elisabeth Heseltine, MSc
Kimmo Peltonen, PhD
Marja Sorsa, PhD
Harri Vainio, MD

Butadiene and styrene are important industrial chemicals, produced in large volumes, and the two compounds often occur together. The subjects of the hazards to health of exposures to butadiene and styrene attracted 163 participants from 17 countries to an international symposium held in Espoo, Finland, on April 18 to 21, 1993. The meeting was organized by the Finnish Institute of Occupational Health, in collaboration with the International Agency for Research on Cancer (IARC) and the Commission of the European Communities to bring together researchers and other interested parties concerned with the exposure assessment, toxicology, and carcinogenicity of butadiene and styrene. The large number of participants indicates the strong interest that the topics inspired; there was good representation from industry.

Butadiene and styrene have similar toxicological properties and both undergo metabolism to biologically active intermediates. The potential carcinogenic and genetic effects of these compounds are timely issues, because much of the information pertaining to those effects is very recent. Such data are essential for evaluating the risks to human health of exposures to these compounds.

A previous meeting on butadiene had been organized by the US National Institute of Environmental Health Sciences in 1988[1]; the carcinogenic risk to humans of exposure to butadiene had also been considered by a working group convened by IARC in 1991.[2] Styrene was the subject of a meeting held by the Finnish Institute of Occupational Health in as early as 1978[3] and was one of the compounds reevaluated by a working

From Communication in Science, Lajarthe, 24290 St Léon-sur-Vézère, France (Ms Heseltine); the Institute of Occupational Health, Topeliuksenkatu 41 a A, 00250 Helsinki, Finland (Dr Peltonen, Dr Sorsa); and the International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France (Dr Vainio).

Address correspondence to: Marja Sorsa, Institute of Occupational Health, Topeliuksenkatu 41 A, 00250 Helsinki, Finland.

0096-1736/93/3511-1089$03.00/0

Subject file : LCVCM

To: **J. Ware, LCVCM**

From: **D. Penney, Corp. R & D**
Date: **February 11, 1994**

Subject: **LCVCM Q & A Document**

This is the final version of the LCVCM Q & A document. I would be interested in knowing about any feedback you receive from employees on this.

CC:

Houston- T. Grumbles, J. Ledvina
LCVCM- M. Lunsford

LCVCM Q&A

1. ***What's the difference between "known human" and "probable human" carcinogens?***

A "known human" carcinogen is one for which there is sufficient evidence from human studies that exposure to the material can cause cancer. A "probable human" carcinogen is one for which there is some, but not sufficient, evidence from human or animal studies that the material can cause cancer in humans.

2. ***Can you get VCM exposure through the skin? What about at concentrations where breathing air is required?***

Exposure to VCM through the skin is not considered a significant route of worker exposure. Experiments with animals have shown a very small amount (about 0.023 %) can be absorbed through the skin at a high concentration (7,000 ppm). Clothing would reduce skin absorption of VCM even more.

3. ***What does short-term exposure mean in the VCM "exposure history" slide?***

The term "Short-term" exposure was used to contrast chemical exposures which last anywhere from a minute or even as long as a few months with those lasting for years.

4. ***Who decides what causes certain kinds of cancer? How is this determination made?***

This decision can be made by an individual, but usually groups of individuals with specialized knowledge (e.g., medicine, toxicology and epidemiology) are better at evaluating the different types of scientific information which can go into this decision. These evaluations most often include information from human and animal studies as well as from studies on other organisms, such as bacteria.

5. ***Who is Sir Richard Doll and what makes him an expert?***

Sir Richard Doll was trained as a mathematician. He has achieved wide recognition in the scientific community for his contributions to the mathematical interpretation of human cancer studies. He holds an academic position at the University of Oxford in England and serves on many health advisory boards. He is widely published in well known scientific journals.

6. ***Can't equal "experts" come up with different opinions when looking at the same data?***

When making judgements about complex issues such as whether a chemical causes cancer in humans, experts can disagree. The matter can be especially complicated because studies often conflict with another and vary in quality. Sometimes these issues cannot be resolved until more scientific information is available.

Subject files: Aberdeen Q+A

VRD 000205003

To: All Employees

From: C. W. Turner
Date: February 4, 1994

VISTA

Interoffice Communication

Subject: **HEALTH CONCERNS**

During September, 1993, Bob Seymour conducted meetings with all employees to discuss health concerns. Numerous questions were raised during those meetings which required additional study and with the help of Dave Penney (Research Manager/Toxicologist of Vista R&D) answers have been compiled and are attached.

Additionally, Joe Ledvina (Director of Health, Safety, and Environmental) will be in the plant on Tuesday, February 8, and will be available to discuss any additional questions that may be raised during the employee meetings.

Please contact me if you would like additional information.

C. W. Turner

C. W. Turner
Plant Manager

/rah

attachment

cc: Bulletin Boards, Department Heads
HWH, JCL - Houston
Dave Penney - Austin

ABERDEEN Q&A

1. **What are the results of the last update to the angiosarcoma registry which was published in 1991? Are any Vista people in the registry? When will the next registry update be available?**

   The angiosarcoma registry is a world-wide registry of all cases of angiosarcoma of the liver which have been attributed to vinyl chloride exposure. As of the last review, which was published in 1991, 161 cases had been entered into the registry. Thirty-nine of these cases were from the U.S., but none of these cases were from Vista. Vista has not had any cases of angiosarcoma of the liver diagnosed in its workers at any site.

   A more recent update of the registry has just been published. Hopefully, we will have a copy of it available to us within the next few months.

2. **Are there studies that show chemical workers have a higher risk of cancer?**

   Yes, there are studies showing that chemical workers exposed to certain chemical processes have a higher risk of some forms of cancer.

3. **Do we have data from each plant on the risk of cancer?**

   Vista maintains medical records on its employees. These records may contain some of this information, however, they have not been studied to determine whether any particular plant is at an increased risk of cancer. This is something that Vista is planning to initiate soon.

4. **How is the information on the cause of death collected in human studies?**

   The cause of death is obtained from the death certificate of the individual. A copy of the death certificate can be obtained from the local health authorities where the death occurred. Often, the most difficult part of the process is in finding the place of death of former employees, particularly if the employee only worked with the company for a short period of time. Sometimes this information can be obtained from company records, other employees or the National Death Registry, which is a registry of the location of all deaths in the U.S.

5. Why are studies typically conducted on deceased individuals? Why not conduct surveys of plant people and see what problems people have?

Most often the focus is on the cause of death because this information is the most feasible to obtain and it provides data about the most serious diseases. Obviously, other diseases, though not life threatening, can have a major impact as well. Surveys can provide this information although the accuracy of the data can be a problem. Often, people do not know the specific disease that they or other individuals may have experienced.

6. Do the studies in the presentation that was given by Dave Penney take into account exposure to other chemicals besides vinyl chloride?

Most of the studies of workers engaged in VCM or PVC manufacturing or processing have not taken potential exposure to other chemicals into account. This is because the primary health concerns have been associated with vinyl chloride.

7. What are the health effects of trichloroethylene (TCE)?

Acute (short-term) TCE exposure has been associated with a number of effects. TCE can cause skin irritation probably due to its ability to dry the skin. Nervous system damage has been attributed to overexposure to TCE. Large doses of TCE produce liver and kidney disorders in animals, but these effects would not be anticipated in the accepted range of occupational TCE exposures. Individuals have died from the accumulation of fluid in the lungs produced by intentionally inhaling high concentrations of TCE.

8. How are animal studies used to determine whether a chemical can cause cancer?

Animal studies are one of many sources of information used to determine whether a chemical causes cancer. Evidence that a chemical causes cancer in animals may be a good indication that the chemical is capable of causing cancer in humans also.

9. Why does it take so long to get data from human cancer studies?

It takes a long time to gather an analyze the data, particularly, when many thousands of individuals are involved. After the study is completed, it is reviewed by other scientists before it is published in the scientific literature. This review can take a long time, but is critical to establishing the validity of the study.

10. Do human cancer studies include data on specific individuals?

Yes, in some studies information is gathered on all individuals who have exposure to a particular chemical or group of chemicals. In other studies, individual information is only gathered on individuals who have the particular disease that is being investigated. In most cases, individual death certificates are used to obtain useful information.

11. Have there have studies of how many people have cancer in the Aberdeen area? Have there been studies of the causes of these cancers?

Not to our knowledge.

12. Has CMA been accused of using bad information in its studies of workers exposed to vinyl chloride? Who pays for the studies? How do we know the studies are not biased on who paid for the studies? Does anyone disagree with the conclusion of these studies?

CMA has not been accused of using bad information in its studies. While it is true that it is the member companies of CMA that pay for these studies, CMA goes to great lengths to assure their scientific integrity. CMA chose to have the study of the vinyl chloride workers published so it would face the scrutiny of scientists who do not have any connection with industry. We do not know of anyone who has challenged the validity of the CMA study.

13. What is the risk of breathing PVC dust?

Data from studies of animals exposed to PVC indicate that PVC itself possesses little or no biological activity. Exposure to high concentrations can cause irritation of the respiratory tract and other conditions typical of a nuisance dust.

14. We used to have benzene in the plant. What are the health effects of benzene exposure?

Acute (short-term) exposure to benzene can also lead to dizziness, abnormal heart beat, fluid in the lungs and irritation of the lungs and the digestive tract. Long-term benzene exposure has been linked with increased risk of leukemia, hindered formation of blood cells and damage of the genetic information of cells of humans.

15. What are the health effects of AMS (alpha-methyl styrene)?

In animals, AMS exposure has been shown to produce adverse effects on both the liver and the kidneys. In humans, AMS has been shown to produce irritation of the eyes, skin and upper respiratory tract. Prolonged exposure of humans to AMS has been shown to lead to sleepiness and other signs of depression of the central nervous system.

16. Do we have records of exposure to employees early in the life of the Aberdeen Plant?

No. Routine sampling to measure individual employee exposure and general area VCM levels was not started until late 1974. At that time, data was developed to measure exposures in the low parts per million range.

17. Is there any specific ppm exposure level where you will get cancer?

It is not possible in most cases to determine a specific exposure level that will result in cancer. The risk of getting cancer at a given exposure level varies from person to person. Most cancer causing agents are considered capable of causing cancer in some people even at very low levels of exposure. However, the risk at such levels of exposure are usually at or lower than other risks which all workers face.

The OSHA permissible limit of 1.0 ppm is based on the OSHA policy of setting exposure limits for carcinogens at the "lowest feasible level". It is not specifically determined based on animal and human data. In fact, American Conference of Governmental Industrial Hygienists consider 5.0 ppm a safe exposure limit for VCM.

18. Is Mr. Paul Hubbard's death included in the CMA studies and did he die of angiosarcoma?

We understand Mr. Hubbard died in 1985 or 1986. His death would not have been included in the last CMA update since it only included deaths which occurred between 1972 and 1982. We do not know the specific cause of Mr. Hubbard's death.

19. Where can I get additional information about the health risks of chemical exposure?

This document is an attempt to answer specific questions that have been raised about the health effects of vinyl chloride exposure. If you have other questions about the health effects of exposure to vinyl chloride or any other chemicals, you may call Chris Markerson (extension #3618) or Dave Penney (512-331-2468).

group at IARC in 1987.[4] Another IARC working group is to consider the carcinogenic risks of exposure to styrene in February 1994. The international symposium reported here was organized to bring together the world's experts on the two topics, to inspire discussion that would lead to a better understanding of the health hazards of the two chemicals. The proceedings, which are to be published shortly as Volume 127 of the *IARC Scientific Publications* series,[5] will be an up-to-date coverage of current information, thus providing a basis for improved strategies for preventing both occupational and environmental exposures to these important chemicals.

The meeting covered seven main areas of research: exposures to butadiene and styrene, measurement of internal doses received by exposed people, measurements of metabolites and of adducts with DNA and protein as markers of exposure, neurotoxicity and reproductive effects, genetic toxicity, carcinogenicity, and implications for public health. This meeting report is based on the presentations of eight rapporteurs and on the subsequent discussion at the closing session of the Symposium. The rapporteurs were Dr D. Anderson, BIBRA Toxicology International, Carshalton, Surrey, England; Dr. W. Anwar, Faculty of Medicine, Ain Shams University, Cairo, Egypt; Dr G. L. Foureman, Environmental Criteria and Assessment Office, Environmental Protection Agency, Research Triangle Park, NC, US; Dr. P. Kalliokoski, University of Kuopio, Finland; Dr T. Kauppinen, Institute of Occupational Health, Helsinki, Finland; Dr P. J. Landrigan, Department of Community Medicine, The Mount Sinai Medical Center, New York, NY, US; Dr R. L. Melnick, National Institute of Environmental Health Sciences, Research Triangle Park, NC, US; and Dr H.-G. Neumann, Institute of Toxicology, University of Würzburg, Germany.

Occurrence and Exposures

Butadiene

The results were presented of a comprehensive study on occupational exposure to butadiene, carried out by the US National Institute for Occupational Safety and Health. The highest exposures were found to occur in the monomer industry, where a mean airborne level of 5.9 ppm (geometric mean, 0.5 ppm) was found (for butadiene; 1 ppm = 2.2 mg/m^3); 7% of the samples showed a level >10 ppm, which is the current US threshold limit value for butadiene, and 20% of samples contained >2 ppm, which is the level proposed by the US Occupational Safety and Health Administration. In the polymer industry, a mean airborne exposure of 1.1 ppm was found (geometric mean, 0.1 ppm); 3% of samples showed >10 ppm and 11%, >2 ppm. Occasional peak concentrations exceeding 200 ppm were found in both the monomer and polymer industries. In end-user industries, however, butadiene could not be detected in the more than 100 samples that were taken.

One paper was presented on environmental exposures to butadiene, which was based on the Urban Air Toxics Monitoring Program of the US Environmental Protection Agency. The survey of butadiene, done in 1990, covered 11 urban areas in which 24-hour samples were collected every 12 days. Butadiene was found in 30% (106 of 349) of samples at an average ambient concentration of 0.71 μg/m^3. The stationary sources from which butadiene is released are pressure relief and process vent discharges, equipment leaks and openings, leaks from storage vessels, waste treatment and disposal, and emergency and accidental releases. In a survey of more than 2000 peak releases from 32 factories, the release frequency was found to range from one to 700 events per year, although more than 75% of the factories had less than five events a year. The estimated median concentration of butadiene 200 meters from the centers of the 27 highest emitting factories was 18.9 μg/m^3; 5 kilometers from the plant centers, the median concentration was 0.13 μg/m^3. On the basis of a study of releases from motor vehicles, the annual average level of exposure was estimated to be 0.56 μg/m^3 in urban areas and 0.30 μg/m^3 in rural settings; the average concentration within a vehicle was estimated to be 3.0 μg/m^3. It was estimated that more than 90% of all butadiene emissions in the United States came from mobile sources, resulting in 10 times higher emissions than from industrial sources.

Styrene

Four papers were presented on exposures of the general population to styrene. The main route of exposure is the air. In Canada, the ambient air contained styrene at mean levels of 0.1 to 2.4 μg/m^3 (for styrene, 1 ppm = 4.2 mg/m^3). The mean concentration in indoor air was 0.3 μg/m^3, but a concentration of 129 μg/m^3 was detected inside one home. In the Netherlands, the average ambient air concentration was reported to be 1.5 μg/m^3. On the basis of that value, the annual intake of styrene from air would be 6.5 mg/person. Smoking is another source of exposure to styrene. A US study indicated that as much as 10 μg of styrene are generated in mainstream cigarette smoke. The annual styrene intake of a person who smoked 20 cigarettes per day would therefore be about 70 mg.

Drinking water appears not to be an important source of exposure: Only 3% of Canadian samples of drinking water contained detectable levels of styrene. Even the highest level found, 0.25 μg/l, would result in an annual intake of only about 0.1 mg/person. Styrene is a natural constituent of foods, albeit at very low concentrations; it may also occur in foods through migration of residual monomer from polystyrene packaging materials: concentrations of 4 to 20 μg/kg have been detected in foods wrapped in polystyrene. Most fruits and vegetables contain concentrations of 0.1 μg/kg or less. Levels of about 1 μg/kg have been detected in wheat, peanuts, and strawberries, and somewhat higher levels, about 5 μg/kg, have been found in black currants, beef, and wine. Coffee and beer can contain 10 to 360 μg/l. The finding of the highest naturally occurring levels of styrene, up to 40 mg/kg, in cinnamon may be due to the fact that this spice contains cinnamic aldehyde, which has structural similarities to styrene. The annual intake of styrene

fro— foods of various kinds can thus be nated to be about 2 mg/person.

In a presentation on occupational exposure to styrene, it was emphasized that level of exposure is closely related to type of industry. Thus, the heaviest exposures occur in the reinforced plastics industry, where manual methods are still widely used for manufacture. Very similar exposure levels, with medians of about 40 ppm, were found in three recent surveys in Canada, Finland, and the Netherlands. Short peak exposures of about 200 ppm are still common in the reinforced plastics industry.

Styrene is used predominantly in the polystyrene manufacturing industry. Average airborne concentrations of styrene in that industry are, however, relatively low, at <5 ppm, although peak concentrations up to 20 ppm can occur during certain phases of production. In styrene-butadiene rubber plants, mean levels of 0.5 to 2 ppm have been found. In a styrene-butadiene latex polymerizing plant, the range of concentrations was 4–7 p— No new data were available on e— ures to styrene in plants where the monomer is produced. Low levels (0.1 to 0.4 ppm) were found in secondary processes, where styrene is released because of the thermal degradation of polymers.

The total annual intake of styrene of the nonsmoking population from all sources would be about 10 mg/person; that among smokers would be about 80 mg/person. These levels are more than 3 orders of magnitude lower than exposures reported in the reinforced plastics industry, where exposure to 40 ppm of styrene would result in an annual intake of about 400 g/person.

Dose Measurement

Metabolic activation of both styrene and butadiene involves oxidation mediated by various forms of cytochrome P450 to monoepoxide intermediates: styrene to styrene oxide and butadiene to monoepoxybutene. Detoxication of both intermediates oc— y hydrolysis, via epoxide hydrolase, or by glutathione conjugation, via glutathione *S*-transferases. Epoxybutene can undergo further oxidation to diepoxybutane or hydrolysis and oxidation to epoxybutane diol. The aim of current research is to establish the dosimetry of the metabolism of the reactive epoxide intermediates of styrene and butadiene in tissues.

Butadiene

The metabolic elimination of butadiene and epoxybutene is saturable, and the rate differs between species. The rate of elimination of butadiene is greater in mice than in rats and that of epoxybutene is greater in rats than in mice. These findings suggest that at steady state the concentrations of epoxybutene are greater in mice than in rats. Data on the kinetics of butadiene activation and epoxide detoxication in vitro in tissues of mice, rats, and human beings have been incorporated into physiologically based pharmacokinetic models based on liver and lung; the next step will be to validate the predictions made on the basis of such models with regard to the doses of carcinogenic intermediates that reach the tissues. The species differences in the uptake and clearance of butadiene are largely controlled by physiological parameters; however, the difference between mice and rats in the doses of epoxybutene that are achieved internally seem to be too small to explain the difference in the carcinogenic effect of butadiene in the two species—mice being clearly more susceptible than rats. More information is required on the metabolism of butadiene in tissues other than liver and lung; for instance, an extremely high level of epoxybutene has been detected in mouse bone marrow. Information is also needed on metabolites other than epoxybutene; data on the formation and detoxication of diepoxybutane would be a useful adjunct to current knowledge. Finally, more studies should be done on human variability and polymorphisms with regard to the enzymes involved in the metabolism of butadiene.

Biological monitoring of exposure to butadiene has been improved markedly in recent years. Two major urinary metabolites are measured: the product of epoxybutene hydrolysis followed by glutathione conjugation, and the product of glutathione conjugation of epoxybutene. Detection of those metabolites in all the species that have so far been studied confirms the hypothesis that the main metabolic pathway of butadiene is through activation to epoxybutene. Species differ, however, in the pathways of detoxication: in mice, the glutathione *S*-transferase route predominates, and in monkeys and human beings, detoxication occurs primarily by epoxide hydrolase. The first metabolite appears to be an effective biomarker of exposure to butadiene because it has been detected in humans exposed to concentrations of butadiene as low as 3 to 4 ppm.

Styrene

Physiologically based pharmacokinetic models also have been developed to analyze the metabolism of styrene and styrene oxide in mice, rats, and human beings. The advantage in comparison with butadiene is that many more data on human exposure to styrene are available, so that the models can be validated. Furthermore, the levels of styrene in blood can be correlated directly with exposures to airborne styrene. The half-life of styrene in blood is about 4 hours, however, so that an increase in body burden during a working week can influence urinary measurements of exposure. The most reliable way to conduct biological monitoring of the exposure of workers to styrene is to measure both mandelic acid and phenylglyoxylic acid in urine samples collected in the morning after exposure and stored frozen.[6]

Conclusion

Tissue dosimetry models provide a first step in understanding the carcinogenicity of butadiene and styrene in different species; such models are in an advanced stage of development for butadiene. They will not, however, provide answers about mechanisms of carcinogenesis. The next step will be to find out what the consequences are of the presence of epoxides in tissues and to elucidate differences in genetic susceptibility to cancer induction.

Protein and DNA Adducts as Markers of Exposure

Better information is also needed about the dosimetry of reactive metabolites as biochemical monitors of tissue doses received by exposed humans. If such information were available, it would no longer be necessary to measure actual uptake, to undertake complicated measurements of environmental levels, or to take into account peak exposures, continuous and intermittent exposures, or the role of individual variation in uptake.

Butadiene

In the case of butadiene, an adduct with N^6-deoxyadenosine has been synthesized and shown by the ^{32}P postlabeling method to be formed in mouse liver after exposure in vivo to butadiene. In another study, diepoxybutane was reacted with adenosine and DNA and shown, also by ^{32}P postlabeling, to induce adducts in hamster cells in vitro. Three studies were reported of adducts with hemoglobin in erythrocytes. A detection limit of about 1 pmol/g of globin was achieved with gas chromatography-mass spectrometry after modified Edman degradation and derivatization with pentafluorophenyl isothiocyanate. In two of the studies, workers exposed to 1 to 3 ppm butadiene had hemoglobin adduct levels of 1 to 10 pmol/g of globin. In another study, however, in which subjects were exposed to butadiene at less than 1 ppm, no such adducts were found. These results represent a great advance in human biomonitoring because they show that the binding product of one of the critical metabolites of butadiene can be measured in exposed human beings.

The question is whether the blood dose of one reactive metabolite can reflect the species differences in susceptibility, whereby butadiene induces tumors more readily in mice than in rats. Hemoglobin adducts of epoxybutene were measured in two studies after continuous exposure of animals by inhalation to levels of 100 to 500 ppm: the adduct levels were 3 and 5 times higher in mice than in rats in the two studies, indicating that the tissue dose of one of the critical metabolites is indeed substantially higher in the more susceptible species.

Styrene

The situation is less clear for styrene. Adducts have been measured in DNA in white blood cells and in hemoglobin in red blood cells. In contrast to previous reports, radioactive styrene and styrene oxide were both reported to form adducts in rats in vivo. The levels of binding were, however, lower than those of many other compounds. Using the ^{32}P postlabeling method and synthesized O^6-deoxyguanosine, a detection limit of about 0.1 adducts per 10^8 normal nucleotides was achieved. When the method was applied to the determination of adduct levels in laminating workers and controls, the workers were found to have 4.5 adducts per 10^7 normal nucleotides, whereas the controls had only 0.5 adducts per 10^7.

In a study in which styrene oxide was reacted with DNA in vitro, one major, three minor, and several trace adducts were found. A detection limit of 1 adduct per 10^7 nucleotides was attained, which was considered to be sufficient to detect styrene oxide-derived adducts in vitro or exposures to high doses of styrene in vivo but still insufficient for monitoring occupationally exposed people.

Hemoglobin adducts at N-terminal valine have been studied, with a detection limit of 10 pmol/g of globin, and adducts have been found with carboxylic acid esters, at a detection limit of 15 pmol/g of globin. Interestingly, N-terminal valine adducts accounted for only 5.2% and carboxylic ester adducts for 15% of total globin adducts. In this study, however, neither of these adducts was found in exposed humans.

Conclusions

In general, hemoglobin adduct measurements are sufficiently developed to be used for human biomonitoring of both butadiene and styrene. The problems that remain with regard to the use of ^{32}P postlabeling in detecting DNA markers of exposure to both compounds are with labeling efficiency and whether white or red blood cells are the appropriate surrogates for target tissues. The methods for measuring adducts of styrene with DNA and protein are therefore still in a developmental stage; they are not yet sensitive enough for monitoring exposures to low concentrations, and they must be validated. Measurements of adducts with the metabolites of butadiene are perhaps sufficient for monitoring biologically effective doses, but much more needs to be known before any conclusions can be drawn about risk.

Reproductive Effects and Neurotoxicity

Butadiene

Only one study addressed the toxic effects of butadiene other than carcinogenicity. That study demonstrated toxicity to developing mouse fetuses as a result of paternal exposure to butadiene: Greater mortality than among controls was seen among offspring sired by male mice that had been exposed subchronically to either 12.5 or 1250 ppm butadiene. More early deaths (evaluated at day 15 of gestation), late deaths (evaluated at day 17 of gestation), and congenital malformations were seen in the offspring of males exposed at both concentrations than in the offspring of unexposed mice. The numbers of early deaths corresponded to the dose; fewer late deaths and congenital malformations were seen at the higher concentration, because of the high rate of early deaths. These results clearly indicate adverse genetic effects of butadiene on the male germ line.

Styrene

Ototoxicity remains the most clearly demonstrated nonsubjective toxic effect of exposure to styrene. One group reported treatment-related functional deficits and pathological lesions in the cochlea of adult male rats that had been exposed to styrene at 800 ppm; no such effect was seen at 200 ppm. Although such clear, unconfounded results have not been seen in exposed humans, self-reported symptoms and cognitive signs in workers

indicate that styrene may elicit neur c effects. A considerable amount of evidence was presented during the symposium to implicate chronic low levels of exposure to styrene in perturbations of the central nervous system and of vision. A mild but dose-related increase in loss of color vision was reported among members of a cohort of workers exposed to styrene at an estimated level of 68 mg/m^3, representing 30% of the current threshold limit value in the United States. Another presentation highlighted the many limitations and contradictions of studies of occupational situations, in which neurotoxic effects have been reported in association with chronic exposures to styrene at low levels. No significant alteration in electroencephalograms was seen in workers exposed to styrene, but self-reported symptoms were clearly related to levels of styrene at the work site and duration of employment in the reinforced plastics industry.

The reproductive and developmental toxicity of styrene in humans ha no clearly demonstrable end p . One presentation showed the limited and contradictory nature of existing epidemiological studies in this area; another, however, identified recent studies on the ability of styrene to cause developmental delays, decreased levels of neurotransmitters, and neurotoxic effects in developing animals. Further work is needed, but to date no evidence has been produced that is sufficient to rule out developmental and reproductive effects of exposures to styrene at the concentrations that human beings encounter.

Genetic Toxicity

Both butadiene and styrene are activated to epoxides that bind to DNA, and both are active in a range of short-term tests.

Butadiene

Several studies were reported of workers exposed to butadiene. In a small group of workers, a correlation w found between the level of metab c in urine and the frequency of mutations at the *hprt* locus, as detected by autoradiography. In a study of individual sensitivity to butadiene, peripheral blood lymphocytes were taken from 170 workers and exposed in vitro to 6-μmol/l diepoxybutane. The mean frequency of sister chromatid exchange was distributed bimodally; cells from 20% of the workers were found to be twice as sensitive as the others to sister chromatid exchange induction. Cells from sensitive workers also contained 4 times more chromosomal aberrations than did those from less sensitive workers. Lymphocytes from 6 of 40 workers employed in the production of butadiene were found to be sensitive to diepoxybutane in vitro. In a study of both smokers and nonsmokers, no increase was seen in the frequencies of chromosomal aberrations, sister chromatid exchange, or micronucleus formation in workers exposed to butadiene.

Butadiene and its epoxide metabolites were examined in a human lymphoblastoid cell line (TK6) and in splenic T cells isolated from B6C3F1 mice. In TK6 cells, all three metabolites were mutagenic at the *hprt* and *tk* loci, but diepoxybutane was mutagenic at doses 2 orders of magnitude lower than epoxybutene or epoxybutane diol. In splenic T cells, the frequency of *hprt* mutations was increased significantly after exposure of mice to butadiene by inhalation or to epoxybutene by intraperitoneal injection. Sequencing studies demonstrated that the frameshift mutations were similar to those induced by ethylene oxide.

Oncogene activation and tumor suppressor gene inactivation were seen in tumors induced in B6C3F1 mice by butadiene. Oncogene activation was shown using polymerase chain reaction products and the restriction enzyme *Bst*UI: six of nine lung carcinomas contained a C → G transversion in codon 13 of the K-*ras* protooncogene, and nine of 21 mammary carcinomas contained the same transversion in codon 13 of H-*ras*. Tumor suppressor genes were studied in lung and mammary adenocarcinomas by examining one marker for loss of heterozygosity. In the mammary tumors, losses were found (by Southern blotting and DNA sequencing) at markers surrounding the *p53* and *Rb-1* genes on chromosomes 11 and 14; in lung tumors, losses were found on chromosome 4. The *p53* gene is inactivated in butadiene-induced mammary carcinomas and is less common in lymphomas and lung tumors in B6C3F1 mice.

Mice exposed chronically to butadiene, treated with radiation, or bearing white spotted or Steel mutations exhibit an identical pattern of disease, which includes a high incidence of thymic lymphomas and leukemia. These findings indicate that the pattern is due to a functional defect in a subpopulation of primitive hematopoetic stem and progenitor cells.

Butadiene induces mutations in tissues of CD2F1 transgenic mice that have either the *lacZ* or *lacI* gene as a recoverable mutational target. Exposure of mice with the *lacZ* gene to butadiene by inhalation increased the mutation frequency in lung by two-fold over that in controls, but no increase was seen in bone marrow or liver. In mice with the *lacZ* gene, the mutation frequency in lung was again increased, that in spleen was increased at exposure levels down to 62.5 ppm, and the frequency in bone marrow was 4 times higher than that in controls after exposure to 625 ppm. Sequence analysis of *lacI* mutations from bone marrow showed a shift from G:C to A:T base pairs. Evidence was also obtained for clonal expansion in vivo.

Styrene

A number of studies were reported on the genetic toxicity of styrene. In 18 workers exposed to styrene, a significant increase in the frequency of chromosomal aberrations was seen when compared with controls. In a group of 52 workers who were exposed to a mean of 7 ppm styrene during the production of fiberglass-reinforced styrene-polyester resins, no adducts of styrene oxide with hemoglobin were detected, and no significant difference was seen between exposed and unexposed workers with regard to numbers of sister chromatid exchanges, high-frequency cells, or

micronuclei. Exposure of 17 workers to styrene at 18 ppm for 8 hours resulted in a doubling of the frequency of DNA single-strand breaks. In a review of 47 published studies on the cytogenetic effects of styrene among exposed workers, 10 showed chromosomal aberrations, five showed increased frequencies of micronucleus formation, and two showed increased frequencies of sister chromatid exchange. Thus, 17 studies showed significant increases in chromosomal damage in exposed as compared with control subjects. The relationship between exposure to styrene and chromosomal aberrations is not, however, quantitative, and the author of the review suggested that other factors in workplaces where styrene is present might be responsible. In another review of the cytogenetic effects of styrene, it was suggested that no concordance among studies could be expected in view of variability in the kinetics of exposure, in individual responses and in the biologically relevant doses received. The association between exposure and both sister chromatid exchange and chromosomal aberrations is seen in laminating industries, for example, where exposures are high, but not in the monomer industry, for example, where exposures are low.

In female B6C3F1 mice and Fischer 344 rats that had been exposed by inhalation to styrene at 0, 125, 250, or 500 ppm for 6 h/day for 14 days, small but statistically significant, concentration-dependent increases in the frequency of sister chromatid exchange were seen in mouse lung and spleen and in mouse and rat peripheral blood lymphocytes because of median rather than high-frequency exchanges; no statistically significant increase in chromosomal aberrations or micronuclei was observed. DNA strand breakage was not observed in rat lymphocytes. In another study, Fischer 344 rats were exposed by inhalation to styrene at 150, 500, or 1000 ppm for 6 h/day 5 days a week for 4 weeks, and to ethylene oxide at 150 ppm as a positive control. No increase was seen in the frequency of sister chromatid exchange or chromosomal aberrations that could be related to treatment.

Cancer

Butadiene

Studies of the carcinogenicity of butadiene in experimental animals were reviewed. Butadiene has a clear carcinogenic effect after relatively short exposure periods and at multiple organ sites in mice exposed by inhalation in long-term studies. Significant effects have been seen at a dose as low as 6.25 ppm. In rats, the effect is less pronounced, and the target organs are different from those in mice.

The epidemiological studies of exposure to butadiene, most of which are of the retrospective cohort design, have indicated slightly increased frequencies of lymphatic and hematopoietic cancers. An update of a cohort mortality study among butadiene production workers was presented in which no new case of lymphosarcoma had been found. The results were therefore very similar to those of the original study, in which excess mortality from lymphatic and hematopoietic cancers was seen, arising mainly from the subcategory of lymphosarcoma and reticulosarcoma. A report was also made of a case-control study, nested within a cohort of styrene-butadiene manufacturing workers, in which a large excess of leukemia was associated with exposure to butadiene and not to styrene. The authors pointed out that use of such a study design made it possible to obtain accurate measures of exposures, which are usually not available for cohort studies. Two new studies were reported of workers potentially exposed to butadiene. In one, of 25 deaths observed among 617 butadiene monomer workers, none was due to hematopoietic cancer; in the other, two deaths from lymphopoietic cancers were observed among long-term workers at an acrylonitrile-butadiene-styrene facility, which was close to the expected value. Further nested case-control studies incorporating careful assessments of exposure might provide useful results in this area.

Styrene

The results of 14 long-term bioassays in which styrene and styrene oxide were tested in several animal species by various routes were reviewed critically. They provided no solid evidence for the carcinogenicity of styrene but convincing evidence that styrene oxide causes tumors of the forestomach, and perhaps also of the liver, in male mice. The possible role of cell proliferation in the induction by styrene oxide of forestomach tumors was studied in rats and found to be both highly focal and variable.

Some of the most important new results on styrene are those of epidemiological studies. The preliminary results of a large, multicenter cohort study carried out at IARC were reported. In the cohort of about 40,000 workers, representing a wide scale of exposures, from none to heavy, the observed mortality from lymphatic and hematopoietic cancers was close to that expected. Furthermore, in a stratified analysis, there was no consistent trend by duration of exposure. When the data were analyzed by time since first exposure, however, suggestive trends were observed; for example, the standardized mortality ratio for leukemia increased from 87 to 196 in a group that had been exposed to styrene for more than 1 year. The exposures of this large cohort to styrene, which originates mainly in the reinforced plastics industry, are highly contrasted, and they have few relevant confounding exposures. A parallel study of industrial hygiene will eventually provide enough information to allow analysis of the data by cumulative exposure, taking into account both level and duration of exposure, and those results may be crucial for assessing the carcinogenicity of styrene to humans.

A study that is part of the multicenter study was also reported in detail separately. That cohort comprises 64,000 employees in 552 Danish companies in which at least part of the work force is involved in the manufacture of reinforced plastics or reinforced plastic products. Slight excesses in the incidence of lung cancer, pleural mesothelioma, nasal cancer, lymphomas, and leukemias were found among men. The cohort has not yet been stratified on the basis of potential exposure to styrene, but the

numbers of cases reported are sufficiently large to study exposure-response patterns of non-Hodgkin's lymphoma and leukemia in men, for example, so that when the analysis is completed the study will be very informative. A nested case-control study within the cohort might also provide interesting information on exposures to styrene and to other compounds in those industries.

A third study that will provide new information once it has been completed is an update of a US cohort of workers potentially exposed to styrene in the reinforced plastics industry. The number of deaths has increased from 499 to about 1750 in the recent update, so that finer stratifications in the analysis are now possible.

Thus, the latest results tend to suggest the existence of an association between lymphatic and hematopoietic cancers and exposure to styrene. Two small studies with lower exposures to styrene did not show excesses, but the exposure-response patterns observed are not consistent. The working group that is to be convened by IARC in January 1994 to reevaluate the carcinogenicity of styrene will have an interesting and difficult task. The final results of some of the studies described above may be of major importance in that evaluation.

Concluding Remarks

Emphasis was laid on the importance of information on carcinogenic mechanisms in evaluating risk. Differences between species in the rate of metabolism of styrene and the low intrinsic potency of styrene oxide to bind to DNA are major elements in any assessment of the risk of styrene to humans. For butadiene, also, the large differences between species with regard to the kinetics of metabolism must be taken into consideration in any extrapolation to humans of findings of carcinogenicity in animals.

After rats were treated with styrene oxide or butylated hydroxyanisole for one month, such that forestomach carcinomas were induced in 84% of animals treated with styrene oxide and 28% of those treated with butylated hydroxyanisole, the two compounds were found to induce cell proliferation to a similar extent, but only the latter induced hyperplastic lesions. The authors concluded that styrene oxide acts through mitogenesis and DNA binding. In a further experiment, labeled styrene was administered by inhalation to mice and rats, and adducts were measured in DNA from liver and lung. The covalent binding index, however, was less than 0.1, which is too low to account for the tumor incidence observed. It was concluded that nongenotoxic components must be involved.

The results of bioassays in animals prompted several attempts to quantify the risk to humans of exposure to butadiene. Two such studies were presented: one based on data in mice and the other on results for rats. The derived estimates differ significantly and appear to depend on animal species, tumor site, dose level, and the mathematical model used. Our understanding of the relevant mechanisms of the carcinogenicity of butadiene thus appears to be inaccurate and incomplete.

The risks associated with exposure to styrene were estimated on the basis of the results of studies in experimental animals, assuming that any possible effect of that compound is due entirely to styrene oxide. Exposure to 20 ppm over 40 years was thus calculated to give rise to a risk of <1 per 10,000. The underlying assumption and other assumptions made in the risk estimation are, however, highly debatable.

In a review of current epidemiological data on the two compounds, occupational exposure to butadiene was found to be strongly associated with carcinogenic risk, but the results with respect to heavy occupational exposure to styrene were considered still to be equivocal.

Research still remains to be done to elucidate the risks to humans of exposures to butadiene and styrene. Studies are needed to identify the possible hazards of end-points, such as reproductive toxicity (in the case of butadiene) and neurotoxicity (in the case of styrene), that are currently not well defined. Physiologically based pharmacokinetic dose-response models should be refined in order to elucidate (1) the relationship between exposure, the dose that reaches the target, and biological effects and (2) the basic biological mechanisms responsible for the effects observed; the latter is crucial to the extrapolation of data from animals to humans and from high to low doses. Biological markers of exposure, effects, and susceptibility in human populations should be developed so that adverse effects can be detected earlier and control action taken to reduce the risks to public health of exposures to butadiene and to styrene.

It has taken a long time to assess the risks to human beings of exposures to butadiene and styrene, chemicals that have been in widespread use for more than 50 years. It is to be hoped that the proceedings of this international symposium will contribute to the implementation of appropriate preventive measures.

References

1. Melnick RL, Bird MG, organizers. Symposium on the Toxicology, Carcinogenesis and Human Health Aspects of 1,3-Butadiene. *Environ Health Perspect.* 1990;86.
2. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Vol. 54, *Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals.* Lyon;1992:237–285.
3. Järvisalo J, ed. Proceedings of the International Symposium on Styrene. Occupational and Toxicological Aspects. Helsinki, 17-19 April 1978. *Scand J Work Environ Health.* 1978;4 (Suppl. 2).
4. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42.* Lyon;1987:345–347.
5. Sorsa M, Peltonen K, Vainio H, Hemminki K, eds. *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127). Lyon: International Agency for Research on Cancer (in press).
6. Pekari K, Nylander-French L, Pfäffli P, Sorsa M, Aitio A. Biological monitoring of exposure to styrene—assessment of different approaches. *J Occup Med Toxicol.* 1993;2:115–126.

Chemical file · 1,3-butadiene

1845 W. Orange Grove Rd. Bldg. #2
Tucson, AZ 85704

References

(1) Mehta PP, Sagar S, Kakkar VV: Treatment of superficial thrombophlebitis: a randomized double-blind trial of heparinoid cream. Br Med J 3:614–616, 1975

(2) Meuleman DG, Hobbelen PM, van Dedem G, et al: A novel anti-thrombotic heparinoid (Org 10172) devoid of bleeding inducing capacity: a survey of its pharmacological properties in experimental animal models. Thromb Res 27:353–363, 1982

Lack of Carcinogenicity in Mice Exposed Once to High Concentrations of 1,3-Butadiene

1,3-Butadiene is a colorless, flammable gas used primarily in the production of synthetic rubber and thermoplastic resins. Approximately 3 billion pounds of this chemical are produced in the United States every year, and approximately 52000 workers are potentially exposed (*1*). Surveys by the National Institute of Occupational Safety and Health (NIOSH) of exposure at facilities that produce or process 1,3-butadiene indicate typical ambient air concentrations of less than 10 ppm averaged over an 8-hour period. However, investigators have documented levels as high as 370 ppm for 15 minutes and 120 ppm averaged over 8 hours (*2*).

Studies of rodent carcinogenicity have demonstrated 1,3-butadiene to be a potent carcinogen in mice, producing a variety of tumors including lymphocytic lymphoma and hemangiosarcoma of the heart and neoplasms of the lung, forestomach, Harderian gland, preputial gland, liver, mammary gland, and ovary (*1-3*). Epidemiological studies have consistently shown associations between exposure to 1,3-butadiene and excess mortality due to lymphatic and hematopoietic cancers (*4-6*). To date, all reports of adequately performed carcinogenicity studies in mice exposed to 1,3-butadiene have shown an increased incidence of tumors. The concentrations studied range from as high as 1250 ppm for 60 weeks (*3*) to as low as 6.25 ppm for 2 years (6 hours per day for 5 days a week). In addition, exposures to 200 ppm for 40 weeks or 625 ppm for 13 weeks were carcinogenic in mice at the same sites identified in the 2-year study (*2*).

Although these data can and are being used to promulgate regulations concerning permissible ambient exposure levels for workers, the data do not allow for predictions of risk associated with a catastrophic release of 1,3-butadiene or during a single short, but unavoidable, occupational high-exposure situation. To address this issue, we performed a study in which groups of 60 male and 60 female $B6C3F_1$ mice (8-10 weeks old at the beginning of the study) were exposed for a single 2-hour period to concentrations of 0, 1000, 5000, or 10000 ppm 1,3-butadiene. Exposure conditions and methods were similar to those reported in earlier studies (*2,3*). The mice were then held for 2 years, at which time they were killed, and tissues and organs examined microscopically (*7*).

The single exposure to 1,3-butadiene did not affect survival at 2 years. The number of mice surviving in each group of 60 female mice was as follows: 45, 36, 38, and 48 for those receiving 0, 1000, 5000, and 10000 ppm, respectively. In each group of 60 male mice, the number of surviving mice was 28, 34, 44, and 34 for those receiving 0, 1000, 5000, and 10000 ppm, respectively. There were no clear chemical-related effects on body weights throughout the 2-year period. There were no statistically significant increased incidences of neoplastic or nonneoplastic lesions attributed to exposure to 1,3-butadiene. A comparison of numbers of mice with tumors of organs that have shown increases in previous studies is shown in Table 1.

The one questionable site was the forestomach of male mice, which showed a nonsignificant trend for squamous cell neoplasms ($P = .079$; logistic regression test). All but one of these neoplasms was a papilloma; one male in the high-dose group had a carcinoma. The historical control incidence of squamous cell neoplasms is 0.74%, with a range of 0%-4%. Thus, the high-dose incidence of 6% exceeded the historical control range. Although the possibility cannot be excluded that these tumors were caused by exposure to 1,3-butadiene, several factors argue against this. Prior studies have shown that male

Table 1. Incidence of primary tumors in $B6C3F_1$ mice exposed to 1,3-butadiene for 2 hours and then held for 2 years*

		Exposure concentration, ppm							
		Male†				Female			
Target	Lesion	0	1000	5000	10000	0	1000	5000	10000
Hematopoietic system	Lymphoma	7/59	8/58	8/58	10/58	13/57	19/56	18/57	13/58
Heart	Hemangiosarcoma	1/59	0/58	0/58	0/58	0/56	0/56	0/57	0/58
Lung	Alveolar-bronchiolar neoplasm	8/59	9/58	12/57	8/58	3/56	4/56	0/57	3/58
Forestomach	Squamous cell neoplasm	0/59	1/58	1/58	3/58	0/57	1/56	0/57	0/58
Mammary gland	Acinar cell neoplasm	0/59	0/58	0/58	1/58	2/57	1/56	3/57	4/58
Ovary	Granulosa cell neoplasm	—	—	—	—	0/53	0/52	1/53	0/56
Liver	Hepatocellular neoplasm	17/59	21/58	21/57	18/58	5/56	6/55	8/57	3/58

*Incidence values are given as the number of tumor-bearing animals/number of animals examined. Tissues or organs from some mice that died early were not examined due to autolysis. No significant differences in tumor incidence were observed between the control group and any of the exposure groups by life table or logistic regression analyses.

†— = not applicable.

and female mice are equally sensitive to the induction of forestomach tumors by 1,3-butadiene, whereas here only the male mice appeared to respond. Secondly, the forestomach has not been the most sensitive tissue for tumorigenesis in earlier studies, again suggesting that this observation is a chance occurrence.

The top exposure concentration used in these studies (10000 ppm) was limited by the need to keep the concentration below the flammable level. Both the 5000 and 10000 ppm concentrations are above the reported saturation level (between 1000 and 2000 ppm) for metabolism of 1,3-butadiene by B6C3F$_1$ mice (*8*). Disregarding this factor, which could limit the production of potentially carcinogenic metabolites, the CT (concentration in ppm × time in hours) product for the top concentration in this study was 20000 (10000 ppm for 2 hours). This CT compares with a CT of approximately 240000 for the previously shortest 1,3-butadiene exposure (625 ppm, 6 hours per day for 5 days a week for 13 weeks) shown to be carcinogenic in mice. Although the results of the current study did not identify a carcinogenic effect associated with an acute high exposure to 1,3-butadiene, it must be recognized that attempts to define NOAELs (i.e., no observed adverse exposure levels) or LOAELs (i.e., lowest observed adverse exposure levels) with an animal model as insensitive as the typical rodent bioassay may underestimate the true risk to humans of exposures of this type.

JOHN R. BUCHER
RONALD L. MELNICK
National Institute of Environmental Health Sciences
Research Triangle Park, N.C.
PAUL K. HILDEBRANDT
PATHCO, Inc.
Gaithersburg, Md.

References

(1) Melnick RL, Huff J: 1,3-Butadiene: toxicity and carcinogenicity in laboratory animals and in humans. Rev Environ Contam Toxicol 124:111–144, 1992
(2) Melnick RL, Huff J, Chou BJ, et al: Carcinogenicity of 1,3-butadiene in C57BL/6 × C3H F1 mice at low exposure concentrations. Cancer Res 50:6592–6599, 1990
(3) Huff JE, Melnick RL, Solleveld HA, et al: Multiple organ carcinogenicity of 1,3-butadiene in B6C3F1 mice after 60 weeks of inhalation exposure. Science 227:548–549, 1985
(4) Matanoski GM, Santos-Burgoa C, Schwartz L: Mortality of a cohort of workers in the styrene-butadiene polymer manufacturing industry (1943-1982). Environ Health Perspect 86:107–117, 1990
(5) Divine BJ: An update on mortality among workers at a 1,3-butadiene facility—preliminary results. Environ Health Perspect 86:119–128, 1990
(6) Santos-Burgoa C, Matanoski GM, Zeger S, et al: Lymphohematopoietic cancer in styrene-butadiene polymerization workers. Am J Epidemiol 136:843–854, 1992
(7) McConnell EE: Pathology requirements for two-year rodent studies. I. A review of current procedures. Toxicol Pathol 11:60–64, 1983
(8) Laib RH, Filser JG, Kreiling R, et al: Inhalation pharmacokinetics of 1,3-butadiene and 1,2-epoxybutene-3 in rats and mice. Environ Health Perspect 86:57–63, 1990

Note

Correspondence to: John R. Bucher, Ph.D., National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709.

Advice to Doctors

Newly diagnosed cancer patients are sometimes told they have terminal disease and have 3 or 6 months or a year or two to live. Why do physicians say this? Because, they say, they must be honest; they must be frank; and the patient and his or her family has a right to know and must prepare for death. The truth is that this physician, in playing God, is trying to protect himself or herself in case of poor results, or wants to take sole credit for saving a life. Either way, the physician is a winner and the patient, family, and friends are the losers.

Doctor, suppose you were able to access a machine and read the local newspaper printed 6 months from today. On the front page you see your picture and read that you were the victim of a drive-by shooting. You were killed the previous night! How would this help you and your family? What would this do to your quality of life this afternoon? Tomorrow? Do you believe that if you had the power to look back the day after that shooting, you would have believed your life was better for having known it would happen? When you tell a patient he or she is likely to die within a certain period of time, you are trying to allow that patient to read a newspaper that is written in the future.

As to honesty, the truth is not that the patient is going to die in 6 months. Only God knows when that particular individual will pass away. That person may be hit by a truck on the way home and be killed today. Every doctor knows stories of "terminal" cancer patients who are alive and well years later. No one knows what is going to be discovered in the next 6 months that could help. In other words, the whole truth is that you, the physician, have never seen a patient with this type of cancer successfully treated. But some have made it, and you can make some phone calls to see if someone somewhere can do something to help.

In a hospital tumor board meeting I attended, the case of a patient who had cancer throughout both lungs was discussed. Surgery, radiation, and chemotherapy were all ruled out. The head oncologist told the attending physician to tell the patient that he had terminal disease and that nothing could be done. I asked why he did not state that they knew of no medical options but that the patient could talk to a minister or look into psychological counseling. The oncologist's answer was that he would rather see the patient die than resort to prayer or psychology. I'm not trying to suggest that prayer or psychology would have helped, but it was obvious that the oncologist would have preferred to see the patient die rather than take the chance of sharing success with anyone else.

Over 15 years ago, I was told by a prominent physician that I had terminal lung cancer and that nothing could be done. He said that I had 90 days to live. Had I believed him, I would have fulfilled his prognosis. I went