U.S. Sperm Trend Conclusions

The letter written by Heinze (*1*) has serious shortcomings. Heinze wrote that

> There is not a single study of healthy men from any fertility center or sperm bank that has reported a decline in sperm counts in the United States.

This is not true. A number of such studies exist. Leto and Frensilli (*2*) documented a decline in sperm counts in potential sperm donors from all over the United States in a longitudinal study.

Heinze stated that

> A study by MacLeod and Wang (*3*) indicates that sperm counts have remained constant in New York since 1938.

That study was dated 1979 and was on men ascertained at a fertility center. Although their sperm counts were stable over the years preceding 1979, it does not necessarily follow that sperm counts of fertile men were stable too.

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U.S. Sperm Trend: Response

I would like to respond to James's comments on my letter "Regional Differences Invalidate U.S. Sperm Trend Conclusions" (*1*).

Perhaps I should have said that

> There is not a single [confirmed] study of healthy men from any fertility center or sperm bank that has reported a decline in sperm counts in the United States.

The study of Leto and Frensilli (*2*) is contradicted by the four longitudinal studies cited in my letter, which report no decline in sperm counts in five regions of the United States over periods ranging from 10 to 30 years (*1*). Earlier data on trends in sperm counts were reviewed by MacLeod and Wang (*3*), who concluded that

> enough data have been presented to indicate that there has not been a substantial change in the numerical aspect of semen quality.

Saidi et al. (*4*), in a recently published review of 29 U.S. studies from the late 1930s to the late 1990s, found "no significant changes in sperm counts during the last 60 years."

MacLeod and Wang (*3*) reviewed all of the U.S. data available up to that time (1979), including data from fertile men as well as from men evaluated at a fertility center. The earliest data on sperm counts in New York City, published in 1938 (*5*), were on prenatal couples (i.e., men of known fertility); mean counts (137×10^6/mL) from this study are virtually identical to the mean counts (131.5×10^6/mL) reported in the most recent study from New York City published in 1996 (*6*), which focused on donors to sperm banks (i.e., men of unknown fertility).

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Comments on "Drinking Water Arsenic in Utah: A Cohort Mortality Study"

Lewis et al. (*1*) compared the mortality of a cohort of members of the Church of Jesus Christ of Latter-day Saints (also known as Mormons) who were exposed to relatively high levels of arsenic through drinking water to the mortality of the general population of Utah. The authors concluded that arsenic exposure may be associated with hypertensive heart disease, nephritis and nephroma, prostate cancer in men, and other heart disease in women. No excess risks were reported for cancers such as those of the skin and bladder, which have been associated with arsenic in other studies (*2*). We believe that the comparison group used in this study, and the weight given on external rather than internal comparisons, complicates the interpretation of the study results.

Mormons are a selected group that differs from other groups of the general population in many ways, including lifestyle factors such as smoking, which are strong determinants of health. Lewis et al. (*1*) acknowledged that the study group is known to have about one-half the mortality rates of the general population for diseases such as respiratory and bladder cancers. Given this strong selection bias, it would be unlikely to find any excess risks for these diseases unless this risk associated with arsenic was very high. Similarly, high standard mortality ratios (SMRs) are likely to be caused by other general lifestyle factors, rather than arsenic in drinking water.

When the external comparison group is very different from the index group and information on potential confounders is not available, the best solution is to perform internal comparisons. If conclusions had been based on internal comparisons, neither hypertensive heart disease (SMRs of 2.4, 1.9, and 2.3 for low, medium, and high exposure to arsenic, respectively), nephritis/nephroma (SMRs of 2.0, 2.1, and 0.9, respectively), nor all other heart diseases (SMRs of 2.3, 1.4, and 0.7, respectively) would probably have been associated with arsenic in this study. Among the four causes that Lewis et al. (*1*) reported to be associated with arsenic, an increasing risk with exposure was only seen for prostate cancer. The authors did mention that internal comparisons are planned. Although such comparisons may be limited by small numbers, any conclusions from this study should await the conduct of such analyses.

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"Drinking Water Arsenic in Utah …": Response

We thank Villanueva and Kogevinas for their letter based on our recent article (*1*). We agree that to interpret the results of this paper it is important to keep in mind the characteristics of the population used to generate the expected numbers. Of the

populations readily available to generate the expected numbers, we considered the white population of males and females from the state of Utah to be the best. We used white male and white female death rates from the state of Utah as the external comparison group. For noncancer causes of death, we used Utah white male and female rates for 1960–1992 to estimate the expected number of noncancer deaths, and we used Utah white male and female rates from 1950 to 1992 to estimate the expected number of cancer deaths. Based on a 1982 report, nearly 73% of the state of Utah is Mormon (*2*), whereas our mortality cohort was 100% Mormon. Given that a majority of those in Utah are Mormon, our study population and the external Utah population would not be expected to differ greatly on average for many lifestyle factors including smoking. Therefore, we believe there are minimal differences between the external comparison group (in our case, white men and women in the state of Utah, which is predominantly Mormon) and our index group (which is by definition 100% white Mormons). To avoid any misunderstanding, we did not use death rates from the U.S. general population as the basis of the expected numbers, which would have been more different from the index group on potentially confounding factors. We made no attempt to generalize our results back to the U.S. population.

Although we agree that Mormons are a select group with many healthy lifestyle habits, we do not think that selection bias had a significant effect in this study, as suggested by Villanueva and Kogevinas. We did not claim that the study group had one-half the rates of mortality for respiratory diseases and bladder cancer than the general population, but rather that Mormon men in general had one-half of the incidence of these smoking-related health effects as compared with U.S. men. The difference in these rates would not contribute to selection bias in the context of our study. Selection bias is caused by systematic differences in characteristics between those who are selected for a study and those who are not (*3*) and results in error in the measure of association. Because we took a nearly complete sample of historically registered Mormons for this part of Millard County, Utah, selection bias (if any) played a very minor role, as over 90% of the people living in these areas at that time were registered in the historic Mormon church membership records. The loss to follow-up for the mortality cohort was also low.

Historically, Utah has had among the lowest mortality rates for bladder cancer and lung and bronchus cancer in the United States (*4*). The lack of a finding for bladder cancer and respiratory diseases is due to the rareness of these events in Utah. For bladder cancer, only five deaths were reported. As we discussed in our paper (*1*), the rates of smoking for other areas in Utah are higher than for Millard County. We would expect the SMR for respiratory conditions (expected number generated from the state of Utah rates) to be less than 1.0. This finding makes sense based on what we know about the two populations (our cohort and the population of Utah) with regard to smoking. In the review paper cited by Villanueva and Kogevinas in their letter (*5*), none of the articles reviewed indicate an excess of skin or bladder cancer from the studies that were conducted in U.S. populations. In addition, a previously conducted case–control study of bladder cancer and arsenic in drinking water in Utah did not find an overall association of inorganic arsenic with risk of bladder cancer (*6*). In assessing the two populations in our mortality analysis, one factor for which this part of Millard County, Utah (from which the index group is drawn), and the rest of Utah (external comparison group) differs is the concentration of arsenic in the water. On average, Millard County has had the highest concentrations of arsenic in the state from both public and private wells over the last 20 years (*7*). Without further information on individual exposure to arsenic in drinking water, one could assume that the concentration of arsenic may play some role in the health of this community; however, a causal association based on this analysis alone would be inappropriate.

Villanueva and Kogevinas suggest that any conclusions from this study should await the conduct of analyses using internal comparisons. However, while we are completing our internal comparisons analysis, we do not think it is incorrect to evaluate the relationships between arsenic concentration and causes of mortality from these results as long as one keeps in mind the source and the characteristics of the external (comparison) population and the fact that this is a single study. Villanueva and Kogevinas indicate that they believe certain increasing effects that appeared in this analysis for hypertensive heart disease, nephritis and nephrosis, and all other heart diseases would not be apparent if an internal comparison group had been used in the analysis. However, it is quite possible to have results for a condition that are in the same direction (both increased or both decreased) from either type of analysis that uses internal or external comparison groups. We plan to note the similarities and differences between our SMR results and the forthcoming relative risk results based on internal comparisons. The relationships between low, medium, and high exposure groups in this analysis are less apparent because of potential differences in the age structure from the subcohort analysis. SMRs are generally not directly comparable, even if the same standard population is used to generate the expected numbers.

Finally, we want to emphasize the importance of conducting population studies and our original goal in conducting the study. Population studies, and more importantly SMR analyses, play an important role in identifying important risk factors or hazards. We were interested in determining whether studies of health effects related to arsenic in drinking water could be conducted in U.S. populations exposed to relatively low concentrations of arsenic, as compared to many international populations that have reported effects, often at higher concentrations. We also were interested in determining which health effects may be more meaningful to study in U.S. populations. This cohort provided the opportunity not only to evaluate cancer effects but also noncancer effects. We believe mortality studies are one way to identify potential hypotheses for further testing. The relationships between the health effects and arsenic in drinking water in this study are consistent with those reported in other populations and should be considered when planning further studies of arsenic and U.S. populations.

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Comments on "Why Not Use It All?"

The recent editorial by George Lucier (*1*) mischaracterizes the two key aspects of the Society of Toxicology (SOT)–European Society of Toxicology (EUROTOX) debate, which was a part of the program of the March 1999 SOT Annual Meeting held in New Orleans, Louisiana. First, the debaters represented neither an SOT motion nor a EUROTOX motion, i.e., this is not a situation where the two societies have taken an official position on an issue. Second, the debate was not intended to persuade the audience to simply accept one side and jettison the data presented by the other side. The SOT–EUROTOX debate provides a public forum for airing different viewpoints and differences in interpretation of data surrounding a scientific issue. It is framed deliberately in a provocative fashion to stimulate an open, thorough discussion. This type of discussion facilitates introspection and leads to an enhanced understanding of the issue at hand.

The particular debate in question focused upon the following hypothetical motion: "The Results of Mechanistic Toxicity Studies Should Supersede Ambiguous Epidemiological Data." This debate was a part of an annual cooperative activity between two of the largest professional organizations of toxicologists in the world: the SOT and EUROTOX. A topic chosen jointly by the program committee of each society is debated at each society's annual meeting, the SOT meeting in March and the EUROTOX meeting in June. The two program committees select a member of their respective society to participate in the debate, and the same individuals debate the issue in the United States and in Europe. In addition to selecting a new topic and new debaters each year, the "side" that each society takes changes yearly, i.e., in even-numbered years EUROTOX speaks for the motion and SOT speaks against it, whereas the SOT speaks for the motion and EUROTOX against it in odd-number years. Importantly, the topic does not represent an official position of either society. Rather, a considered extreme "pro" and "con" side of the issue is set initially to force each side to marshal their best rationale. Furthermore, substantial time for audience participation is an integral component of the program. Over the years we have learned that this format facilitates an open discussion that entails the presentation of a full range of views leading to a more thorough understanding of the issue at hand. Often an individual debater may speak to an issue in which he or she has an extensive record of publication; however, this is not always the case. The prime objective is to select debaters who will develop strong arguments for the side they are taking in a fashion analogous to an attorney making the best argument for his or her client.

Contrary to Lucier's editorial (*1*), this format not only permits, but indeed demands, full consideration of all relevant data sets. The scientific expertise of the chosen debaters plus the public nature of the debate, combined with ample time for both questions and comments from the audience, ensures that this occurs. It is not a simple case of choosing between two opposite poles. Experience has demonstrated the scientific value of the debate. It serves to enhance critical, constructive thinking concerning the issue at hand. Typically, this session draws a packed room and, judging by the attentiveness of the audience and their enthusiastic participation in the discussion, it is a highly valued component of our annual meeting.

We welcome more open dialog on the value of this and other specific components of the SOT annual meeting program, which is intended to provide an international forum for discussion of important and sometimes controversial issues related to the science of toxicology.

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"Why Not Use It All?": Another View

I join enthusiastically in Lucier's well crafted editorial argument (*1*) that full assessment of the carcinogenic potential of chemical compounds requires examination of epidemiologic, toxicologic, and mechanistic data. To ignore information from any of these three sources would be wasteful, short-sighted, and not in the best interests of protecting public health.

There is, however, a fourth dimension of carcinogenic risk assessment that has not to date received adequate consideration. This is the developmental dimension. The young of all mammalian species have exposures and vulnerabilities to chemical carcinogens that are qualitatively and quantitatively different from those of adults. The special susceptibilities of human babies were examined in detail in the 1993 National Academy of Sciences report *Pesticides in the Diets of Infants and Children* (*2*).

The EPA Guidelines on Carcinogenic Risk Assessment, on which Lucier comments in his editorial (*1*), pay only scant attention to developmental biology. The current draft of these guidelines continues to embody the outmoded fiction that the entire American population can be represented by an adult white male who weighs 70 kg. Until our national policy on carcinogen risk assessment moves beyond this limiting assumption and begins to require explicit consideration of pediatric exposures and risks, there will be little incentive for researchers to explore pathways of exposure, patterns of disease, or mechanisms of carcinogenesis in the young. We are not yet using all of the data.

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Air Toxics Concentrations of Methyl Chloride

On behalf of the Methyl Chloride Industry Association (MCIA; which comprises the following domestic producers of methyl chloride: Dow Chemical Company, Dow Corning Corporation, General Electric Company, and Vulcan Materials Company), I would like to alert you to certain incorrect statements concerning methyl chloride contained in "Public Health Implications of 1990 Air Toxics Concentrations across the United States" (*1*). In this letter, I will briefly summarize these incorrect statements and provide a

more detailed explanation of the basis for MCIA's position.

Woodruff et al. (*1*) incorrectly suggest that industrial air emissions of methyl chloride present a significant health risk. On the basis of 1990 data for the Toxics Release Inventory (TRI) and the Cumulative Exposure Project (CEP), Woofruff et al. purport to identify listed hazardous air pollutants (HAPs) that are present in the environment above levels of concern based on cancer and noncancer effects. The authors further state that methyl chloride is one of eight pollutants identified as having "modeled concentrations exceeding the benchmark concentrations for cancer in 100% of the census tracts" (*1*).

These statements are inaccurate for the following reasons. First, methyl chloride air emissions and resulting concentrations should not be compared to a cancer health benchmark because available data are not sufficient to conclude that methyl chloride poses a human cancer hazard. Methyl chloride has been classified by the U.S. Environmental Protection Agency (U.S. EPA) as only a Group C possible human carcinogen (*2*); this is based on no human data and insufficient animal data. Further, the International Agency for Research on Cancer (IARC) (*3*) found that the evidence of carcinogenicity of methyl chloride to humans and to animals is inadequate; therefore, IARC classifies methyl chloride in Group 3 (not classifiable). A U.S. EPA Scientific Peer Review Panel (*4*), convened for a rulemaking proceeding under 112(g) of the Clean Air Act, agreed that compounds classified as Group C (possible) carcinogens should not be grouped with "known" and "probable" human carcinogens. The available data simply are not sufficient to justify evaluating or classifying methyl chloride based on a perceived cancer hazard.

Second, when background concentrations from natural sources are removed from the analysis, methyl chloride emissions do not exceed benchmark levels in 100% of the census tracts. Perhaps up to 99% of ambient air concentrations of methyl chloride are due to releases from natural sources, rather than releases from manufacturing and use (*5*). Although in their Table 2 Woodruff et al. (*1*) acknowledge that the alleged exceedances for methyl chloride are due almost entirely to background concentrations, rather than man-made sources, they nevertheless purport to identify "HAPs representing the highest potential health risks" with the idea that

> Future regulatory and scientific activities can begin to focus on these pollutants to address and further evaluate their public health significance.

Given the almost insignificant amount of methyl chloride emissions from industrial sources, efforts to reduce methyl chloride emissions from industrial sources will not meaningfully reduce ambient concentrations of methyl chloride. Woodruff et al. misleadingly suggest otherwise.

Woodruff et al. (*1*) also misleadingly suggest that the CEP represents the U.S. EPA's final analysis. This is not correct. The CEP is an analysis performed by the U.S. EPA that compared modeled ambient air concentrations of HAPs in urban census tracts to chronic health effects benchmarks. HAPs were ranked according to the number of urban census tracts in which the modeled concentration was above the health benchmark. Much of the needed health effects information was previously compiled for the U.S. EPA's proposed rule making under Section 112(g) of the Clean Air Act Amendments of 1990. In the 112(g) proposal, the U.S. EPA proposed a relative hazard ranking of all HAPs. However, this rule making was never finalized and the U.S. EPA never responded to public comments submitted or to the views expressed by the Scientific Peer Review Panel concerning the inappropriateness of classifying Group C carcinogens with Group A and Group B carcinogens. Because the analysis and conclusions contained in the CEP were never subject to peer review, it is therefore not a reliable source of information, nor does it represent the U.S. EPA's final analysis of the data.

The editors of *EHP* have an obligation to ensure that the statements contained in its publications are factually accurate and not misleading. This obligation is paramount, particularly when a paper is drafted by a U.S. EPA staff scientist and therefore has the potential to be mistakenly viewed by readers as an official U.S. EPA position. The misleading statements included in the paper are of particular concern because they have been mistakenly relied upon by the public and other publications. For example, *Rachel's Environment & Health Weekly* (*6*) appears to have relied on the *EHP* paper as the basis for a statement that

> EPA … published a report in 1998 saying that 100% of the outdoor air in the continental U.S. is contaminated with eight cancer-causing industrial chemicals at levels that exceed EPA's "benchmark" safety standards.

The paper further identified methyl chloride as a "carcinogen" that is "known to cause cancer." Woodruff et al. (*1*) is cited as the reference for these misleading statements.

We request that such misleading information not be published again in subsequent papers appearing in *EHP* and that this letter be published to provide the public with a more accurate presentation of the facts concerning methyl chloride. If you have questions concerning these comments or require further information, please contact me.

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Air Toxic Concentrations: Response

We appreciate Browning's interest in our paper "Public Health Implications of 1990 Air Toxics Concentrations across the United States" published in the May 1998 issue of *EHP* (*1*). In this paper we compared estimated concentrations of 148 air toxics, derived from dispersion modeling of air toxics emissions, to previously defined benchmarks for cancer and noncancer effects.

As stated in the paper, the goal of the analysis was to provide a relatively comprehensive assessment of the potential public health impacts of air toxics (referred to in the Clean Air Act as "hazardous air pollutants" or HAPs) based on available information. To conduct this analysis, we used emissions data from stationary and mobile sources in an atmospheric dispersion model to estimate 1990 outdoor concentrations of 148 HAPs for every census tract in the contiguous United States. For many HAPs, the estimated concentrations also included a background concentration, which represents the impacts of long-range transport, resuspension of historical emissions, and nonanthropogenic sources, that would be present without local anthropogenic 1990 emissions. Background concentrations were based on measurements taken in locations

remote from the impact of local anthropogenic sources and were applied uniformly to all census tracts.

The estimated concentrations were compared to previously defined benchmarks for cancer and noncancer effects (*2*). For this analysis, a HAP was considered to be a potential human carcinogen if it was classified by the U.S. EPA (*3*) as Group A (known), B (probable), or C (possible), or by the International Agency for Research on Cancer (IARC) as Group 1 (known), 2A (probable), or 2B (possible). The description of the IARC categorization for carcinogens is found in the preamble of each IARC Monograph (*4*). This is consistent with the prescribed risk-based standards for risks resulting from exposures to known, probable, and possible carcinogens in the Clean Air Act Amendments of 1990 [section 112(f)]. The benchmark concentration for carcinogens was set equal to a concentration associated with a one-in-a-million cancer risk for lifetime exposure. We then assessed the number of exceedances, or census tracts with estimated concentrations greater than the one-in-a-million benchmark, for each HAP.

The initial assessment of the carcinogenicity of methyl chloride was reported in a document prepared by the U.S. EPA Office of Research and Development (*5*). In this document methyl chloride was classified as a group C carcinogen (possible human carcinogen) on the basis of kidney tumors found in mice exposed via inhalation. Therefore, we considered methyl chloride to be a possible human carcinogen on the basis of the U.S. EPA classification.

The Section 112(g) technical support document (*6*) referred to by Browning did not classify any HAPs as carcinogens, but rather adopted existing agency assessments for use in its hazard ranking. The procedures for adopting assessments for the section 112(g) document were peer reviewed by an external expert panel, but this panel did not engage in further review of individual pollutant assessments that had already been through various forms of external and internal peer review. The analysis of Caldwell et al. (*2*) referenced in our paper built on and extended the principles used in the Section 112(g) document (*6*) to assemble hazard information on air toxics. One of these principles was to use existing reviewed toxicologic data. Although it was beyond the scope of our paper (*1*) to review the toxicologic data for each HAP, the general assessment procedures, as well as the specific methyl chloride weight-of-evidence classification and benchmark concentration, were presented by Caldwell et al. (*2*). Although the U.S. EPA classification of methyl chloride differs from that of IARC, the tiering approach adopted by Caldwell et al. considered the U.S. EPA classifications first and then used IARC assessments for pollutants lacking a U.S. EPA classification.

Browning correctly quotes the "Results" of our paper (*1*): methyl chloride was one of several pollutants that had

> modeled concentrations exceeding the benchmark concentrations for cancer in 100% of the census tracts.

Immediately after this statement, we explained that this result was due to the fact that the estimated background concentrations (applied to every census tract) alone were greater than the benchmark concentrations for these pollutants. We further explored the results for these pollutants by considering the number of exceedances when background is disregarded. Table 2 in our paper (*1*) clearly displayed our finding that when the background concentration was disregarded, estimated 1990 methyl chloride concentrations exceeded the cancer benchmark in about 110 (out of 60,000) census tracts in the contiguous United States. This information is all clearly presented in the same paragraph that contains the statement quoted by Browning.

Our main objective in conducting this analysis was to estimate concentrations experienced in ambient air, regardless of source, to help define the potential scope of impacts on public health. As we stated in the paper,

> Future regulatory and scientific activities can begin to focus on these pollutants to address and further evaluate their public health significance.

In our paper (*1*), we did not recommend any specific course of action for methyl chloride or any other pollutant.

We agree that greater confidence should be placed in results for pollutants classified as known and probable human carcinogens than for those classified as possible human carcinogens. However, as we have stated in our work, we believe it is important to include as much information about the potential hazards of as many HAPs as possible. To do otherwise would be to initially assume that there is no risk and would not reflect prudent public health practice. As we stated in our paper (*1*), it is appropriate to follow up with further research to investigate these relationships more closely.

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Correction

In the July **Focus** article, "A Healthy Home Environment?" [*EHP* 107:A352–A357 (1999)], the sentence "Natural gas in the United States does not contain carbon, but CO may form if the gas is burned without an adequate air supply" should have read "Natural gas in the United States also contains carbon, and CO may form if the gas is burned without an adequate air supply." *EHP* regrets the error.