To the editor:

The causal relation between benzene exposure and multiple myeloma

The evidence cited by Bergsagel et al in their recent review does not at all support their conclusion that “there is no causal relationship between exposure to benzene or benzene-containing solvents and multiple myeloma.” The data they present in their Tables 3 and 4 is akin to a fishing expedition in waters known to be sterile. It is unreasonable to ask the question of whether benzene causes multiple myeloma (MM) in a cohort in which the benzene effect, if any, is too weak to observe an increase in the relative risk of acute myelogenous leukemia (AML). AML is known to be caused by benzene and has a higher background incidence and likely a shorter latency period than MM, making the causal relation between benzene and AML much easier to detect epidemiologically. Although not stated by Bergsagel et al, the same epidemiological approach that did not find a statistically significant increase in MM also did not find an increase in AML in this cohort. It is as if the authors asked the question of whether cigarette smoking causes MM but chose to address it in a cohort in which the extent of cigarette smoking was sufficiently small that there was no increase in lung cancer. The laboratory equivalent would be to draw negative conclusions from a study in which a positive control turned out to be negative.

Consideration of ionizing radiation should be sufficient to expose the fallacy of the authors’ assumption that just because different hematological neoplasms have different manifestations and clinical courses they must have different etiologies. For example, atom bomb survivors and other radiation-exposed cohorts have shown multiple hematological and nonhematological neoplasms, all with different manifestations and clinical courses, arising from the same insult. Similarly, Damashek’s coining of the term “myeloproliferative syndrome” reflects the recognition of the relatedness of a number of clinically dissimilar cancers.

Bergsagel et al fail to discuss the key points that make biologically plausible the causal relation between benzene and MM, or to cite a published article by one of us specifically discussing this question. While not conclusive of causality, it is known that benzene metabolites are capable of causing cancer (AML) in the organ system in which plasma cells are usually located; that the lymphocyte is particularly sensitive to benzene toxicity; that circulating lymphocytes, which are primarily B-lymphocytes, demonstrate benzene-induced chromosomal abnormalities consistent with cancer-causing effects; and that the B-lymphocyte is the precursor of the plasma cell.

The authors are correct that there is a lack of conclusive epidemiological evidence causally linking benzene to MM, although the pliofilm worker study they discount is certainly suggestive. If MM can be caused by benzene, an obvious question is why has AML, but not MM, been observable in classic epidemiological studies of exposed workers? Four major possible explanations are 1) the relatively lower background incidence of MM, which limits the power of epidemiologic studies to detect an effect, 2) the relatively longer latency period for MM, 3) the imprecision of metrics for estimation of exposure in observational epidemiologic studies, and 4) the possibility of a relatively higher potency for benzene in causing AML than for other tumors, similar to that observed for AML resulting from ionizing radiation and chemotherapy.

Despite there being no question that benzene causes AML, most cohort studies of benzene-exposed work forces have not shown a statistically significant increase in AML. Clearly this is at least in part due to the relatively low levels of benzene exposure for most of these large work forces, to the limited number of cases in most studies, as well as to the fact that a number of studies did not separate out cases by histologic type. The background incidence of AML is sufficiently low that even a doubling of risk would be difficult to observe in most workplace cohorts due to their lack of size. A case in point is the study of close to 20,000 workers at 8 oil refineries in Britain in which 31.96 acute leukemia deaths were expected and only 30 were observed (SMR = 0.95) (6). Yet the nested case-control analysis of those individuals dying of leukemia found a greater likelihood of moderate to high levels of benzene exposure during their working lifetime (OR = 2.0). One epidemiological approach that avoids problems caused by the healthy worker effect is to determine the proportionate mortality ratio (PMR). Dement et al in a study of refinery workers in which the PMR for leukemia was 175 showed an increased PMR of 124 for MM in refinery workers, although this finding was not statically significant.

Another key issue explaining the lack of association and weakness of association between benzene and AML or MM in most occupational studies is the imprecision of the estimates of exposure. This imprecision almost invariably results in a bias of the findings toward the null—it is far easier and more likely that a negative study will be produced than a positive study.

As noted by the authors, the MM incidence in China and in Japan is far lower than the incidence in the United States and Western Europe. Accordingly, the low incidence of MM in the recent Chinese studies cited by benzene-exposed workers by Bergsagel et al is not surprising. Also misleading is the authors’ description of the Decoufle et al study as having “reported only one death from MM in 259 petrochemical workers who were exposed to benzene.” A better description is that of the 58 deaths in this cohort, two were related to MM, one of whom died from treatment-related acute leukemia. This study should not be cited as evidence of a lack of a causal relation between benzene and MM.

A recent case-control study, not referenced by Bergsagel et al, observed a statistically significant (OR = 2.4, p = .039) association of MM with employment in the chemical industry. Also deserving consideration is a Canadian cohort study of 156,242 male farmers in which there was a statistically significant association in the highest exposure group between MM and a surrogate of fuel oil use (OR = 1.7, 95% CI 1.1-2.7), but not herbicides.

The first law of toxicology is that the dose makes the poison. Fortunately, we now rarely find large cohorts of workers who are heavily exposed to benzene in countries that have an appreciable background incidence of MM. What we still see in the United States are individual cases of MM in people who have had heavy exposure to benzene at exposure levels that are far higher than occur in the large well-controlled workplace cohorts that are a requisite for classical epidemiology studies.

The current controversy about MM is reminiscent of the situation from the 1940’s through the 1970’s in which both biological plausibility and individual case reports led hematology
textbooks to list benzene as a likely cause of AML. Until the 1976 study of pliofilm workers, however, epidemiologists fought this designation, due to the absence of a sufficiently large well-studied cohort with enough benzene exposure to lead to a statistically significant increase in leukemia deaths. This unwillingness to address biological data was instrumental in the delay of decades in adopting rigorous controls to protect workers against benzene. While we agree that the causal relation between benzene and MM remains unproven, there are sufficient data to make this association highly probable.

Bernard D. Goldstein
Stuart L. Shalat
Environmental and Occupational Health Sciences Institute (EOHSI)
EOHSI is a jointly sponsored program of UMDNJ-Robert Wood Johnson Medical School and Rutgers, The State University of New Jersey

References

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Response:

Benzene and multiple myeloma: scientific evidence

Goldstein and Shalat overstate the conclusion of our review. Our conclusion was that “there is no scientific evidence to support a causal relationship between exposure to benzene or other petroleum products and the risk of developing multiple myeloma.” In fact, Goldstein and Shalat agree with us and reiterate the same conclusion in the fourth paragraph of their letter.

Goldstein and Shalat miss the point by using the radiation analogy. Epidemiologic data show that exposure to radiation induces cancer in more than one site. This is not true in studies of even highly exposed benzene workers. Further, the probable mode of action of benzene is quite different from that of radiation. Benzene does not induce point mutations which, in the case of radiation, partially explains why it is associated with cancers at more than one site. We did not reference Dr. Goldstein’s review1 because it was outdated and written before the most recent reanalyses of the pliofilm cohort.2,3 These analyses found no association between MM and exposure to benzene.

Goldstein and Shalat state: “‘AML is known to be caused by benzene and has a higher background incidence and likely a shorter latency period than MM making the causal relation between benzene and AML much easier to detect epidemiologically.’” This statement is incorrect. The incidence rate of AML is lower than the rate for MM in the USA. According to the NCI SEER data4 the age-adjusted incidence rate, 1987-91, for AML in males was 2.9/100,000 (1.4/100,000 for age <65 and 17.1/100,000 for age 65+). The corresponding rates for MM were 5.5/100,000 (2.1/100,000 for age <65 and 36.3/100,000 for age 65+). It is not clear where Goldstein and Shalat obtained relevant data for the latency period for MM, since no agent has been causally associated with this disease. The latency period cannot be determined if no causative factor has been identified.

Goldstein and Shalat argue that benzene exposure levels in the petroleum industry are too low to detect an increased risk of MM. In our review we cite Wong and Raabe,5 who identified three refineries with a significant increase in leukemia mortality (SMR = 1.91, 95% CI: 1.39-2.56, 43 observed deaths), but no increase in MM mortality (SMR = 1.02, 95% CI: 0.68-1.46, 29 observed deaths). Thus, Goldstein and Shalat’s argument that the reason for not finding an increase in MM mortality in petroleum workers is due to low benzene exposure (as indicated by a lack of leukemia increase) is incorrect.

Goldstein and Shalat cite a nested case-control study of leukemia (not MM) in the United Kingdom,6 implying that we should have examined nested case-control studies for the issue of MM. Among studies of petroleum workers there were only two nested case-control studies with quantitative exposure levels.7,8 We reviewed both studies in our paper, and found no exposure-response relationship between exposure and MM.

Goldstein and Shalat also cite a proportional mortality study.9 This study design is inferior to the cohort study design, primarily because information on the population at risk is missing, and, as such, proportional mortality ratios (PMRs) do not measure risk per se.10,11 Furthermore, the particular proportional mortality study cited by Goldstein and Shalat was based on an incomplete sample of death certificates among employees at 3 Texas refineries. All 3 refineries have been studied with the more appropriate cohort study design.12-15 and were included in the review by Wong and Raabe.6 The small mortality study of 259 petrochemical workers,16 cited by Goldstein and Shalat consisted of only one death from MM (as the underlying cause of death). Goldstein and Shalat argue that there was another death with MM as the secondary cause of death. In cohort mortality studies, only the underlying causes of death are analyzed, since the expected deaths are based on comparison rates of underlying causes of death only. If one includes secondary causes of death as well in a study, then similar rates based on multiple causes from the general population must be used for comparison. Neither the original authors (Decouflé et al) nor
Goldstein and Shalat offer such multiple causes of death rates for comparison. Goldstein and Shalat also cite a population-based case-control study in West Virginia.\(^1\) First, the occupation information was based entirely on death certificates, which might not be accurate. Second, “employment in the chemical industry” is an extremely broad and heterogeneous classification, and is not identical to or specific for “exposure to benzene.” Goldstein and Shalat argue that we should not expect to find an increase in MM in a study unless there was a corresponding increase in AML, (as an indicator for “sufficient” benzene exposure). In the West Virginia case-control study, the odds ratios for “employment in the chemical industry” were 2.39 (95% CI: 1.04-5.48) for MM and 1.09 (95% CI: 0.40-2.96) for AML. Since there was no increase of AML in the West Virginia study (i.e., insufficient benzene exposure), the increase in MM could not have been related to benzene. Further, in our paper we reviewed 7 case-control studies that examined the specific relationship between exposure to benzene, or benzene-containing solvents, and MM. In these studies, exposure information was obtained from interviews or employment/pension records, and not from death certificates. The risk ratios from these studies ranged from 0.5 to 1.1, supporting the conclusion that there is no relationship between benzene exposure and MM.

Finally, Goldstein and Shalat cite a cohort study of farmers in Canada by Semenciw et al, in which MM was analyzed in relation to agricultural practices.\(^1\) Goldstein and Shalat state: “there was a statistically significant association in the highest exposure group between MM and a surrogate of fuel oil use (OR = 1.7, 95% CI: 1.1-2.7), but not herbicides.” First, this was a cohort study, and the risk estimates were relative risks and not odds ratios. Second, the reported relative risk of 1.69 (95% CI: 1.08-2.65) was for the group of farmers who spent more than $900 in 1970 for fuel and oil for farming. Goldstein and Shalat assume that these farmers were exposed to high levels of benzene, and that the observed increased risk could be attributed to benzene and not to any other factor in the farm environment, such as fertilizers or herbicides. This assumption is not valid. Without knowing the specific fuels or oils used, it cannot be stated with any level of certainty that the farmers were exposed to appreciable amounts of benzene. Goldstein and Shalat point out that the increased MM was not due to herbicides used, it cannot be stated with any level of certainty that the farmers were exposed to appreciable amounts of benzene. Goldstein and Shalat argue that we should not expect to find an increase in MM in a study unless there was a corresponding increase in AML, (as an indicator for “sufficient” benzene exposure). In the West Virginia case-control study, the odds ratios for “employment in the chemical industry” were 2.39 (95% CI: 1.04-5.48) for MM and 1.09 (95% CI: 0.40-2.96) for AML. Since there was no increase of AML in the West Virginia study (i.e., insufficient benzene exposure), the increase in MM could not have been related to benzene. Further, in our paper we reviewed 7 case-control studies that examined the specific relationship between exposure to benzene, or benzene-containing solvents, and MM. In these studies, exposure information was obtained from interviews or employment/pension records, and not from death certificates. The risk ratios from these studies ranged from 0.5 to 1.1, supporting the conclusion that there is no relationship between benzene exposure and MM.

In summary, Goldstein and Shalat do not offer any scientific data to refute our conclusion. We stand by the conclusion in our paper that “there is no scientific evidence to support a causal relationship between exposure to benzene or other petroleum products and the risk of developing multiple myeloma.”

Daniel E. Bergsagel
Ontario Cancer Institute/Princess Margaret Hospital
University of Toronto
Toronto, ON, Canada

References
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Bernard D. Goldstein Stuart L. Shalat