Benzene and Leukemia: The 0.1 ppm ACGIH Proposed Threshold Limit Value for Benzene

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The American Conference of Governmental Industrial Hygienists (ACGIH) has proposed a threshold limit value (TLV) for benzene of 0.1 ppm. Individuals representing the American Petroleum Institute (API) and the Chemical Manufacturers Association (CMA) have argued that 1) the risk assessment by Rinsky *et al.* which ACGIH partially relied upon for its proposed TLV overestimates the risk; however, at the exposures levels of interest (e.g., 0.1 to 1.0 ppm) for establishing a benzene TLV, the Rinsky *et al.* assessment provides lower estimates of leukemia risk than most others; 2) ACGIH should not use the Dow study for direct observational evidence of leukemia risk associated with low-level benzene exposure because of confounding exposure; however, it is unlikely that confounding exposures played a role in the excess of leukemia demonstrated in the study, and the Dow cohort was exposed to an average benzene concentration of about 5.5 ppm benzene for 7.0 years (38.5 ppm-years), while some of the individuals in the study who died from leukemia were exposed to an average of only 1.0 ppm without the opportunity for high-peak exposures; 3) the Occupational Safety and Health Administration (OSHA) established an 8-hour time-weighted average (TWA) of 1.0 ppm in 1987, and there is no new evidence that would justify reducing the TWA below that level; however, the OSHA TWA of 1.0 ppm was based on economic feasibility and the level of excess risk remaining at 1.0 ppm, i.e., 10 excess leukemia deaths per 1000 workers over an occupational lifetime (45 years) according to OSHA's preferred estimate leaves behind a risk considered significant by OSHA. In addition, chromosomal studies among workers and in animals exposed to benzene indicate that low-level exposure, i.e., 1.0 ppm, is associated with elevated cytogenetic damage. On the basis of adverse health effects data alone, in this author's opinion, it would be poor science and poor public health policy to establish a benzene TLV greater than 0.1 ppm. Infante, P.F.: Benzene and Leukemia: The 0.1 ppm ACGIH Proposed Threshold Limit Value for Benzene. Appl. Occup. Environ. Hyg. 7(4):253–262; 1992.

Introduction

In July 1990, the American Conference of Governmental Industrial Hygienists (ACGIH) published[1] a "Notice of Intended Change—Benzene," whereby it proposed a revision of its current threshold limit value (TLV) for benzene from an atmospheric concentration of 10 ppm to 0.1 ppm as a time-weighted average (TWA) with a Skin notation and the designation as an A1 carcinogen—confirmed human carcinogen. The ACGIH document is well written and is based on a sound scientific evaluation of the literature. The proposed TLV of 0.1 ppm benzene is based upon: 1) the results of quantitative risk assessments of leukemia, with special emphasis on the Rinsky *et al.*[2] assessment using the National Institute for Occupational Safety and Health (NIOSH) case–control data; 2) direct inspection of observational data pertaining to benzene exposure levels associated with leukemia cases/deaths from the Dow Chemical Company[3,4] cohort mortality study; 3) benzene exposure levels associated with chromosomal breakage in epidemiologic and toxicologic studies.

On March 26, 1991, presentations made before the ACGIH Chemical Substances TLV Committee by individuals[5–9] representing the American Petroleum Institute (API) and the Chemical Manufacturers Association (CMA) recommended that ACGIH establish a TLV higher than 0.1 ppm based upon the following arguments: 1) the risk assessment by Rinsky *et al.*[2] gives too high a risk when compared with the assessment done by Brett *et al.*[10] using the same case–control data source and model, but with different benzene exposure assumptions than those used by Rinsky *et al.*; 2) ACGIH should not use the Dow study[3,4] for direct observational data indicating low-level benzene exposure and leukemia because of speculation that benzene exposure levels may have been higher than those cited in the report and because of possible confounding exposures; and 3) the Occupational Safety and Health Administration (OSHA) established an 8-hour TWA of 1 ppm in 1987, and there is no new evidence that would justify reducing the TWA below that level.

The parties mentioned above also submitted written opinions to ACGIH prior to the meeting in support of their views. The API and CMA presentations and written comments did not address the toxicologic and epidemiologic

The views expressed herein are those of the author and do not necessarily represent those of the Occupational Safety and Health Administration.

studies of low-level benzene exposure and chromosomal breakage. This article addresses each of the major comments listed above in the broad categories of 1) quantitative risk of cancer associated with benzene exposure; 2) direct observation of low-level benzene exposure and leukemia/lymphoma; and 3) health evidence justifies an exposure limit below 1 ppm benzene. In addition, a section on low-level benzene exposure and chromosomal breakage that was addressed by ACGIH, but not by API or CMA, is also addressed.

Quantitative Risk of Cancer Associated with Benzene Exposure

Argument that the leukemia risk based on the case–control study by Rinsky et al.[2] *gives too high a risk when compared to the assessment done by Brett* et al.[10] *on the same data set.*

Rinsky *et al.*[2] estimated the odds of death from leukemia in relation to cumulative benzene exposure based on a nested case–control study. They selected nine leukemia deaths from their cohort and matched them each with ten controls based on year of birth and year first employed in Pliofilm®. They selected a logistic regression model to estimate the odds ratio for leukemia in relation to cumulative benzene exposure. Their analysis indicates that 45 years of exposure to 1 ppm benzene (45 ppm-years) would result in an odds ratio (relative leukemia mortality rate) of 1.76. This odds ratio translates into a leukemia rate that is 76 percent greater than that of the unexposed population and would be equivalent to 5.3 extra leukemia deaths per 1000 workers exposed to 1 ppm benzene over an occupational lifetime (45 years). As indicated in the ACGIH justification[1] for its proposed revision to a TLV–TWA of 0.1 ppm, the odds ratio for occupational exposure to 0.5 ppm benzene for 45 years is 1.3 according to Rinsky *et al.*[2] which translates into 2.3 extra leukemia deaths per 1000 workers—a level of excess risk considered significant by OSHA[11] and other regulatory agencies. Based partly upon this analysis, ACGIH proposed a benzene TLV–TWA of 0.1 ppm, which Rinsky *et al.*[2] determined to be associated with an odds ratio of 1.05 that can be translated into an excess risk of 0.4 leukemia deaths per 1000 workers exposed over an occupational lifetime.

Brett *et al.*[10] conducted a similar type of analyses to that of Rinsky *et al.* using the same model and study population as the latter group. For each of the leukemia deaths in the Rinsky *et al.* study, Brett *et al.* selected slightly different sets of controls. The preferred set of controls selected by Brett *et al.* were matched on date of birth, date of entering Pliofilm, and employment at the same plant. (Rinsky *et al.* did not match on employment at the same plant.) In addition, Brett *et al.* did not use the exposure assumptions of Rinsky *et al.*, but rather used the highest benzene exposure estimates as determined by Crump and Allen.[12] The preferred estimate of risk by Brett *et al.*[10] suggests that occupational exposure to 1 ppm benzene for 45 years would result in 0.5 extra leukemia deaths per 1000 workers. Exposure to 0.5 ppm benzene over 45 years would result in 0.3 extra leukemia deaths per 1000 workers.[7] Thus, in relation to benzene exposures of interest (0.1 to 1.0 ppm) in establishing an ACGIH TLV, one could argue, as did API and CMA, that the estimates provided by Rinsky *et al.*[2] are too high. [Their estimates of risk (10) at the lower end of the range of benzene exposures of interest, however, are slightly lower than those provided by most other risk assessments.] Conversely, one could argue that the estimates of leukemia risk by Brett *et al.*[10] are too low, particularly in light of the results of the other risk assessments on benzene and leukemia as discussed below.

Why are there differences between the risk assessments by Rinsky et al.[2] *and by Brett* et al.[10] *when the authors used the same database?*

The major difference in leukemia risk assessment between the results of the Rinsky *et al.*[2] and those of Brett *et al.*[10] stems from a difference in exposure estimation for periods when no benzene exposure data are available. Which set of assumptions is closer to the "truth" will never be known. Rinsky *et al.* made reasonable exposure assumptions. The Crump and Allen[12] exposure assessment used by Brett *et al.*[10] is also reasonable. Whichever estimate one chooses to use is a matter of personal preference that is not based upon any available data analysis.

Furthermore, regardless of the number of additional estimates of benzene exposure to the Rinsky *et al.* cohort[2] that may be developed in the future, it is unlikely that they will be any more precise than those already available. For example, Paustenbach[6] made a presentation during the ACGIH TLV benzene deliberations whereby he claims to have made "recent advances in understanding the exposures of workers in the Pliofilm cohort." This effort included:

- Interviews with three former Pliofilm workers from one of the facilities studied that was located in St. Marys, Ohio. [*Note:* In 1976, a NIOSH team of investigators interviewed employees and members of management and reviewed the Pliofilm process while it was still in operation.]
- Review of the Kipen *et al.*[13] study discussed below.
- Review of a 1942 labor conference transcript that discussed exposure situations and acute toxicity among rubber workers, but not necessarily those who were studied by Rinsky *et al.*[2]

All these aspects of exposure were evaluated as part of the OSHA hearing. Nothing presented by Paustenbach[6] is new in terms of actual data or information. The only new aspect is the different assumptions made in his report about exposure for times when no actual exposure data are available.

The potential effect on the risk estimates of unaccounted benzene exposure was discussed thoroughly as part of the OSHA hearing and is discussed in detail in the final OSHA benzene standard.[11] The analyses by Brett *et al.*[10] were presented at the OSHA benzene hearing. OSHA concluded[11] "that there was some additional exposure, but

the data indicate that it did not make any substantial difference in the risk estimates ... internal analysis of the data show that any extra dose received by the cohort was not large enough to make a difference in the estimates." For example, in the prospective analysis of the Rinsky *et al.* cohort performed by Crump and Allen,[12] additional, unreported, atmospheric benzene exposures in the Pliofilm operations and unaccounted for atmospheric benzene exposure in non-Pliofilm jobs or from skin absorption while workers were employed either in the Pliofilm operation or on jobs outside of Pliofilm that occurred more or less uniformly across the study cohort would manifest themselves in estimates of the intercept from the risk analysis as being larger than 1.0 and/or in an excess (relative to the control population) of leukemias in the lower exposure groups. In fact, neither of these conditions occurred. Estimates of the intercept in the five analyses by Crump and Allen[12] that used only the Rinsky *et al.* data were 0.87, 0.82, 0.88, 0.18, and 1.11. All but one of these estimates of intercept is less than 1.0, and the exception is from the analysis that was considered the least reliable by Brett *et al.*,[10] i.e., the "window dose analysis." Thus, the Rinsky *et al.* data provide evidence against uniform exposures from other sources at a magnitude to affect leukemia rates in the study cohort.[11]

A paper published in 1989 by Kipen *et al.*[13] purports to show the benefits of using peripheral blood counts for the reconstruction of previous benzene exposure levels experienced by the Rinsky *et al.*[2] cohort in the 1940s. The authors concluded that there was a significant inverse relationship between benzene exposure (as determined by their preferred estimate of exposure, i.e., the Crump and Allen maximum exposure estimate,[12] but not by the Rinsky *et al.* estimate) and white blood cell (WBC) count among benzene-exposed workers in the NIOSH study. Based upon this analysis, Kipen *et al.* concluded that their preferred estimate of benzene exposure to the NIOSH cohort (as performed by Crump and Allen[12]) was better than that done by NIOSH.

If such an analysis was correct, it would support use of the exposure assumption preferred by Brett *et al.*[10] for their logistic regression analysis of the Rinsky *et al.* case–control study.[2] Although the Kipen *et al.* analysis[13] represents a creative approach, there is potential for tremendous selection bias in the study as the investigators based their analyses upon 128 (11%) of about 1200 rubber workers included in the cohort study. It is not known whether this small portion of workers' blood analyses represents the total population that was studied. However, it is likely that the results are not representative because the average WBC count for the group studied was 9300/mm^3. The normal range of WBC count for the general population is 5000/mm^3 to 10,000/mm^3, with an average of about 7500/mm^3. Thus, it is perplexing that a group of individuals exposed to such a potent bone-marrow depressant as benzene would have an average count so much higher than normal.

In the report, Kipen *et al.* stated,[13] "... we do not have an explanation for this aberration in the data set." A possible explanation is that workers whose blood counts were on the low side of normal were removed from the job if their count did not improve. Hence, workers with low counts were not available for succeeding blood tests. Those who remained on the job in the mid- to late-1940s, a period when most of the secular increase took place, and had at least five WBC counts taken (a criterion for selection into the Kipen *et al.* study[13]) were those who had blood counts that were either normal or on the high side of normal. Thus, the Kipen *et al.*[13] findings may be the result of selection bias and they cannot be used to support any particular exposure estimate.

In response to the Kipen *et al.* paper,[13] Hornung *et al.*[14] of NIOSH presented analyses of WBC counts among the NIOSH cohort. They concluded that the temporal increases observed among the NIOSH cohort cannot be attributed to a reduction in benzene exposure because preemployment blood counts showed the same temporal increase in WBCs. In the opinion of Hornung *et al.*,[14] the temporal increase was more likely due to changes in laboratory practice during the 1940s.

Should the Rinsky et al. *or the Brett* et al. *analysis be relied upon by ACGIH to determine the risk of leukemia related to benzene exposure and hence the TLV?*

During the OSHA benzene hearing, the Rinsky *et al.*[2] study was characterized by witnesses representing both industry and labor as one of the most thoroughly studied occupational cohorts in existence.[11] Based upon all of the evidence submitted to the OSHA record, OSHA was also of the opinion that the study was carefully conducted. OSHA concluded that both the Rinsky *et al.* risk assessment[2] and the Brett *et al.* risk assessment,[10] using the NIOSH case–control data and a logistic regression model, were well conducted.

OSHA, however, did not rely upon either of these analyses for its best estimate of leukemia risk for several reasons.[11] First, the model was not developed for cancer dose–response analysis. The assumption of a log-linear relationship between dose of benzene and relative odds of developing leukemia will cause any variation in the estimate of dose to result in an exponential change in the associated risk. This type of model seemed to be biologically less plausible than a linear model which also fit the case–control data set. Second, the use of a model resulting in an exponential change in risk with a change in dose introduces more uncertainty. This is of particular concern in light of the argument about different estimates of exposure by API, CMA, and Rinsky *et al.* for members of the Rinsky *et al.* study.[11] Third, the studies by Rinsky *et al.*[2] and Brett *et al.*[10] were based only on one of the three available studies that had good information on benzene dose. Thus, it seemed preferable to base estimates of risk using all three of the high-quality epidemiologic studies that contained data in a format that allowed for reasonable estimates of benzene dose.[2–4,15]

ACGIH should rely upon the Crump and Allen as-

sessment to estimate leukemia risk from benzene exposure.

OSHA relied upon the risk assessment by Crump and Allen,[12] which used the Crump and Allen maximum exposure assessment, for its preferred estimate of risk for the following reasons. Crump and Allen combined data from all three of the high-quality epidemiologic studies with good benzene exposure data;[2–4,15] thus, the best available data were used to determine excess risk. They demonstrated that the data from all three studies fit a linear model well. Furthermore, the linear model projected excess leukemia risks that were more mid-point estimates as compared to the logistic regression model when considering both low and high ranges of cumulative dose. There also appeared to be a biological basis for a linear model because benzene had shown a linear relationship for chromosomal breakage and cancer in animals.[11]

As shown in Table I, the Crump and Allen risk assessment[12] projects a risk of 10 excess leukemia deaths per 1000 workers as a result of 1 ppm benzene exposure for 45 years. The risk at 0.1 ppm for 45 years would be 1 per 1000 (ten times lower) since the relationship is linear at low doses. These findings are similar to those reported by others who used a linear model to estimate leukemia risk associated with benzene exposure.[12,16–19]

TABLE I. Estimated Excess Leukemia Deaths per 1000 Workers Exposed to Benzene for 40–45 Years (1 ppm or 10 ppm) Using Relative Risk and Cumulative Exposure Model[A]

Study	40 ppm-yrs (95% C.I.[B])	400 ppm-yrs (95% C.I.)
Rinsky[2]	6.6 (2.1–15)	63 (21–129)
Wong[15]	13 (0.1–31)	121 (1–243)
Rinsky,[2] Wong,[15] and Ott[3]	10 (4–22)[C]	95 (37–186)[C]

[A]Source 29 CFR Part 1910.[11]
[B]C.I. = confidence interval.
[C]Indicates 45 ppm-yrs and 450 ppm-yrs, respectively.

The only risk assessment, besides Crump and Allen,[12] which used all three of the high-quality studies with good dose data available to estimate risk is that of Austin *et al.*[17] This study estimated an excess of 53 leukemia deaths per 1000 workers as a result of 300 ppm-years of benzene exposure. Since these authors used a cumulative dose concept and a linear model, as has the majority of the risk assessments for benzene,[12,16–19] the risk associated with 0.1 ppm exposure for 45 years would be 0.8 excess leukemia deaths per 1000 workers. This estimate is virtually the same as the 1 extra leukemia death per 1000 workers estimated by Crump and Allen.[12]

Thus, the quantitative risk assessment that OSHA relied upon for its best estimate of risk,[12] or that by Austin *et al.*,[17] provides estimates of risk associated with 0.1 ppm benzene exposure for 45 years that OSHA considers significant, i.e., 1 per 1,000. For the reasons cited above, ACGIH should use the Crump and Allen[12] risk assessment based upon the relative model for its preferred estimate of dose–response for benzene and leukemia. OSHA did not set a permissible exposure limit (PEL) below 1.0 ppm because it was not economically feasible to do so.

Some factors that may result in an underestimate of cancer risk associated with benzene exposure which are not accounted for in any of the risk assessments.

1. Benzene-related diseases other than leukemia have not been counted in most quantitative risk assessments.

The risk of disease from benzene exposure based on leukemia only serves to underestimate risk. However, diseases other than leukemia have not been included in most risk assessments of benzene-exposed workers. Benzene exposure may cause other, "nonmalignant" blood diseases and lymphoma.[2–4,15,20,21] By considering just the ratio of leukemia to multiple myeloma (23:9) in the four major cohort studies of benzene-exposed workers where such data were provided,[2,4,15,22] one could add an additional 39 percent of excess cancer deaths to the quantitative risk.

2. The use of a cumulative dose concept to estimate benzene exposure in relation to bone marrow toxicity, chromosomal aberrations, and cancer.

All of the risk assessments for benzene and leukemia have used a cumulative dose concept for estimating risk. Given the type of exposure data that are available, it would be difficult, if not impossible, to develop what may be considered a more meaningful dose concept for benzene, based upon toxicologic study results. Several toxicologic studies, as indicated in Table II, demonstrate that the mode of exposure to benzene has a significant effect on benzene's toxic response. Thus, the risk of disease from benzene exposure to a group of individuals might be underestimated, depending upon the manner in which dose is received on a particular job in relation to the manner in which the dose was received in the epidemiologic study used to estimate quantitative risk.

For example, Irons[23] has shown that the administration of an important benzene metabolite, hydroquinone, can cause bone marrow depression as a result of intermittent exposure to 45 percent of a dose from which the animals' bone marrow was refractory. Likewise, the study by Dempster *et al.*[24] demonstrates that anemia results from 33 percent of a dose that did not cause a reduction in red blood cells and depends upon the mode of exposure. Luke *et al.*[25] have demonstrated a greater suppression of polychromatic erythrocytes (PCEs), a reflection of recently induced bone-marrow damage, as a result of a lesser benzene dose given intermittently.

Cancer response in experimental animals also has been related to mode of exposure. Snyder *et al.*[26] have demonstrated that 64 percent of a benzene dose given intermittently results in the same cancer response as the full dose given on a more continuous basis. These study results again demonstrate that the mode of exposure to benzene is related to the severity of response for several toxic endpoints including cancer. In these studies, less cumulative

TABLE II. Effect of Mode of Benzene Exposure on Type and Severity of Toxic Response

1. Irons:[23] Benzene metabolite (hydroquinone) results in bone-marrow depression as a result of 45% of a dose from which animals bone marrow was refractory.
2. Dempster *et al.*:[24] Anemia results from 33% of a dose that did not cause red blood cell reduction:
   10 days × 100 ppm (1000 ppm-days) = anemia
   3 days × 300 ppm (900 ppm-days) = anemia
   3 days × 1000 ppm (3000 ppm-days) = refractory
   1 day × 3000 ppm (3000 ppm-days) = refractory
3. Luke *et al.*:[25] A greater suppression of PCE[A] as a result of a lesser benzene dose given intermittently:
   Exposed DBA mice for 13 weeks to 300 ppm benzene
   Regimen 1 = 5 days/week × 6 hours/day
   Regimen 2 = 3 days/week × 6 hours/day
   Significantly > suppression of PCEs with Regimen 2
4. Snyder *et al.*:[26] Cancer in animals:
   CD-1 mice:
   1195 ppm × 50 days Cont.[B] = 59,750 ppm-days
   298 ppm × 129 days Int.[C] = 38,442 ppm-days
   64% of dose given Int., but at lower levels, results in same tumor response as the full dose given at higher levels, but continuously.
   C57B1 mice:
   1195 ppm × 50 days Cont. = 59,750 ppm-days
   300 ppm × 181 days Int. = 54,300 ppm-days
   90% of a dose given "Int." results in a significant increase in tumors, whereas larger dose given Cont. does not.

The studies indicated above demonstrate that a cumulative dose model may underestimate risk of bone marrow toxicity or cancer.
[A]PCE = polychromatic erythrocytes
[B]Cont. = dose administered 5 days/week for 10 weeks.
[C]Int. = dose administered 5 days/week followed by 2 weeks no dose.

benzene dose caused more disease and the same cumulative dose caused different cancer response rates depending upon the intermittency of the exposure.

With regard to epidemiologic data, the analyses by Wong[15] might lead one to conclude that only cumulative dose is important in determining a relation between benzene exposure and lymphopoietic cancer. His analyses demonstrate a significant dose–response for lymphopoietic cancer and benzene when the data were analyzed by cumulative benzene dose, but not when the duration of exposure or peak exposure were used as surrogates of dose. However, duration of exposure can only be a meaningful measure of dose when all cohort members had the same level of exposure during their entire employment period. Since benzene exposure levels have generally declined over calendar time periods, duration of exposure cannot, therefore, be a meaningful measure of benzene dose.

Although the benzene peak exposure analysis did not demonstrate a significant dose–response in the Wong study, the relative risk was 3.38 for lymphopoietic cancer at the lowest-peak-exposure level (< 25 ppm) in the report.[27] Hence, the relative risk was already elevated at the lowest maximum peak evaluated in the study. The inability of Wong to demonstrate a dose–response by maximum-peak-exposure level may be a reflection of the peak levels he arbitrarily chose to evaluate for dose–response. For example, if it had been possible to have chosen peak levels of < 5 ppm, < 10 ppm, and < 25 ppm, etc., Wong may have been able to demonstrate a dose–response by peak exposure level. However, his data set was too small to conduct such a refined analysis.

Direct Observation of Low-Level Benzene Exposure and Leukemia/Lymphoma

The Dow study by Ott/Bond provides direct evidence of leukemia as a result of low-level benzene exposure, and nonmalignant blood diseases as a result of slightly higher levels of exposure.

As mentioned in the ACGIH benzene documentation,[1] the risk of low-level benzene exposure does not need to be estimated from formal quantitative cancer risk assessment. The Dow[3,4] study provides direct evidence that low-level benzene exposure is associated with an increased risk of leukemia. As shown in Table III, the average benzene exposure received by the cohort was 5.5 ppm for 7.0 years, or 38.5 ppm-years cumulative dose. Thus, a 0.1 ppm exposure limit for 45 years (4.5 ppm-years) would provide slightly less than a tenfold protection factor. The average exposure for the five leukemia cases, 6 ppm for 12 years, or 72 ppm-years of exposure, was higher than that for the entire cohort. As shown in Table III, leukemia cases #2 and #5 were only exposed to an average of 1 ppm, while cases #1 and #3 were only exposed to an average of 5 ppm. Case #4 was exposed to an average of 18 ppm.

Written comments provided to the Chemical Substances TLV Committee by Dr. Bond[8] suggest that the Dow cohort[3,4] may have been exposed to benzene levels higher than those provided in the published reports of the study. However, the authors of the Dow cohort have previously published the best available data on benzene exposure to the cohort. As appropriately stated by Bond, exposure prior to 1960 "may have been considerably higher than we assumed for purposes of our investigation. ... we have no data that would validate or invalidate this assumption."[8]

TABLE III. Myelogenous Leukemia Deaths Among Workers Exposed to Benzene by Exposure Level, Years Exposed, Cumulative Dose, and Latency

Case No.	Average Benzene Exposure (ppm)	Years Exposed	Cumulative Benzene Dose (ppm-yrs)	Latency (Years)
1	5.0	10.7	54.0	11
2	1.0	1.5	1.5	15
3*	5.0	5.0	25.4	15
4	18.0	19.5	351.0	37
5	1.2	23.3	28.0	39
Average (Cases)	6.0	12.0	72.0	
Entire Cohort	5.5	7.0	38.5	

Observed myelogenous leukemia deaths = 4
Expected myelogenous leukemia deaths = 0.9
SMR = 444
*Underlying cause of death classified as pneumonia, AML listed under other significant conditions
Source: Ott *et al.*[3] and Bond *et al.*[4]

Thus, data that would invalidate the estimates of benzene exposure in the published reports do not exist.

The question of whether low-level exposure to benzene could cause leukemia was also a concern of the CMA during the OSHA rulemaking on benzene. The Association asked Dr. Brian MacMahon to evaluate the literature. Dr. MacMahon concluded that it is more probable than not that benzene exposures as low as 10 ppm and below increase the risk of leukemia in a meaningful way.[28] He was most impressed with the Dow study as showing increased leukemia risk as a result of exposures below 10 ppm in rendering his opinion. His report was submitted by CMA to the OSHA benzene docket and considered in the Agency's deliberations.

In Dr. Bond's statement to the ACGIH[8] and in the original Ott *et al.* report[3] of the Dow cohort study, it is mentioned that one of the individuals who developed leukemia as a result of only 1.0 ppm benzene exposure for 1.5 years also worked between 1948 and 1950 in a sawmill that manufactured veneer. Bond[8] and Ott *et al.*[3] cite Milham[29] as a source indicating that this occupational exposure is associated with an increased risk of myelocytic leukemia. The implication is that this leukemia death as observed among the Dow workers exposed to benzene may have been caused by the individual's working in the sawmill. The supportive documentation for this statement is simply incorrect.

Data from the cited Milham report[29] for the category of exposure titled "sawmill and other mill workers" do not indicate an excess of mortality from leukemia. The only cancers shown to be in excess according to Milham are cancers of the pancreas and the testis. In addition, the International Agency for Research on Cancer (IARC) reviewed epidemiologic studies of workers in "The Lumber and Sawmill Industries (Including Logging)." IARC concluded[3,30] that "The epidemiological data are not sufficient to make a definite assessment of the carcinogenic risks of employment in the lumber and sawmill industries." The only cancer risks of possible concern mentioned by IARC[3,30] in association with this industry were nasal cancer, soft tissue sarcoma, and histiocytic lymphoma. Thus, the implication that one of the leukemia deaths associated with low-level benzene exposure, as observed in the Dow study, may have been the result of his employment in a sawmill for 1 to 2 years is without merit.

Data from the Bond *et al.*[4] study also indicate a significantly elevated risk of death (3 observed versus 0.7 expected, $p < 0.05$) from nonmalignant blood diseases. The individuals who died from these diseases experienced slightly higher levels of benzene exposure than those who died from leukemia. One death was observed from aplastic anemia (TWA = 4.6 ppm benzene for 8.2 years of exposure); one death was observed from "pernicious anemia," which is megaloblastic anemia[11] according to tissue evaluation (TWA = 30.1 ppm benzene for 15.3 years of exposure); and one death was observed from myelofibrosis (TWA = 19.3 ppm benzene for 26 years of exposure).

Levels of benzene exposure associated with leukemia and lymphoma in recent occupational cohort mortality studies

Fifteen or more years ago, many of the cases of leukemia reported in the literature were associated with relatively high levels of benzene exposure. For example, the series of leukemia cases reported by Vigliani[31] indicate that workers were exposed to average benzene levels of about 200–500 ppm, while the leukemia cases reported in the earlier days by Aksoy[32] indicate that workers experienced benzene levels in the range of about 150–210 ppm.[33] These relatively "old" case reports have lead some scientists to conclude that only high levels of benzene exposure can cause leukemia. These reports, however, have no bearing on direct observations indicating an association between leukemia and low-level benzene exposure.

As benzene exposures in the workplace have been tremendously reduced over the past 50 years, individuals exposed to low-level benzene, in the range of only a few parts per million and less, are now known to have developed leukemia and lymphoma. Table IV shows the average benzene exposure levels associated with leukemia cases as derived from the epidemiologic cohort studies of benzene-exposed workers where such information was reported.[2–4,15,34] As indicated, 34 percent of the leukemia deaths were observed among workers whose average exposures were characterized as being below 6 ppm; 48 percent were reported to have been exposed below 16

TABLE IV. Average Benzene Exposure Levels for Leukemia Cases by Study as Indicated in Published Reports

Average Benzene Exposure Level (ppm)	Studies					Percent of Total
	Yin[34]	Rinsky[2]	Bond[4]	Wong[15]*	Total	
0.1–5	7	1	4	5	17	34
6–15	4	1	1	1	7	14
16–30	7	3	0	0	10	20
31–60	6	4	0	0	10	20
60+	6	0	0	0	6	12
All levels	30	9	5	6	50	

*Based on 6 cases where data available

TABLE V. Average Benzene Exposure Levels for Leukemia and Lymphoma Cases by Study as Indicated in Published Reports

Average Benzene Exposure Level (ppm)	Studies					Percent of Total
	Yin[34]	Rinsky[21A]	Bond[40B]	Wong[15C]	Total	
0–5	7	1	5	10	23	35
6–15	4	4	1	2	11	17
16–30	7	4	2	3	16	24
31–60	6	4	0	0	10	15
60+	6	0	0	0	6	9
All levels	30	13	8	15	66	

[A]Leukemia and multiple myeloma.
[B]Leukemia and "nonmalignant" blood diseases.
[C]Leukemia and lymphoma, based on 15 cases where data available.

ppm.

Table V presents the same type of analysis for leukemia, other "nonmalignant blood diseases," and lymphoma were reported by exposure level. The distribution of diseases is about the same; 35 percent were exposed to benzene concentrations below 6 ppm, and 52 percent were exposed to average levels below 16 ppm.

In its justification for a 0.1 ppm TLV, ACGIH cited the Dow study for direct-observational evidence of benzene's ability to cause leukemia as a result of low-level exposure. The Chemical Substances TLV Committee,[1] however, failed to include similar evidence from the Wong study.[15] In the Wong study,[15] where data were provided for workers who were continuously exposed, 10 of 15 deaths from lymphopoietic cancer were exposed to average benzene concentrations of 5 ppm or less. Data in Table 16 of the Wong report[15] indicate that three of the individuals who died from lymphopoietic cancer were only exposed to average benzene concentrations of 0.5 ppm.

The data presented above collectively indicate that low-level exposure to benzene carries with it a risk of developing leukemia, lymphoma, and nonmalignant blood diseases, although the latter group of diseases were associated with exposures at the high end of the low-exposure range.

Periodic peak exposure and intermittent lower level exposure as related to the development of leukemia and other diseases in workers exposed to benzene.

Reports that have indicated elevated risk of leukemia[2–4,15,34] or excessive chromosomal breakage[35] as a result of low-level benzene exposure have sometimes been followed by statements, without documentation, that the elevated risks observed in the studies were the result of unaccounted for high-peak benzene exposure levels.[4,8,36] These comments have been speculative from the standpoint of exposure level. They also do not take into account the influence of mode of benzene exposure as it relates to hematopoietic diseases. Data now suggest that intermittency of exposure, whether the exposure be high or relatively low, may be a major factor in the induction of leukemia and other diseases associated with benzene exposure.

The experimental studies cited above, the results of which are shown in Table II, support the conclusion that intermittent exposure to a lesser total amount of benzene can cause relatively more bone marrow toxicity,[23,24] chromosomal aberrations,[25] and cancer.[26] For example, the study by Luke *et al.*[25] indicates that 3 days of benzene exposure followed by 4 days of nonexposure caused more suppression of polychromatic erythrocytes than 5 days of exposure to the same daily dose followed by 2 days of nonexposure. Likewise, the study by Snyder *et al.*[26] demonstrates a greater cancer response in C57B1 mice as a result of 181 days of interrupted exposure at 300 ppm as compared with 51 days of more continuous exposure at about 1200 ppm benzene (Table II).

While few epidemiologic data are available to evaluate the influence of intermittent and peak benzene exposure on subsequent disease, the study by Wong[27] shows that peak exposures above 100 ppm are not associated with any greater odds of developing leukemia than peak exposures below 25 ppm. In the more detailed version of his paper submitted to OSHA,[27] the data in Table 41 indicate that the odds ratio (O.R.) for lymphopoietic cancer for those who experienced peaks greater than 100 ppm was 3.01, while the O.R. for those who experienced benzene peak exposure levels below 25 ppm was 3.38. Likewise, the study of refinery workers by Devine and Barron[37] indicates no excess risk to the cohort overall; however, those who experienced jobs where intermittent exposure would occur (utility workers and pipefitters) demonstrated significantly elevated O.R.s (4.6 and 2.7, respectively) for leukemia. Data on the level of peak benzene exposures that may have been associated with jobs indicating an elevated leukemia risk in the latter study, however, were not reported. In the latter study,[37] it is possible that these peak exposures were high, and as a result, those who received intermittent exposure may also have received the relatively greatest cumulative dose of benzene. Therefore, the Devine and Barron[37] study results raise the possibility that intermittent exposure played a role in the elevated risk of leukemia observed; however, it is not possible to separate the effect of intermittent exposure from the effect of total cumulative dose.

Additional observations, however, indicate an association between intermittent, low-level, peak exposure to benzene and lymphopoietic cancer. The short period of low-level benzene exposure for some of the individuals in the studies who developed leukemia[2-4,15,34] make it less likely that their exposure estimates would be in error. For example, case #2 in the Ott/Bond study, as shown in Table III, was only exposed for 1.5 years to an average of 1 ppm. This individual worked in an area of the plant categorized as "potential exposure to very low concentrations of benzene (< 2 ppm TWA dosage: 18 ppm-months)." With regard to the potential for intermittent, low-level exposure to benzene in the Wong study,[15] his Table 16 indicates that case #8 (multiple myeloma) and case #11 (chronic myelogenous leukemia) were exposed to average benzene concentrations of 0.5 ppm for 2.3 years and 1.2 years, respectively. Their maximum peak exposures to benzene were categorized as below 25 ppm.

Since some of the individuals in the cohort studies who ed from leukemia and lymphoma did not experience high peak benzene exposures, they must have experienced low exposures. These exposures would be received on an intermittent basis as is usually the case in the occupational setting. Workers are not exposed continuously to the "average" level over an 8-hour shift. Also, their daily exposure fluctuates from one day to the next.

Thus, the fourfold risk of myelogenous leukemia associated with low-level exposure in the Ott/Bond study[3,4] and the low benzene exposure levels associated with a number of the leukemia/lymphoma deaths in the Rinsky *et al.*,[2] Wong,[15] and Yin *et al.*[34] studies may perhaps be enhanced by the intermittent nature of exposures as they occur on the job. Since benzene exposures have been reduced in the workplace over the past four decades, intermittent, low-level exposure to benzene may present a greater absolute risk of benzene-related diseases than brief, periodic, high-level exposure.

Low-Level Benzene Exposure and Chromosomal Aberrations

As part of its justification for its 0.1 ppm TLV, ACGIH cited studies in humans and experimental animals related to chromosomal damage as a result of low-level benzene exposure. Commentors representing API and CMA did not address this concern during their presentations before the Chemical Substances TLV Committee. Nevertheless, chromosomal damage has been observed in workers exposed to low average levels of benzene. The data in Figure 1, taken from Picciano,[35] demonstrate an elevated frequency of chromosomal breakage at exposure levels down to 1 ppm. When the study results were reported to the U.S. Environmental Protection Agency (EPA),[36] it was stated that industrial hygiene data indicated that benzene peak exposures exceeded 100 ppm and that this peaking in exposure was presumably responsible for the observed clastogenic effects among the benzene-exposed workers. However, data later supplied by the company indicated that high-level benzene exposures to most of these workers could not be substantiated and could not have accounted for the elevated frequency of chromosomal breakage seen in the study.[38]

While there can always be argument that unaccounted for exposures were experienced by the workers in the Picciano study[35] or any other study that shows adverse effects from low-level benzene exposure, this matter may be resolved in the laboratory where exposure can be controlled. In this regard, experimental study has also demonstrated that low-level benzene exposure can cause chromosomal aberrations. The Chemical Industry Institute of Toxicology study by Erexson *et al.*,[39] as cited in the ACGIH benzene documentation, demonstrates a significant increase in chromosomal breakage as a result of exposure to 1 ppm benzene. For a substance known to cause bone marrow toxicity and lymphohematopoietic cancer, the chromosomal studies alone showing an increase in breakage at 1 ppm should lead one to consider setting an exposure limit based on health below 1 ppm.

Health Evidence Justifies an Exposure Limit Below 1 ppm

In comments on the ACGIH Notice of Intended Change—Benzene received from CMA,[9] the issue is raised about ACGIH using a "no increased risk" standard in recommending a 0.1 ppm TLV for benzene. This argument is moot in relation to occupational benzene exposure because the estimated excess risk associated with the proposed 0.1 ppm TLV is about 1 per 1000 workers for leukemia only. The risk would be higher if other benzene-associated diseases were included in the risk assessments.

Argument is raised that OSHA set a PEL of 1 ppm in 1987 and that there is no new evidence that would justify reducing the TLV to a lower level. OSHA, however, set a PEL of 1.0 ppm because it was not economically feasible

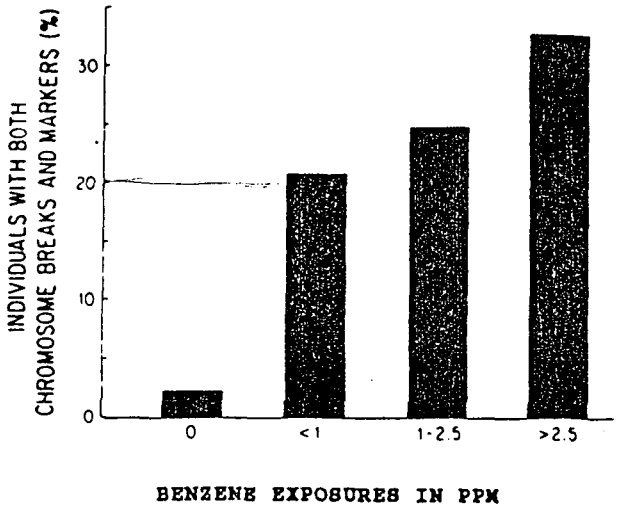

FIGURE 1. Comparison of the distribution of individuals with both chromosome breaks and markers as a function of benzene exposure. Source: D.J. Picciano.[35]

to set a lower limit. The OSHA standard,[11] however, includes other provisions to help lower the risk. These include: 1) an action level of 0.5 ppm as an incentive for manufacturers to go below this level in order to save on costs of compliance with the additional ancillary provisions of the standard; 2) medical surveillance to help identify some of the individuals more susceptible to benzene-related blood diseases so they can be removed from exposure; 3) exposure monitoring; and 4) training and education about the hazards of benzene and appropriate work practices to use when it is present as part of the manufacturing process.

Recommendations

ACGIH has done a rigorous job in its documentation of a 0.1 ppm TLV–TWA for benzene. It should, however, consider the Crump and Allen risk assessment for estimation of excess leukemia in its final evaluation since these authors used all of the available data from the three epidemiologic cohort studies that included data on benzene dose. ACGIH should acknowledge that risk based upon leukemia underestimates total disease risk from benzene exposure because it does not include lymphoma, aplastic anemia, and other cytopenias. Likewise, the final documentation should include a discussion of factors that may be related to potential underestimation of risk, such as use of a cumulative dose concept, in the quantitative risk assessments for leukemia.

Finally, in this author's opinion, it would be poor science and poor public health policy to establish a TLV greater than 0.1 ppm based on the health data currently available. Therefore, the ACGIH should not establish a TLV for benzene above 0.1 ppm.

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