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RES — ADMIN.

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RLR		MJ
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MLaD		HDL

ARVP/ 8/16

August 1, 1979

DORIS L. COLLINS, WIDOW OF
JOHN F. COLLINS, DECEASED,
VS AMERICAN MOTORISTS
INSURANCE COMPANY

PRIVILEGED AND
CONFIDENTIAL

Mr. David W. Ledyard
P. O. Box 1632
Beaumont, Texas 77704

Dear Sir:

The enclosed attachment is for your information and possible use in the subject case.

The information is a portion of the American Petroleum Industry comments on EPA's Water Quality Criteria as proposed in the March 15, 1979, Federal Register. Serious flaws are pointed out in both fundamental methodology and data handling in the EPA's Carcinogen Assessment Group's September 12, 1978, "Final Report on Population Risk to Ambient Benzene Exposure." This group's report was based on analysis of three reports (Infante, Aksoy and Ott) that related leukemia to benzene exposure.

We understand you have copies of the depositions taken from four employes of Texaco's Port Arthur Research Laboratories by Mr. Joe Tonahill last November. We would appreciate receiving copies of these depositions,

Yours very truly,

AJS-LSR

Attachment

cc: Loyd Godbold ✓

BLIND COPIES: JRS-JPD-HLH
TRS-RH
HGH

COMMENTS

of

AMERICAN PETROLEUM INSTITUTE

on

WATER QUALITY CRITERIA PROPOSED BY THE U.S. ENVIRONMENTAL PROTECTION AGENCY

as published in

Federal Register, Vol. 44, No. 52,
March 15, 1973, pp. 15926-15981

June 13, 1979

Evaluation of Proposed Ambient Water Quality Criteria For The Protection of Human Health

Benzene

Prepared by

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June 13, 1979

The EPA water quality criteria document on benzene has fairly completely reviewed the literature on benzene and human health effects. It uses the EPA's Carcinogen Assessment Group's (CAG's) September 12, 1978, "Final Report on Population Risk to Ambient Benzene Exposure" as its basis for deriving the criterion for benzene.

The CAG report calculated that the lifetime risk of dying from leukemia from a lifetime exposure to 1 ppm benzene in the ambient air was 2.4%. Using this value, EPA has in the water quality criterion document on benzene arithmetically calculated with a number of assumptions the concentration of benzene in a 2 liter daily water consumption that would relate to an equivalent lifetime risk of 10^{-5}. EPA has determined that the lifetime risk of 10^{-5} would not be exceeded if the benzene concentration was 15 ug/liter. Therefore, EPA has proposed 15 ug/l as the criterion for a 10^{-5} risk, 1.5 ug/l as the criterion for a 10^{-6} risk, and 0.15 ug/l as the criterion for a 10^{-7} risk.

CAG REPORT

The CAG report was based on analysis of three reports -- Infante (1977), Aksoy (1974,76,77) and Ott (1977) -- that related leukemia to benzene exposure. This analysis is seriously flawed in both fundamental methodology and in data handling such that it is inappropriate to serve as a basis for determining criteria for benzene.

Basic underlying methodologic assumptions that are questionable include (1) that a demonstrable carcinogenic effect at any level implies a carcinogenic effect at every level of exposure; i.e., is non-threshold; (2) that the extrapolation from known data to zero exposure is a straight line; and (3) that the appropriate model of significant exposure is the lifetime cumulative dose. Occupational health studies have demonstrated leukemia risks only at exposure exceeding about 100 ppm benzene in air. The risk model attempts to quantitate risk at levels more than six orders of magnitude below where they have been demonstrated. Specific comments of methodology are discussed by Dr. Downs.

The Infante, Aksoy, and Ott studies were considered by the CAG report because they each provided data for estimates of (1) rate of leukemia mortality of study population based on number of cases observed and size of study population; (2) comparative rate of leukemia mortality in reference population; (3) degree, index, or measure of exposure to benzene; and (4) risk estimate of excess leukemia mortality in relationship to exposure estimate.

The CAG report has incorrectly and/or uncritically used data from or applied calculations to the three studies in a manner that has artifically increased the risk estimate determined from each study and thus also from the three studies taken together.

INFANTE STUDY

1. Study Population and Cases

Infante, et al. have studied the mortality experience of a group of workers employed between 1940-1949 in the production of Pliofilm. The study's strengths are described as including that the workers' exposure was almost exclusively restricted to benzene and that the cases observed were acute myelogenous leukemia, or AML (the cell type most frequently attributed to benzene exposure). This is not entirely correct.

The study considered the mortality experience of groups of workers at two plants. Only at Plant B was the exposure almost exclusively to benzene, and at Plant B there were no cases of AML. All the cases of AML occurred at Plant A where workers had exposure *to* multiple toxic chemicals including benzene. Not only was the distribution of AML different between the plants, but also the crude leukemia mortality rates differed with Plant A's far exceeding that of Plant B's -- 17/1,000 in Plant A vs 5/1,000 in Plant B. Page 9 of the CAG report states in error that the crude leukemia mortality rates are similar.

The group of 746 workers studied in the Infants report is only a fraction of the benzene exposed population at these plants. The groups missing from the study include 404 dryside workers: the unknown number of pipefitters, mechanics, and maintenance workers who had direct contact with benzene but who were on a different payroll; and an unknown number of workers at

Plant A who left employment during the years 1940-1943. Since the total exposed population had not been studied, the leukemia mortality rate in the total exposed population is unknown.

The study reported seven cases of leukemia mortality among the group studied. The CAG report has inappropriately increased the number of cases to nine by adding two cases reported by the local physician (Dr. Sakol) to have been mis-recorded cn the death certificate. There is no valid reason to include these two cases who appear not to be members of the group that was studied, but of another group. Dr. Infante has specifically (Lancet/ letter) reported that one of the men was not a member of the study group and Dr. Sakol indicated in oral testimony that two of his cases were pipefitters, a group excluded from the report. Further, it is a violation of good epidemiologic practice to "correct the diagnosis" of death certificates in the study group but not in the comparison group. For these reasons, it is wrong for CAG to increase the case count from seven to nine.

2. Comparison Population and Risks.

The authors of the original study derived their expected number of leukemia deaths frcm the person-year distribution of their study group -- initially reported as 1.33 leukemia deaths when the vital status of only 75% of the group was ascertained snd then later revised to 1.25 leukemia deaths when the vital status or' 958 of the group ha3 been ascertained. The appropriate calculation of relative risk (R = observed/expected) would have

been 7/1-25 = 5.60, rather than 9/1-25 = 7.20 as CAG had calculated. The appropriate value for excess relative risk (R - 1) would have been 4.60, not 6.20. The changes that CAG made have artificially increased the calculated excess relative risk by 358 -- [$\frac{(6.20 - 4.60)}{4.60}$ = 35%].

3. Exposure Estimate

The CAG report indicated that the study had no valid estimation of worker exposure, but guessed that the levels were less than the prevailing recommended occupational limits at the various time periods. The exposure data from monitoring surveys, however, showed otherwise. Studies in 1948, when the standard was 35 ppm, found levels of 120 ppm at one common worksite and of 500 ppm in an area where "one or more employees would spend approximately one hcur per day." In 1956, when the standard was still 35 ppm, three-quarters of the work areas tested had levels as high as 100 ppm and over half of the work areas tested had mean concentration greater than the standard, Between 1963 and 1974, 43% of the surveys showed levels above the limits (10-25 ppm) acceptable at those times. One-quarter of the surveys showed means greater than the acceptable limit. Studies in 1973 and 1974 still showed levels of 200-250 ppm where workers spent up to 30 minutes at a time without a respirator. Exposures measured in 1974 showed 20 ppm benzene, [twice the limit of 10 ppm] in the "dry" area whose workers were excluded in the Infante

report as unexposed. The available data indicate that the exposure estimates used in the report are much too low.

The CAG has estimated a lifetime mean benzene concentration for these workers of 2.81 ppm, but as the "data" upon which it is built are only hypothetical, the estimate is fairly meaningless.

4. Risk Estimate

Because of the lack of detailed exposure data, a credible quantitative risk estimate related to exposure levels cannot be calculated. It is evident from the data available that exposures were frequently much greater than the recommended exposure limits. Thus, an estimate based on the CAG assumption that exposure levels were not greater than recommended would yield an artificially high estimate of the risk of dying from benzene exposure based on the Infante data.

The equation for estimating the per ppm risk of dying from benzene exposure (B) is

$$B = \frac{D(R - 1)}{\bar{X}}$$

where D is the probability of dying from the types of cancer benzene is alleged to cause (all leukemias in this study with D = .00672), R - 1 is the excess relative risk, and $\bar{X}$ is the calculated mean lifetime benzene exposure level in ppm (airj.

$$B = \frac{(.00672)(5.60 - 1)}{2.81} = .01102 \text{ per ppm benzene}$$

(i.e., 1.1% chance of dying due to a lifetime exposure *to* 1 ppm benzene)

This calculated risk is less than that calculated by CAG and is itself high, because the exposure levels were assumed to be lower than they apparently were. The CAG estimate of B = 0.14854 is 35% [$\frac{(.014854 - .01102)}{.01102}$ = 35%] greater than that calculated above.

ARSOY STUDY

1. Study Population and Cases

Aksoy has reported leukemia cases connected with benzene exposure in Istanbul, Turkey. Between 1967 and 1974, he found 31 cases of leukemia among shoe workers in Istanbul. Accepting the Turkish government's estimate of 28,500 workers in the shoe, slipper, and handbag industry in Istanbul, Aksoy has estimated an annual incidence of 13.7 cases of leukemia per 100,000 person-years of observation -- 31/(28,500 persons x 8 years x 10^{-5}).

At the OSHA hearings, Aksoy contrasted the cell type distribution of 40 cases of leukemia in persons exposed to benzene with 50 cases in persons not exposed to benzene. Thirty-five of the 40 cases of leukemia in benzene exposed persons were non-lymphoid types. Applying this ratio to the annual estimated leukemia incidence 13.7 x (35/40) would lead to 11.9 cases of non-lymphoid leukemia per 100,000 persons annually.

2. Comparison Population and Risks

Aksoy reports the total incidence rate of leukemia in the general Western European population as 6 per 100,000 persons

annually. He feels that the recorded rate of 2–3 per 100,000 persons annually for Istanbul is inappropriately low, based on his own experience and knowledge of the cancer reporting efficacy in Istanbul. Aksoy has found that 46% of his non-benzene exposed leukemia cases are non-lymphoid types. Applying this proportion to the general estimate would give an estimated expected incidence of 6(46/100), or 2.76 non-lymphoid leukemia cases per 100,000 persons annually.

The observed incidence (11.9×10^{-5}) of non-lymphoid leukemia is statistically significantly greater than the expected incidence (2.76×10^{-5}). However, the relative risk (R) is 4.31 (11.9/2.76 = 4-31), not 19.9 as indicated by the CAG report.

The CAG report had inappropriately quadrupled the relative risk estimate first by using the $2\text{–}3 \times 10^{-5}$ rate rather than the 6×10^{-5} mortality rate for the reference population and second by adjusting for an age difference that did not exist. The CAG report doubled the risk by comparing the median age (36 years) of the benzene related leukemia deaths with the median age (about 70 years) of all deaths rather than the median age (37 years) of Aksoy's non-benzene related leukemia deaths. The proportion of leukemia deaths that are due to non-lymphoid leukemia is no different for 36 year olds than for 37 year olds. Dr. Aksoy stated at the OSHA hearings (TR. 156) that "their (exposed and unexposed leukemia cases) ages correspond to each other."

The relative risk (R) of non-lymphoid leukemia death is 4.31, not 19.9 as CAG has calculated. The excess relative risk (R - 1) of non-lymphoid leukemia death is 3.31, not 18.9 as CAG calculated. The CAG approach increases the calculated excess relative risk estimate by 471% -- (18.9 - 3.31)/3.31 = 471%.

3. Exposure Estimates

Aksoy has reported on the incidence of non-lymphoid leukemia among workers exposed to benzene in glues in the shoemaking industry in Istanbul. The shoe making industry in Istanbul is a cottage industry where the workshop is in the home and the family is exposed to the workshop fumes throughout the entire day and night. The working conditions in these shops are described by Aksoy as "unhygienic and poorly ventilated."

In his published reports Aksoy states that the benzene exposure of his patients "during working hours was 150-210 ppm and even more (to 640 ppm, rarely) when benzene containing adhesives were used" and "outside working hours ranged between 15 and 30 ppm." The CAG report used the data as if the levels were 150-210 ppm during working hours while benzene containing adhesives were used, 15-30 ppm during working hours while benzene containing adhesives were not used, and 0 ppm during non-working hours. CAG ignored the very high level of benzene measured in the workshop and calculated a geometric mean of the two exposure levels, calling it the average work hour exposure concentration:

$$\left[\frac{(15 - 30)}{0.2} \times \frac{(150 - 210)}{0.2}\right]^{1/2} = 63.6.$$

This value of 63.6 ppm benzene would be more appropriately called the average work day concentration and is a low estimate. Weighted averages using similar methodologies would produce higher estimates of the average work day concentration.

Assuming, as does CAG, an average work year of 300 days and an average duration of exposure of 9.7 years (average for Aksoy's leukemia cases) and further assuming an average observation period of 34.2 years* (average for Aksoy's leukemia cases), an estimated lifetime average benzene exposure ($\bar{X}$) for Aksoy's leukemia patients is

$$\bar{X} = 63.6 \times \frac{300}{365} \times \frac{9.7}{34.2} \quad \text{(workday exposure)}$$

$$+ 22.5 \times \frac{65}{365} \times \frac{9.7}{34.2} \quad \text{(non-workday exposure)}$$

$$+ 0 \times \frac{365}{355} \times \frac{24.5}{34.2} \quad \text{(assumes no exposure during years not in industry)}$$

$$\bar{X} = 14.83 + 1.14 + 0 = 15.97 \text{ ppm} = 16 \text{ ppm}.$$

This is a low estimate of $\bar{X}$ based OR the data above, for it also ignores the highest levels recorded. Inclusion of measurements as high a5 640 ppm would significantly raise the estimate of $\bar{X}$.

* The CAG used 50 years as an average period of operation, although Aksoy's cases only average 34.2 years.

4. Risk Estimate

The equation for estimating the per ppm risk of dying from benzene exposure (B) is

$$B = \frac{D(R - 1)}{\bar{X}}$$

where D is the probability of dying from types of cancer benzene is alleged to cause (non-lymphoid leukemia in this study with D = .004517), R - 1 is the excess relative risk, and $\bar{X}$ is the calculated mean lifetime benzene exposure level in ppm air,

B = ,004517 (4.31 - 1)/16 = .000934/ppm benzene

This estimate ignores the measurements of exposure up to 640 ppm, the consideration of which would reduce further the apparent per ppm benzene risk. Nonetheless, the value for B calculated by CAG is more than 20 times greater $\left[\frac{0.020252 - .000934}{0.000934} = 20.68\right]$ than that calculated above.

OTT STUDY

1. Study Population and *Cases*

Ott has studied the mortality experience of chemical workers exposed to benzene. He reported one leukemia death in a worker exposed to no other suspect carcinogen, one leukemia death in a worker exposed also to other suspect carcinogens, and one broncho-pneumonia death in a worker with leukemia who was not known to be exposed to other suspect carcinogens.

2. Comparison Population and Risks

Using U.S. mortality rates, Ott calculated an expected observation of 0.9 leukemia death among the benzene exposed workers not exposed to other suspect carcinogens. He observed one such death for a non-statistically significant relative risk of 1.1. Similarly, among all the workers including those exposed to other suspect carcinogens, one would expect to observe one leukemia death. Ott observed two leukemia deaths for a non-statistically significant relative risk of 2.0.

The CAG report has considered the third case with death from pneumonia as a leukemia death and has thus reported an incidence ratio as a mortality ratio. This ignores the possibility of a "cure" from leukemia and the competing risk of death by other causes. Therefore, it is not appropriate as an estimate of mortality risk.

3. Exposure Estimate

The CAG report has made a weighted average of the estimate occupational exposure of the workers in Ott's study and then converted that average to an estimate of lifetime average exposure. The CAG report estimates a lifetime average exposure of 0.171 ppm.

4. Risk Estimate

The equation for estimating the per ppm risk of dying from benzene exposure (B) is

$$B = \frac{D(R - 1)}{\bar{X}}$$

where D is the probability of dying from the type of cancer benzene is alleged to cause (myelogenous in this study with D = 0.002884), R - 1 is the excess relative risk, and X is the lifetime average exposure level in ppm air.

$$B = 0.002884 \frac{(1.1 - 1)}{0.17}$$

$$= 0.001687/\text{ppm benzene}$$

for workers exposed only to benzene, and

$$B = 0.002884 \frac{(2.0 - 1.0)}{.17}$$

$$= 0.016865/\text{ppm benzene}$$

for workers also exposed to other suspect carcinogens.

Use of either of these numbers is misleading for they imply a risk where no statistically significant risk has been demonstrated. The failure of the methodology to provide confidence limits to the individual risk estimates makes the results meaningless, as they conclude a risk estimate based on a nondemonstrated risk.

Nonetheless, the CAG approach has developed a risk estimate of 0.04635/ppm benzene that is more than 25 times as great as $\frac{0.04635}{.001687} = 26.51$ the mortality risk estimate that might be calculated for benzene exposed workers not known to be exposed tc other suspect carcinogens.

SUMMARY RISK ESTIMATE

A per ppm risk estimate (B) has been calculated for each of the three studies. The pooled estimate of the per ppm risk estimate (B) for benzene is calculated by CAG as the geometric mean of the three values. Similarly,

$$B = [B(\text{Infante}) \times B(\text{Aksoy}) \times B(\text{Ott})]^{1/3}$$

$$B = [(.01102) \times (.000934) \times (.001687)]^{1/3}$$

$$B = [(11.02) \times (.934) \times (1.687)]^{1/3} \times 10^{-3}$$

$$B = [17.364]^{1/3} \times 10^{-3} = 2.51395 \times 10^{-3}$$

$$B = .002589/\text{ppm}$$ benzene.

However, because of the methodological problems and assunptions mentioned above, this number itself is also quite suspect.

The summary risk estimate calculated by CAG was 0.024073/ppm benzene, which is nearly 10 times as large as (.024074/.002589 = 9.3) the risk estimate calculated above.

CRITERICN DERIVATION

The EPA water quality criterion document on benzene has calculated the concentrations of benzene in water that would correspond to an extra 1/100,000 - 1/10,000,000 risk of leukemia death due to the daily ingestion of 2 liters of such waters over a lifetime. The calculation of these concentrations is based on an estimate of the risk (B) of such leukemia mortality from lifetime daily exposure to 1 ppm benzene in air.

Risk (R) = Risk (B) per ppm in air x Daily Exposure (X) in ppm air

If B = 0.002589/ppm benzene in air and R is set to equal 10^{-5}, then the daily benzene exposure equivalent ($\bar{X}$) is,

$$\bar{X} = R/B$$

$$= 10^{-5}/.002589/ppm$$

$$= .00386 \text{ ppm (air)}$$

$$= .00386 \text{ ppm (air)} \times \frac{3.25/mg/M^3}{\text{ppm (air)}} \times \frac{1M^3}{hr} \times \frac{24 \text{ hr}}{day}$$

$$= .301 \text{ mg/day} = 301 \text{ ug benzene/day}$$

Assuming that the proportion absorbed from inhalation and from ingestion is similar, a 301 ug daily benzene ingestion in two liters of water would suggest a water concentration of 150 ug/liter for a risk of 10^{-5} with a minor adjustment for fish consumption. This concentration (150 ug/l) is 10 times as great as that calculated by the EPA document.

PERSPECTIVE ON HUMAN EXPOSURE TO BENZENE

The EPA ambient water quality criteria document gives the following information on current human daily exposure to benzene.

~~Source~~	Benzene Concentration	Daily ~~Volume~~	Average ~~Daily Amount~~
Ambient Water	0 - 0.3 ppb (1 ug/l)	2 liters	0.3 ~~250.0~~ ug
Food			
Ambient Air	1.03 ppb (3.25 ug/M^3)	1 M^3/hr x 24 hr	80.3 ug
Total			330.6 ug

Whether there is or is not a human risk from benzene exposure in drinking water at current levels, it is evident that ordinary ambient levels of benzene in water represent a very

small part -- [$\frac{0.3}{330.6}$ = 0.09%], less than 0.1%, of the human and occupational exposure to benzene. Current total U.S. average daily benzene exposure is similar to that estimated to produce a risk of 10^{-5} and current benzene water exposure amounts correspond to a risk of less than 10^{-8}.

CONCLUSION

The CAG estimate of risk from leukemia is found to be suspect and does not serve as a suitable basis for determining the water quality criterion for benzene. Re-calculation using corrected data lowers the risk estimate by a factor of 10.

Further, the role of ambient water benzene levels is seen to be miniscule in the overall picture of human exposure to benzene.