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15. Supplementary Notes

16. Abstract (Limit: 200 words) This testimony concerned data contained in a study dealing with mortality in the chemical industry as a result of exposure to benzene (71432) causing increased incidences of lymphatic and hematopoietic cancer. NIOSH took the position that exposure to peak concentrations of benzene at less than 25 parts per million (ppm) was associated with a relative risk of 3.38 for these diseases. It was not specified whether these peak exposures occurred alone or as part of an otherwise constant exposure pattern. The relative risk was still well above 1.0. Two other cases classified in the continuous exposure group had spent most of their work time in intermittent exposure jobs and only a modest amount of time in continuously exposed jobs. The absence of a dose/rate effect was not a particularly surprising finding to NIOSH, and was not considered to discount the need for a limit on short term exposures. Cumulative dose was important and the ability of benzene to accumulate in the body must be carefully examined. Once inside the body, benzene is not uniformly distributed, but concentrates in the bone marrow of experimental animals where it can be metabolized. Benzene metabolites can covalently bind to bone marrow DNA and inhibit RNA synthesis. Single exposures to benzene at low doses have produced increased in the numbers of micronuclei and sister chromatid exchanges in rats. Benzene metabolites have been shown to produce an increased frequency of sister chromatid exchanges in cultured human lymphocytes. Responses to additional specific questions concerning NIOSH's view of benzene research were provided.

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NIOSH Comments to DOL

COMMENTS OF THE NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION PROPOSED RULE: OCCUPATIONAL EXPOSURE TO BENZENE

Part 2

29 CFR 1910
Docket No. 11-059C

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Director
National Institute for Occupational Safety and Health
March 1986

Following the presentation of the NIOSH testimony on benzene, Mr. King, representing the Chemical Manufacturers Association, asked a number of questions concerning the NIOSH interpretation of the report; "An Industry-wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene" by Wong. Mr. King's questions arose as a result of the NIOSH position that exposure to peak concentrations of benzene at less than 25 ppm were associated with a relative risk of 3.38 for developing lymphatic and hematopoietic cancer. Mr. King asked a number of questions concerning this issue with respect to the NIOSH understanding of Table 41 of the Wong study.

Based on our review of the Wong study, Table 41 describes the leukemia and hematopoietic cancer mortality experience of the cohort in terms of the workers' exposures to peak concentrations. Based on the number of observed deaths, Table 41 refers to all cohort members whether they were continuously exposed or only intermittently exposed. Furthermore, the relative risk provided by Wong for mortality from leukemia and hematopoietic cancer did not increase with increasing peak exposure.

From this it can be concluded that excess cancer deaths are related to peak exposures regardless of the nature of those peaks. In other words, regardless of how the peak exposures occurred, either alone or as part of an otherwise constant exposure pattern, the relative risk is still well above 1.0. Unfortunately, Wong did not present a separate analysis of the cohort's mortality experience with respect to intermittent or continuous exposure.

It is also of some interest to examine Table 44 of the Wong study; "Characteristics of 22 Deaths from Lymphatic and Hematopoietic Cancer." Of the 22 deaths, 3 occurred among workers with no benzene exposure, 4 among those intermittently exposed, and the remainder among those continuously exposed. Of particular interest are cases number 3 and 6. These two cases are included among the continuously exposed group. With the exception of these two workers, all the other cases in the continuously exposed group spent their entire tenure in continuously exposed jobs. Worker number three had 0.9 years of total exposure; however, only 0.2 years of that time was in continuously exposed jobs, the remaining 0.7 years was spent in intermittently exposed work in the "medium" exposure category (25-100 ppm). Case number 6 had a total tenure of 5.8 years, 1.9 years of which were in continuously exposed jobs, while 3.9 years spent in intermittently exposed jobs also in the "medium" exposure category.

Since Wong did not have data available that could be used to characterize the full extent of the intermittent exposures, it is not possible to directly compare ppm-months of exposure between the continuously

and intermittently exposed workers. If such comparison could be made, one possible outcome might be that these two workers actually had a higher cumulative dose as a result of intermittent exposure, and therefore might reasonably be classified in the intermittently exposed group. Other than to increase the SMRs in Table 24, it is not known what effect such a change in classification would have on Wong's conclusions.

Mr. King also asked a number of questions concerning the absence of a dose rate effect following analysis of peak exposure mortality. The absence of a dose-rate effect is not a particularly surprising outcome. As we stated in our testimony, it is significant that lymphatic and hematopoietic cancer mortality is in fact associated with peak exposure; that the incidence does not increase with dose-rate and does not discount the need for a limit on short term exposures.

As the Wong study points out, cumulative dose is an important consideration in benzene induced cancer. Thus, the ability of benzene to accumulate in the body and manifest adverse biologic effects should be carefully examined.

Mary White testified that if a worker inhaled 10 ppm of benzene for 8 hours, at a ventilation rate of 20 L/min, a worker's body burden of benzene would be 306 mg. This value is higher than expected, most likely because White assumed 100% retention rather than using the more commonly accepted value of about 50% (Srbova, et al., 1950; Hunter, 1966). As noted in our testimony, Berlin (1985) determined that the half-time of removal of benzene from experimental subjects exposed at 4 ppm or 8 ppm was 2.5 hours. Berlin's model assumed that uptake and removal involved distribution through three theoretical compartments. Berlin also determined that removal from the second compartment was much slower, approximately 24 hours, and that removal from the third compartment may take as long as 90 hours.

Using the data for elimination of benzene developed by Berlin (1985); a ventilation rate of 20 L/min, and an assumed 8-hour benzene exposure of 1 ppm, the daily and weekly body burden of benzene can be calculated as follows:

(20 L/min)(480 min/day)(1 cu m/1,000 L)(3.1 mg benzene/cu m)

For the purpose of this calculation, it is also assumed that steady state concentrations of benzene in the body are reached very soon after exposure begins, and that 50% of inhaled benzene is retained. Using these assumptions, it can be calculated that at the end of an 8-hour workshift, the body burden of benzene will be 19.88 mg. Using Berlin's value of 2.5 hours for $t_{1/2}$ for removal of benzene from the first compartment yields 9.94 mg of benzene as the amount remaining. It is of particular interest to know what the body burden will be 16 hours after termination of exposure; 16 hours is the time between the end of the first workshift and the beginning of the next.

Using 24 hours as $t_{1/2}$ for the second compartment, the amount of benzene remaining in the body can be found by using the value obtained 13.5 hours after $t_{1/2}$ for the first compartment and subtracting it from the amount remaining 2.5 hours after exposure. This yields (9.94 mg - 2.8 mg) 7.1 mg, which is the amount of benzene in the body of a worker at the beginning of the next workshift. At the end of the second workshift, the worker's body burden will be about 27 mg of benzene and he will start the next shift with about 10 mg. By the end of the fifth workshift (e.g., 5 p.m. on a Friday) the same worker's body burden will be about 32 mg of benzene. One point of this exercise is to quantitatively demonstrate the amount of benzene the body accumulates over a workweek. Furthermore, using Berlin's estimate of 90 hours as t 1/2 for the third compartment, it can be calculated that this same worker will begin his next workweek (e.g., 9 a.m. Monday) with a body burden of about 6 mg of benzene.

A similar calculation can be performed for a worker that has an airborne exposure to benzene of 1 ppm and builds 150 tires per day; a task demonstrated by Susten et al. (1984) to lead to the percutaneous absorption of about 7 mg of benzene. This value also assumes that only about 50% of the absorbed benzene is retained in the body. Under this reasonable scenario, the worker would end the work shift with a body burden of about 27 mg of benzene; 20 mg as a result of inhalation for 8 hours at a concentration of 1 ppm, and about 7 mg as a result of skin contact with a solvent containing 0.5% benzene while building 150 tires. This additional exposure adds about 8.3% to the total body burden of the worker. Thus, a worker exposed to benzene as described in this paragraph would begin the second week of work with about 6.5 mg of benzene, opposed to the estimated 6 mg resulting from inhalation exposure only. After many years of such exposure this additional burden may gain increased significance.

It is also of some interest to examine a third scenario in which a worker is exposed to benzene only once per day for 15 minutes at a concentration of 32 ppm, a theoretically possible exposure if there is no limit on short term exposure concentrations, but there is compliance with an 8 hour Time Weighted Average concentration of 1 ppm. A worker exposed to benzene in this manner would end an 8-hour workshift with a total body burden of 0.35 mg of benzene. This value assumes that elimination of benzene from the body begins as soon as exposure ceases, and that the 15 minutes over which the worker was exposed is negligible compared to the total workshift of eight hours. Although it is not necessary for the purpose of the remainder of this presentation to calculate either the body burden at the end of a workweek, which contains five such exposures, or the body burden expected at the beginning of the next workweek, it is obvious that under an exposure regimen such as this, benzene will still accumulate in the body of a worker.

Once benzene enters the body it is not uniformly distributed. Rickert et al. (1979) demonstrated that the concentration of benzene in the bone marrow of rats following inhalation was about 3 times greater than the concentration in blood, and about 3.7 times the concentration found in the liver.

Bone marrow can metabolize benzene. Gollmer et al. (1984) demonstrated that microsomal cytochrome P-450 and monoxygenase isolated from rabbit bone marrow convert benzene to phenol about 4 times faster than the liver, and that the activity of this bone marrow system is not induced by exposure. The data of Gollmer et al. (1984) are significant because they demonstrate that hepatic metabolism of benzene with subsequent transport of toxic metabolites to the bone marrow is not necessary.

That a single benzene exposure at 32 ppm for 15 minutes may have biologic significance is supported by the findings of Erexson et al. (1985a) of CIIT. In their work with mice and rats these workers demonstrated the ability of a single benzene exposure to be toxic to the bone marrow. In their studies, rats were exposed to benzene in air for one 6-hour period at either 0.1 ppm, 0.3 ppm, 1.0 ppm, 3.0 ppm, 10 ppm, or 30 ppm. No effects were observed among rats exposed at 0.1 ppm or 0.3 ppm. Among rats exposed at 1.0 ppm, however, Erexson et al. observed an increase in the incidence of sister chromatid exchanges. This finding was described by the investigators as having borderline statistical significance. After exposures at 3.0 ppm, 10.0 ppm, and 30.0 ppm the increased frequency of sister chromatid exchanges was clearly statistically significant when compared to controls. A statistically significant increase in bone marrow polychromatic erythrocyte micronuclei was observed following exposure to benzene at 1.0 ppm and higher.

These results are of interest because of the low concentrations used and the fact that they were observed after only a single exposure. The total body burden of benzene that resulted in these effects can be compared to the benzene body burden calculated for a worker exposed to benzene at 32 ppm for 15 minutes. Under that scenario it was calculated that the worker's body burden of benzene would be about 0.35 mg. Using a ventilation rate of 0.73 L/min. for a rat, and assuming that 50% of the inhaled material is retained, a rat exposed to 0.1 ppm benzene for 6 hours would have a body burden of about 0.04 mg; at 0.3 ppm, about 0.12 mg; at 1.0 ppm about 0.41 mg; and at 3.0 ppm about 1.2 mg. The amount of benzene in rats exposed at 1.0 ppm for 6 hours compares favorably to the amount accrued by a worker exposed at 32 ppm for 15 minutes, 0.41 mg v. 0.35 mg. The concentration-time products are also similar; 360 ppm-min. for rats and 480 ppm-min. for the theoretical example described above.

Assuming a human body weight of 70 kg and a body weight of .2 kg for a rat, the body burden can be calculated to 0.008 mg/kg for humans and 2.05 mg/kg for rats. Although the body burden in rats is 256 times that in humans, when expressed as mg/kg body weight the calculation overlooks the possibility that a 32 ppm exposure for 15 minutes may cause benzene to reach the bone marrow faster and at an initially greater concentration than a 1 ppm exposure for 6 hours.

Despite this, the fact that benzene accumulates in bone marrow and other tissues, even after a single exposure, is a concern for the worker who would encounter daily peak exposures for several years.

Using stromal cell survivability as an indicator of benzene and benzene-metabolite induced toxicity, Gaido and Wierda (1984) reported that the order of toxicity was: hydroquinone>benzoquinone>benzenetriol>catechol> phenol. These data are significant in view of the data of Rickert et al. (1979) who demonstrated that hydroquinone persists in the bone marrow longer, and at a greater concentration than other benzene metabolites, catechol was second.

Benzene metabolites can also covalently bind to bone marrow DNA and inhibit RNA synthesis. These findings were reported by Kalf et al. (1985) who incubated rabbit bone marrow cells with various benzene metabolites. They reported that the order of inhibition of bone marrow mitochondrial RNA (m + RNA) synthesis was: p-benzoquinone>phenol>hydroquinone>catechol> benzene. They also reported that DNA adducts of deoxyadenosine were formed by p-benzoquinone, hydroquinone, phenol and 1,3,4,-benzenetriol.

Arfellini et al. (1985) described the results of studies of in vivo and in vitro binding of [U-^{14}C] benzene in rats and mice. Rats were injected with the labeled material in benzene at a dose of 6.35 u moles/kg body weight. Using a body weight of 250 gm., each rat received about 3.6 u moles (280 ugm) of labeled material. Mice, weighing about 25 gm each, received about .36 u moles, or about 28 micrograms of labeled benzene. The results (obtained 22 hours after administration of the material) of the in vivo studies are summarized below.

picomoles benzene/mg DNA

Tissue	Rat	Mouse
liver	.14	.30
kidney	.56	.27
lung	.14	.04
spleen	.65-.68	.63
bone marrow	.70	.36

Although this study demonstrates in vivo alkylation of DNA, the study is incapable of distinguishing whether it is benzene itself or one or more of its metabolites that is actually bound to the DNA. Nevertheless, the data clearly show that the greatest amount of radioactivity is associated with bone marrow and splenic DNA.

Morimoto and Wolff (1980) have also demonstrated the ability of benzene and its metabolites to cause increases in sister chromatid exchanges and to affect cell division in cultured human lymphocytes. Of the compounds tested, they reported that catechol was the most potent in ability to induce sister chromatid exchanges and delay cell division. This conclusion was based on determination of the concentration required to double SCEs, cause a twelve-hour delay of cell cycle, and to cause a 60% reduction in mitotic index. Hydroquinone also exhibited strong ability to affect these changes, although to a lesser extent than catechol, but far more so than phenol.

Inhibition of rabbit bone marrow messenger RNA (mRNA) synthesis by benzene metabolites was demonstrated by in vitro studies conducted by Post et al. (1984). Using micromolar concentrations of benzene metabolites these investigators reported that the order of inhibitory activity was: p-benzoquinone=hydroquinone>>catechol>1,2,4,-benzenetriol>>phenol.

Erexson et al. (1985b) also examined the ability of benzene and its metabolites to induce increases in the frequency of sister chromatid exchanges in cultured human lymphocytes. Based on their studies these investigators reported that the relative potencies were: catechol>p-benzoquinone>hydroquinone>1,2,4,-benzenetriol>phenol>benzene.

Watanabe et al. (1980) examined a small group of female workers that had been exposed to benzene at concentrations as high as 40 ppm for 1-20 years in an attempt to find an increase in the frequency of sister chromatid exchanges. Rather than the expected outcome, the investigators reported a decrease in the frequency of SCEs. They speculated that this finding may indicate that at relatively low concentrations, benzene or its metabolites may be interfering with DNA replication. This early theory is consistent with the findings of Post et al. (1984) who reported that benzene metabolites inhibited mRNA synthesis.

Based on this brief analysis, the following conclusions may be drawn:

- Regardless of the exposure regimen, as long as it is routine, benzene and its metabolites will accumulate in the body;
- Benzene is lipophilic, thus it is not surprising to find three times more benzene in the bone marrow than in the blood;
- Bone marrow can metabolize benzene to phenol and quinone at a rate four times that found in liver. Therefore, production of toxic metabolites in the liver and their subsequent transport to bone marrow does not appear to be a necessary step in the mechanism of benzene induced bone marrow toxicity
- Benzene metabolites are toxic to bone marrow stromal cells, they bind to bone marrow DNA and inhibit synthesis of both mtRNA and mRNA and may interfere with DNA replication. Benzene metabolites also form adducts with d-adenosine and d-guanosine.
- Single exposures to benzene at low doses produced increases in the numbers of micronuclei and SCEs in rats.
- Benzene metabolites produce an increased frequency of SCEs in cultured human lymphocytes.

Based on these data, a plausible mechanism for benzene induced toxicity following exposures at either low concentrations or perhaps intermittent peak concentrations would involve inhalation, preferential deposition in the

bone marrow, metabolism to phenol and other metabolites, inhibition of mRNA synthesis, inhibition of DNA replication and formation of DNA adducts: possibly resulting in transformation of normal cells to cancer cells. The fact that an increased frequency of SCEs is found apparently among only those exposed at relatively high concentrations is not inconsistent with this proposed mechanism. At higher exposures DNA alkylation may be so wide spread that even under conditions of diminished repair and replication, exchanges are still occurring at a detectable rate.

The data reviewed here also indicate that it is the amount of benzene delivered to the target tissue and not necessarily the rate at which it is delivered that is most important when considering benzene induced toxicity. The need for a limit on high exposures over short periods of time (i.e., peak exposures) is clear.

The following responses, Numbers 1-11, are provided in answering questions asked by Arthur Sampson of Kirland and Ellis in his March 31, 1986, letter to Mr. Robert Rinsky, NIOSH.

1. Mr. Sampson correctly points out an inconsistency in the way the work history of George Nockengost was counted for the cohort and case control studies, and for the case description in the 1981 paper. A review of the microfilm record revealed a very bad photograph of the original work history folder. (This was the document used to code work histories.) After reviewing his record I have made the decision to interpret his pliofilm work history to be dept 50, op 21 from 6/15/42 to 1/26/43; dept 50, op 13 from 1/26/43 to 4/3/43; dept 50 op 16 from 4/3/43 to 2/14/45; and then, continued as coded in the BN3 computer file. These changes are factored into the re-analysis that is enclosed.

2. As a result of a coding error in Gerald Helmkee's file, the work history beginning 3/30/48 to 7/19/49 was left out of the study. The computer files have been corrected, and these changes have been factored into the re-analysis that is enclosed.

3. The dose file constructed was specific for plant, department, and job operation. For Plant 1, job operations in Departments 146 and 146A (codes 01 and 02) had corresponding dose assignments in the dose file; for Plant 2, job operations in Departments 146, 146-A, 046, and 046-1 (codes 01, 02, 50, and 51) had corresponding dose assignments. Mr. Sampson specifically asked, "Are you sure that there are no cases other than Mr. Helmkee's where exposure jobs were assigned to other department codes?" My answer is that I am not sure. As in any file of this size, I am certain other coding mistakes exist, however, I do not know where these mistakes are. Consequently, I do not know if any other dose assignments have been similarly affected. From the verification sampling we performed, I am satisfied that the number of such errors are well within reasonable requirements for use in the epidemiologic study.

Mr. Sampson also asked, "Could this problem exclude some exposed workers (from the) analysis?" Obviously, the answer is, theoretically, yes. To determine if this possibility affected the analysis, I ran a distribution on the numbers of work histories by plant, department, and operation codes that were not represented in the dose file, among the 99 cases and controls. Among these 99 persons, there were no job operations that should have been considered exposed that were not.

The reason for using department codes 01, 02, 50, and 51 in the dose file, was actually to include more people in the cohort, rather than exclude people. For instance, we felt a person with the job title "miscellaneous" ought to be attributed some amount of exposure so that his person-years were counted if he worked in any of the departments 01, 02, 50, 51. This procedure undoubtedly over-estimated person-years and resulted in an under-estimate of the SMR's. There would have been no justification to include a person who had the job title "miscellaneous" in, for example, a pliofilm accounting job.

4. Not including the 30 ppm value recorded in the quencher on 6/4/69, the histogram on page 229 of the 1981 report was an error. It was missing from Appendix 3 of the 1985 paper because this paper used the histogram from the 1981 paper. The exposure matrix has been corrected by changing the 1969 value to a measured value of 30 and changing the 1968 value to an interpolated value of 33. This was factored into the re-analysis that is enclosed.

   The data that are referenced in Table 11 are the worksheets of the NIOSH Industrial Hygienist that were made from the environmental data we obtained from Goodyear. I do not know why the 1970 value on these worksheets indicates only one measurement of 8 ppm, because the raw data reflect two 2 measurements; one of 8 ppm and one of 5 ppm. The 1981 histogram correctly displays the means of these two measurements, as does the dose matrix of the August 9th, 1985, paper.

5. The exposure matrix represents our effort to reconstruct the past exposures. I acknowledge that there could be other valid interpretations of the data. Other assumptions of what the doses were may also be valid. This is why we presented all of our assumptions in such detail. I would point out, however, that our dose assignments were made without knowledge of how the assignments would affect the cumulative doses of either the cases or controls. I would not change our exposure estimates on the basis of Mr. Pax's personnel record.

6. The fact that "hematopoietic deaths" occurred among persons in the cohort does not in itself suggest any exposure level. I am aware of the belief by some, but not of any evidence, that such disease can manifest only after high exposure to benzene. Our exposure

estimates were based on historical environmental monitoring data and not on pre-conceived notions of disease outcome. As stated in number 5 above, there could well be different and legitimate differences in the interpretation of the environmental data.

7. I do not know if this fibrous glass cohort has ever been updated. I do not know the current SMR's for leukemia in that cohort. I chose to use the United States population as my referent population, and then conduct a case control study from within the cohort.

8. I was aware that Goodyear did blood testing on more than just their pliofilm workers. At the time of our initial surveys, I made inquiries as to the availability of any records of blood work on the Akron population. I recall being unable to locate the records. More recently, I have called Goodyear with the same question. My recollection of the surveys have been confirmed. I have never collected any records other than those in the individual personnel folders. I have no correspondence on the subject.

9. The January 31, 1985, report was a very early draft of my work. I do not know how anyone obtained a copy of this draft. No one was authorized to distribute my preliminary work. As I recall the primary difference in the results of the January and August papers came from a technical problem in the life table computer program and the way in which it handled some work histories that overlapped some dates of death. Also, there were refinements made to the dosage matrix subsequent to the January draft, however, I recall these refinements made very little difference in the results.

10. I have no documents or correspondence that reflect efforts to identify additional solvent exposures in non-Pliofilm jobs. I attempted to determine this information by interviewing people and by searching Goodyear files. I found nothing reliable on which to base any estimates of exposure outside of pliofilm.

11. I have no documents that reflect NIOSH's efforts to identify dermal exposure.

The following answers respond to questions asked during the March 20, 1986, hearings.

1. A copy of Mr. Thomas Filloon's resume, at the time of his employment at NIOSH, was requested. Since Mr. Filloon is a Commissioned Officer of the U.S. Public Health Service, a resume is not available. Mr. Filloon was hired based on his application to the Public Health Service and an interview with NIOSH staff.

2. Page 35-36 in the transcript of the NIOSH testimony. There were a lot of data, including the storage data (Figure 13 of the 1981 paper) that were not incorporated into Appendix 5 of the 1985

paper. Measurements taken by the company at "Presses Open", the title for Figure 12. were used by NIOSH in the assignment of doses to exposure classes. Specifically, reference Q in appendix 5 of the 1981 paper describes how these values were used.

3. In regard to page 92 in the transcript of the NIOSH testimony, "stripper" refers to the "stripper roll", which was part of the casting unit.

4. On page 99 in the transcript of the NIOSH testimony, Table 5 in the "Exhibits for Cross-Examination of Mr. Robert Rinsky" refers to the work history of Mr. John Gravens. There were a number of documents in each individual's personnel folder. NIOSH clerks were instructed to code from the work histories recorded on the jacket that contained all the other documents. It seems to me that in the case of Mr. Gravens, there was a duplicate jacket, which appeared to be hand copied. However, it is not an exact duplicate in that certain early work histories were not included. Our staff apparently did not notice this discrepancy, and coded from the less complete jacket, ignoring these earlier jobs where there was benzene exposure. I have determined that these jobs should have been counted. The computer files have been corrected and this data has been factored into the re-analysis that is enclosed.

Other comments:

The enclosed report, "Benzene and Leukemia: An Epidemiologic Risk Assessment" incorporates the corrections specified in my answers to the questions above, and corrections of the inconsistencies in the dose file pointed out in submissions by witnesses representing the American Petroleum Institute. Changes in the dose file caused a reduction in the total cohort size by 31 people, i.e. from 1196 to 1165. With these modifications most of the odds ratios have changed slightly, however, the conclusions remain exactly as they were in the August paper. NIOSH has also learned of an additional leukemic death that occurred in 1984. This death is considered in the discussion section on page 19 of the manuscript.

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