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COMMENTARY

# Occupational Exposure to Benzene: A Review of Carcinogenic and Related Health Effects Following the U.S. Supreme Court Decision

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The recent US Supreme Court decision (*Industrial Union Department v American Petroleum Institute*, 48 USLW 5022, decided July 2, 1980) on the Occupational Safety and Health Administration's (OSHA) proposed standard for lowering exposure to benzene in the occupational setting has been a topic of recent discussion in both the lay [Doninger, 1980: Fishbein, 1980: The New York Times, 1980] and scientific media [Smith, 1980]. As a result of this decision, there appears to be some confusion about the actual toxicity and carcinogenicity of benzene.

A plurality ofjustices in a 5 to 4 decision stated that OSHA had neither made nor rejected any factual determinations demonstrating "significant risks," to be defined by the Agency, at the current standard of 10 parts per million (pprn); nor had OSHA made or rejected any factual determinations of significant benefits from lowering the standard to 1 ppm. The Supreme Court decision, however, should not be taken to imply that adverse health effects do not occur as a result of exposure to benzene below the current 10 ppm standard. In light of a possible misinterpretation of health effect data related to benzene exposure. we present here both a historical perspective on the current US standard and an updated review of the pertinent literature addressing the carcinogenic. mutagenic. and related toxic effect5 of benzene.

## PERSPECTIVE ON THE CURRENT STANDARD

The current OSHA standard for occupational exposure to benzene, adopted in 1971, is an 8–hour bme-weighted average (TWA) of 10 part5 per million (ppm), with an acceptable ceiling concentration of 25 ppm (29 CFR 1910.1000, Table 2-2). Excursions above the ceiling are allowed to a maximum peak concentration not to exceed 50 ppm for more than 10 minutes in any 8–hour work period.

Evidence received by OSHA after 1971 indicated that workers exposed to benzene were at an increased risk of developinn leukemia. In addition. benzene

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previously had been linked to other serious adverse health effects. including aplastic anemia, pancytopenia, other hematological disorders, and chromosomal aberrations. The primary route of exposure is thought to be through the inhalation of benzene vapor [IARC, 1974], although little information is available which adequately addresses the potential for benzene to be absorbed through the skin [NIOSH. 19741.

Consequently. in February 1978. OSHA promulgated a revised standard for occupational exposure to benzene [OSHA. 1978]. This standard allowed for an 8–hour ume weighted average (TWA) of 1 ppm with a ceiling limit of 5 ppm. It was estimated that more than 35,000 workers were exposed to benzene at TWA concentrations greater than 1.0 ppm. The standard was based on a determination by OSHA that the available scientific evidence established that employees exposed to benzene were at an elevated risk of developing leukemia, nonmalignant blood disorders and chromosomal damage. A lower court vacated the revised (1 ppm) standard, and the Supreme Court recently upheld the lower court's decision. As a result, the standard adopted in 1971 is currently in effect.

## BENZENE CARCINOGENICITY

### Epidemiologic Evidence

The evidence in the 1977 OSHA benzene record clearly demonstrated that benzene is a human leukemogen. In making this determination, OSHA relied upon an evaluation of all the evidence and not on any one particular study. Participants in the rulemaking for the most part did not challenge benzene's leukemogenicity, and neither did the US Court of Appeals for the Fifth Circuit when it vacated the standard. Within the scientific community, there is little dispute over benzene's carcinogenicity. For instance, the International Agency for Research on Cancer [1979] has classified benzene as a chemical for which there is sufficient evidence to support a causal association between exposure and cancer in humans. Numerous other scientific reports concur with this conclusion [CEQ, 1980: Cole and Goldman. 1975; NIOSH. 1977: NTP. 1980].

Two cohort studies have demonstrated an increased incidence of leukemia in workers exposed to benzene. The first is a study by Infante et al [1977a] of workers exposed to benzene in the production of Pliofilm, a rubber film material, in two Ohio industrial facilities. There was a paucity of information regarding atmospheric levels of benzene to which workers may have been exposed. but the available data indicated that average benzene levels generally ranged from less than 10 ppm to 100 ppm.

All white males who had been directly exposed to benzene at any time between 1940 to 1949 and who were alive on January 1, 1950 were included in the cohort. The vital status of these workers was determined through June 30. 1975. Causes of death were determined from death certificates. Medical records were also reviewed. Those benzene-exposed workers with unknown vital status. comprising 25% of the total cohort, were assumed to be alive so that the relative risk of developing leukemia would be biased toward an underestimate.

Observed deaths among the benzene-exposed cohort were compared with expected numbers of deaths calculated from both the general US white male population death rates. adjusted for age and calendar time period. and from the death rates of a comparison group of fibrous-glass workers employed in Ohio during the same period of time.

The investigators identified a significant excess of deaths from leukemia when compared to either the general US white male population (SMR = 507, 7 observed deaths vs 1.38 expected, p less than 0.002). or to the fibrous-glass workers (SMR = 473. 7 observed vs 1.48 expected, p less than 0.002).

Subsequent to this initial report, the benzene-exposed population was followed further [Infante et al. 1977b]. As the vital status of workers previously assumed to be alive changed with the identification of their deaths, the number of person-years of observation they could contribute to the cohort inevitably decreased. As a consequence, this reduction in the number of person-years of observation necessarily resulted in a reduction in the number of expected deaths due to leukemia.

Because acute myelogenous leukemia and its acute variants are the cell types of leukemia most frequently associated with benzene exposure, Infante et al [1977] reanalyzed their data in order to take into account the distribution of specific cell types of leukemia. Of the seven observed leukemia deaths. one was classified as chronic myelogenous leukemia and six as acute myelogenous or monocytic leukemia. The number of expected deaths from acute and monocytic leukemia was estimated on the basis of National Cancer Institute mortality rates for these cell types of leukemia [Burbank, 1971]. The total expected number of deaths from acute and monocytic leukemia was calculated to be 0.70. When compared to the six observed cases of acute myelogenous and monocytic leukemia, this yielded an SMR of 857. This SMR is considered to be conservative for two reasons. First, the rates used for determining the expected number included cell types other than acute myelogenous and monocytic leukemias, such as acute lymphatic leukemia. Second, a 29 year-old cohort member, whose cause of death was listed as chronic myelogenous leukemia and therefore not included in this analysis, died within 2 years of his initial exposure to benzene. Since there was such a short time interval between initial exposure and death, it is possible that this individual may have died from acute myelogenous leukemia.

A second cohort study of 594 males exposed to benzene in three chemical production areas of a Michigan plant was conducted by Ott and his colleagues at the Dow Chemical Company [Ott et al. 1977]. All individuals who began employment at any time between 1940 and 1970 were included in the cohort The vital status of these workers was determined through 1973. Three leukemia cases were observed among the cohort members; all were myelocytic and two were classified as acute myelocytic leukemia. Because one of these leukemia cases was coded on the death certificate as having died from bronchopneumonia. the expected number of leukemia cases was generated on the basis of morbidity data from the Third National Cancer Survey rather than mortality data. Using this analysis. the three myelocytic leukemia cases were reported to be significantly in excess of the expected number, 0.8 (p less than 0.047).* All three leukemia cases were exposed to atmospheric benzene concentrations averaging less than 10 ppm. In addition to the three leukemia cases. two deaths due to anemia. one aplastic and one pernicious. were also observed among members of this cohort.*

A few studies have suggested that acute myelogenous leukemia and its variants are more likely than other types of leukemia to occur in relation to benzene exposure [Goldstein. 1977]. However. the benzene-exposed populations have been

*On the basis of these results, the Dow Chemical Company [1977] initiated a global policy of reducing benzene exposure in its operations to a ceiling value of 10 ppm

of insufficient sample size, and thereby of inadequate sensitivity, to detect excesses in other types of leukemia that may not demonstrate a relative risk as high as myelomonocytic leukemias. When the expected number of a specific cell type of leukemia is less than one. as it was in the Infante et al [1977b] and Ott et al [1977] studies, only relative nsks that are of considerable magnitude will be recognized as significant.

Nevertheless. several studies and case reports have linked various types of leukemia to benzene exposure. Browning [1965] searched the literature and found 61 reported cases of leukemia among persons who had been exposed to benzene. The classifications of these leukemia cases were as follows: 6 acute myeloid. 1 subacute myeloid. 21 chronic myeloid, 7 lymphatic, 14 aleukemic, and 12 erythroleukemic. In addition, Vigliani and Forni [19761 stated that in Paris from 1950–1965.43 cases of leukemia had been identified in subjects with chronic benzene exposure; 23 were classified as acute leukemia, 13 were classified as chronic myeloid leukemia, and 8 were classified as chronic lymphocytic leukemia.

Aksoy [ 19801recently described cases of various types of malignanciesamong 47 shoe workers chronically exposed to benzene and 16 persons employed in other industries where benzene had been used in Turkey. Of the 42 cases of leukemia, only 16 (38%) were acute myeloblastic leukemia. The other types of leukemia in descending order of frequency were: acute erythroleukemia, preleukemia, acute lymphoblastic leukemia, acute monocytic leukemia, chronic myeloid leukemia, acute myelocytic leukemia and acute undifferentiated leukemia. In addition, malignancies other than leukemia were found among persons chronically exposed to benzene, including nine cases of malignant lymphoma, three cases of multiple myeloma and five cases of lung cancer.

Ishimaru et al [1971] conducted a study of 303 leukemia cases and 303 matched controls among adult survivors of the atomic bomb explosions in Hiroshima and Nagasaki. Japan. The risk of leukemia was found to be significantly higher among those employed in occupations where various solvents. including benzene. or medical x-ray were used as compared to those without such exposure. The relative risk was 1.8 times higher for chronic leukemia and 2.9 times higher for acute leukemia.

At the OSHA benzene hearing in 1977. some witnesses presented epidemiologic studies which failed to detect an excessive cancer nsk among workers exposed to benzene However. in all of these studies methodologic deficiencies made it apparent that they could not be relied upon for an evaluation of potential adverse effects from occupational exposure to benzene. Specifically, the authors could not specify the proportions of workers in their study populations that ever had been exposed to benzene. Further, for those who may have been exposed, there was no knowledge of when their exposure took place. making an assessment of the adequacy of latency period difficult. if not impossible. to determine.

In one such study, Thorpe [ 19741 analyzed deaths due to leukemia among 38,000 employees of eight European affiliates of a major petroleum corporation. Eighteen cases of leukemia between 1962 and 1971 were reported by company physicians in response to a questionnaire. The author compared the 18 reported leukemia deaths with an expected number of 23.23 leukemia deaths. generated using WHO age-specific mortality rates Presumably because of inadequate records, the author applied WHO mortality rates to the age distribution of the UK

affiliate. Workers in the other European affiliates were assumed by the author to have the same age distribution as those in the UK. Thorpe concluded that no excess in leukemia mortality could be damonstrated among these employees.

However, it is unknown exactly how many of these workers had a history of exposure to benzene. The number of persons potentially exposed to benzene was estimated on the basis of job assignments, but the author acknowledged that it was often difficult to distinguish exposed from nonexposed workers. Industrial hygiene measurements of worker exposure were generally not available. For a large number of individuals known to have died, the cause of death was not known. Furthermore, for those individuals whose causes of death were reported, there was no verification of cause of death. This is an important consideration because an individual with leukemia may die from another immediate cause such as an acute infectious disease, and the fact that the individual had leukemia may be overlooked when the cause of death is coded.

These deficiencies preclude any judgment on the relationship of benzene exposure and leukemia from this study of European affiliates of a major petroleum corporation. Nevertheless, some individuals [American Petroleum Institute, 1980] continue to cite this study as evidence of a threshold level for the induction of leukemia among workers exposed to benzene.

### Studies in Animals

At the time of the 1977 OSHA benzene rulemaking, the evidence was not sufficient to demonstrate cancer induction in laboratory animals following exposure to benzene. A study by Lignac [1932] showed that 8 out of 33 mice developed leukemia or Kundrat's lymphosarcoma 4 to 11 months after the first subcutaneous injection of benzene. Because no control animals were included in the study, no conclusions could be drawn from its results. Other attempts to induce cancer in benzene-exposed animals had been unsuccessful up until 1979.

Since the close of the record in the 1977 OSHA benzene rulemaking. two independent laboratories have reported henzene-induced cancers in rodents. Maltoni and Scarnato [1979] observed a significant excess in Zymbal gland tumors female Sprague-Dawley rats who were administered daily doses of 250 mg/kg body weight benzene by stomach tube (8/32 exposed vs 0130 control, p less than 0.05). In C57BL mice exposed by inhalation to 300 ppm benzene 6hours/day, 5 days/week for up to 16 months. Snyder et al [1980] detected a statistically significant increase (p less than 0.005) in hematopoietic neoplasms, specifically thymic lymphomas.

Thus. a statistically significant increase in tumors has been demonstrated in twodifferent species of laboratory animals. Sprague-Dawley rats and C57BL mice. following exposure to benzene.

## NONMALIGNANT BLOOD DISORDERS

The most commonly reported, but not necessarily the most frequently occurring, adverse health effects associated with chronic exposure to benzene is an alteration in the levels of erythrocytes. leukocytes. or thrombocytes in the circulating blood [OSH.4. 1978]. Pancytopenia is a term used to refer to a decrease in all three of these hematologic components. and the term is frequently used inter-

changeably with aplastic anemia. The relatively more frequent reporting in the literature of cases of aplastic anemia than of leukemia in association with benzene exposure may be a reflection of the shorter biological lag time associated with the clinical appearance of aplastic anemia as compared to the eventual clinical manifestation of leukemia. The incidence of these toxic manifestations of benzene exposure presumably is further underreported in more recent times as physicians are less likely to report blood abnormalities already known to be associated with benzene exposure.

Numerous studies were included in the 1977 OSHA benzene record which showed blood disorders among occupationally exposed workers and laboratory animals exposed to benzene. However. several issues remained unresolved at the close of the record.

First, the incidence of nonmalignant blood disorders resulting from benzene exposure is uncertain. Jandl [1977] who testified on behalf of Organization Resources Counselors Inc, estimated that about 10 and possibly 20 patients die annually from nonmalignant disease as a result of benzene exposure. However, Goldstein suggested that the true incidence of nonmalignant disease resulting from benzene exposure. such as pancytopenia, may be seriously underestimated because the possible importance of exposure to benzene may be overlooked [1977]. OSHA concluded that the data available did not permit an accurate quantitative assessment of the morbidity or mortality from benzene-induced nonmalignant blood disorders.

Second, the evidence in the record demonstrated no consensus of opinion as to whether benzene-induced nonmalignant blood disorders persist after cessation of benzene exposure. However, it is well recognized that a large number of patients with aplastic anemia die as a result of this disease. In 1977, 1,153 recognized deaths due to aplastic anemia (ICD no 284, 8th revision) occurred in the United States (US Department of Health and Human Services. unpublished). OSHA stated that it was not appropnate to conclude that nonmalignant blood disorders would revert to the individual's normal values in all cases following the cessation of exposure to benzene.

Finally, some hearing participants argued that a no-effect level for nonmalignant blood disorders could be established at an atmospheric benzene concentration greater than 10 ppm. because they believed it was unclear what health effects occur below 20 ppm. After reviewing the evidence in the 1977 benzene record, OSHA [1978] stated that there was no dispute that nonmalignant bone marrow toxicity can result from exposure to benzene above 25–40 ppm. Further, OSHA recognized that several studies reported blood abnormalities associated with benzene exposure levels below 25 ppm, at levels perhaps as low as 10 ppm. Reasoning that a relatively higher dose would result in an increased nsk. that a lower dose would result in a reduced risk, and that there is a wide range of human sensitivity to benzene, OSHA concluded that a minimum effect level for benzene could not be determined for nonmalignant blood disorders.

## CHROMOSOMAL ABERRATIONS

The record for the 1977 OSHA benzene rulemaking included several reports of chromosomal damage in benzene-exposed workers, both with and without clinical symptoms. For example. Forni et al [1971b] performed chromosome

studies on 34 workers in a rotogravure plant and 34 controls matched by age and sex. Ten of the rotogravure workers had been exposed to benzene and toluene and the remaining 24 had been exposed to toluene only. The investigators reported a statistically significant increase in both stable and unstable chromosomal aberrations in the benzene-exposed group compared with either the controls or the toluene-exposed group. In another investigation by Forni et al [1971a], 25 workers who had been diagnosed 1 to 18 years earlier as having chronic benzene poisoning were studied for chromosomal aberrations. At the time of the chromosome study, most subjects showed practically normal blood counts. Compared with matched controls, the former benzene-hemopathy cases had a significantly increased frequency of unstable and stable chromosomal aberrations. Follow-up studies revealed a general decrease in unstable chromosome aberrations and a persistence or increase in stable aberrations over time.

In addition, after the closing of the 1977 OSHA benzene hearing record, Kilian and Daniel of the Dow Chemical Company's Bio-Medical Research Laboratory released the results of a cytogenetic study of Dow employees exposed to benzene [Holder, 1978]. This study, discussed in the section on effects from low-level exposure to benzene, clearly demonstrated a significant increase in structural chromosomal aberrations resulting from average benzene exposures below atmosphere concentrations of 10 ppm.

Two other studies further suggest that benzene can cause chromosomal damage at low levels. Girard et al [1970] performed a cytogenetic study on workers exposed in a French paint factory where benzene solvents were used. Atmospheric exposures to benzene were measured ranging from trace amounts up to 14 ppm. Of 50 workers examined, 21 were considered to have an increase in the number of chromosome fractures and 4 were considered to have a large number of various anomalies, although no control workers were examined. Hartwich and Schwanitz [1972] studied 9 workers who were exposed to benzene in the open air. The authors stated that the maximum workplace concentration of 25 ppm was never reached, even under unfavorable conditions. Of the 100 cells examined per worker, the proportion with chromosomal deviations ranged from 8% to 12%. and averaged 10.4%. Concurrent controls were not examined, but the authors stated that the average aberration rate from studies by other investigators of blood donors was 5.1%

Interpreting the evidence on chromosomal damage in both human and experimental studies, OSHA stated that chromosomal damage represented an adverse biological event which may pose or reflect a potential health risk and as such, must be considered in the larger realm of adverse health effects associated with benzene. OSHA did not actually link chromosomal aberrations with demonstrable adverse health effects. However, a large body of scientific data suggests that an increased rate of chromosomal aberrations is of serious concern since chromosomal abnormalities have been associated with at least one-half of all spontaneously aborted fetuses [Stein et al. 1975] and with several congenital syndromes that also show an increased risk of malignancy [Mulvihill, 19751. In addition, chromosomal breakage, whether of genetic or environmental origin, has been associated with leukemia [Mulvihill, 1975]. The EPA [1979] Health Effects Research Laboratory recently described chromosomal aberrations as "a major cause of heritable human disease, and their occurrence is often associated with cancer."

## HEALTH EFFECTS AT LOW-LEVEL EXPOSURE TO BENZENE

In ruling on the evidence in the 1977 OSHA record demonstrating health effects at low-level exposure to benzene, the Supreme Court did not attempt to substitute its scientific judgment for that of the agency's. instead, the Supreme Court based its decision on legal issues involving the intepretation of the Occupational Safety and Health Act of 1970 (29 USC 651 et seq). A close scientific review of the evidence in the 1977 OSHA benzene record, as well as the new evidence since the close of the record, reveals that there are data which demonstrate serious adverse health effects resulting from low-level exposure to b

In the Ott et al study [1977], discussed in the section on epidemiologic evidence of carcinogenicity, all three individuals diagnosed as having leukemia and the individual with the diagnosis of aplastic anemia had worked in jobs where benzene exposure was characterized by the authors as low (TWA = 2 to 9 ppm) or very low (TWA less than 2 ppm). Further, the period of exposure to benzene for these cases was relatively short, ranging from 18 months to 10 years.

A second study from the Dow research laboratories has demonstrated an increase in chromosomal aberrations among workers who had been exposed to average benzene concentrations of less than 10 ppm [Holder, 1978]. These findings were released shortly after the 1977 OSHA benzene record was closed, and therefore could not be cited by OSHA in support of the recommended 10 ppm standard. The results of this study were later published by Picciano [1979]. Data from cytogenetic studies on 52 benzene-exposed workers were compared with data from 44 pre-employment controls. The results showed that the percentage of workers who had cells with chromosome breaks was significantly greater for the benzene-exposed group (Chi-square = 10.24, df = 1, p less than 0.005). In addition, the percentage of workers who had both chromosome breaks and marker chromosomes was ten-times higher among the benzene-exposed workers (Chi-square = 8.96, df = 1, p less than 0.005).

Picciano later presented an analysis of the cytogenetic results by level of exposure to benzene [1980]. This analysis showed chromosomal damage at exposures averaging below 2.5 ppm as well as a dose-response relationship between chromosomal damage and benzene exposure level. The percentage of individuals with both chromosome breaks and markers was 3% for nonexposed persons, 21% for persons exposed to levels up to 1.0 ppm, 25% for persons exposed from 1.0 to 2.5 ppm. and 33% for workers exposed to levels from 3.5 ppm up to 10 ppm

Thus. data currently available demonstrate the induction of leukemia and chromosomal damage as a result of exposure to benzene at average concentrations below 10 ppm.

## THRESHOLDS FOR CARCINOGENICITY

During the 1977 OSHA benzene rulemaking, the major dispute was whether or not a threshold level existed for benzene exposure in relation to leukemia. Some participants argued that in workplaces where an excess in leukemia was demonstrated among benzene-exposed workers. the atmospheric levels of benzene were several times higher than the current TWA of 10 ppm. Furthermore. it was claimed that no excess in leukemia incidence had been definitely established among workers exposed to levels of benzene below 10 ppm.

OSHA responded to these comments by stating that once the carcinogenicity of a substance has been established qualitatively, any exposure must be considered to be attended by an increased risk of developing cancer. The epidemiologic studies which were cited in support of a cancer threshold, the agency stated, were characterized by a number of flaws in both design and methodology. OSHA concluded that it was not possible to demonstrate a threshold or to establish a safe level for exposure to benzene. As a result, OSHA stated that it was its belief that occupational exposure to benzene at low levels poses a carcinogenic risk to workers.

Whether or not safe or no-effect levels can be set for exposure to carcinogens was one of many important issues discussed during OSHA's recent rulemaking on the identification, classification, and regulation of potential occupational carcinogens, referred to as the OSHA Cancer Policy [1980]. During the lengthy rulemaking proceedings, a number of witnesses expressed strong support for OSHA's proposed position that threshold, safe, or no-effect levels cannot be established for carcinogens. The following comments summarize the opinions expressed by most of the witnesses who participated in the proceedings.

Dr. Marvin Schneiderman of the National Cancer Institute stated, 'There is as yet no evidence whatsoever that thresholds exist for the irreversible process of carcinogenesis. . . . Unless some new, compelling information appears, the concept of threshold serves no useful purpose in regulatory decisions." Dr. Matthew Meselson of Harvard University commented, "It is conceivable, but my belief is that it should be assumed in general that there is no such thing as a threshold." Quoting the minutes of the Ad Hoc Committee on Testing for Environmental Chemical Carcinogens, Dr. Harold Stewart of the National Institutes of Health and chairman of the committee added, "In the case of the human population, with the completely unknown variations in sensitivity to any chemical carcinogen, and the impossibility of knowledge of other variables that may affect responsiveness to these agents, attempts to establish threshold levels for carcinogenicity are unrealistic." [OSHA, 1980].

After reviewing all of the evidence in the record for the Cancer Policy, OSHA concluded that no threshold levels could be established for carcinogens. Specifically. OSHA concluded that there was substantial evidence in the record which demonstrated that. 1) carcinogenic procesces differ from other typec of toxic effects in being irreversible and originating from minute foci or even from single cells. so that there is no theoretical reason to expect a threshold even for an individual; 2) the various defense mechanisms advanced as theoretical bases for thresholds, such as DNA repair, detoxification. and immunosuppression. are unlikely to be efficient enough to ensure a threshold: 3) even if thresholds do exist for individual humans, it would not be expected that such thresholds exist for populabons of exposed persons due to individual human variatlons in susceptibility, and the potential additive and synergistic effects with other carcinogens. intrinsic. and extrinsic factors: 4) the evidence presented for the existence of thresholds for specific carcinogens was inconclusive or erroneous: and finally. 5) no reliable method is known today for establishing a threshold that could apply to an exposed group of workers.

Thus. OSHA's earlier conclucion that no threshold could be established for benzene exposure is supported by the consensus of the scientific community, as expressed by the extensive evidence submitted into the OSHA record for the

**Cancer Policy. Furthermore, the earlier position OSHA took concerning benzene is consistent with the conclusions drawn by the Agency after consideration of all evidence in the record for the Cancer Policy.**

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