

IV. ENVIRONMENTAL DATA

Environmental Concentrations

In the past, where benzene was used in large quantities, extremely high concentrations of atmospheric benzene vapor could exist in the working environment. This was due in part to the lack of toxicological knowledge about benzene and the lack of enforcement of control procedures. During the winter months when the doors and windows of the plants were closed and normal ventilation was minimized, concentrations of benzene vapor could reach very high levels. The literature indicates atmospheric concentrations well over 16,000 ppm. [13] As the knowledge of the toxicity of benzene increased and better industrial hygiene practices were conducted in the United States, the levels of benzene in the workroom atmosphere decreased. During the 1930's and 1940's, these concentrations were lowered through the use of product substitution, improved ventilation, and other engineering practices. Specifically, in 1939, Greenburg et al [17] cited benzene exposure levels ranging from 10-1,060 ppm in 3 plants of the rotogravure printing industry in New York City. Also in 1939, a report by Bowditch and Elkins [18] gave levels of benzene vapor concentrations extending from 100 to greater than 500 ppm in 6 plants engaged in the manufacture of artificial leather, rubber goods, or shoes during the 1936-1939 period.

In 1961, Pagnotto et al [12] reported measurements of benzene concentrations up to 125 ppm in the workroom atmosphere of 8 rubber coating plants, the highest concentrations of benzene occurring in the saturating rooms.

From additional data supplied by Pagnotto [written communication, 1972], benzene concentrations in the plant listed in Table XII-9 ranged from 95-260 ppm in the churn room operations and from 65-200 ppm at the spreader machines during 1935 through 1937. The use of the benzene solvent was discontinued in 1937. In 1960, when surveys of this industry were resumed, benzene containing naphtha solvents had been substituted for the benzene solvent used earlier, the percentage of benzene in the naphtha solvents being 3% and 7.5% by volume. During the 1960-1963 period, environmental benzene concentrations for spreader and churn operations consistently averaged 20-25 ppm and frequently were lower. Measurements as high as 140 ppm were noted in the saturator operation. These benzene containing naphtha solvents continued to be used until 1965 when toluene containing solvents were introduced. In another plant using a solvent containing 5% benzene, environmental concentrations of 125 ppm were recorded. Improvements in ventilation reduced air levels to approximately 6 ppm (range 3-13 ppm) within 6 months. Urine phenol levels in the workers attested to the reduced environmental concentrations. These significant reductions in the measured benzene concentrations emphasize the efficacy of substitution and ventilation procedures as methods of control.

Parkinson [84] in 1971 reported on an investigation on the possibility that a hazard to health existed in the handling of gasoline, particularly at retail gasoline service (filling) stations. A working group consisting of representatives from approximately 6 British petroleum firms planned the investigation, conducted at typical retail service stations and bulk loading installations during the summer of 1969, mostly during warm weather and while there was a relatively high demand for

gasoline. A series of 30-minute personal samples were taken at a sampling rate of 1 liter/minute during the entire work period of service station operators, and during the entire period of loading or discharging of gasoline for bulk installation operators or tank truck (road car) drivers. In addition, urine samples for phenol analysis were collected at the beginning and end of the working period. Nine service stations were surveyed, 4 of which were large and open with a high annual sales volume of gasoline, and 4 that were "typical filling stations" of medium size and somewhat enclosed with average annual sales. One station represented a site in dense urban areas, being very enclosed and with a relatively high annual sales volume of gasoline. Benzene content of gasolines ranged from 2.8-5.8% by volume, in weather situations ranging from sunny to changeable, with variable temperature and wind conditions. Environmental benzene concentrations ranged from 0.2-3.2 ppm from 121 total tests taken. Normal handling procedures at bulk loading facilities with gasolines ranging from 0.4-6.8% benzene by volume resulted in environmental benzene concentrations ranging from 0.1-7.7 ppm for 70 total determinations. One seemingly nonrepresentative sample of 19.5 ppm was also found. Loading and discharging of road tankers with gasoline containing added benzene (10-33% by volume) produced airborne benzene concentrations ranging from 1.4-9.4 ppm. The highest urinary phenol levels observed were 18 mg/liter for the service station operations, 10 mg/liter for the bulk loading facilities handling normal gasoline, and 48 mg/liter in the handling of gasoline containing added benzene. It was concluded that benzene concentrations measured during normal operations in a variety of service stations were such that it was difficult to conceive that any benzene inhalation hazard

existed. Even though environmental benzene and urinary phenol levels for bulk loading operations were higher than for the filling station findings, the values recorded were considered to be well within the UK ceiling limit of 25 ppm, even during abnormally warm weather.

Sherwood [85] in 1972 reported on benzene exposures during loading and weighing operations of rail tankers with gasoline from storage tanks. The loading operator was adjacent to open ports on top of the tankers and the weighing operator worked in a small room at ground level between pair of railroad tracks. During loading operations, some benzene vapor escaped through the open tanker ports and rather than being dispersed, entered the weighing room at ground level when there was little or no wind. The mean concentrations to which workers were exposed during loading operations were 1.6 and 2.5 ppm, equivalent to 1.1 and 1.3 ppm on a time-weighted average basis over an 8-hour workday. The weighing operator was exposed to a mean concentration of 20 ppm which, when calculated on a time-weighted averaged basis, was equivalent to 14 ppm over an 8-hour workday. Modifications were made to reduce exposures in the weighing operation to levels below those encountered by the loaders.

Published environmental data on benzene concentrations in other industries is lacking beyond the brief statements provided in the medical reports on benzene poisoning discussed in Section III. These medical reports indicate a marked decrease in benzene exposure levels since World War I when concentrations extended into the thousands of ppm. [13] By the late 1930's, levels had dropped to hundreds of ppm, [17,18] and more recently to the tens of ppm. [12,22,56,86]

The substitution of process materials or equipment is frequently the most effective approach to reduce or eliminate benzene vapor exposures in industry. Oftentimes substitution of less toxic materials is one of the most overlooked methods of controlling exposure to a hazardous substance. The effectiveness of this method has been demonstrated in the rubber coating industry.

Where substitution of benzene containing solvent mixtures for other less hazardous solvents is not practical, consideration should be given to isolation of processes and installation of local exhaust ventilation in the major process sections where vaporous benzene emissions occur.

Environmental Sampling and Analytical Method

Many methods have been used in the past to determine the concentration of benzene vapor in air. Methods of collection have included absorption in scrubbers by nitrating solutions, [87,88] direct collection of whole-air samples, [89] and adsorption on silica gel [90-94] or activated carbon. [95,96] Analytical methods have included colorimetry which involves nitration followed by reaction with various ketones, [87,88,97] direct ultraviolet spectrophotometry, [91,98,99] direct estimation by means of colorimetric indicator tubes, [100,101] based on the colorimetric reaction between benzene and formaldehyde in the presence of sulfuric acid, and gas chromatography. [95,96,102-104]

Of the various methods of collection, adsorption on activated charcoal offers the greatest efficiency and ease of collection. The use of scrubbing liquids is inconvenient for obtaining personal breathing-zone samples, especially when 2 or more scrubbers must be connected in series to

assure high collection efficiency. The use of plastic-film bags for collecting whole-air samples may result in loss of samples due to adsorption or permeation of the benzene vapor through the plastic. In addition, aromatic hydrocarbons such as benzene are easily displaced from silica gel by water vapor, resulting in the possible loss of sample when using silica gel in a humid atmosphere.

Of the various methods of analysis, gas chromatography is believed to offer the greatest specificity and sensitivity. The various colorimetric methods, and even the direct spectrophotometric methods, are subject to interferences from a wide variety of compounds, and removal of these interferences is tedious and, in many cases, incomplete. The use of colorimetric indicator tubes must be considered only a semiquantitative technique, useful only on that basis.

Sorbability of Benzene on Charcoal

A concentration of 25 ppm of benzene was dynamically generated in a NIOSH laboratory to test the sorbability of benzene on charcoal. The following tests were performed:

(a) Single Section Charcoal Tubes

To obtain an approximate breakthrough value, a charcoal tube containing only one section of charcoal (100 mg) was used to collect benzene from the air. The 25-ppm mixture was drawn through the tube at a rate of 1 liter/minute and a flame ionization detector was placed downstream of the tube to monitor the benzene vapor coming through the tube. Concentrations coming through the tube were recorded by a strip chart recorder and the point at which the signal noticeably deflected from

the initial reading was defined as the point of breakthrough. The average breakthrough volume was 66 liters, obtained from several tubes under these conditions.

(b) Double Section Charcoal Tubes

These tests were performed using the normal charcoal tubes containing two sections of activated charcoal. Samples were collected at 25 ppm of benzene at a flow rate of 1 liter/minute and for various lengths of time ranging from 10-200 minutes. Breakthrough was defined as the point in sampling at which 0.1 mg of benzene was collected on the 50-mg (backup) section of charcoal. The data points are listed in Table IV-1.

A plot was made of total volume sampled vs weight of benzene on the backup section of charcoal, a parabolic regression analysis was performed, and a curve was plotted. The volume on the curve corresponding to 0.1 mg of benzene on the backup section was selected as the point of breakthrough and was determined to be 68 liters.

From these data, it appears that 68 liters is a very conservative value, since no tube had more than 0.1 mg on the backup section until at least 90 liters of air had been drawn through the tube. Therefore, a sample volume of 10 liters (1 liter/minute for 10 minutes) as prescribed in the recommended sampling method provides excellent recovery of the sampled benzene. At this sampled volume of 10 liters, no appreciable amount of benzene will pass to the backup filter and the small amount which does adsorb is well below the defined breakthrough point (0.1 mg).

TABLE IV-1

ADSORPTION OF BENZENE ON CHARCOAL SECTIONS
TO DETERMINE BREAKTHROUGH

Tube No.	Volume sampled (liters)	Benzene Concentration	
		Front section (mg)	Backup section (mg)
20-16	10	0.79	0.001
20-12	15	1.24	0.001
20-9	20	1.74	0.004
20-10	25	2.11	N.D.*
20-11	30	2.46	N.D.*
20-15	35	3.08	N.D.*
20-14	40	3.55	0.011
20-8	45	4.01	0.010
20-13	50	4.38	0.014
20-7	55	4.96	0.034
20-5	60	5.20	0.060
20-3	65	5.58	0.013
20-4	70	6.33	0.031
20-1	75	6.60	0.052
20-2	80	7.25	0.070
20-6	90	7.81	0.150
20-20	100	8.72	0.019
20-19	120	10.10	0.033
20-17	150	12.40	0.605
20-18	200	13.83	2.971

*N.D. - No detectable benzene on the backup section.

Accuracy and Precision Data

(a) Analytical Method, Not Including Sampling Error

Ten samples from the breakthrough tests were used to determine the accuracy and precision of the analytical method alone (not including sampling error). The 25-ppm benzene concentration was prepared by continuously injecting benzene from a motor-driven syringe into a flowing air stream. The flow rate of the air sampled through the charcoal tube was controlled at 1 liter/minute by a calibrated critical orifice.

TABLE IV-2

DATA FOR ACCURACY AND PRECISION OF
THE ANALYTICAL METHOD
(NOT INCLUDING SAMPLING ERROR)

Tube No.	Total benzene collected (mg)	Volume sampled (liters)	Measured conc. (ppm)
20-7	4.96	55	28.2
20-8	4.01	45	27.9
20-9	1.74	20	27.2
20-10	2.11	25	26.4
20-11	2.46	30	25.7
20-12	1.24	15	25.9
20-13	4.38	50	27.4
20-14	3.55	40	27.8
20-15	3.08	35	27.5
20-16	0.79	10	24.7

Mean (\bar{x}) of the 10 measured values = 26.9 ppm

Standard deviation (s) = 1.1 ppm

Accuracy: Systematic error = $\frac{\bar{x}-25}{25} \times 100 = 7.6\%$

Precision (relative standard deviation) =
 $\frac{s}{\bar{x}} \times 100 = 4.2\%$

The information in Table IV-2 is obtained from a small sampling, but provides a typical example of the accuracy and precision of the method excluding any sampling error.

(b) Analytical Method Using Personal Sampling Pump

(1) No in-line resistance

The accuracy and precision of the overall sampling and analytical method was determined (Table IV-3) on samples using approved coal mine dust personal sampling pumps having no pulsation dampeners and a rotameter calibrated with no in-line resistance. Ten charcoal tube samples were taken using 5 different pumps (two samples/ pump) at different times during the day.

(A) Sampling procedures

The charcoal tube tips were broken off and the tube was connected to the pump inlet with a 3-foot length of polyvinyl tubing. With pump operation, the rotameter ball was set for the desired flow rate (1 liter/minute), and the benzene-containing air (25 ppm) was sampled for 10 minutes.

Theoretical sampling volume = 10 liters/tube

Generated concentration = 25 ppm

Temperature of sampling = approximately 25 C

Pressure = approximately 745 mm Hg

TABLE IV-3

DATA FOR ACCURACY AND PRECISION OF ANALYTICAL METHOD
USING PERSONAL SAMPLING PUMP
(NO IN-LINE RESISTANCE)

<u>Tube No.</u>	<u>Total benzene collected (mg)</u>	<u>Measured conc. (ppm)</u>
A1	0.69	21.6
B1	0.65	20.3
C1	(lost)	-
D1	0.69	21.6
E1	0.79	24.7
A2	0.68	21.3
B2	0.55	17.2
C2	0.71	22.2
D2	0.67	21.0
E2	0.77	24.1

Mean (\bar{x}) = 21.6 ppm

Standard Deviation (s) = 2.2 ppm

Accuracy: Systematic error = $\frac{25 - \bar{x}}{25} \times 100 = 13.6\%$

Precision (relative standard deviation) = $\frac{s}{\bar{x}} \times 100 = 10.1\%$

(2) With In-line Resistance

Ten charcoal tube samples were collected using the same procedure as in (1) above, except that pump calibration was performed with a charcoal tube in line. The results are listed in Table IV-4.

TABLE IV-4
DATA FOR ACCURACY AND PRECISION OF
ANALYTICAL METHOD USING PERSONAL SAMPLING PUMP
(WITH IN-LINE RESISTANCE)

<u>Tube No.</u>	<u>Total benzene collected (mg)</u>	<u>Measured conc. (ppm)</u>
A3	0.71	22.2
B3	0.79	24.7
C3	0.71	22.2
D3	0.70	21.9
E3	0.80	25.0
A4	0.51	16.0
B4	0.79	24.7
C4	0.77	24.1
D4	0.77	24.1
E4	0.73	22.9

Mean (\bar{x}) = 22.8 ppm

Standard Deviation (s) = 2.7 ppm

Accuracy: Systematic error = $\frac{25 - \bar{x}}{25} \times 100 = 8.8\%$

Precision (relative standard deviation) = $\frac{s}{\bar{x}} \times 100 = 11.6\%$

The accuracy of the tests with in-line calibration was approximately 5% better than that in (1) above which lacked the in-line calibration. The data, however, were insufficient to show whether the difference was statistically significant.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The uses for benzene greatly expanded following World War I and an increasing number of reports of chronic benzene poisoning of workers appeared in the literature.[1,16-18] By 1947, the maximum allowable concentration for worker exposure to benzene had been reduced from 75 ppm to 35 ppm in the State of Massachusetts. [57] This was predicated upon the findings of Hardy and Elkins [57] of abnormal blood pictures in workers exposed to average benzene concentrations probably not over 60-80 ppm. This level was later adopted by the Maine Department of Health and Welfare in 1954 [105] and the Florida Industrial Commission in 1957. [106]

The American Conference of Governmental Industrial Hygienists recommended 100 ppm in 1946. [107] Subsequently, the value was successively reduced to 50 ppm in 1946, [108] 35 ppm in 1948, [109] and 25 ppm in 1957 [110] as a time-weighted average level where it remained until 1963 when a "C" designation was added [111] which indicated a ceiling limit that should not be exceeded. This value is the current recommended ceiling for an 8-hour/day, 40-hour/week exposure period. [112] The Conference believes this level to be low enough to prevent serious blood changes. [112]

The American National Standards Institute recommends a time-weighted average of 10 ppm for an 8-hour workday with a ceiling of 25 ppm and an acceptable peak exposure of 50 ppm for a duration of not more than 10 minutes if encountered not more than once during an 8-hour workday. [113] The ceiling of 25 ppm is considered acceptable to avoid changes in the

blood-forming tissues. The acceptable excursion level and duration is apparently based purely on judgment; examination of the literature by NIOSH has failed to find data to support such an excursion above a ceiling.

The American Industrial Hygiene Association's Hygienic Guide for benzene [5] recommends a maximal atmospheric concentration (8 hours) for benzene of 25 ppm with 100 ppm not to be exceeded for any period of time. The MAC of 25 ppm is based upon the particularly insidious and irreversible effects of long-term low-level exposure.

The current workroom air standard established under the Occupational Safety and Health Act of 1970 is an 8-hour time-weighted average of 10 ppm (29 CFR Part 1910.93 published in the Federal Register, volume 37, page 22139, dated October 18, 1972, as amended). The standard is based on American National Standards Institute Z37.4-1969. [113]

In 1971, a conference of the International Labour Office (ILO) adopted a Convention [114] and Recommendation [115] concerning protection against hazards of poisoning arising from benzene which specified an environmental concentration in the workplace not to exceed a ceiling value of 25 ppm (80 mg/cu m) for benzene or products containing benzene at more than 1% by volume. Restrictions on the use of benzene specified that whenever harmless or less harmful substitute products were available, substitution was mandatory; however, specifically excluded from the restriction were (1) the production of benzene, (2) the use of benzene for chemical synthesis, (3) the use of benzene in gasoline, and (4) analytical or research work carried out in laboratories.

Permissible levels in the range of 100 or 110 mg/cu m (31 or 35 ppm) for benzene vapor in the workplace have been established in Bulgaria,

Chile, France, Hungary, Malagasy Republic, Morocco, and Poland. [116] A level of 80 mg/cu m (25 ppm) exists for the Federal Republic of Germany, whereas the Democratic Republic of Germany has set 50 mg/cu m (16 ppm). Unusually high permissible levels were established by Uruguay at 1,000 mg/cu m (310 ppm) and Bolivia at 320 mg/cu m (100 ppm). Spain has set separate limits for men and women of 220 mg/cu m (70 ppm) and 110 mg/cu m (35 ppm), respectively. [116] The maximum permissible concentration in the USSR was 50 mg/cu m (16 ppm) in 1957 [58] and 20 mg/cu m (6 ppm) [116,117] in 1959, apparently based on the experimental work in rats reported in 1956 by Novikov. [69] Currently, the limit is 5 mg/cu m (2 ppm) based on findings of a definite lowering of the phagocytic activity of leukocytes reported by Kozlova and Volkova [58] in humans, along with other unspecified data in unknown species. [118] Although most nations have not established a formal environmental standard for benzene, 71 countries have existing legislation which governs the use of benzene or recognizes worker compensation claims resulting from benzene exposure. [116]

Basis for Recommended Environmental Standard

Published definitive epidemiologic data are lacking on workers exposed to benzene vapor at any concentration for prolonged periods of time. The US and European literature dealing with the effects of benzene on exposed workers consists primarily of medical reports rather than documented, comprehensive epidemiologic studies encompassing both clinical and environmental findings.

The report of Pagnotto et al, [12] along with the followup data (see Epidemiologic Studies) from investigations in the rubber coating industry

during the 1960-1963 period showed that environmental benzene concentrations consistently averaged between 20 and 25 ppm for spreader and churn operations. Levels occasionally reached 39 ppm. Some workers had hemoglobin levels below 13.5 g/100 ml of blood and other unspecified minor deviations from normal had been observed. These findings may indicate borderline blood problems. Some of the workers in the rubber coating plant had been exposed to benzene for a number of years and the borderline hematological changes are of equivocal significance in these workers.

Hardy and Elkins [57] found that levels of benzene exposure ranging from 40-80 ppm with an estimated average of 60 ppm in the artificial leather industry had produced deviations in more than 1 blood element in 16 out of 52 workers exposed. In addition, average inorganic sulfate to total sulfate ratios from urinalyses were interpreted as representing hazardous conditions for workers exposed to benzene concentrations of not over 60 ppm.

The chronic exposures of rats, rabbits, and guinea pigs to 80-88 ppm concentrations of benzene for periods extending from 32-269 days by Wolf et al [68] evoked a leukopenia with changes in the number of nucleated cells in the bone marrow. These investigators stated that the "no effect level" for benzene is "well below 80 ppm" on the basis of their findings with the 3 species of test animals.

Nau et al [67] reported that there was a decrease in the WBC of rats after 756 hours of exposure to a 50 ppm concentration of benzene for 8 hours/day, 5 days/week. The animals also developed lower leukocyte DNA values, a depression of myelocytic activity, and an increase in the proportion of erythrocyte precursors in the bone marrow.

Deichmann et al [66] induced a moderate but definite leukopenia in rats exposed 5 hours/day, 4 days/week to 44 and 47 ppm concentrations of benzene for periods of 5-8 weeks. No leukopenia developed in rats exposed to from 15-31 ppm.

In summary, the exposures of industrial workers to benzene at concentrations averaging 60 ppm and of animals (rats) at 40-50 ppm has induced hematological changes in these subjects. Suggestive but by no means conclusive changes were noted from data in the rubber coating industry workers at 20-25 ppm. At levels of 80-88 ppm, leukopenia and proportional increases in nucleated cells in the bone marrow occurred in animals and at about 60 ppm, changes in total RBC's and WBC's, Hgb, polymorphonuclears, lymphocytes, and eosinophils were noted in humans. On the basis of this evidence, it is felt that exposures of workers should be kept below 25 ppm.

There are conflicting reports concerning the increased susceptibility of women to benzene poisoning. [16,21,22,39,60] Hunter [21] considered that his study cast considerable doubt on theories of the existence of female hypersusceptibility to benzene. Savilahti [39] also found no significant differences between sexes in susceptibility to benzene poisoning. Of the studies suggesting greater susceptibility of women to benzene poisoning, [22,60] comparisons between men and women either cannot be made or figures are too few to be meaningful. Smith [16] reported menstrual function to be undisturbed in the majority of her positive or suspected cases of benzene poisoning. She did not judge the few incidences of menstrual irregularities to be of concern.

It is concluded from study of the relevant reports that an increased susceptibility to benzene of pregnant women or their offspring has not been demonstrated. The risk of exposure of pregnant women to benzene at levels below 100 ppm has not been defined. The literature contains statements such as that of Cassan and Baron [60] in 1956 that a pregnant woman must be removed not only from the work station but from the room where work with a benzene exposure risk is performed. Their statement is based (in part) on the measurement of RBC between 4.0 and 4.25 million in two pregnant women following their removal to another part of the room from the work station where they used a benzene varnish on electrical equipment. There are special requirements placed on the hemopoietic system of women in general, and especially during pregnancy. Although no definite hypersusceptibility to benzene vapor has been shown in women, pregnant women, or their offspring, it may be prudent to avoid exposing pregnant women to benzene. In the study by Smith, [16] the ages were quite evenly distributed between 17 and 52 years. Susceptibility to benzene poisoning was about equally marked between young and old, so youth was not considered to be a predisposing factor in benzene poisoning.

In view of the borderline hematological changes which occur in both man and animals from exposures to benzene and of the consequences which result from overexposure, it is considered that a conservative limit must be recommended. Therefore, in order to provide protection of workers to the effects of benzene poisoning over a working lifetime, it is recommended that an environmental limit for benzene of 10 ppm as a time-weighted average for up to a 10-hour workday, 40-hour workweek be adopted. In addition, in order to preclude acute effects from benzene, it is considered

that exposures of workers should be kept at or below 25 ppm; therefore, a ceiling is recommended for which benzene concentrations shall not be permitted to exceed 25 ppm.

It is recognized that many workers handle small amounts of benzene or are working in situations where, regardless of the amount used, there is only negligible contact with the substance. Under these conditions, it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily to protect worker health under more hazardous circumstances. Concern for worker health requires that protective measures be instituted below the enforceable limit to insure that exposures stay below that limit. For these reasons, "exposure to benzene" has been defined as exposure above half the environmental limit, thereby delineating those work situations which do not require the expenditure of health resources for environmental and medical monitoring and associated recordkeeping. Half the environmental limit has been chosen on the basis of professional judgment rather than on quantitative data that delineate non-hazardous areas from areas in which a hazard may exist. However, because of non-respiratory hazards such as those resulting from skin irritation or eye contact, it is recommended that appropriate work practices and protective measures be required regardless of the air concentration.

Finally, because of the shortage of exposure-effect data, there is a great need for detailed, comprehensive epidemiological investigations of benzene. The cause and effect relationship between benzene and aplastic anemia seems firmly established. Whether the alterations in marrow function observed from benzene exposure actually induce malignant changes

is not conclusive; nevertheless, the possibility that benzene can induce leukemia cannot be dismissed. The limited comparisons made for benzene worker populations in Italy [41] and France [55] indicate the distinct possibility that benzene may be carcinogenic. Limited population comparisons in the United States are not known to have been performed. Comprehensive studies on the long-term relationships of benzene worker populations with mortality and morbidity information on the incidence of leukemia in the population-at-large are greatly needed.

Basis for Biologic Monitoring

Biologic monitoring represents a technique by which absorption of benzene or its metabolites can be determined to verify whether a risk of benzene intoxication exists.

Benzene vapor is absorbed rapidly through the lungs from which the chemical is then distributed and either metabolized or rapidly excreted in the exhaled air. [64,77,119,120] Approximately 40% of absorbed benzene is excreted through the lungs; the remainder is metabolized. [119] It is widely distributed in the body tissues and tends to concentrate in tissues with a high fat content. [64] Most of the metabolized benzene is oxidized in the body to phenols which, in turn, are conjugated in the liver with sulfate ions and excreted in urine. [2]

Benzene in the blood and expired air along with urinary metabolites from benzene were considered as indices for biologic monitoring.

(a) Blood

Although measurements of benzene in the blood have been performed, [121] they have not been generally employed to correlate with the level of

environmental exposure. The measurement of benzene in the blood is not a good index of exposure, first, because benzene has a short and unpredictable duration in the blood and second, because there is no satisfactory correlation between the concentration of inhaled benzene and levels of benzene in the blood, at least from prolonged exposure. [116]

(b) Breath

Measurement of benzene by breath analysis is promising. In the 1967 report by Stewart et al, [37] of 10 workers accidentally overexposed to benzene (85-115 ppm) for 3 months [see Section III (b)(1)], frequent breath analysis was performed along with environmental monitoring. The statistical correlation between the concentration of benzene in the expired air and that of the daily vapor exposures was so reliable that post-exposure breath analysis was considered to be a rapid diagnostic index of benzene exposure.

Hunter [122] reported that exposures of benzene vapor in adult males at 300 mg/cu m (100 ppm) for 1-4 hours resulted in expired air concentrations of 180-220 mg/cu m. After the subjects were removed from the exposure, benzene could be detected in exhalations for up to 24 hours afterward with an instrument sensitive to 0.02 mg/cu m. Thus, Hunter felt that detection of benzene in expired air after industrial exposures was possible, and an indication of the intensity of the industrial exposure could be obtained from the concentrations found at known times after work.

Sherwood and Carter [102] reported in 1970 that immediately after sedentary exposure to 25 ppm for 4.5 hours (115 ppm-hr), the concentration in the breath was about 2 ppm. Breath sampling was employed successfully to evaluate the exposures of 3 workers during gasoline loading operations.

[85] A 1972 report indicated that consumption of ethyl alcohol soon after benzene exposure resulted in an accelerated elimination of benzene in the breath. [123] A rise in rapidly excreted phenol in the urine was also noted. The possibility that alcohol could accelerate elimination of benzene with possible protective effects was speculated upon. Limited comparisons of exhaled breath samplings with phenol-in-urine analyses have also been reported. [9]

Although breath analysis is claimed to give close correlations of environmental exposure levels to concentrations of benzene in the exhaled breath under experimental conditions, the rapid rate at which benzene is initially eliminated in the breath would seem to present difficulties in ascertaining accurate postexposure times under many occupational field conditions for which exhaled benzene concentrations could be related to environmental exposure levels for purposes of standards evaluation. Sufficient data involving decay curves for known exposure concentrations and times are generally unavailable; therefore, although breath analysis may be used to augment other biological analytical methods, there is, at present, inadequate information to recommend it as a primary method for biologic monitoring. Other methods are better supported by existing data.

(c) Urinalysis

(1) Sulfate Ratios

The urine sulfate ratio test is based on the premise that benzene is partially metabolized to organic derivatives conjugated with sulfate radicals. [124] As the sulfates increase due to exposure to benzene, there is a corresponding decrease in the ratio of inorganic to total sulfates. At one time, urine sulfate ratios were considered to be a

good measure of benzene exposure [125]; however, more recent methods have shown sulfate ratios to be less specific than the measurement of urinary phenols. [124]

(2) Urinary Phenol

The mechanism of formation and elimination of phenol conjugates has been studied by Dutton, [120] and reviewed by Williams. [77] In a review on the tolerance limit for benzene, Truhaut [126] discusses reported findings and presents, in a schematic form, the metabolic transformation of radioactively tagged benzene in the rabbit; most of the pathways also occur in humans (Figure XII-2). [34] Phenol is the major detoxification product eliminated in the urine. Almost 40% of the retained benzene is excreted in urine as phenol, 3% as pyrocatechol, and 1% as hydroquinone with the excretion of these metabolites being completed within 24-48 hours following a single exposure to benzene vapor. [77]

Teisinger and Fiserova-Bergerova [127] found that the measurement of total content of urinary phenol was superior to the measurement of the urine sulfate ratio as an index of benzene exposure. In addition, data was provided (Tables XII-12 and XII-13) by the Bethlehem Steel Corporation in response to a NIOSH request in the Federal Register of April 22, 1972, for information not readily available in the literature. Their conclusions also confirmed the superiority of urine phenol methods over the determination of urine sulfate ratios as an index of benzene absorption.

Docter and Zielhuis [128] suggested that "normal" values for urinary metabolites (phenol and phenol congeners) in individuals not exposed to benzene vary from 5-10 mg/liter with an upper limit of 15-20 mg/liter. Other estimates of the normal unexposed urinary phenol excretion are those

of Deichmann and Schafer, [129] 11-42 mg; and Walkley et al, [124] an average of 30 mg/liter. Thus, urinary phenol levels in unexposed persons are well below the recommended biologic level of 75 mg/liter.

The general rate of urinary excretion of a compound is dependent on many variables, such as physical exertion, excretory water availability, and sometimes diurnal and seasonal variations; therefore, small samples need to be corrected for variations in urine concentration. In the worker environment, problems of quality control and especially contamination are more easily managed with methods of "spot" surveillance programs than with collection of large volumes from multiple voidings which extend over periods of 24-48 hours.

Although the majority of retained benzene is excreted in the urine as phenol and conjugated phenols within 24 hours, samples obtained at or near the end of a working day present an excellent measure of exposure to benzene. [12] Close agreement generally results between observed environmental benzene concentrations obtained from laboratory analysis and equivalent air levels derived from urinary phenol measurements (see Tables XII-9, XII-10, and Figure XII-1).

An environmental benzene concentration of 25 ppm was reported by Walkley et al [124] to cause a urinary phenol concentration of 200 mg/liter in the people exposed. This would be equivalent to 170-190 mg/liter by the method of Sherwood and Carter [102] according to a written communication from Elkins in 1972. Docter and Zielhuis [128] found that people exposed to 25 ppm benzene produced 170-195 mg/liter of urinary phenol, while those exposed to 10 ppm produced a phenol concentration in the urine of 70-80 mg/liter. Buchwald [130] reported that an environmental benzene

concentration of 25 ppm would result in 195-225 mg/liter of phenol when adjusted to a specific gravity of 1.024.

It is on the basis of these studies that the recommended level of 75 mg/liter of phenol in urine sampled at or near the end of the workday has been selected to correlate with the recommended occupational environmental standard of a time-weighted average of 10 ppm of benzene. Phenol results obtained from samples taken at the beginning of the workday provide a measure of benzene retention and possibly metabolism of phenol-producing substances other than benzene. Such findings are valuable for comparison purposes with results obtained at the end of the workday but should not be related with 75 mg/liter of phenol as a basis for judging unacceptable absorption of benzene. Biologic monitoring, therefore, provides a valuable measurement technique to verify benzene exposure in the individual worker.

Basis for Biologic Sampling and Analytical Method

Several colorimetric methods have been used for the estimation of phenol in the urine. [124,131-134] In recent years, however, gas chromatographic techniques have been adopted extensively because of the advantages of specificity and rapidity of analysis. [102,135]

The following analytical techniques were given special consideration:

(a) A sensitive colorimetric method for phenol was developed by Walkley, Pagnotto, and Elkins, [124] a modification of the test of Theis and Benedict, [131] in which diazotized paranitroaniline was used as a color reagent. The results of this test were significant when the test was applied to urine samples collected at, or near, the end of the working

period. It is advisable to adjust all phenol values to a definite specific gravity to obtain good correlation [134]; the authors used a specific gravity value of 1.024. The phenol method [124,128] gave a more reliable picture of overall benzene exposure than data obtained from environmental air analyses. The authors pointed out that the test should not be used as an exclusive measure of exposure but that it is useful in validating results of overall benzene exposure. This method has the disadvantage of including paracresol in the determination; thus phenol values are reflections of both benzene absorption and paracresol content in the urine.

(b) A gas chromatographic procedure to determine more accurately the normal urinary excretion of phenol and to relate excretion to defined exposures was devised by Van Haaften and Sie. [135] Urine samples were heated in the presence of phosphoric acid to hydrolyze the conjugated phenols. The liberated phenols were separated in a polyethylene-glycol column and determined by means of a flame ionization detector. The procedure was accurate from 1 to 1,000 mg/liter of urinary phenols or cresols. Sherwood and Carter, [102] presented a gas chromatographic procedure to differentiate phenol and its conjugates from ortho-, meta-, and paracresols in urine. Urine was hydrolyzed with perchloric acid at 95 C. The phenols and cresols were then extracted with isopropyl ether for analysis by gas chromatography. The phenol concentration was determined by comparing the peak areas. Phenol was eluted in 100 seconds, orthocresol in 130 seconds, and meta- and paracresols in 320 seconds at a carrier gas flow rate of 60 ml/min.

The gas chromatographic methods have high specificity and provide for rapid determination of phenol in the urine. Detection of less than 0.1

ppm of benzene in air and 1 mg/liter of urine phenol is possible. The method of Sherwood and Carter [102] is the recommended method; it is described in Appendix III.