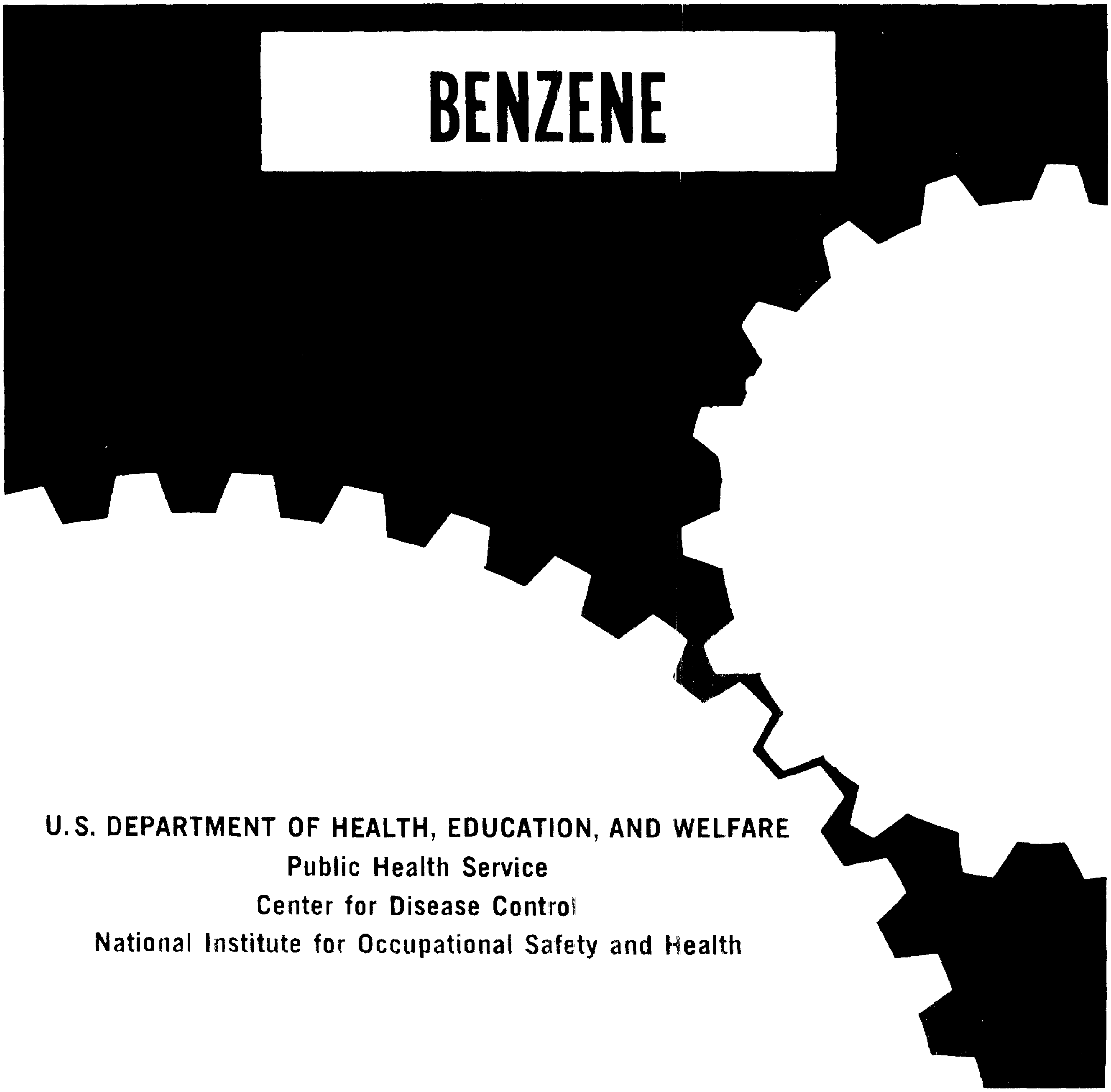
criteria for a recommended standard . . . .

OCCUPATIONAL EXPOSURE
TO
BENZENE



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

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1974

HEW Publication No. (NIOSH) 74-137

PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices.

It is intended to present successive reports as research and epidemiologic studies are completed and sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on benzene by members of my staff, the valuable and constructive comments presented by the review consultants on benzene, the ad hoc committees of the American Academy of Occupational Medicine and the Society of Toxicology, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by Professor William A. Burgess, NIOSH consultant on respiratory protection. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on benzene. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.

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The Office of Research and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for benzene. George D. Clayton and Associates developed the basic information for consideration by NIOSH staff and consultants under contract No. HSM-99-72-26. Douglas L. Smith, Ph.D., served as criteria manager and had NIOSH program responsibility for development of the document.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR BENZENE

Table of Contents

Page

PREFACE

REVIEW COMMITTEES

I. RECOMMENDATIONS FOR A BENZENE STANDARD

III. BIOLOGIC EFFECTS OF EXPOSURE

IV. ENVIRONMENTAL DATA

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards 68

Table of Contents
(continued)

I. RECOMMENDATIONS FOR A BENZENE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to benzene in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of workers for up to a 40-hour workweek over a working lifetime; compliance with the standard should therefore prevent adverse effects of benzene on the health and safety of workers. The standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. The standard will be subject to review and revision as necessary.

These criteria and recommended standard apply to occupational exposure of workers to the aromatic hydrocarbon C6H6, hereinafter referred to as "benzene." Synonyms for benzene include benzol, benzole, coal naphtha, cyclohexatriene, phene, phenyl hydride, and pyrobenzol. Benzin, petroleum benzin, and benzine are terms used for a mixture of saturated aliphatic hydrocarbons and should not be confused with benzene.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to benzene shall be controlled so that workers shall not be exposed to benzene at a concentration greater than 10 parts per million parts of air (32 milligrams per cubic meter of air) determined as a time-weighted average (TWA) exposure for up to a 10-hour workday, 40-hour workweek with a ceiling of 25 parts per million parts of air (80 milligrams per cubic meter of air) as determined by a sampling time of 10 minutes.

(b) Sampling and Analysis

Procedures for sampling, calibration of equipment, and analysis of environmental samples shall be as provided in Appendix I or by any method shown to be equivalent in accuracy, precision, and sensitivity to the method specified.

(c) Exposure

"Exposure to benzene" means exposure to a concentration of benzene above one-half the recommended environmental standard. Exposures at lower environmental concentrations will not require adherence to the following sections except for Sections 4 (b)(c), Skin and Eye Protection, and 6(a)(d)(e) of Work Practices. Procedures for identification of exposure areas can be accomplished by time-weighted average (TWA) determinations by methods described in Appendices I and II or by any method shown to be equivalent in accuracy, precision, and sensitivity to the methods specified.

If "exposure" to other chemicals also occurs, for example to toluene, provisions of any applicable standards for the other chemicals shall also be followed.

Section 2 - Medical

Medical monitoring (biologic monitoring and medical examinations) shall be made available to workers as outlined below.

(a) Biologic Monitoring

Biologic monitoring shall be provided to all workers subject to "exposure to benzene." It consists of sampling and analysis of urine for total phenol content. Such monitoring shall be performed to ensure that no worker absorbs an unacceptable amount of benzene. Unacceptable absorption of benzene posing a risk of benzene poisoning is demonstrated at levels of 75 mg phenol/liter of urine (with urine specific gravity corrected to 1.024) or greater as sampled and determined by the method specified in Appendix III, or alternative methods shown to be equivalent in accuracy and precision. "Spot" urine specimens of about 100 ml shall be collected as close to the end of the working day as feasible. Any urine specimens with a specific gravity less than 1.010 shall be discarded and another sample obtained.

To satisfy the biologic monitoring requirement, every worker subject to "exposure to benzene" shall have urine sampling and analysis made available to him at quarterly intervals. The schedule of biologic monitoring may be altered if indicated by the results of a professional industrial hygiene survey. If environmental sampling and analysis demonstrate that environmental levels are at, or greater than, the environmental limit, the interval of biologic monitoring shall be increased so that a phenol analysis shall be conducted every 2 weeks on every worker. This increased frequency shall be continued for at least 2 months after the high environmental level has been demonstrated.

If a worker's urine phenol level is found to be 75 mg/liter or greater, calculated to a specific gravity of 1.024, two followup urine samples shall be obtained within 1 week after receipt of the results, one as close to the beginning and one as close to the end of the same working day as possible. If the original elevated finding is confirmed, steps to reduce the worker's absorption of benzene shall be taken promptly. Steps to be considered should include improvement of environmental controls, of personal protection or personal hygiene, and the use of administrative controls. For those workers with confirmed high biologic levels of phenol as determined from the biologic sampling, a medical examination for possible benzene poisoning shall be considered and the OSHA area industrial hygienist shall be informed.

Biologic monitoring shall also be provided where the OSHA area industrial hygienist has reason to believe operations produce unusual exposure excursions or that environmental samples do not adequately describe worker exposure.

(b) Medical Examinations

Medical examinations shall be provided for all workers subject to "exposure to benzene" or when unacceptable absorption of benzene is demonstrated as judged by biologic monitoring. An evaluation of the advisability of a worker's using negative- or positive-pressure respirators shall also be made.

(1) Preplacement and Annual

Comprehensive preplacement and annual physical examinations, to include medical histories, shall be provided for all workers. Initial examinations for presently employed workers shall be offered within 6 months of the promulgation of a standard incorporating these recommendations and annually thereafter. The medical history should include information on previous exposures to benzene and any other hematologic toxin; blood dyscrasias including, but not limited to, genetically related hemoglobin alterations, bleeding abnormalities, and abnormalities in the function of formed blood elements; renal disease; liver disease; alcoholic intake; and infection. Laboratory examinations at the time of the preplacement examination shall include, but shall not be limited to:

(A) Complete blood count, including hematocrit, hemoglobin, mean corpuscular volume, white blood cell count including a differential count, and platelet estimation from the differential slide.

(B) Reticulocyte count.

(C) Serum bilirubin.

(D) Urinary phenol.

(2) Quarterly

Each worker exposed to benzene shall have laboratory examinations provided at 3-month intervals as prescribed for the preplacement and annual examinations but not necessarily including the reticulocyte count and serum bilirubin requirements.

(3) Monthly

Monthly laboratory examinations, or more or less frequently as indicated by professional judgment, as prescribed for the quarterly requirements, shall be provided if, in the opinion of the responsible physician, a worker shows alterations in the formed elements of the blood as compared with previous results which are judged as sufficient to warrant more frequent observations. This schedule shall continue for at least 3 months thereafter until there is evidence of return to normal values (see Appendix IV) or other reasons indicate discontinuance.

(4) Two-Week Intervals

Each worker exposed to benzene in excess of a time-weighted average concentration which exceeds the standard shall have the laboratory examinations provided every 2 weeks as prescribed for the preplacement and annual examinations. If evidence of benzene poisoning is developed from these examinations, the worker should be kept under a physician's care until the worker has completely recovered or maximal improvement has occurred. Ordinarily, this is mandatory in most workmen's compensation jurisdictions.

Each employee who absorbs unacceptable amounts of benzene as indicated by biologic monitoring shall be examined as soon as practicable after such absorption is demonstrated and confirmed, and at least monthly thereafter, until his urine phenol levels have returned to normal, ie, below 75 mg/liter of urine.

Medical records shall be maintained for persons employed in work involving exposure to benzene and shall include information on all biologic determinations and on all required medical examinations. Medical records with pertinent supporting documents shall be maintained at least 20 years after the individual's employment is terminated. These records shall be available to the medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employee or former employee, and of the employer.

Section 3 - Labeling (Posting)

The following sign shall be affixed in a readily visible location at or near entrances to areas in which there is the likelihood of occupational exposure to benzene:

DANGER!

BENZENE

EXTREMELY FLAMMABLE:
Keep away from heat, sparks, and open flame.

VAPOR HARMFUL
High concentrations of vapor
are hazardous to health.
Provide adequate ventilation.

This warning sign shall be printed both in English and in the predominant language of non-English-speaking workers, unless they are otherwise trained and informed of the hazardous areas. All illiterate workers shall receive such training.

Section 4 - Personal Protective Equipment and Protective Clothing

Engineering controls shall be used to maintain benzene exposures below the prescribed limit. Administrative controls may also be used to reduce exposure. Requirements for personal protective equipment shall be as approved under provisions of 29 CFR 1910 (37 FR 22102, Subpart I, October 18, 1972, as amended).

(a) Respiratory Protection

This subsection shall apply whenever a variance from the standard recommended in Section 1(a) is granted under provisions of the Occupational

This subsection shall apply whenever a variance from the standard

Safety and Health Act, or in the interim period during the application for a variance. When the limits of exposure to benzene prescribed in subsection (a) of Section 1 cannot be met by controlling the concentration of benzene in the work environment, an employer must utilize, as provided in this subsection, a program of respiratory protection to effect the required protection of every worker exposed. Respirators shall also be provided and used for nonroutine operations (occasional brief exposures above the ceiling of 25 ppm and for emergencies); however, for these instances, a variance is not required, but the requirements set forth below continue to apply. Appropriate respirators as described in Table I-1 shall only be used pursuant to the following requirements:

(1) For the purpose of determining the type of respirator to be used, the employer shall measure the atmospheric concentration of benzene in the workplace when the initial application for variance is made and thereafter whenever process, worksite, climate, or control changes occur which are likely to increase the benzene concentration. The employer shall ensure through proper respirator selection, fit, use, and maintenance that no worker is being exposed to benzene in excess of the standard.

(2) The respirator and cartridge or canister used shall be of the appropriate class, as determined on the basis of exposure to benzene.

(3) A respiratory protective program meeting the general requirements outlined in section 3.5 of American National Standard Practices for Respiratory Protection Z88.2-1969 shall be established and enforced by the employer. In addition, Sections 3.6 (Program

Administration), 3.7 (Medical Limitations), and 3.8 (Approval) shall be adopted and enforced.

(4) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employee uses the respirator provided.

(5) Respiratory protective devices described in Table I-1 shall be those approved under provisions of 30 CFR 11 (37 FR 6244, March 25, 1972) as amended.

(6) Respirators specified for use in higher concentrations of benzene are permitted in atmospheres of lower concentrations.

(7) Employees shall be given instruction on the use of respirators assigned to them, day-to-day maintenance and cleaning of the respirators, and how to test for leakage.

(8) Emergency and escape-type respirators shall be made immediately available at the work stations for each worker.

TABLE I-1

REQUIREMENTS FOR RESPIRATOR USAGE - BENZENE

Maximum Use Concentration (Multiples of TWA limit)	Respirator Type for Benzene
Less than or equal to 10x	(1) Chemical cartridge respirator with organic vapor cartridge(s) and quarter or half mask. (2) Type C supplied air respirator, demand type (negative pressure), with quarter or half mask.
Less than or equal to 100x	(1) Gas mask with chin style canister for organic vapors. (2) Gas mask with front or back mounted chest type canister for organic vapors. (3) Type C supplied air respirator, demand (negative pressure), with full facepiece. (4) Self-contained breathing apparatus in demand mode (negative pressure) with full facepiece. (5) Combination supplied air respirator, pressure-demand type, with auxiliary self-contained air supply and full facepiece.
Greater than 100x	(1) Self-contained breathing apparatus in pressure-demand mode (positive pressure). with full facepiece. (2) Type C supplied air respirator, pressure-demand or continuous flow type with full facepiece or hood. (3) Combination supplied air respirator, pressure-demand type, with auxiliary self-contained air supply with full facepiece.

TABLE I-1
(continued)

REQUIREMENTS FOR RESPIRATOR USAGE - BENZENE

Maximum Use Concentration (Multiples of TWA limit)	Respirator Type for Benzene
Emergency (No concentration limit)	(1) Self-contained breathing apparatus in pressure-demand mode (positive pressure) with full facepiece.
	(2) Combination supplied air respirator, pressure-demand type, with auxiliary self-contained air supply and full facepiece.
Evacuation or escape (No concentration limit)	(1) Self-contained breathing apparatus in demand or pressure-demand mode (negative or positive pressure).
	(2) Gas mask with organic vapor canister and mouthpiece respirator.

(b) Skin Protection

(1) Benzene-wetted clothing shall be removed promptly and benzene-exposed parts of the body shall be washed thoroughly.

(A) Workers wearing benzene-wetted clothing shall not be permitted to smoke or go near heaters or open flames.

(B) Benzene-wetted clothing shall not be placed in proximity of flames, heaters, or spark-producing equipment, and shall be free of vapor before being reworn.

(2) Workers shall be warned to avoid situations during extremely cold weather in which liquid benzene could freeze on clothing and vaporize on entering warm areas, thus posing a serious health or fire hazard to the wearer.

(3) Protective clothing, consisting of coveralls or similar full-body clothing should be worn and should be changed at least twice weekly.

(4) If operations require continued exposure to liquid benzene, workers shall wear impervious clothing, gloves, or coverings to protect potentially exposed areas of the body. Consideration shall be given to the heat stress factors involved when wearing impervious clothing.

(c) Eye Protection

Eye protective equipment shall be provided by the employer and used by the employee where eye contact with liquid benzene is likely to occur from spill, splash, or spray.

(1) Selection, use, and maintenance of eye protective equipment shall be in accordance with provisions of the American National Standard Practice for Occupational and Educational Eye and Face Protection, ANSI Z87.1-1968.

(2) Spectacle-type safety goggles-- metal or plastic rim safety spectacles with unperforated side shields, or suitable all-plastic safety goggles equipped with approved impact-resistant glass or plastic lenses shall be worn when there is danger of benzene contact with the eye. Prescription lenses shall be provided for those employees who need them.

(3) Face shields-- full length, 8-inch minimum plastic shields with forehead protection may be worn in place of, or in addition to, goggles. If there is danger of material striking the eyes from underneath, or around the sides of the face shield, safety goggles shall be worn as added protection.

Section 5 - Informing Employees of Hazards from Benzene

At the beginning of employment in a benzene area, employees exposed to benzene shall be informed of hazards, relevant symptoms of overexposure, appropriate emergency procedures, and proper conditions and precautions for safe use of benzene. The information shall be posted in the work area, and maintained on file, and be readily accessible to the worker at all places of employment where benzene is involved in unit processes and operations or is released as a product, byproduct, or contaminant.

A continuing educational program shall be instituted to ensure that all workers have current knowledge of job hazards, proper maintenance procedures and cleanup methods, and that they know how to correctly use respiratory protective equipment and protective clothing.

Information as required shall be recorded on US Department of Labor Form OSHA-20 "Material Safety Data Sheet" or a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Smoking

Smoking materials, including personal matches and lighters, shall be prohibited in all areas where there is benzene.

(b) Emergency Procedures

(1) Fire fighting procedures shall be established and implemented to meet foreseeable events; these shall include procedures for emergencies involving release of benzene vapor.

(2) Where there is the possibility of benzene contact on the eyes or skin, safety showers, eye-wash fountains, and cleansing

facilities shall be installed and maintained to provide prompt, immediate access by the workers.

(3) Appropriate respirators shall be immediately available for wear during emergency situations and evacuation or escape.

(c) Exhaust Systems and Enclosure

Exhaust ventilation and process enclosures shall be used wherever practicable to control workplace concentrations. Spark-proof fans and systems shall be designed and maintained to prevent the accumulation or recirculation of benzene into the workplace. In addition, necessary measures shall be taken to ensure that discharge outdoors will not produce a health hazard to humans, animals, or plants.

(d) General Housekeeping

Emphasis shall be placed upon cleanup, inspection and repair of equipment and leaks, proper storage of materials, and assurance that escape routes are kept clear. Sanitation shall meet the requirements of 29 CFR 1910.141, as amended.

(e) Disposal

(1) All local, state, and federal regulations concerning waste disposal into landfills, streams, municipal treatment plants, or impounding basins shall be followed.

(2) Benzene or benzene-containing materials shall not be discharged where there is a potential for vapor ignition.

(f) Food

Food preparation and eating should be prohibited in benzene work areas.

(g) Restricted Access to Benzene Areas

Entry to any area where there is the possibility of exposure to benzene shall be permitted only on the basis of need; all persons entering shall be protected as required for workers regularly assigned to that area.

Section 7 - Monitoring and Reporting Requirements

Workroom areas where it has been determined, on the basis of an industrial hygiene survey or the judgment of a compliance officer, that environmental levels do not exceed one-half the environmental standard shall not be considered to have benzene exposure. Records of these surveys, including the basis for concluding that air levels are not above one-half the environmental standard, shall be maintained until a new survey is conducted. Surveys shall be repeated when any process change indicates a need for reevaluation or at the discretion of the compliance officer. Requirements set forth below apply to areas in which there is benzene exposure.

Employers shall maintain records of accidental benzene release requiring evacuation. In addition, records of environmental exposures to benzene shall be maintained based upon the following sampling and recording schedules except as otherwise indicated by a professional industrial hygiene survey. In all monitoring, samples representative of the exposure in the breathing zone of employees shall be collected. An adequate number of samples shall be collected to permit construction of a time-weighted average (TWA) exposure and ceiling concentration for every operation or process. The minimum number of representative TWA determinations for an operation or process shall be based on the number of workers exposed as provided in Table I-2 or as otherwise indicated by a professional industrial hygiene survey.

Periodic environmental sampling and biologic sampling shall be timed so that results from both procedures will reflect representative worker exposures to benzene.

(a) Initial and Recurrent Sampling Procedures

(1) The first environmental sampling shall be completed within 6 months of the promulgation of a standard incorporating these recommendations.

(2) Samples shall be collected and analyzed at least quarterly for the evaluation of the work environment and to determine adherence to the recommended standard.

(3) Employees or their representatives shall have the opportunity to observe environmental monitoring.

(b) Special Sampling Procedures

(1) Environmental monitoring of an operation or process shall be repeated at 15-day intervals when the benzene concentrations have been found to exceed the recommended environmental standard. In such cases, suitable control measures shall be instituted, and monitoring shall continue at 15-day intervals until 2 consecutive surveys indicate the adequacy of the controls.

(2) Environmental samples shall be taken within 30 days after installation of a new process or process change.

(c) Recordkeeping Procedures

(1) Records of all sampling and medical examinations shall be maintained for at least 20 years after the individual's employment is

terminated. Records shall indicate the type of personal protection devices, if any, in use at the time of sampling. Records shall be maintained and classified so that each employee shall be able to obtain information on his own environmental exposure.

TABLE I-2

SAMPLING SCHEDULE

Number of Employees Exposed	Minimum Number of TWA Determinations
1-20	50% of the total number of workers
21-100	10 plus 25% of the excess over 20 workers
over 100	30 plus 5% of the excess over 100 workers

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from exposure to benzene. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to ". . . develop criteria dealing with toxic materials and harmful physical agents and substances which will describe . . . exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultations with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. It should be pointed out that any recommended criteria for a standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

These criteria for a standard for benzene are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of benzene or its release as an intermediate, byproduct, or impurity therefrom as applicable under the Occupational Safety and Health Act of 1970.

The standard was not designed for the population-at-large, and any extrapolation beyond general occupational exposures is not warranted. It is intended to (1) protect against injury from benzene, (2) be measurable by techniques that are valid, reproducible, and available to industry and official agencies, and (3) be attainable with existing technology.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

The first major industrial use of benzene was as a solvent in the rubber industry just preceding World War I. [1] During World War I, benzene production was stimulated greatly by the demand for toluene in the manufacture of explosives. The large quantities of benzene which were produced resulted in its more widespread use as a starting point for the manufacture of various organic compounds. This situation led to greatly increased uses of benzene as a solvent in the artificial leather, rubber goods, and rotogravure printing industries, and as a starting material in organic syntheses. [1]

Benzene is a clear, colorless, noncorrosive, highly flammable liquid with a strong, rather pleasant odor. Its physical properties are given in Table XII-1. Today, it is obtained primarily from the petroleum industry where it is produced as a petrochemical from paraffinic hydrocarbons. [2,3] It is also recovered from the gases and coal tar in coke oven operations. The major impurities in commercial benzene (benzol) are toluene and xylene although the commercial form may also be contaminated with phenol, thiophene, carbon disulfide, acetyl nitrile, pyridine, and other substances. "Benzol 90" contains from 80-85% benzene, 13-15% toluene, and 2-3% xylene. The "90" designation refers to the percent of total liquid, by volume, which distills below 100 C.

Industries and processes using benzene include coke and gas, chemical, printing and lithography, paint, rubber, dry cleaning, adhesives, petroleum, and coatings. [2,4] Benzene is also used extensively in chemical laboratories as a solvent and reactant in numerous chemical applications. [1,5]

During 1967, nearly 800 million gallons of benzene were produced in the United States [3] and by 1969, this figure had increased to 1,185 million gallons with approximately 16% of the production derived from coal. [6] About 87% of the benzene output is used chiefly as an intermediate in producing other organic chemicals such as phenol, cyclohexane, and styrene (see Table XII-2). [3] The remaining amount (13%) is used primarily in the manufacture of detergents and pesticides with small amounts of benzene being used in solvents and paint removal formulations. Benzene is also present in gasoline. [7,8] Petrols (gasolines) in the United Kingdom were reported by Sherwood [9] to be as high as 6% in benzene content and an ad hoc report [10] on European gasolines showed that most of the gasolines tested during 1970 to 1972 were in the 5% range with some up to 16%. Benzene analyses reported in 1972 [11] of 37 unleaded and low-lead gasolines from 15 companies in the United States showed a range from 0.3-2.0% benzene content by volume with an average of 0.8%.

Benzene may also be a component in commercial grades of toluene, xylene, and multicomponent solvent mixtures whose composition varies with intended usage. [5] It is a significant component, ie, 3% or more, in numerous hydrocarbon mixtures such as the aromatic petroleum naphthas whose boiling ranges encompass that of benzene. [5,12]

Although benzene is used generally in enclosed systems wherever possible, exposures can occur from liquid transfer operations, from equipment leakage, from carryover losses, and in maintenance operations.

Exposures also occur from its use as a solvent component in small plant open systems. [1,5]

NIOSH estimates that 2,000,000 persons in the work force have potential exposure to benzene.

Historical Reports

The early uses of benzene, particularly as a solvent, resulted in widespread exposures of workers to its vapor with levels regularly around 500 ppm and some in excess of 1,000 ppm (3,200 mg/cu m). [13]

In 1909, three 14-year old Maryland girls became ill and, within 1 month, 2 of them died following exposure for a period of 4-5 months to the vapors of a commercial grade of benzene used as a rubber solvent in sealing tin cans. [14] Leukopenia was the most striking feature of the blood examination. One girl entered the hospital with a leukocyte count of 1,280 cells/ cu mm which dropped to 480-600/cu mm before death. The second girl was hospitalized with a count of 560 which dropped to 140/cu mm before death. In both cases, there were relative decreases in the polymorphonuclear elements of 43% and 18%, respectively, and the red blood cell counts dropped to 640,000/cu mm in the first girl, and to 1,150,000/cu mm in the second. Both deaths occurred 6-7 days after admission to the hospital. No mention was made of the outcome of the third case.

Numerous other early reports of fatal cases of benzene poisoning have been mentioned in review articles by Greenburg in 1926 [1] and Hamilton in 1931. [15]

Early cases of chronic benzene poisoning include those reported in England by Legge in 1920 [13] of 2 men engaged in spreading balloon fabric with rubber. Legge's report provided the first measurements of benzene levels in workroom atmospheres to which workers were exposed on a chronic basis. The exposure levels were determined by the firm's chemist and for many of the operations they ranged from 2.1-8 parts/ 10,000 (210-800 ppm) with a peak concentration of 1,050 ppm measured "in front of a fan and at back of machine, machines on both sides, both spreading." However, Legge pointed out that considering the amount of benzene which was being consumed in the poorly ventilated spreading room, the concentration at the end of 1 hour could theoretically have been as high as 16,800 ppm.

With the expanded use of benzene in industry after World War I, an increasing number of reports of chronic benzene poisoning of workers began to appear in the literature. [1,16-18] Because of the seriousness of benzene poisoning, investigations were directed to the many aspects of the cause, recognition, and control of the disease; the results from this research were prominent in the occupational health literature. [19-22] The growing recognition of the hazard associated with the use of benzene led gradually to the substitution of other solvents and an accompanying decrease in the incidence of cases of benzene poisoning.

Effects on Humans

(a) Effects of Inhalation

Browning [23] reported that fatal cases have usually occurred when benzene was inhaled in enclosed spaces such as in tanks containing residues of benzene, and that 13 such cases were reported in Great Britain between 1941 and 1959. The effects observed following such severe exposures were convulsive movements and paralysis followed by unconsciousness. Milder forms of acute intoxication produced an initial state of euphoria followed by giddiness, headache, nausea, a staggering gait and, if not removed from exposure, a state of unconsciousness. Recovery depended upon the severity of the exposure.

Gerarde [24] noted that breathlessness, nervous irritability, and unsteadiness in walking may persist for a period of 2-3 weeks; furthermore, delayed effects may arise and persist long after the acute incident. The postmortem findings in cases of acute benzene poisoning include extensive petechial hemorrhage in the brain, pleurae, pericardium, urinary tract, mucous membranes, and skin.

Flury [25] stated that single exposures to benzene vapor in the atmosphere at 20,000 ppm may be fatal within 5-10 minutes; 7,500 ppm will produce toxic effects if inhaled for 0.5-1 hour and an exposure to 3,000 ppm may only be tolerated for 0.5-1 hour.

(b) Effects of Oral Exposure

Cases of illness or death resulting from the accidental ingestion of a fluid containing benzene have been reported. [26,27] Liquid benzene causes a local irritation of the mucous membranes of the mouth, throat, esophagus, and stomach. [24] The subsequent absorption of ingested benzene into the blood leads to signs and symptoms of systemic intoxication. [24] The ingestion of a tablespoonful of benzene has been known to cause collapse, bronchitis, and pneumonia. Ingestion as a route of entry of benzene in industrial situations is unlikely except in accidental or intentional situations.

(c) Effects of Skin Exposure

Dermal contact with liquid benzene may cause erythema and blistering of the skin and a dry, scaly dermatitis may develop on prolonged or repeated exposure. [24] Investigations of the percutaneous absorption of benzene have been very limited and from which only qualified estimates can be made.

In 1946, Cesaro [28] reported no observable change in the urinary inorganic sulfate to total sulfate ratio as evidence of absorption of benzene during 20- to 30-minute exposures of the arms or whole bodies of male human subjects to cotton soaked with benzene.

Conca and Maltagliati [29] in 1955, also reported no urinary sulfate changes and detected no benzene in the expired breath of 3 men whose arms had been immersed in benzene for 25-35 minutes. A colorimetric method of unstated sensitivity was used for the breath analyses.

In 1961, Hanke et al [30] reported the rate of human skin absorption of liquid benzene applied under a closed cup as 0.4 mg/sq cm/hr using an ultraviolet spectrophotometric method to determine the amount of benzene remaining from a known quantity exposed to the skin for 10-15 minutes under controlled conditions. This compared with later findings by his coworkers of 22-23 mg/sq cm/hr for ethylbenzene [31] and 14-23 mg/sq cm/hr for toluene. [32] These findings support the belief that liquid benzene is poorly absorbed through the intact skin.

(d) Absorption, Distribution, Metabolism, and Excretion

Srbova et al [33] in 1950 reported on 23 human volunteers exposed to benzene vapor at levels ranging from 47-110 ppm. The subjects inhaled a mixture of air and benzene, usually for 2 hours (occasionally for as long as 3 hours), during which time samples of inhaled and exhaled air were taken every 15 minutes and analyzed polarographically. Blood and urine samples were also collected and analyzed at different times. The absorption of benzene was reported to be greatest during the first 5 minutes, decreasing rapidly thereafter, and becoming constant after approximately 15 minutes of exposure. After 1 hour, approximately 50% of the inhaled benzene was absorbed. Following benzene exposure, 30-50% of the absorbed benzene was eliminated through the lungs, only 0.1-0.2% was eliminated unchanged through the kidneys, and the remainder was metabolized. Complete equilibrium between the concentrations of benzene in the air and in the blood was not achieved because the duration of the experiments was too short. Benzene removal through of the lungs was also followed in 10 subjects with 16.4-41.6% of the retained benzene being eliminated within 5-7 hours. The rate of benzene elimination was greatest during the first hour and decreased slowly thereafter.

Teisinger et al [34] in 1952 reported on exposing 15 human subjects to an average benzene vapor concentration of approximately 100 ppm for 5 hours. They reported an average retention of 46% of the inhaled benzene, elimination of 12% through the lungs following exposure, and only 0.1-0.2% of the unmetabolized benzene eliminated in the urine. Approximately 29% of the absorbed benzene was metabolized and excreted in the urine in the form of phenol, 2.9% as pyrocatechol, and 1% as hydroquinone.

In 1946, Duvoir et al [35] reported that in subjects exposed to 6,000 ppm of benzene 28-34% was retained and absorbed into the blood. The authors found that approximately 55-60% of the benzene in the blood became fixed in the bone marrow, fatty tissues, and the liver. The remaining 40-

45% was excreted unchanged through the lungs. The absorbed portion was then metabolized through oxidation to phenol and diphenols and eliminated as such or as esters of sulfuric and glucuronic acids. Through this metabolic process, benzene decreased the organic sulfate reserve.

Hunter, [36] using gas chromatographic analysis, stated that at a benzene concentration of approximately 35 ppm a healthy adult male reached a relatively steady state in approximately 5-7 minutes. Approximately 47% of the benzene in the inhaled air was absorbed. The major portion of the urinary phenols was conjugated with glycine, sulfuric acid, or glucuronic acid with up to 8% of the phenols being excreted in the free form.

According to Gerarde, [2] benzene saturation of the circulating blood is very rapid, reaching a 70-80% saturation level within 30 minutes. Relatively complete saturation, however, may require as much as 2-3 days. The author suggested that the fatty tissue, which has a great affinity for benzene, removes and stores the benzene carried by the blood; however, this fatty tissue in many instances has a very meager blood supply and requires a relatively long period to attain equilibrium.

Benzene is best known in industrial exposure situations for its chronic forms of poisoning and specifically for its injurious effect on the hematopoietic system.

Erf and Rhoads [20] presented in 1939 the results of blood findings in 9 individuals, 6 of whom were rotogravure printers employed in a plant from which Greenburg et al [17] also reported on an investigation (see Epidemiologic Studies). The authors stated that "no correlation between the severity of disease and the intensity of exposure can be made." The duration of exposure ranged from 6 months to 3 years, with the symptoms of poisoning being present from 1-6 months before medical aid was sought. The hematologic findings varied; however, anemia, leukopenia, thrombocytopenia, and elevated reticulocyte levels were present in all cases. Biopsy tissue from the sternal bone marrow of 8 of the patients showed microscopic changes varying from a hypoplasia with immature cellular elements to a hyperplasia with normal maturation. Following 2-5 months of treatment, 8 of the 9 patients were clinically improved; the ninth subject developed leukemia and died. In 1918, the man had worked with his brother in a studio where benzene was used. During that year his brother developed epistaxis and anemia and died. The man then changed his occupation without further exposure to benzene until 17 years later when he obtained employment in the rotogravure plant where he was exposed to benzene vapor for 14 hours a day. Upon hospitalization, leukemia was diagnosed. He did not respond to treatment, the WBC increased in number to 137,000/cu mm with the majority being identified as myelocytes, and the spleen and all peripheral lymph nodes became enlarged. After 5 weeks of therapy he left town and died 2 months later in another city. Post-mortem examination revealed a diffuse infiltration of the organs with immature myeloid cells, a finding typical of myeloid leukemia.

In 1967, Stewart et al presented information concerning 10 chronically exposed benzene workers. Only an abstract of the paper was reported [37]; subsequent publication of the data of potential importance has not resulted. The workers, chronically exposed to benzene (less than 25 ppm) for several years, were accidentally overexposed (85-115 ppm) to benzene for a period of 3 months. Six complained of fatigue and all showed signs of mild anemia. Nine of the 10 recovered in 4-8 months after which time they were returned to the benzene area and were maintained under a strict medical surveillance program. It included continuous breathing-zone monitoring and frequent analysis of breath for benzene vapor.

Epidemiologic Studies

The signs and symptoms of chronic benzene poisoning can effectively be described from a report by Helmer [38] in 1944. Because of the difficulties in importing appropriate solvents during World War II, the use of benzene increased markedly in a Swedish plant which manufactured rubber raincoats. Work was performed on a conveyor belt with alternate sewing and gumming, the latter being done mainly by hand on open tables using a solution of 10% rubber in heated benzene. The total amount of benzene used was unspecified; however, at full worker capacity, about 50 kg of benzene evaporated in an 8 1/2-hr workday. The atmospheric benzene concentration was estimated to be approximately 17 mg/liter (5,320 ppm) based upon its rate of consumption and even distribution over the premises. The work force had been reduced to one-third of normal along with reduction in the total output (8 kg benzene consumption/workday) when inspections were conducted by the State Institute of Public Health. With the decreased benzene consumption and fan-installed improved ventilation, environmental analysis showed a benzene content of 0.44-0.70 mg/liter of air (140-220 ppm). There had been no mechanical provisions employed for exhaust ventilation before cases of benzene poisoning were encountered. The study showed that 184 workers (169 women and 15 men) from the rubber plant, of which 60 workers (58 women and 2 men) were entered on the sick list suffering from chronic benzene poisoning. In those workers afflicted, headaches (73%) and fatigue (88%) were prominent, persisting for many months, even after the blood picture had improved markedly. The subjects complained of having to lie down after performing very simple household chores and not even being able to take short walks. There was an increased tendency to bleed; cutaneous hemorrhages were noted (48%), mainly in the legs and arms. The hemorrhages were often large with initial spreading, and would appear without demonstrable trauma. Other abnormal bleeding occurred in the gums and nose, as well as irregular, sometimes more frequent and copious menses. The latter affected only women who had suffered more serious blood changes. Other common troubles included nervousness, vertigo, somnolence or sleeplessness, shortness of breath, and palpitations. Dyspeptic disorders, nausea, vomiting, and loss of appetite appeared in 22% of the cases. Two subjects complained of a benzene taste in the mouth. Skin changes were manifested in the form of itching, possibly with pruriginous papules or slight dermatitic changes. There was a loss of weight in 9 cases, some up to 10 kg (approximately 22 pounds) in one year. There were reports of prickling sensations in the arms and legs. Eight subjects complained of smarting in the eyes. It was pointed out, both by Helmer [38] in this study and by Greenburg et al, [17] that symptomatic effects often do not correlate with objective findings. Symptomatic effects may be absent, even in serious cases of chronic benzene poisoning.

The unique aspect of chronic benzene poisoning resulting from exposure to benzene vapor over prolonged periods of time is its effect on the blood-forming system. There is a distressing lack of exposure-effect data in the literature; therefore, only approximations of worker exposure can be made. One exception is the early account in 1926 by Greenburg [19] in which he reported on the complete blood counts (CBC) of workers exposed to concentrations of benzene ranging from 90-1800 ppm (undescribed sampling and analytical method) in 18 workrooms during both winter and summer seasons. The data enable estimates of the effects of local ventilation and seasonal changes on the benzene content in the air. Even so, concentrations were reported as averages; ranges are unknown but may have an important bearing on individual workers, especially those determined to be positive (see below). Summaries of the blood findings and average benzene-in-air concentrations are presented in Tables XII-3 and XII-4. Originally, the most important early sign of benzene poisoning was thought to be the change in the white blood cell (WBC) count. Greenburg considered cases as positive which showed less than 5,500 WBC/cu mm (7,500-9,000 was considered the normal count). A reduction of the WBC count to less than 4,000 and the red blood cell (RBC) count to less than 4 million /cu mm was found in 10 of 26 workers. Three of 8 workers studied in detail showed less than 50% polymorphonuclear leukocytes, 2 showed a lymphocyte population greater than 45%, and 2 showed eosinophils of more than 5%. In all groups listed in Table XII-3, there were workers who showed a picture of chronic benzene poisoning as judged by reductions in the WBC count. The hazard from the use of benzene was evidently not entirely removed at average benzene concentrations in the vicinity of 70-90 ppm. Variations were noted in the individual susceptibility to benzene poisoning as well as to wide variations in the quantities of benzene used during the year; therefore, only qualified estimates can be made to correlate the benzene exposure levels with the clinical findings.

In 1939, Greenburg et al [17] reported on the results of blood examinations performed on 332 workers exposed to benzene vapor in 3 rotogravure plants. In Plant A, exposures ranged from 50 to over 1,000 ppm; in Plant B, from 24-675 ppm, and in Plant C, from 11-57 ppm in the first floor pressroom, from 182-298 ppm in the proofroom, and from 25-200 ppm in the 11th floor pressroom. The method of sampling and analysis was not described. The extensive results of the blood tests were grouped for the workers from the 3 plants which prevents relating the blood findings to the reported exposure levels in the separate process areas. Of the 332 workers examined, 130 were found to be suffering with varying degrees of benzene poisoning, 22 of these to a severe extent whereas 43 were early cases. The RBC count was less than 4.5 million in 48% of these subjects, the platelets were less than 100,000 in 33%, and the WBC count was less than 5,000 in 15% of the total workers, in 30% of the early cases, and in 86% of the 22 severe cases of poisoning. The hemoglobin (Hgb) was less than 13 g/100ml of blood in 15% of 235 workers examined.

From the detailed blood studies which were performed on 102 of the workers, the incidence of significant abnormalities has been summarized and is presented in Table XII-5. In the early mild cases, the most frequent changes were a reduction in RBC (72.1%) and an increase in average cell size (58.1%). Since macrocytosis was also shown (24.3%) in the 9 otherwise negative cases, it was suggested that an increase in mean corpuscular volume (MCV) and a reduction in the RBC count constituted a more sensitive index of benzene poisoning than did WBC reduction. Various combinations of the 5 most commonly used blood tests (Table XII-6) indicated that 82% of poisoning cases could be revealed by a combination of MCV and RBC determinations. It was possible to detect poisoning in even more workers when the determinations were combined with WBC counts (93%) and finally, 97% when thrombocyte examinations were added.

Savilahti [39] described in 1956 the clinical findings of 147 workers exposed to benzene for more than 10 years in a shoe factory where air analyses at 3 working stations 6 months preceding the medical study provided average benzene values of 318, 433, and 470 ppm, respectively. Hematologic abnormalities were found in 73% of the workers; thrombocytopenia, 62%; leukopenia, 32%; anemia, 35%; and anemia, leukopenia, and thrombocytopenia simultaneously in 31 subjects. Of those affected, 1 died and 120 became asymptomatic within 3 months following removal from exposure to benzene. Of the remainder, 1 patient was still in the hospital after 1 year, 6 were at home on sick leave, and 20 continued to show relatively minor hematologic symptoms.

Juzwiak [40] published in 1969 the results of blood examinations on 585 persons employed in 13 shoe plants where they were exposed to benzene vapor. From 1960 to 1963, "Butapren" glue was used, consisting of (literally translated) 40% extraction benzene (probably petroleum benzin), 26% technical benzene, 2% toluene, 26% ethyl and butyl acetates, and other "harmless components." Fluctuations in mean benzene concentrations from 0.1-0.5 mg/liter of air (31-156 ppm) were reported. In 1964, the toluene content of the glue was increased to 29% to replace the technical benzene entirely; nevertheless, mean benzene concentrations of 0.13-0.14 mg/liter (41-44 ppm) were still recorded. In addition to the toluene, gasoline was also known to be present in the chemical composition of the glue. Commercial toluene and gasoline regularly contain benzene. Seventy-three

present in the chemical composition of the glue.

percent of the workers were reported to have reduced RBC counts, 8.5% had reduced WBC counts, and 91% had reduced Hgb levels. Again, the lack of adequately documented environmental data in support of medical findings precludes any confident correlation of exposure and effect.

Cases of leukemia reportedly due to benzene exposures first appeared in the literature of the 1930's. [17,22] Mallory et al, [22] in 1939, presented necropsy or biopsy protocols from 19 cases having chronic exposure to benzene. They pointed out that early phases of benzene poisoning were not exemplified in their report since all but 3 of the cases were fatal and the early death of 1 of the remainder was expected, based on a diagnosis of aleukemic leukemia. None of the reported cases had less than 6 months' contact with benzene vapor and only 4 cases had less than a year's exposure. Table XII-7 lists the presumptive duration of contact and interval between the last contact and death or biopsy in the 19 cases of chronic benzene poisoning. Of special note are 2 cases of verified leukemia:

(1) The subject had been exposed to benzene for 10 years and, according to the authors, had shown hematologic evidence of benzene poisoning. He developed a typical picture of acute myeloid leukemia in the last 3 months of his life. Autopsy showed the characteristic myeloid infiltration of the liver, spleen, and bone marrow. In addition, a true leukemic tumor, 4 cm in diameter, was localized in the liver.

(2) A boy of 12, a painter's son, played in his father's shop, frequently using a paint remover known to contain benzene to remove coats of paint from toys. He developed a clinical picture of aplastic

anemia but tissue biopsy revealed a typical leukemic replacement of the marrow.

The authors described "a neoplastic tendency" for benzene as evidenced by the degree of aplasia, excessive mitotic figures, and all development having no counterpart in normal tissues but common to malignant tumors. They concluded that the evidence that chronic exposure to benzene produced leukemia in human beings was incomplete but sufficient to command serious consideration.

Vigliani and Saita [41] reported in 1964 on 6 cases of benzene-associated leukemia which had been observed by them. Meager environmental data were presented which applied to 2 of the cases.

(1) A 38-year-old man became an operator in a rotogravure firm which used inks containing 40% benzene. According to the authors, the benzene concentration in the department where the man worked varied between 0.60 and 2.10 mg/liter of air (190-660 ppm). Four years later, he was hospitalized with generalized depression of the formed elements of the blood. Post-mortem findings were myeloid metaplasia of the liver and spleen.

(2) A 24-year-old man began work in the same rotogravure department as the operator described above. Seven years later (1945), when the first worker died of leukemia, some of the other workers in the department showed signs of benzene poisoning and were examined; however, benzene poisoning was apparently not suspected in this man and he was not examined. It is not known whether he had been examined prior to the death of his colleague. In 1949, at the same time the plant replaced benzene with other solvents, he showed a slight leukopenia. Subsequent quarterly

routine medical examinations showed him normal until 1961 when serious signs and symptoms of leukemia appeared. In spite of intensive therapy, death occurred approximately 1 year after the clinical appearance of the disease.

The incidence of benzene-induced chromosome changes in peripheral blood lymphocytes or bone marrow has received increased interest. [42-49] Significantly increased rates of "unstable" and "stable" chromosome aberrations were observed and were still present several years after cessation of exposure to benzene. [48] Followup studies showed a tendency toward a decrease in unstable chromosome changes and a persistence or an increase in stable changes. Occasional abnormal clone formations were observed. These changes are similar to those reported in individuals with past exposure to ionizing radiations, both therapeutic [50] and accidental. [51-53] According to Forni et al, [48] the implications of the chromosome findings with respect to the problem of benzene leukemia are not clear. Persistent chromosome changes in lymphocytes seem simply to indicate that damage has occurred. However, stable chromosome changes in the bone marrow might give rise to leukemic clones, as has been demonstrated in 2 reported cases of benzene-associated leukemia. [44,45] An interesting case involving pregnancy was reported by Forni et al [48] in which a patient, while severely pancytopenic and with severe hemorrhagic problems, delivered an apparently normal boy. All chromosome studies in the patient showed an increased rate of chromosome aberrations; however, a cytogenetic study of the peripheral blood performed on the newborn boy did not show chromosomal abnormalities. In 1969, the patient had another pregnancy and delivered a normal daughter.

In reviewing reports of chromosomal aberrations observed by Pollini and Columbi, [42] Vigliani and Saita [41] suggested a possible mutagenic effect on blood cells which may help to explain the appearance of leukemia during the course of a benzene hypoplastic anemia. The authors made no conclusion concerning the existence of a true "benzene leukemia" because of a lack of extensive analysis of the incidence of leukemia among workers exposed to benzene as compared with that of a carefully evaluated control group. In a leukemia survey reported by Thorpe, [54] emphasis was placed on the need for improvement in the recording and storage of biological observations, job histories, occupational exposures, and demographic data. A comparison by Vigliani and Saita [41] of the incidence of acute leukemia among the general population in Milan from 1959 to 1961, however, indicated an incidence of about 1 case among 20,000 people. Statistics from the Italian National Institute for Insurance Against Accidents and Occupational Diseases as reported by Vigliani and Saita [41] showed a sharp rise in the reported cases of acute leukemia among local residents in 1962 to 1963, coinciding with the increase in cases of benzene poisoning in workers. The rise in leukemia cases was about 20 times higher than expected. The incidence of leukemia was especially striking when the fatal general population cases were considered: out of 26 deaths, 11 were due to leukemia and 15 to aplastic anemia. [41] Their figures corresponded well with those of Cavignaux [55] for 1960 and 1961 which pointed out the high incidence of leukemia among cases of benzene poisoning in France. Vigliani and Saita [41] emphasized that, "Great caution must be exercised before admitting the benzene etiology of chronic myeloid or lymphatic types of leukemia."

Browning [23] has tabulated 60 cases of leukemia among benzene workers in her 1965 text. She found no correlation between the original authors' reported medical findings and benzene exposure levels.

In a 1969 report of the health status of 765 female workers in the leather industry in Lodz, Poland, Butarewicz et al [56] provided data showing blood changes in 18.6% of 350 workers exposed to a benzene-containing adhesive, as compared with blood changes in only 5% of 246 workers exposed to a benzene-free glue and 3.5% in 169 control female workers who were not exposed to either of the adhesives. The atmospheric benzene levels were not well defined, the highest concentrations noted in one of the zones being reported as more than 1.2 times (37 ppm) the maximum permissible concentration of 100 mg/cu m (31 ppm). There were wide variations in the air analyses as a function of the season, room temperature, the number of dryers operating, and the efficiency of the ventilation; therefore, essentially no exposure-effect comparisons can be made. Such a large population of workers exposed to benzene in recent years would have provided an excellent opportunity for the development of correlative data between blood changes and other medical findings with measured environmental exposures to benzene.

The study of Hardy and Elkins [57] in 1948 emphasized that benzene poisoning, as evidenced by laboratory blood studies, frequently occurred without any indication of clinical signs or symptoms. A small Massachusetts rubber coating firm experienced the death of an employee which was diagnosed as benzene poisoning. Subsequently, a blood study was performed on all 52 workers employed by the company. Sixteen workers showed deviations in more than 1 blood element. The results of air analyses, taken on 3 different occasions, are listed in Table XII-8 and indicate what the authors termed remarkable uniformity. There had been no significant changes in the ventilation of the plant or in the plant's operational procedures during the 8-year period preceding the complete blood study; however, during the wartime period of 1942-1946, most of the men had put in considerable overtime work, "averaging much more than eight hours a day." According to the authors, [57] of the 16 men with abnormal blood pictures, 6 worked in the coating room and, in all probability, were exposed to average benzene concentrations of not over 60 ppm; 2 men who worked in the mixing room were possibly exposed to 80 ppm; and 1 man who cleaned the cans may have had a considerably higher exposure. Followup studies of the 16 workers, either 4 months or 10 months later, showed only 4 workers with relatively normal hematologic values at the time the report was written, 10 months after benzene exposure ceased entirely. It was concluded from this study that the maximum allowable concentration of 75 ppm of benzene which was accepted by the State of Massachusetts at that time was too high, and subsequently the figure of 35 ppm was used.

Additional data on effects of benzene on the blood picture were provided in 1961 by Pagnotto et al [12] from a study of the Massachusetts rubber coating industry. By that time, the use of benzene as an industrial solvent in large quantities had diminished considerably; however, petroleum naphthas containing varying amounts of benzene up to 9.3% were used heavily in the rubber coating industry. Their study covered 11 plants which involved practically all the large Massachusetts plants and some of the smaller ones. Of 65 environmental determinations taken, only 4 were recorded above 40 ppm, the highest being 125 ppm. Air sampling and

smaller ones. Of 65 environmental determinations taken, only 4 were

analyses were performed by collecting the benzene vapor on silica gel and analyzing the desorbed benzene by ultraviolet spectrophotometry. In addition, urinary phenol determinations were performed on 162 workers and compared with the atmospheric exposure levels as shown in Figure XII-1. According to the authors, it was apparent from the air-urine correlation that the phenol test was a good index of benzene exposure. A limited number of Hgb determinations were also performed on workers in 3 of the plants. The results of the blood tests on 47 men representing spreader, saturator, and churn operations showed in Plant A, 5 out of 27 workers had Hgb levels below 13.5 g/ 100 ml of blood and 2 out of 32 had RBC under 4 million/cu mm. In Plant B, 1 worker out of 9 examined showed deviations in Hgb and RBC below the criteria listed for Plant A. No abnormal findings were reported in Plant C.

The domestic and foreign literature dealing with the effects of benzene on exposed workers consists primarily of medical reports rather than documented, comprehensive frequency and distribution studies encompassing both medical and environmental findings. Published definitive epidemiologic data have been difficult to find on workers exposed to benzene vapor at specific concentrations for prolonged periods of time.

Kozlova and Volkova [58] in 1960 reported on observed changes of the formed elements of the blood and phagocytic activity of leukocytes in workers exposed to benzene in a leatherette factory over a study period of 5 years, 1953-1957. The blood changes were studied in 252 production workers; phagocytic activity of leukocytes was also determined from 157 of the subjects. Environmental concentrations of benzene fluctuated from 150-1,000 mg/cu m (47-310 ppm) during the first 3 years of the study. At the end of 1955, environmental concentrations were reduced due to installation of improved control measures, and in 1957, exposure levels reportedly did not exceed 80-150 mg/cu m (25-47 ppm) average concentrations. Worker job assignments remained relatively unchanged during the course of the 5-year period. Phagocytic activity of leukocytes was measured by the average number of bacteria engulfed by neutrophils in a 1 1/2 billion suspension of Bacillus Fridmani. For analysis of the data, 3 groups were selected based upon environmental benzene levels in the plant areas. Group I, consisting of 121 workers, was exposed at benzene concentrations exceeding 250 mg/cu m (about 78 ppm) which was more than 5 times the then existing maximum permissible concentrations of 50 mg/cu m (16 ppm). Group II consisted of 60 workers exposed to concentrations of 100-200 mg/cu m (31-62 ppm), 2-4 times the maximum permissible concentration, and Group III, 71 workers not having production assignments involving benzene but whose exposures were from 75-125 mg/cu m (24-39 ppm) due to benzene vapor in the proximity of the main production areas. The Group III exposure levels were 1 1/2 to 2/1/2 times the maximum permissible concentration. Marked alterations of blood formed elements were reported for all groups and the authors [58] noted that decreased leukocyte and thrombocyte counts were observed more frequently in workers employed 5-10 years than were changes in erythrocyte composition. Furthermore, it was stated that with prolonged contact with small concentrations of benzene (Group III exposure levels), leukocyte depression occurred prior to depression of the erythrocytes. In Groups I and II, the prevalence of neutropenia was closely related to the length of worker employment. Because of the leukocyte depressions observed, and particularly with the neutrophils, it was believed that phagocytic activity provided a measure of individual susceptibility to benzene. Phagocytic activity was decreased in 86% of Group I workers and 60% of Group III workers. It was found that phagocytic activity of the leukocytes, as a rule, decreased in the majority of workers sooner than blood alterations were noted. It was suggested that phagocytic activity of the leukocytes was a more sensitive test for benzene poisoning than was observation of morphological changes of the blood.

Horiuchi et al [59] presented in 1963 the effects of benzene exposure in 373 male workers engaged in paint manufacture of coating operations in 14 workshops. Thirty-minute breathing zone samples were taken along with clinical laboratory tests which included complete blood cell counts, specific gravities of whole blood and serum, urinary coproporphyrin and total sulfate ratios, and subjective clinical symptoms obtained by a questionnaire. Workshops were grouped according to the range of benzene concentrations encountered as: Group I, 6.6-78.5 ppm; Group II, 3.4-35.9 ppm; Group III, 0.3-22.1 ppm; and Group IV, trace-1.8 ppm. From the frequency of "abnormal" findings (unspecified as to what constituted abnormal) it was concluded that effects noted in Group IV were essentially the same as for workers not exposed to benzene. Based on the higher incidence of abnormal findings in Groups I and II compared with Group III, the authors concluded that the maximium allowable concentration of benzene in the workroom air should be below the maximum encountered in Group III, that is, approximately 20 ppm.

Followup studies [LD Pagnotto, written communication, October 1972] of the rubber coating industry originally reported by Pagnotto et al [12] were made through 1963 and results are summarized in Table XII-9 for Plant

A for which the most complete information was available. Two naphtha solvents were used in Plant A, (3% and 7.5% benzene by volume) until 1965 when toluene-containing solvents were introduced. Table XII-9 lists 12 of 35 workers who were involved in the study. Although information is minimal, the table provides information as to environmental benzene concentrations and worker exposures as measured by urine phenol levels over a 3 1/2 year period from 1960 through 1963. Environmental benzene concentrations for spreader and churn operations consistently averaged between 20 and 25 ppm and frequently were lower. The saturator operation indicated fluctuations as high as 140 ppm and it appears that saturator environmental levels in the vicinity of 70-90 ppm were encountered rather frequently. Of particular significance is the generally close agreement observed between environmental benzene concentrations obtained from laboratory analysis and equivalent air levels for individual worker exposures as determined from Table XII-10. This again indicated the value of urinary phenol determinations as a measure of exposure to benzene.

Blood Hgb levels of some of the workers are listed in Table XII-11. The data are very meager and no firm conclusions can be drawn from the information. In one of the 1961 studies, 27 workers were tested and 6 were found to have Hgb levels below 13.5 g/100 ml of blood. In the 1963 study, 12 of 24 workers examined were reported to have normal blood pictures. The remainder were said by the company to show minor deviations from normal, although these differences were unspecified and the information was unavailable. Blood studies from Worker L were reported to have had an appreciable deviation from the normal. There was no knowledge of his blood picture prior to being hired by the rubber coating firm. He was removed

appreciable deviation from the normal. There was no knowledge of his blood

from the job in 1963. Worker H was the saturator operator reported in Table XII-9 and had the highest benzene exposures. He was still working at the saturator job in June, 1967.

(a) Sex, Pregnancy, and Age

In 1939, Hunter [21] reported on a study of 70 male and 19 female workers exposed to benzene whose histories, physical examinations, routine urine and complete blood examinations were conducted over a period of 4 years. The workers were divided into 3 main classifications consisting of group 1, those showing a normal blood picture; group 2, those showing only 1 abnormal feature; and group 3, those showing 2 or more deviations from the normal. Two of the 10 fatal cases in the study were female. In one factory where 43 workers were studied, although the only fatal case was a young girl, 26 of the workers were men (60.5%) and about 28 of them (64%) had a depression of the polynuclear percentage. The author found no supporting evidence that women were more liable to development of benzene poisoning than men and suggested that facts from the study cast considerable doubt on whether a female hypersusceptibility to benzene existed. Hunter emphasized that the early diagnosis of benzene poisoning depends upon an evaluation of the complete blood picture rather than upon the existence of a leukopenia alone. No environmental exposure data were given in this report.

Mallory et al [22] in a companion paper to that of Hunter suggested from either necropsy or biopsy material obtained from 4 females and 12 males that hypoplastic reactions might be more common in the female than in the male, thus supporting an opinion at the time that females were more susceptible than males to the effects of benzene poisoning. The authors recognized that their figures were too few to be conclusive.

In 1928, Smith [16] reported on a study of 79 women, 25 with confirmed chronic benzene poisoning and 5 suspected cases. Complete histories were obtained which were designed to reveal past and present exposure to benzene. In addition, complete blood counts were taken, consisting of Hgb, RBC, and WBC, including differential counts. Findings were not compared with those of male workers but the results did not differ from those reported in men by other investigations. The age spread of the women studied was quite evenly distributed from 17-52 years. The author found that susceptibility to benzene poisoning appeared to be about equally marked among young and older women and that youth did not seem to be a predisposing factor in the development of benzene poisoning. In addition, the menstrual function was undisturbed in the majority of positive and suspected cases. The few incidences of menstrual irregularities were not considered to be of concern.

In 1956, Cassan and Baron [60] mentioned the greater susceptibility of women to benzene poisoning, particularly when they were pregnant. Because the study involved women exclusively, no firm conclusions may be drawn from this report regarding sex differences in susceptibility to benzene poisoning.

Savilahti [39] reported in 1956 that he did not find any correlation between age, sex, and symptoms of benzene poisoning in the study of 147 workers (98 women, 49 men). Subjects showing abnormal blood changes ranged in age from 16-66 (average=36) while those unaffected were from ages 18-66 with an identical average age. Twenty-four of the 41 female workers and 18

in age from 16-66 (average=36) while those unaffected were from ages 18-66

of the 35 male workers became ill; thus, no significant differences were observed between age or sex.

Animal Toxicity

(a) Acute Exposures

Lazarew et al [61] reported in 1931 that liquid benzene could be absorbed through a rabbit's paw by measuring the weight increase resulting from the absorption of benzene vapor by activated silica gel from the exhaled air after preliminary removal of water and carbon dioxide by phosphorus pentoxide and soda lime. The animal served as its own control by providing an exhaled air sample through a tracheal canula for analysis preceding the 30- to 60-minute exposure. The weight increases of the silica gel adsorption tubes during the experimental runs were 2-3 times greater than the controls. No quantitative data were available and the degree of benzene absorption is unknown.

In 1944, Carpenter et al [62] described their observations of ten rabbits undergoing anesthesia with 35,000-45,000 ppm of benzene vapor in air. The average time required for light anesthesia was 3.7 minutes, 5.0 minutes for excitation and tremors; death ensued in approximately 36 minutes.

In 1965, Jonek et al [63] reported on a histochemical study of enzymatic changes in the central nervous system of mice subjected to acute benzene poisoning by single inhalation exposures at the 60 mg/liter (18,750 ppm) and compared the findings to those observed in a control group. Changes in the activity of enzymes suggested a selective influence of benzene on oxidation in neurons. This reaction was not the same in all neurons; some showed enzymatic activity similar to that observed in the control group, while in others, activity was less than that in the controls or even absent. The authors postulated that the observed changes in the enzyme activities may be the result of a direct lesion of the lipoprotein membranes of the structural elements of the cells by benzene or the products of benzene metabolism.

(b) Chronic Exposures

In 1941, Schrenk et al [64] reported, in an extensive study of dogs exposed continuously (24 hr/day), intermittently (4- or 8-hr/day), and singly to benzene vapor, that (1) the initial absorption of benzene was extremely rapid (nearly complete within 30 minutes) with later absorption approaching equilibrium more slowly (over several hours), (2) a linear relationship existed between the concentration of benzene in the air and the equilibrium concentration in the blood, (3) distribution of benzene throughout the body occurred rapidly, (4) the fat, bone marrow, and urine contained approximately 20 times the concentration of benzene as the blood, (5) benzene concentration in the muscle and vital organs was 1-3 times that in the blood, and (6) the RBC contained approximately twice the amount of benzene found in the plasma. The blood benzene values were determined by either a nitration method or a rather involved method in which carbon dioxide was formed from the combustion of benzene and ultimately measured by changes in electrical conductivity through precipitation as barium carbonate from a barium hydroxide solution. The method provided 70-112% recoveries of added known amounts of benzene. The blood samples were drawn before and after the repeated daily exposures to benzene. The exposures ranged from 2-37.5 hours for different animals. The results of this work showed that for each 100 ppm of benzene vapor in air, the equilibrium blood concentration in terms of milligrams of benzene/100 ml of blood was 0.21. When the concentration of benzene in blood and air were calculated in mg/liter, the coefficient of distribution obtained by dividing the blood concentration by the air concentration was found to be 6.58.

Desoille et al [65] described in 1967 the effects of exposure to benzene on virgin and pregnant guinea pigs from a dose of 0.1 g/kg using benzene in olive oil and injected subcutaneously each day for a period of 9 weeks. A study of the variations of RBC and WBC counts was made before, during, and after pregnancy. Pregnancy did not enhance the hemotoxic effects of benzene.

Deichmann et al [66] in 1963 published results after exposing 8 groups of rats to analyzed benzene concentrations extending from 15-831 ppm for periods ranging from 5 weeks to 7 months. A significant leukopenia resulted after 2-4 weeks of exposure to the 3 highest exposure groups of 831, 65, and 61 ppm. Exposure to mean concentrations of 47 and 44 ppm, 7 hours/day, 5 days/week, in separate experiments induced a moderate but definite leukopenia after 5-8 weeks of exposure. The WBC dropped from 12.1 to 10.4 thousand/cu mm in the males and from 11.3 to 9.4 thousand/cu mm in the females when exposed to 47 ppm (range, 33-55). In the groups exposed to 44 ppm (range 40-50), the WBC dropped from 15.2 to 10.0 thousand/cu mm in the males and from 11.8 to 7.7 thousand/ cu mm in the females. No leukopenia was observed in the groups of rats exposed to average concentrations of 31, 29, or 15 ppm or in the controls.

Nau et al [67] exposed rats to a benzene concentration of 1,000 ppm for 23.5 hours/day, 7 days/week. After 183 hours of exposure, the rats appeared to be in "poor" condition and suffered a loss in body weight. They hemorrhaged from the nose and mouth, the stomach was distended, the gut was empty, and the blood vessels of the lungs, liver, kidneys, intestines, and omental tissues were engorged. The WBC fell from a mean value of 22,650 to 5,425/cu mm by the 105th day, and there was a reversal of the polymorphonuclear-lymphocyte ratio from 22:57 in the preexposure period to 54:46 at the end of 105 days of exposure. Microscopic studies of the bone marrow showed an increase in the proportion of RBC precursors. Nau et al [67] also showed a decrease of WBC (no values given) after about 90 days of repeated daily exposures of 8 hours/day, 5 days/week at the 200 ppm level, but there was no change in the polymorphonuclear-lymphocyte ratio. Microscopic examination of the bone marrow showed some depression of myelocytic activity and stimulation of erythrocytic activity. Rats similarly exposed at 50 ppm had a decrease in the WBC (no values given).

In addition, the development of bilateral cataracts was reported in 50% of the rats after 600 hours of exposure to the 50-ppm concentration of benzene. However, observation was not found in the rats exposed to 200 ppm of benzene undergoing the same 8-hour/day, 5-day/week regimen after 750 hours of exposure. The rats exposed to 50 ppm also developed, as did the rats at the 200 ppm exposure level, lower leucocyte DNA values, depression of myelocytic activity, and a stimulated erythrocytic activity in the bone marrow.

Wolf et al [68] published in 1956 the results of their toxicologic studies of benzene and certain of its alkylated derivatives. These investigators noted slight histopathologic changes in the blood and testes of rabbits consisting of leukopenia and degeneration of the seminiferous tubules when exposed to 80 ppm concentrations of benzene for 243 days; in the bone marrow, blood, spleen, and testes of guinea pigs exposed to 88 ppm for 269 days; in the blood and kidneys of guinea pigs exposed to 88 ppm for 32 days; and in the blood and spleen of rats exposed to 88 ppm for 204 days. On the basis of these results, the authors concluded that the no-effect level was below 80 ppm.

Following the belief that the central nervous system has a regulatory effect on hematopoietic activity, and that functional disturbances of the central nervous system preceded changes occurring in either blood morphology or the hematopoietic system to chronic benzene intoxication, Novikov [69] in 1956 reported on changes in conditioned reflex activity in 6 rats exposed at 64 mg/cu m (20 ppm) of benzene vapor and an additional 6 animals exposed at 13 mg/cu m (4 ppm) for 6 hours/day, 6 days/week, for 5 1/2 months. As could be expected with a central nervous system depressant, there was a delay in conditional response time after exposure to benzene; this delay was observed in rats exposed at 20 ppm but not at 4 ppm. It was suggested by the author [69] that the results presented could serve as a physiological basis for an allowable benzene concentration limit in atmospheric air.

Horiuchi et al [70] reported in 1967 on the effects of benzene inhalation on spontaneous behavior in 15 mice as measured by spontaneous motor (wheel-turning) activity. This study was initiated as a result of reports in the USSR literature on behavioral responses. Mice were exposed 6 hours/day for 20 days to benzene concentrations at 10 ppm and 100 ppm. Observations were also made on changes in body weight, RBC's, WBC's, and thrombocyte counts. Thirty days after cessation of benzene exposure, examinations of the bone marrow, spleen, liver, and kidneys were performed. A decrease in wheel-turning activity was observed by the 5th day in the 5 mice exposed at 100 ppm. The 5 mice exposed at 10 ppm and 100 ppm showed decreases in the RBC and WBC counts, but values overlapped those of the controls. In addition, degenerative changes of the bone marrow were reported in all mice exposed to benzene at 100 ppm and slight degenerative changes in 2 of 5 mice exposed at 10 ppm. The authors emphasized that further study was needed. No attempt was made to relate the animal results to human exposure, but it was concluded that the benzene concentration necessary to prevent effects in mice was below 10 ppm.

(1) Nutrition

Experimental studies with dogs and rats conducted by Shils and Goldwater [71] showed that an inadequate protein intake predisposes to increased susceptibility to benzene poisoning. They stated that no appreciable effect of varying the fat content of the diet has been demonstrated convincingly. On this basis, they recommended that the benzene workers have well balanced meals containing sufficient of high quality protein. This recommendation was made with a view to the role of the sulfur-containing amino acids and of choline in influencing the fat content of the liver and the reparative processes in the liver.

(2) Proneness to Infections

Reports on this subject are limited to several studies made in the 1913-1917 period. Winternitz and Hirschfelder [72] reported that rabbits with leukopenia from benzene had strikingly reduced resistance to pneumonia. Kline and Winternitz [73] emphasized the lowering of resistance that accompanies leukopenia. Animals with leukopenia from benzene succumbed in 41 hours to 5 ml of a 20-hour culture of pneumococcus introduced intratracheally, while animals injected subcutaneously with 1 ml of toluene/kg of body weight did not have leukopenia, had normal resistance to infection, and survived. Weiskotten and Steensland [74] noted that active acute infection appeared spontaneously in rabbits injected with benzene. The authors suggested that the lowering of resistance by benzene may activate latent or quiescent infection. White and Gammon [75] reported that rabbits exposed to benzene vapor administered from a wide-mouthed bottle with absorbent cotton on the bottom were less resistant to tuberculous infection than were unexposed rabbits. Camp and Baumgartner [76] found that rabbits whose leukocyte counts had been lowered to below 1,000/cu mm succumbed in 1 1/2 to 4 days from inflammatory reactions resulting from irritation of an ear scratch with croton oil or from an intramuscular injection of carmine.

(c) Metabolism

Phenol is the chief metabolite of benzene in the urine and, to a lesser extent, hydroquinone and catechol have been found [77]; yet, although the toxic effects of benzene have been attributed to its phenolic metabolites, [23, 78] subcutaneous administration of phenol, catechol, and hydroquinone in rats failed to produce any hematopoietic toxicity even at doses approximating an LD50. [79] Posner et al [80] in 1961 demonstrated a microsomal enzyme that metabolized benzene and it has been concluded from studies in rats that metabolism by hepatic microsomal enzymes is necessary for the observed bone marrow toxicity. [79] Also, benzene itself, rather than its hydroxylated derivatives, is probably responsible for the microsomal stimulation. [81] Drew and Fouts [82] in 1974 demonstrated that pretreatment of rats with phenobarbital increased the rate of hepatic microsomal metabolism of benzene 10-fold. On the basis that the LC50 for inhaled benzene and the LD50 for injected benzene were not affected by pretreatment of rats with phenobarbital, a protective effect from barbiturateinduced microsomal metabolism was not demonstrated. Lee et al [83] in 1974 presented a study which was undertaken to determine which stage in erythrocyte development was most sensitive to benzene in the belief that benzene interfered with erythrocyte production. Based upon the 24- or 72-hour uptake of 59Fe in the circulating erythrocytes of mice having benzene pretreatment at selected time intervals, the possible damage to stem cells, pronormoblasts, normoblasts, or reticulocytes was determined. Using the appearance of 59Fe as an index of red cell development, it was determined that single doses of benzene selectively damaged pronormoblasts and normoblasts without affecting stem cells or reticulocytes. Thus, benzene seemed to damage red cell percursors which underwent both differentiation and maturation, rather than those concerned principally with differentiation (stem cells) or maturation (reticulocytes).

Correlation of Exposure and Effect

Liquid benzene on the skin may cause erythema and blistering, and a dry, scaly dermatitis may develop on prolonged or repeated exposure. [24] Investigations of the percutaneous absorption of benzene have failed to detect changes in the urinary inorganic to total sulfate ratio [28] or of benzene in the expired breath. [29] According to Hanke et al, [30] the rate of benzene absorption through the human skin was found to be 0.4 mg/sq cm/hr as compared with later findings by others of 14-23 mg/sq cm/hr for toluene. [32] These findings, along with supporting evidence determined in rabbits by Wolf et al [68] indicate that liquid benzene is poorly absorbed through the intact skin. Therefore, skin absorption of benzene is not considered an important route of entry in the occupational situation; however, it is important to avoid skin contact with benzene to prevent local effects. Similarly, ingestion of liquid benzene is generally of concern only in cases of accidental swallowing or attempted suicide.

Absorption of benzene through inhalation is by far the most important route of entry in industrial exposures. Repeated exposures of workers over a prolonged time to high concentrations of benzene have occurred under conditions of poor ventilation combined with heated benzene to accelerate evaporation. [38] In a plant which manufactured rubber raincoats, an atmospheric benzene concentration was estimated to be 5,320 ppm. Sixty workers out of 184 suffered from chronic benzene poisoning in the reported study. [38] Rats exposed experimentally to 1,000 ppm of benzene [67] by Nau et al showed hemorrhaging from the nose and mouth, engorgement of the blood vessels, stomach distention, and markedly reduced WBC levels. Animals were exposed (23.5 hours/day, 7 days/week) for 183 hours to the benzene vapor. Such an exposure is not representative of the normal work schedule but it does indicate the toxic effects of benzene at a concentration to which humans are known to have been exposed.

Worker exposures to benzene concentrations from approximately 300-700 ppm consistently show marked blood dyscrasias. [19,39,41] Reduced WBC and RBC counts were noted by Greenburg [19]; Savilahti [39] found thrombocytopenia, leukopenia, and anemia in from 32-62% of 147 workers; and

Vigliani and Saita [41] described 2 cases of benzene-associated leukemia along with other workers who showed signs of benzene poisoning in a rotogravure plant which used inks containing 40% benzene. Deichmann et al [66] found significant leukopenia in rats exposed to 831 ppm of benzene vapor for periods of 5 weeks and longer. In another animal study, Nau et al [67] showed decreased WBC's and altered myelocytic and erythrocytic activity of the bone marrow in rats exposed to 200 ppm, 8 hours/day, 5 days/week, for 750 hours of exposure.

Alterations in the blood picture also have occurred at benzene exposure levels in the vicinity of 100 ppm. Juzwiak, [40] in 1969, stated the results of blood examinations on 585 persons employed in 13 shoe plants. Exposure levels from benzene contained in a glue mixture fluctuated in mean concentrations from 31-156 ppm. The author found reduced RBC counts, WBC counts, and Hgb levels. Although 91% of the workers had reduced Hgb levels, only 8.5% had reduced WBC counts. It is difficult to correlate the medical findings with the airborne exposures because of the lack of adequately documented environmental data.

Although Greenburg's findings [19] were published in 1926, they represent some of the most meaningful studies available showing approximate correlations of environmental benzene concentrations and chronic benzene poisoning (see Table XII-3). Greenburg considered cases as positive which showed less than 5,500 WBC/cu mm. In all groups studied, there were workers who presented a picture of chronic benzene poisoning as judged by reductions in the WBC count. Greenburg concluded that keeping the average concentration of benzene in the workroom air below 100 ppm (presumably just below this level) still involved a substantial hazard to workers. Effects at 80-88 ppm were noted in animals by Wolf et al [68] in 1956 in rats, rabbits, and guinea pigs exposed intermittently to benzene vapor for periods varying from 204 to 269 days. On the basis of results from their study, the no-effect level was concluded by the authors to be below 80 ppm.

Hardy and Elkins [57] found evidence of deviations in more than one blood element in 16 of 52 workers from blood studies in a plant using naphtha solvents. For 8 years preceding their blood study, the plant's operational procedures and ventilation had undergone no significant changes. Six of the men with abnormal blood pictures were exposed to average benzene concentrations of not over 60 ppm and two other men were exposed to possibly 80 ppm. Additional data from further studies of the rubber coating industry from 1960 through 1963 were supplied by Pagnotto in a 1972 written communication. Environmental benzene concentrations consistently averaged between 20 and 25 ppm and frequently were lower for spreader and churn operations. From minimal blood data, 6 of 27 workers tested were found to have Hgb levels below 13.5 g/100 ml of blood in one of the 1961 studies (see Table XII-11). In the 1963 study, 12 of 24 workers were said to show minor deviations from normal although these differences were unspecified. Rats exposed by Deichmann et al [66] at mean concentrations of 44 ppm (range 40-50), 7 hours/day, 5 days/week, had WBC levels decreasing from 15.2 (preexposure) to 10.0 thousand/cu mm (after 5-8 weeks) in the males and from 11.8 (preexposure) to 7.7 thousand/cu mm in the females. No leukopenia was observed in rats exposed to average concentrations of 15 or 31 ppm.

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)	Benzene Concentration 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)

Tube No.	Total benzene collected (mg)	Measured conc. (ppm)
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)

Tube No.	Total benzene collected (mg)	Measured conc. (ppm)
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 relevent 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 <u>Federal Register</u> 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.

VI. REFERENCES

1. Greenburg L: Benzol poisoning as an industrial hazard--I. The chemistry and industrial uses of benzol--II. Acute benzol poisoning. Public Health Reports 41:1357-75, 1926

2. Gerarde HW: The aromatic hydrocarbons, in Patty FA (ed): Industrial Hygiene and Toxicology, rev ed 2. New York, Interscience Publishers, 1962, vol II, pp 1219-40

3. Stanford Research Institute: Chemical Economics Handbook. Menlo Park, California, pp 618.5021A-E, 618.5022A-B

4. Benzene (Benzol). Inhalation of Concentrated Vapors May Cause Acute, Chronic or Fatal Poisoning. Controlling Chemical Hazards, Ser No 6. US Dept of Labor, Div Labor Standards, 1946, 24 pp

5. Benzene, Hygienic Guide Series. American Industrial Hygiene Association, Hygienic Guides Committee, 1970

6. 1970 chemical production data. Chem Eng News 49:12A, 1971

7. Chemical Safety Data Sheet SD2-Benzene, rev 3. Washington, DC, Manufacturing Chemists Association, 1960, 15 pp

8. Weast RC (ed): Handbook of Chemistry and Physics-- A Ready Reference Book of Chemical and Physical Data, ed 52. Cleveland, The Chemical Rubber Publishing Co, 1971

9. Sherwood RJ: Benzene: The interpretation of monitoring results. Ann Occup Hyg 15: 409-21, 1972

10. Benzene in motor gasoline. International Study Group for Conservation of Clean Air and Water, Western Europe (Stichting Concawe), The Hague, 1973

11. Bowden JN: Status of unleaded and low-lead gasoline composition--Interim report FLRL No 16, AD 747421. Aberdeen Proving Ground, Md, US Army Coating and Chemical Laboratory, 1972

12. Pagnotto LD, Elkins HB, Brugsch HG, Walkley EJ: Industrial benzene exposure from petroleum naphtha--I. Rubber coating industry. Am Ind Hyg Assoc J 22:417-21, 1961

13. Legge TM: Chronic benzol poisoning. J Ind Hyg 1:539-41, 1920

14. Selling L: Benzol as a leucotoxin-- Studies on the degeneration and regeneration of the blood and haematopoietic organs. Johns Hopkins Hosp Rep 17:83-136, 1916

15. Hamilton A: Benzene (benzol) poisoning. Arch Pathol 11:434-54, 1931

16. Smith AR: Chronic benzol poisoning among women industrial workers--A study of the women exposed to benzol fumes in six factories. J Ind Hyg 10:73-93, 1928

17. Greenburg L, Mayers MR, Goldwater L, Smith AR: Benzene (benzol) poisoning in the rotogravure printing industry in New York City. J Ind Hyg Toxicol 21:395-420, 1939

18. Bowditch M, Elkins HB: Chronic exposure to benzene (benzol)--I. The industrial aspects. J Ind Hyg Toxicol 21:321-30, 1939

19. Greenburg, L: Benzol poisoning as an industrial hazard--VII. Results of medical examination and clinical tests made to discover early signs of benzol poisoning in exposed workers. Public Health Reports 41:1526-39, 1926

20. Erf LA, Rhoads CP: The hematological effects of benzene (benzol) poisoning. J Ind Hyg Toxicol 21:421-35, 1939

21. Hunter FT: Chronic exposure to benzene (benzol)--II. The clinical effects. J Ind Hyg Toxicol 21:331-54, 1939

22. Mallory TB, Gall EA, Brickley WJ: Chronic exposure to benzene (benzol)--III. The pathologic results. J Ind Hyg Toxicol 21:355-77, 1939

23. Browning E: Toxicity and Metabolism of Industrial Solvents. New York, Elsevier Publishing Company, 1965, pp 3-65

24. Gerarde HW: Toxicology and Biochemistry of Aromatic Hydrocarbons. New York, Elsevier Publishing Company, 1960, pp 97-108

25. Flury F: [II. Modern occupational intoxications. IIa. Modern occupational intoxications from the aspect of pharmacology and toxicology.] Arch Exp Path Pharmakol 138:65-82, 1928 (Ger)

26. A new domestic poison. Lancet 1:105, 1862

27. Averill C: Benzole poisoning. Br Med J 1:709, 1889

28. Cesaro AN: [Is absorption of benzene through the skin possible?] Med Lavoro 37:151-56, 1946 (Ital)

29. Conca GL, Maltagliati A: [Transcutaneous absorption of benzene.] Med Lavoro 46:194-98, 1955 (Ital)

30. Hanke J, Dutkiewicz T, Piotrowski I: [The absorption of benzene through the skin in men.] Med Pracy 12: 413-26, 1961

31. Dutkiewicz T, Tyras H: A study of the skin absorption of ethylbenzene in man. Br J Indust Med 24:330-32, 1967

32. Dutkiewicz T, Tyras H: [The quantitative estimation of toluene skin absorption in man.] Arch Gewerbepathol Gewerbehyg 24: 253-57, 1968 (Ger)

33. Srbova J, Teisinger J, Skramovsky S: Absorption and elimination of inhaled benzene in man. Arch Ind Hyg Occup Med 2:1-8, 1950

34. Teisinger J, Bergerova-Fiserova V, Kudrna J: [The metabolism of benzene in man.] Procovni lekarstvi 4:175, 1952 (Pol)

35. Duvoir MR, Fabre A, Derobert L: [The significance of benzene in the bone marrow in the course of benzene blood diseases.] Arch Mal Prof 7:77, 1946 (Fr)

36. Hunter CG: Aromatic solvents. Ann Occup Hyg 9:191-97, 1966

37. Stewart RD, Dodd HC, Baretta ED, Schaeffer AW, Mutchler JE: Chronic overexposure to benzene vapor. Toxicol Pharmacol 10:381, 1967; abst

38. Helmer KJ: Accumulated cases of chronic benzene poisoning in the rubber industry. Acta Med Scand 118:354-75, 1944

39. Savilahti M: [More than 100 cases of benzene poisoning in a shoe factory.] Arch Gewerbepathol Gewerbehyg 15:147-57, 1956 (Ger)

40. Juzwiak I: [Studies on the state of health of shoe plant workers exposed to benzene and its homologues.] Med Przemyslowa 20:67-72, 1969 (Pol)

41. Vigliani EC, Saita G: Benzene and leukemia. N Engl J Med 271:872-76, 1964

42. Pollini G, Colombi R: [Medullary chromosome damage in aplastic anemia caused by benzol.] Med Lavoro 55: 241-55, 1964 (Ital)

43. Tough IM, Court Brown WM: Chromosome aberrations and exposure to ambient benzene. Lancet 1:684, 1965

44. Forni A, Moreo L: Cytogenetic studies in a case of benzene leukaemia. Eur J Cancer 3:251-55, 1967

45. Forni A, Moreo L: Chromosome studies in a case of benzene-induced erythroleukaemia. Eur J Cancer 5:459-63, 1969

46. Tough IM, Smith PG, Court Brown WM, Harnden DG: Chromosome studies on workers exposed to atmospheric benzene. Eur J Cancer 6:49-55, 1970

47. Forni A, Pacifico E, Limonta A: Chromosome studies in workers exposed to benzene or toluene or both. Arch Environ Health 22:373-78, 1971

48. Forni A, Cappellini A, Pacifico E, Vigliani EC: Chromosome changes and their evolution in subjects with past exposure to benzene. Arch Environ Health 23:385-91, 1971

49. Hartwich G, Schwanitz G: [Chromosome studies after chronic exposure to benzol.] Dtsch Med Wochenschr 97:45-49, 1972 (Ger)

50. Buckton KE, Jacobs PA, Court Brown WM: A study of the chromosome damage persisting after x-ray therapy for ankylosing spondylitis. Lancet 2:676-82, 1962

51. Bender MA, Gooch PC: Persistent chromosome aberrations in irradiated human subjects. Radiat Res 16:44-53, 1962

52. Bender MA, Gooch PC: Persistent chromosome aberrations in irradiated human subjects--II. Three and one half year investigation. Radiat Res 18:389-96, 1963

53. Goh K-O: Total-body irradiation and human chromosomes--Cytogenetic studies of the peripheral blood and bone marrow leukocytes seven years after total-body irradiation. Radiat Res 35:155-70, 1968

54. Thorpe JJ: Epidemiologic survey of leukemia in persons potentially exposed to benzene. J Occup Med 16:375-82, 1974

55. Cavignaux L: [Confirmed intoxications.] Cah Med Interprof 2: 28-31, 1962 (Fr)

56. Butarewicz L, Gosk S, Gluszczowa M: [Examination of the state of health of women workers in the leather industry, especially from the gynecological point of view.] Med Przemyslowa 20:137-48, 1969 (Pol)

57. Hardy HL, Elkins HB: Medical aspects of maximum allowable concentrations--Benzene. J Ind Hyg Toxicol 30:196-200, 1948

58. Kozlova TA, Volkova AP: [The blood picture and phagocytic activity of leucocytes in workers having contact with benzol.] Gig Sanit 25:29-34, 1960 (Rus)

59. Horiuchi K, Horiguchi S, Aratake K: Studies on the maximum allowable concentration of benzene in the air of workshops. Osaka City Med J 9:79-90, 1963

60. Cassan G, Baron J: [Usefulness of blood tests in workers exposed to benzene.] Arch Mal Prof 17:602-604, 1956 (Fr)

61. Lazarew NW, Brussilowskaja AJ, Lawrow JN, Lifschitz FB: [Cutaneous permeability for petroleum ether and benzene.] Arch Hyg 106:112-22, 1931 (Ger)

62. Carpenter CP, Shaffer CB, Weil CS, Smyth HF Jr: Studies on the inhalation of 1:3-butadiene with a comparison of its narcotic effect

with benzol, toluol, and styrene, and a note on the elimination of styrene by the human. J Ind Hyg Toxicol 26:69-78, 1944

63. Jonek J, Olknowski Z, Zieleznik B: Histochemical studies on the spinal cord of mice poisoned with benzene. Acta Histochem 20:286-96, 1965

64. Schrenk H, Yant WP, Pearce SJ, Patty FA, Sayers RR: Absorption, distribution and elimination of benzene by body tissues and fluids of dogs exposed to benzene. J Ind Hyg Toxicol 23:20-34, 1941

65. Desoille H, Philbert M, Albahary C: [Hormonal influences in chronic benzene intoxication in guinea pigs. Influence of gestation on white and red blood cell counts in guinea pigs with and without moderate benzene intoxication during the entire gestation period.] Arch Mal Prof 28:329-39, 1967 (Fr)

66. Deichmann WB, MacDonald WE, Bernal E: The hemopoietic tissue toxicity of benzene vapors. Toxicol Appl Pharmacol 5:201-24, 1963

67. Nau CA, Neal J, Thornton M: C9-C12 fractions obtained from petroleum distillates--An evaluation of their potential toxicity. Arch Environ Health 12:382-93, 1966

68. Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL, Oyen F: Toxicological studies of certain alkylated benzenes and benzene--Experiments in laboratory animals. Arch Ind Health 14:387-98, 1956

69. Novikov YV: [Effect of small benzene concentrations on higher nervous activity of animals in chronic experiments.] Gig Sanit 21:20-25, 1956 (Rus); also in USSR Literature on Air Pollution and Related Occupational Diseases--A survey. BS Levine (transl), USPHS, 1960, vol 2, pp 185-91

70. Horiuchi K, Horiguchi S, Morioka S: Maximum allowable concentration of benzene in an animal experiment. Osaka City Med J 13:1-8, 1967

71. Shils ME, Goldwater LJ: Nutritional factors affecting the toxicity of some aromatic hydrocarbons with special reference to benzene and nitrobenzene compounds--A review. J Ind Hyg Toxicol 31:175-89, 1949

72. Winternitz MC, Hirschfelder AD: Studies upon experimental pneumonia in rabbits--Parts I to III. J Exp Med 18:657-65, 1913

73. Kline BS, Winternitz MC: Studies upon experimental pneumonia in rabbits--V. The role of the leucocyte in experimental pneumonia. The relation of the number of organisms injected to the mortality. J Exp Med 18:50-60, 1913

74. Weiskotten HG, Steensland HS: Action of benzol--IV. Spontaneous infections with special reference to the diphasic leucopenia (rabbit). Exp Res 37:215-23, 1917

75. White WC, Gammon AM: The influence of benzol inhalations on experimental pulmonary tuberculosis in rabbits. Trans Assoc Amer Phys 29:332-337, 1914

76. Camp WE, Baumgartner EA: Inflammatory reactions in rabbits with a severe leucopenia. J Exp Med 22:174-92, 1915

77. Williams RT: Detoxification Mechanisms. New York, Wiley and Sons, 1959, pp 188-94

78. Cornish HH, Ryan RC: Metabolism of benzene in nonfasted, fasted, and aryl-hydroxylase inhibited rats. Toxicol Appl Pharmacol 7:767-71, 1965

79. Mitchell JR: Mechanism of benzene-induced aplastic anemia. Fed Am Soc Exp Biol 30:561, 1971; abst

80. Posner HS, Mitoma C, Udenfriend S: Enzymatic hydroxylation of aromatic compounds. Arch Biochem Biophys 94:269-79, 1961

81. Saito FU, Kocsis JJ, Snyder R: Effect of benzene on hepatic drug metabolism and ultrastructure. Toxicol Appl Pharmacol 26:209-17, 1973

82. Drew RT, Fouts JR: The lack of effects of pretreatment with phenobarbital and chlorpromazine on the acute toxicity of benzene in rats. Toxicol Appl Pharmacol 27:183-93, 1974

83. Lee EW, Kocsis JJ, Snyder R: Acute effect of benzene on 59Fe incorporation into circulating erythrocytes. Toxicol Appl Pharmacol 27:431-36, 1974

84. Parkinson GS: Benzene in motor gasoline--An investigation into possible health hazards in and around filling stations and in normal transport operations. Ann Occup Hyg 14:145-53, 1971

85. Sherwood RJ: Evaluation of exposure to benzene vapour during the loading of petrol. Br J Ind Med 29:65-9, 1972

86. Blaney L: Early detection of benzene toxicity. Ind Med Surg 19:227-28, 1950

87. Dolin BH: Determination of benzene: Detection and estimation of benzene in the presence of toluene, xylene, and other substances. Ind Eng Chem, Anal Ed 15:242-47, 1943

88. Levine BS (ed): Quantitative determination of benzene in the air. USSR Literature on Air Pollution and Related Occupational Diseases 8:47-51, 1963

89. Smith BS, Pierce JO: The use of plastic bags for industrial air sampling. Am Ind Hyg Assoc J 31:343-48, 1970

90. Ovrum P: Determination of atmospheric benzene concentration by displacement following adsorption on silica gel. Br J Ind Med 13:210-13, 1956

91. Elkins HB, Pagnotto LD, Comproni EM: The ultraviolet spectrophotometric determination of benzene in air samples adsorbed on silica gel. Anal Chem 34:1797-1801, 1962

92. Van Mourik JHC: Experiences with silica gel as adsorbent. Am Ind Hyg Assoc J 26:498-509, 1965

93. Feldstein M, Balestrieri S, Levaggi DA: The use of silica gel in source testing. Am Ind Hyg Assoc J 28:381-85, 1967

94. Buchwald H: Activated silica gel as an adsorbent for atmospheric contaminants. Occup Health Rev 17:14-18, 1965

95. Fraust CL, Hermann ER: Charcoal sampling tubes for organic vapor analysis by gas chromatography. Am Ind Hyg Assoc J 27:68-74, 1966

96. Reid FH, Halpin WR: Determination of halogenated and aromatic hydrocarbons in air by charcoal tube and gas chromatography. Am Ind Hyg Assoc J 29:390-96, 1968

97. Baernstein HD: Photometric determination of benzene, toluene, and their nitro derivatives. Ind Eng Chem, Anal Ed 15:251-53, 1943

98. Maffett PA, Doherty TF, Monkman JL: A direct method for the collection and determination of micro amounts of benzene or toluene in air. Am Ind Hyg Assoc Quart 17:186-88, 1956

99. Analytical Abstracts Committee: Analytical Abstracts, Benzene. American Industrial Hygiene Association, 1965

100. Koljkowsky P: Indicator-tube method for the determination of benzene in air. Analyst 94:918-20, 1969

101. Ash RM, Lynch JR: The evaluation of gas detector tube systems--Benzene. Am Ind Hyg Assoc J 32:410-11, 1971

102. Sherwood RJ, Carter FWG: The measurement of occupational exposure to benzene vapour. Ann Occup Hyg 13:125-46, 1970

103. Levadie R, Harwood JF: An application of gas chromatography to analysis of solvent vapors in industrial air. Am Ind Hyg Assoc J 21:20-24, 1960

104. Whitman NE, Johnston AE: Sampling and analysis of aromatic hydrocarbon vapors in air: A gas-liquid chromatographic method. Am Ind Hyg Assoc J 25:464-69, 1964

105. Rules and Regulations on Sanitation of Factories and Mercantile Establishments, Rule 59. Maine Department of Health and Welfare, December 9, 1954.

106. Regulations for the Control and Prevention of Occupational Disease in Industry, Regulation 4. Florida Industrial Commission, December 16, 1957.

107. American Conference of Governmental Industrial Hygienists: Transactions of the Eighth Annual Meeting. Cincinnati, Ohio, ACGIH, 1946, p 40

108. American Conference of Governmental Industrial Hygienists: Transactions of the Ninth Annual Meeting. Cincinnati, Ohio, ACGIH, 1947, p 44

109. American Conference of Governmental Industrial Hygienists: Transactions of the Tenth Annual Meeting. Cincinnati, Ohio, ACGIH, 1948, p 31

110. American Conference of Governmental Industrial Hygienists: Transactions of the Nineteenth Annual Meeting. Cincinnati, Ohio, ACGIH, 1957, p 47

111. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Substances in Workroom Air Adopted by ACGIH for 1963. Cincinnati, Ohio, ACGIH, 1963.

112. American Conference of Governmental Industrial Hygienists: Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3. Cincinnati, Ohio, 1971, ACGIH, p 22

113. United States of America Standards Institute: Acceptable Concentrations of Benzene Z37.4-1969. New York, 1969, 8 pp

114. Convention 136 concerning protection against hazards of poisoning arising from benzene, adopted by the Conference at its 56th session, International Labour Conference, Geneva, June, 1971

115. Recommendation 144 concerning protection against hazards of poisoning arising from benzene, adopted by the Conference at its 56th session, International Labour Conference, Geneva, June, 1971

116. Benzene: Uses, Toxic Effects, Substitutes. Meeting of Experts on the Safe Use of Benzene and Solvents Containing Benzene, May 16-22, 1967. International Labour Office, Geneva, 1968

117. Smelyanskiy ZB, Ulanova IP: [New standards for permissible levels of toxic gases, fumes, and dust in the air of work areas.] Ind Hyg Occup Dis No 5:7-15, 1959 (Rus)

118. Volkova ZA: [The relationship between human health and environmental conditions (at work and in everyday life) as a method for verifying the safety criteria for human exposure to chemical substances.] Consultation on methods used in the USSR for establishing biologically safe levels of toxic substances, World Health Organization, OH/WP/72.5, December 1972 (Rus)

119. Parke DV, Williams RT: Studies in detoxication--The metabolism of benzene--(a) The determination of benzene; (b) The elimination of unchanged benzene in rabbits. Biochem J 46:236-42, 1953

120. Dutton GJ: Uridine diphosphate glucuronic acid as glucuronyl donor in the synthesis of "ester," aliphatic and steroid glucuronides. Biochem J 64:693-701, 1956

121. Guertin DL, Gerarde HW: Toxicological studies on hydrocarbons-- IV. A method for the quantitative determination of benzene and certain alkylbenzenes in blood. Arch Ind Health 20:262-65, 1959

122. Hunter CG: Solvents with reference to studies on the pharmacodynamics of benzene. Proc Roy Soc Med 61:913-15, 1968

123. Sherwood RJ: One man's elimination of benzene (C6H6). Proceedings of the 3rd Annual Conference on Environmental Toxicology, AMRL TR-72-130, Dayton, 1972

124. Walkley JE, Pagnotto LD, Elkins HB: The measurement of phenol in urine as an index of benzene exposure. Am Ind Hyg Assoc J 22:362-67, 1961

125. Elkins HB: The Chemistry of Industrial Toxicology, ed 2. New York, John Wiley & Sons, 1959

126. Truhaut R: [Determination of a tolerable limit of benzene in work environment.] Arch Mal Prof 29:5-22, 1968 (Fr)

127. Teisinger J, Fiserova-Bergerova V: [Comparative value of the determination of urinary sulfates and phenol for the evaluation of the atmospheric benzene concentration.] Arch Mal Prof 16:221-32, 1955 (Fr)

128. Docter JH, Zielhuis RL: Phenol excretion as a measure of benzene exposure. Ann Occup Hyg 10:317-26, 1967

129. Deichmann W, Schafer LJ: Phenol studies. Am J Clin Pathol 12:129-43, 1942

130. Buchwald H: The expression of urine analysis results--Observations on the use of a specific gravity correction. Ann Occup Hyg 7:125-36, 1964

131. Theis RC, Benedict SR: The determination of phenols in the blood. J Biol Chem 61:67-71, 1924

132. Buchwald H: The colorimetric determination of phenol in air and urine with a stabilized diazonium salt. Ann Occup Hyg 9:7-14, 1966

133. Gibbs HD: Phenol tests--III. The indophenol test. J Biol Chem 72:649-64, 1927

134. Rainsford SG, Lloyd Davies TA: Urinary excretion of phenol by men exposed to vapour of benzene--A screening test. Br J Ind Med 22:21-26, 1965

135. Van Haaften AB, Sie ST: The measurement of phenol in urine by gas chromatography as a check on benzene exposure. Am Ind Hyg Assoc J 26:52-58, 1965

136. White LD, Taylor DG, Mauer PA, Kupel RE: A convenient optimized method for the analysis of selected solvent vapors in the industrial atmosphere. Am Ind Hyg Assoc J 31:225-32, 1970

137. Kupel RE, White LD: Report on a modified charcoal tube. Am Ind Hyg Assoc J 32:456, 1971

138. Standard recommended practice for use of the terms precision and accuracy as applied to the measurement of a property of a material, ASTM E 177-71. Philadelphia, American Society of Testing and Materials, 1971, 18 pp

139. Levine L, Fahy JP: Evaluation of urinary lead determinations. I. The significance of the specific gravity. J Ind Hyg Toxicol 27:217-23, 1945

140. Wintrobe MW: Clinical Hematology, ed 6. Philadelphia, Lea and Febiger, 1967

141. Berlin NI, Waldmann TA, Weissman SM: Life span of the red blood cell. Physiol Rev 39: 577-616, 1959

142. Conn RB: Normal laboratory values of clinical importance -- normal hematologic values, in Beeson PB, McDermott W (eds): Cecil-Loeb Textbook of Medicine, ed 13. Philadelphia, WB Saunders Co, 1971

VII. APPENDIX I

METHOD FOR
SAMPLING AND ANALYTICAL PROCEDURES
FOR DETERMINATION OF BENZENE

The following sampling and analytical method for analysis of benzene in air employs adsorption on charcoal, followed by desorption, and gas chromatographic measurement. This is a modified method derived from White et al [136] and Kupel and White. [137] Additional data are contained in Part IV under Sorbability of Benzene on Charcoal and Accuracy and Precision Data.

Atmospheric Sampling

(a) Equipment Used

The sampling train is composed of a charcoal tube, a vacuum pump, and a flowmeter. A personal sampler pump or a dependable hand pump, eg, a detector tube pump may be calibrated to produce the desired volume of air.

(b) Calibration of Sampling Instruments

Air sampling instruments may be calibrated with a wet test meter or other suitable reference over a normal range of flowrates and pressure drops. The calibration is conducted at least annually and at any time following repairs or modifications to the sampling system. Similarly, wet test meters should be calibrated upon procurement, at least annually, and after each repair. Calibration curves shall be established for each sampling pump and shall be used in adjusting the pumps prior to field use. The volumetric flowrate through the sampling system shall be spot checked and the proper adjustments made before and during each study to assure obtaining accurate airflow data.

(1) Flowmeter Calibration Test Method

(A) With the wet test meter in a level position, check to ascertain that the water level just touches the calibration point on the meter. If the water level is low, add water 1 to 2 F warmer than room temperature to the fill point and run the meter for 30 minutes before calibration.

(B) Check the voltage of the pump battery with a voltmeter to assure adequate voltage for calibration. Charge the pump battery if needed.

(C) Break the tips of a charcoal tube to produce openings of a least 2 mm in diameter.

(D) Assemble the calibration train in series, with the test meter, then the charcoal tube, and finally the pump.

(E) Turn the pump on, adjusting the rotameter float to a selected reading on the rotameter scale. Wait until the float indicates a steady reading.

(F) The pointer on the meter should turn clockwise and indicate a pressure drop of not more than 1.0 inch of water. Operate the system for 10 minutes before starting the calibration. If the pressure is greater, recheck the system.

(G) Data for the calibration include the serial number; meter reading, start and finish; starting time, finish time, and elapsed time; air temperature; barometric pressure; serial number of the pump and rotameter; the name of the person performing the calibration; and the date.

(H) Adjust the rotameter float to at least 3 other readings and record the pertinent data in step G at each reading.

(I) Correct the readings to standard conditions of pressure and temperature by means of the gas law equation.

(J) Use graph paper to plot the actual airflow and the rotameter readings. Determine the rotameter reading which will result in a 1 liter/minute flowrate for the pump being calibrated.

(c) Sampling Procedure

The equipment should be set up in a proper locale. The tips of the charcoal tube are broken off producing openings of at least 2 mm in diameter; the filled end of the tube is inserted toward the pump. The tube should always be in a vertical position during sampling. The pump is started and a 10-liter sample is taken at a flowrate of 1 liter/minute. Slower flowrates may be used to lengthen the sampling period but the 1 liter/minute rate should not be exceeded. After the sample is taken, each end of the tube should be capped (plastic caps are provided with commercial tubes). The samples will remain stable for at least 2 weeks which permits shipment for analysis; however, samples should be analyzed as soon as possible in keeping with good laboratory practices.

Analytical

(a) Principle of the Method

A known volume of air is drawn through a charcoal tube to trap the organic vapors present. The charcoal in the tube is transferred to a small test tube and desorbed with carbon disulfide and an aliquot of the desorbed sample is injected into a gas chromatograph. The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

(b) Range and Sensitivity

The lower limit for benzene with instrument attenuation and splitter techniques is 0.01 mg for each sample. This value can be lowered by reducing the attenuation or by eliminating the splitter. The upper limit value for benzene is 6.0 mg/sample. This value is the number of milligrams of benzene which the front section will collect before a significant amount passes to the backup section. The charcoal tube consists of 2 sections of activated charcoal separated by a section of urethane foam [see description in (f)(2)]. If a particular atmosphere is suspected of containing a large amount of contaminant, it is recommended that a smaller than normal sampling volume be taken.

(c) Interferences

(1) When the amount of water in the air is so great that condensation actually occurs in the tube, organic vapors will not be trapped. Only water present as a mist is a problem, not water vapor.

(2) Any compound with the same retention time in the gas chromatograph as benzene at the operating conditions described in this method could be considered an interference. This type of interference can be overcome by changing the operating conditions of the instrument.

(d) Accuracy and Precision

The accuracy and precision determined by a representative laboratory test with benzene (see also Accuracy and Precision Data in Part IV) was found to be:

	Accuracy	Precision
Motor driven laboratory pump	7.6%	4.2%
Approved coal mine personal sampling pump (calibrated with no in-line resistance)	13.6%	10.1%
Approved coal mine personal sampling pump (calibrated with charcoal tube in line)	8.8%	11.6%

The accuracy includes single-day systematic error by 1 operator. Precision represents the single-day accuracy on several different tubes and includes tube-to-tube deviation under controlled laboratory conditions. [138]

(e) Advantages and Disadvantages of the Method

The sampling device is small, portable, and involves no liquids: one basic method is provided for determining many different organic solvents. Interferences are minimal and most can be eliminated by altering chromatographic conditions. In addition, the analysis is accomplished using a rapid instrumental method.

One disadvantage of the method is that the amount of sample which can be obtained is limited by the amount of benzene which the tube will hold before overloading as indicated by benzene recovery at the outlet end of the tube. Also, the precision is limited by the reproducibility of the pressure drop across the tubes, which affects the flowrate, thus causing the volume to be imprecisely measured.

(f) Apparatus consists of:

(1) An approved coal mine dust personal sampling pump or any vacuum pump whose flow can accurately be determined at 1 liter/minute or less for an area sample.

(2) Charcoal tubes: Glass tubes with both ends flame-sealed, 7 cm long with a 6-mm O.D. and a 4-mm I.D., containing two sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The absorbing section contains 100 mg of charcoal, the backup section, 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of glass wool is placed in front of the absorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute. Tubes with the above specifications are commercially available.

(3) Gas chromatograph equipped with a flame ionization detector.

(4) Column (20 ft x 1/8 in) with 10% FFAP stationary phase on 80/100 mesh acid washed DMCS Chromosorb W solid support.

(5) A mechanical or electronic integrator or a recorder and some method for determining peak area.

(6) Small glass-stoppered test tubes or equivalent tubes.

(7) Syringes: 10 μliter syringe, and other convenient sizes for preparation of standards.

(g) Reagents

(1) Spectroquality carbon disulfide

(2) Benzene, preferably chromatoquality grade.

(3) Bureau of Mines Grade A helium.

(4) Prepurified hydrogen.

(5) Filtered compressed air.

(h) Procedure

(1) Cleaning of Equipment

All equipment used for the laboratory analysis should be washed in detergent followed by tap and distilled water rinses.

(2) Collection and Shipping of Samples

Both ends of the charcoal tube are broken to provide openings of at least 2 mm (one-half the I.D. of the tube). The smaller section of charcoal in the tube is used as a backup section and is, therefore, placed nearest the sampling pump. Tubing may be used to connect the back of the tube to the pump, but no tubing must ever be placed on the front of the charcoal tube. Because of the high resistance of the charcoal tube, the sampling method places a heavy load on the personal sampling pump; therefore, it should not be assumed that the pump will run a full 8 hours without a recharging of the battery.

One or more charcoal tubes serving as blanks are treated in the same manner as the sample tubes (break, seal, ship) except that no air is drawn through them.

If bulk samples are submitted in addition to charcoal tubes, they are to be shipped in a separate container.

(3) Analysis of Samples

(A) Preparation

Each charcoal tube is scored with a file and broken open in front of the first section of charcoal. The glass wool is removed and discarded, the charcoal in the first (larger) section is transferred to a small stoppered test tube, the foam separating section is removed and discarded, and the second section is transferred to another test tube. The two charcoal sections are then analyzed separately.

(B) Desorption

Prior to analysis, 0.5 ml of carbon disulfide is pipetted into each test tube to desorb the benzene from the charcoal. Desorption is complete in 30 minutes if the sample is stirred occasionally.

EXTREME CAUTION MUST BE EXERCISED AT ALL TIMES WHEN USING CARBON DISULFIDE BECAUSE OF ITS HIGH TOXICITY AND FIRE AND EXPLOSION HAZARDS. IT CAN BE IGNITED BY HOT STEAM PIPES. ALL WORK WITH CARBON DISULFIDE MUST BE PERFORMED UNDER AN EXHAUST HOOD.

(C) Gas chromatographic conditions

Typical operating conditions for a gas chromatograph are:

(i) 85 cc/min (70 psig) helium carrier gas flow.
(ii) 65 cc/min (24 psig) hydrogen gas flow to detector.
(iii) 500 cc/min (50 psig) airflow to detector.
(iv) 200 C injector temperature.
(v) 200 C manifold temperature (detector).

(vi) 90 C oven temperature isothermal.

(vii) Use either dual column differential operation or uncompensated mode.

(D) Injection

To eliminate difficulties arising from blowback or distillation within the syringe needle, the solvent flush injection technique is employed to inject the sample into the gas chromatograph. The 10-μl syringe is first flushed with solvent several times to wet the barrel and plunger, then 3 μl of solvent is drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. Next, the needle is removed from the solvent and the plunger is pulled back about 0.2 μl to separate the solvent flush from the sample with an air pocket to be used as a marker. The needle is then immersed in the sample and a 5-μl aliquot is withdrawn. Prior to injection in the gas chromatograph, the plunger is pulled back a short distance to minimize sample evaporation from the needle tip. Duplicate injections should be made of each sample and the standard. No more than a 3% difference should result in the peak areas that are recorded.

(E) Measurement of area

The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement and preliminary sample results are read from a standard curve prepared as outlined below.

(i) Standards Preparation and Desorption Efficiency

(1) Preparation of Standards

It is convenient to prepare standards in terms of mg/ 0.5 ml of carbon disulfide because this is the quantity used for benzene desorption from the charcoal. To prepare a 0.3 mg/ 0.5 ml standard, 6.0 mg of benzene (converted to microliters for easy measurement) is injected into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The excess quantity of benzene is used to minimize error due to carbon disulfide volatility. A series of standards is then prepared, varying in concentration over the desired range, and analyzed under the same gas chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration vs average peak area.

(2) Determination of Desorption Efficiency

The desorption efficiency, ie, the percentage of benzene desorbed from the charcoal, is determined only once, provided the same batch of charcoal is always used.

Activated charcoal, equivalent to the amount in the first section of the sampling tube (100 mg), is measured into a 2-in, 4-mm I.D. glass tube, flame-sealed at one end, and capped with a paraffin film or equivalent at the open end. A known volume of benzene, usually equivalent to that present in a 10-liter sample at a concentration equal to the federal standard, is injected directly into the activated charcoal with a microliter syringe and the tube again capped with more paraffin film. A minimum of 5 tubes are prepared in this manner and allowed to stand for at least 1 day to assure complete adsorption of the benzene onto the charcoal.

These tubes are desorbed and analyzed in exactly the same manner as the sampling tubes.

The results of each analysis are compared to the standards to determine the average percentage (desorption efficiency) that is desorbed. The desorption efficiency is then used as a factor in all sample analyses. The desorption efficiency, determined in this manner, has been shown to be essentially the same as that obtained by analysis of a known amount of benzene vapor trapped on the charcoal and the determined value, therefore, is used because of its simplicity. Each laboratory should determine its own desorption efficiency. For comparison purposes, NIOSH determined a value of 96% for benzene on one batch of charcoal.

(j) Calculations

(1) Read the weight in milligrams corresponding to each peak area from the standard curve. No correction is necessary for the volume injected, since it is the same for both the sample determination and the standard curve.

(2) The weight of benzene on the front section of the blank is subtracted from the weight determined for the front section of each sample; a similar procedure is followed for the backup sections. Amounts present on the front and backup sections of the same tube are then added together to determine the total amount detected in the sample. This total weight is then divided by the desorption efficiency to determine the corrected total number of milligrams in the sample. Milligrams are converted into ppm by volume in the air sampled by the following equation at 25 C and 760 mm Hg:

$$\text{ppm} = \frac{24{,}450 \text{ ml/mole} \times \text{mg/liter}}{\text{molecular wt}}$$

For a 10-liter air sample of benzene:

$$\text{ppm} = \frac{24{,}450 \text{ ml/mole} \times \text{mg in sample/10 liters}}{78.11 \text{ g/mole}}$$

$$\text{ppm} = 31.30 \times \text{mg in sample}$$

VIII. APPENDIX II

METHODS FOR DETERMINATION OF EXPOSURE AREAS TO BENZENE

Estimation of Concentration with Detector Tubes

(a) Atmospheric Sampling

(1) Equipment Used

A typical sampling train consists of a detector tube with a corresponding sampling pump. A specific manufacturer's pump may only be used with his detector tubes.

(2) Sampling Procedures

A specific procedure depends on the manufacturer's instructions but normally consists of breaking both tips off a detector tube, inserting the tube into the pump, and taking a specific number of strokes with the pump.

(3) Handling and Shipping of Samples

Detector tubes are not stable with time; the stain in some tubes fades in a few minutes. The tubes should be read immediately in accordance with the manufacturer's instructions and charts; no attempt should be made to save the used tubes.

(b) General Principles

Gas detector tubes contain a chemically impregnated packing which indicates the concentration of a contaminant in the air by means of a chemically produced color change. The color changes are not permanent or stable, so the stained tubes must be read immediately after the samples are taken. The length of stain or the color intensity is read according to the manufacturer's instructions. This may involve comparing the stain with a chart, a color comparator, or a direct concentration reading from calibration marks on the tube. Detailed descriptions are provided by individual manufacturer's instructions.

Tubes obtained from commercial sources which bear the certified seal of NIOSH are considered to adhere to the requirements as specified for Approval of Gas Detector Tube Units in 42 CFR Part 84 (37 F.R. 19643). A user may perform his own calibration on commercially acquired tubes by generating accurately known concentrations of benzene in air and correlating concentration with stain length or color intensity.

(c) Range and Sensitivity

Certification standards require that certified tubes have a range from 1/2-5 times the time-weighted average concentration. The sensitivity varies with tube brands.

(d) Interferences

Interferences vary with tube brands. The manufacturer's instructions must be consulted.

(e) Accuracy

Certification standards by NIOSH under the provisions of 42 CFR Part 84 (37 F.R. 19643) specify reliability to within ±25% of the actual concentration in the range 0.75-5 times the standard and ±35% in the range from 0.5 up to, but not including, 0.75 times the standard.

(f) Advantages and Disadvantages

Unlike the charcoal tube method, the use of detector tubes (and portable instruments) is relatively inexpensive and rapid; there is far less time lag than that experienced with laboratory analytical results.

Rapid detecting units are valuable for determining whether a hazardous condition exists at a given location so that workers may be evacuated or suitable protective devices provided. In addition, industrial operators and process engineers need inexpensive and rapid tools for day-to-day evaluation of the atmospheric levels in a work area.

The accuracy of detector tubes is limited; at best they give only an indication of the contaminant concentration. In evaluating measurements performed with detector tubes, interferences, difficulty of end-point readings, and possible calibration inaccuracies must all be considered.

Measurement with Portable Instruments

(a) Atmospheric Sampling

(1) Equipment Used

Two classifications of portable meters that are applicable to atmospheric sampling are direct reading instruments and analytical instruments. Combustible gas meters and flame ionization meters are portable, direct reading instruments; portable variable-path infrared analyzers and gas chromatographs are both field analytical instruments. Any of the 4 meters mentioned are acceptable for benzene determinations if they are properly calibrated before use.

(2) Sampling Procedures

The most important sampling step is the meter calibration. Careful calibration must be performed either in the laboratory prior to on-site use or in the field using a container of specific benzene concentration. If calibration charts are inaccurate, erroneous readings will be made.

The actual field sampling is conducted according to the manufacturer's instructions. Readings should be corrected if necessary for variables such as temperature, humidity, atmospheric pressure, etc, and recorded along with time, place, temperature, etc.

(b) General Principles

Analysis is dependent on the type of meter used. The portable direct reading meters require no analysis because they usually provide usable concentration readings directly. Results obtained from the variable-path infrared analyzer and the gas chromatograph must be recorded, further analyzed, and compared with standards to obtain concentration values.

(c) Range and Sensitivity

The range and sensitivity vary with the instrument used; in general, the portable analysis meters are more sensitive than direct reading units.

(d) Interferences

Again, these vary with the instrument used. Water vapor or combustible gases interfere with benzene identification using combustible gas meters. Mixtures of any carbon containing compounds, other than benzene, will interfere in flame ionization determinations.

(e) Advantages and Disadvantages

The benefits and drawbacks of portable instruments are essentially the same as for detector tubes discussed previously. Where recording capability is possible, direct reading instruments have the advantage of continuous record availability.

IX. APPENDIX III

BIOLOGIC METHOD FOR SAMPLING AND ANALYSIS OF BENZENE

The recommended biologic method for urinalysis is derived from Sherwood and Carter. [102] It has been designed to determine the concentration of phenol and its conjugates, sulfate and glucuronide, in urine. It also determines orthocresol and meta- and paracresols. Urine is hydrolyzed with perchloric acid at 95 C, and the phenols and cresols are extracted with isopropyl ether and determined by gas chromatography.

Collection of Urine Samples

"Spot" urine specimens of about 100 ml are collected as close to the end of the working day as possible. If any worker's urine phenol level exceeds 75 mg/liter, procedures are instituted immediately to determine the cause of the elevated urine phenol levels and to reduce benzene exposure to the worker. Weekly specimens are collected as described above until 3 consecutive weekly determinations indicate that urinary phenol levels are below 75 mg/liter.

After thoroughly washing their hands with soap and water, workers shall collect urine samples from single voidings in clean, dry specimen containers having tight closures and at least a 120-ml capacity. Collection containers may be glass, waxcoated paper, or other disposable types if desired. Following collection of urine specimens, 1 ml of a 10% copper sulfate solution is added to each sample as a preservative, and samples are immediately stored under refrigeration, preferably at 0-4 C.

Refrigerated specimens will remain stable for approximately 90 days. If shipment of samples is necessary to perform analyses, the most rapid method available shall be employed utilizing acceptable packing procedures as specified by the carrier. Proper identification of each specimen shall include as a minimum, the worker's name, date, and time of collection.

Analytical

(a) Principle of the Method

Urine samples are treated with perchloric acid at 95 C to hydrolyze the phenol conjugates, phenyl sulfate, and phenyl glucuronide, formed as detoxification products following benzene absorption. The total phenol is extracted with diisopropyl ether and the phenol concentration is determined by gas chromatography analysis of the diisopropyl ether extract.

(b) Apparatus

(1) Gas chromatograph with a flame ionization detector and equipped with a 5-foot x 3/16-inch column packed with 2 w/w polyethylene glycol adipate on universal 'B' support. Operating conditions are as follows:

Column temperature	150 C
Detector temperature	200 C
Injection port temperature	200 C
Carrier gas	Nitrogen
Carrier gas flowrate	60 ml/min

(2) Water bath

(3) Glass-stoppered, 10-ml volumetric flasks

(4) 1-ml, 2-ml, and 5-ml volumetric pipets

(5) 5-μl syringe

(c) Reagents

(1) Phenol

(2) Perchloric acid

(3) Diisopropyl ether

(4) Distilled water

(d) Procedure

(1) Hydrolysis of Phenol Conjugates

Pipet 5 ml of urine into a 10-ml, glass-stoppered, volumetric flask. Add perchloric acid, mix by swirling, and transfer the lightly stoppered flask to a water bath at 95 C. After 2 hours, remove the flask from the water bath and allow to cool at room temperature.

(2) Diisopropyl ether extraction of phenol and cresols.

Pipet 1 ml of diisopropyl ether into the flask and adjust the volume to 10 ml with distilled water. Shake vigorously for 1 minute to extract the phenol and cresols. Allow the aqueous and ether layers to separate.

(3) Gas chromatographic analysis for phenol

Inject 5 μl of the diisopropyl ether layer into the gas chromatograph and record the attenuation and area of the phenol peak. Under the conditions described, phenol is eluted in 100 seconds, o-cresol in 130 seconds, and m- and p- cresols in 320 seconds.

(e) Standards Preparation

A 50 mg/liter standard aqueous solution of phenol is prepared. A 5-ml aliquot of the standard solution is then subjected to the hydrolysis, extraction, and gas chromatographic analysis procedures described under Procedure above.

(f) Calculations

Determine the phenol concentration in the urine by comparing the gas chromatographic peak area of the sample with that of the 50 mg/liter standard and adjust the value to a specific gravity of 1.024.

(g) Specific Gravity Correction

Due to the magnitude of correction which is required, samples having uncorrected specific gravities less than 1.010 shall be rejected and another sample shall be obtained.

Based on a survey of a large population in the United States in connection with urinary lead excretion, Levine and Fahy [139] found the mean specific gravity to be 1.024. Many investigators throughout the world now use this figure. Buchwald [130] in 1964 determined the mean specific gravity for residents in the United Kingdom to be 1.016, a value now frequently used for Northern Europeans. The importance of specific gravity adjustments can be seen in that a specific gravity of 1.016 will give results having two-thirds the value of those corrected to 1.024. It is important, therefore, that a value be chosen for standardization; since greater acceptance seems to be for 1.024, this value has been selected for adjustment of urinary concentrations of benzene recommended for biological monitoring.

$$\text{corrected concentration} = \frac{\text{observed concentration} \times 24}{\text{last 2 digits of sp gr (eg, } 1.0\underline{21}\text{)}}$$

X. APPENDIX IV

SPECIAL MEDICAL CONSIDERATIONS

The literature on the subject of benzene intoxication, both acute and chronic, has been reviewed elsewhere in this document. Levels of exposure permitted in the standards set by this document have been shown to reduce the danger of acute intoxications to a minimum. [1,24,23] Barring accidental exposure, the need for constant monitoring for signs and symptoms of acute intoxication is unnecessary. The toxic effects of chronic low level exposures are not as well documented and, as has been discussed, exposures to 40 ppm have caused hematologic changes in animals. [66] The need for constant and complete monitoring of the organ systems known to be affected by chronic benzene exposure is, therefore, prudent and necessary.

The hematologic system is especially singled out by benzene's toxic effects. There is no agreement in the literature as to which parameter of hematologic function is the first indicator of early benzene intoxication. Monitoring a number of components, therefore, becomes necessary.

The life span of the erythrocyte has been calculated by various methods to be approximately 120 days. [140] This means that if erythrocyte production were to stop suddenly, as in the development of aplastic anemia, 0.83% of the red cell mass would be lost daily. In the asymptomatic individual exposed to very low concentrations of benzene, measurements of the red cell mass could safely be done every 3 months. In workers exposed to higher concentrations, the risk of developing aplastic anemia increases, and more frequent determinations become necessary. In the event of red cell agenesis, 2 weeks would be a sufficient time to reduce the red cell mass by 12%. A longer delay in discovering this condition would be deleterious to the prognosis; thus, monitoring the red cell mass in individuals with higher levels of exposure to benzene should be done at intervals not exceeding 2 weeks. Macrocytosis has also been stated to be the second most frequent toxic effect of benzene on the bone marrow [140]; therefore, bone marrow monitoring for macrocytosis by the measurement of appropriate corpuscular indices at the most frequent practical period is indicated.

No such simple means for estimating the decay of the white blood cell mass in the case of WBC agenesis is available because, to date, the life span of neutrophils has not been measured successfully, despite estimates of less than 12 days. [140] It is difficult to rationally set a maximum period beyond which it would be dangerous to delay measurement. Quarterly intervals in exposed individuals are felt to be maximum intervals prudent in this situation, reflecting the expense and difficulty of the differential WBC count, but measurement at shorter intervals is desirable where practical.

The life span of platelets has been variously estimated as from 9-12 days. These data are imprecise because of the difficulty inherent in the measurements. For those individuals exposed to greater than the maximum suggested TWA, a bimonthly measurement would seem sufficient to find a marked platelet reduction by estimation of platelets from a smear of peripheral blood. This finding might precede symptoms. However, by the time the abnormality is sufficiently advanced, the worker may already be complaining of symptoms caused by a decreased clotting function; therefore, no test more frequently than quarterly is recommended for a platelet determination.

Increased turnover of erythrocytes, probably through hemolysis, has been reported. [140,141] Counts of reticulocytes (immature, still nucleate red blood cells) give a rough estimate of the rapidity of erythrocyte turnover. Obtaining this value on a quarterly basis is suggested in workers having exposures from 1-10 ppm of benzene and annually in others. Hemolysis is discovered early by laboratory estimation of the breakdown products of hemoglobin, of which bilirubin is the easiest to measure. Again, the frequency of the determination is predicated upon the level of individual exposure.

Normal Hematologic Values

The generally accepted ranges of normal for the hematologic tests discussed in the body of this document are presented in Table XII-14 and are derived from values reported by Conn. [142] It should be noted that these values do not represent a definition of normal, but are only a rough guideline. Interpretation of laboratory results should be made on the basis of that laboratory's established normal range for the procedure as performed there. The values listed in Table XII-14 are applicable only to adults.

XI. APPENDIX V.

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material containing benzene shall be provided in the appropriate section of the Material Safety Data Sheet or approved form. If a specific item of information is inapplicable, the initials "n.a." (not applicable) should be inserted.

(a) Section I. Source and Nomenclature.

(1) The name, address, and telephone number of the manufacturer or supplier of the product.

(2) The trade name and synonyms for a mixture of chemicals, a basic structural material, or for a process material; and the trade name and synonyms, chemical name and synonyms, chemical family, and formula for a single chemical.

(b) Section II. Hazardous Ingredients.

(1) Chemical or widely recognized common name of all hazardous ingredients.

(2) The approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, 10-20 by volume; 10% maximum by weight.

(3) Basis for toxicity for each hazardous material such as an established standard in appropriate units.

(c) Section III. Physical Data.

Physical properties of the total product including boiling point and melting point in degrees Fahrenheit; vapor pressure in millimeters of mercury; vapor density of gas or vapor (air=1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water=1); volatility, indicate if by weight or volume, at 70 degrees Fahrenheit; evaporation rate for liquids (indicate whether butyl acetate or ether=1); and appearance and odor.

(d) Section IV. Fire and Explosion Hazard Data.

Fire and explosion hazard data about a single chemical or a mixture of chemicals, including flash point, in degrees Fahrenheit; flammable limits in percent by volume in air; suitable extinguishing media or agents; special fire fighting procedures; and unusual fire and explosion hazard information.

(e) Section V. Health Hazard Data.

Toxic level for total compound or mixture, effects of exposure, and emergency and first-aid procedures.

(f) Section VI. Reactivity Data.

Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

(g) Section VII. Spill or Leak Procedures.

Detailed procedures to be followed with emphasis on precautions to be taken in cleaning up and safe disposal of materials leaked or spilled. This includes proper labeling and disposal of containers holding residues, contaminated absorbents, etc.

(h) Section VIII. Special Protection Information.

Requirements for personal protective equipment, such as respirators, eye protection, clothing, and ventilation, such as local exhaust (at site of product use or application), general, or other special types.

(i) Section IX. Special Precautions.

Any other general precautionary information.

U.S. DEPARTMENT OF LABOR
Occupational Safety and Health Administration

Form Approved
OMB No. 44-R1387

MATERIAL SAFETY DATA SHEET

Required under USDL Safety and Health Regulations for Ship Repairing, Shipbuilding, and Shipbreaking (29 CFR 1915, 1916, 1917)

SECTION I

MANUFACTURER'S NAME	EMERGENCY TELEPHONE NO.
ADDRESS *(Number, Street, City, State, and ZIP Code)*	
CHEMICAL NAME AND SYNONYMS	TRADE NAME AND SYNONYMS
CHEMICAL FAMILY	FORMULA

SECTION II - HAZARDOUS INGREDIENTS

PAINTS, PRESERVATIVES, & SOLVENTS	%	TLV (Units)	ALLOYS AND METALLIC COATINGS	%	TLV (Units)
PIGMENTS			BASE METAL		
CATALYST			ALLOYS		
VEHICLE			METALLIC COATINGS		
SOLVENTS			FILLER METAL PLUS COATING OR CORE FLUX		
ADDITIVES			OTHERS		
OTHERS					

HAZARDOUS MIXTURES OF OTHER LIQUIDS, SOLIDS, OR GASES	%	TLV (Units)

SECTION III - PHYSICAL DATA

BOILING POINT (°F.)		SPECIFIC GRAVITY (H_2O=1)	
VAPOR PRESSURE (mm Hg.)		PERCENT, VOLATILE BY VOLUME (%)	
VAPOR DENSITY (AIR=1)		EVAPORATION RATE (__________ =1)	
SOLUBILITY IN WATER			
APPEARANCE AND ODOR			

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (Method used)	FLAMMABLE LIMITS	Lel	Uel

EXTINGUISHING MEDIA

SPECIAL FIRE FIGHTING PROCEDURES

UNUSUAL FIRE AND EXPLOSION HAZARDS

(Continued on reverse side)

SECTION V - HEALTH HAZARD DATA

THRESHOLD LIMIT VALUE	
EFFECTS OF OVEREXPOSURE	
EMERGENCY AND FIRST AID PROCEDURES	

SECTION VI - REACTIVITY DATA

STABILITY	UNSTABLE		CONDITIONS TO AVOID
	STABLE		
INCOMPATABILITY *(Materials to avoid)*			
HAZARDOUS DECOMPOSITION PRODUCTS			
HAZARDOUS POLYMERIZATION	MAY OCCUR		CONDITIONS TO AVOID
	WILL NOT OCCUR		

SECTION VII - SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED
WASTE DISPOSAL METHOD

SECTION VIII - SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION *(Specify type)*		
VENTILATION	LOCAL EXHAUST	SPECIAL
	MECHANICAL *(General)*	OTHER
PROTECTIVE GLOVES	EYE PROTECTION	
OTHER PROTECTIVE EQUIPMENT		

SECTION IX - SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING
OTHER PRECAUTIONS

PAGE (2)

GPO 934-110

Form OSHA-20
Rev. May 72

TABLE XII-1

SIGNIFICANT PHYSICAL PROPERTIES OF BENZENE

Formula	C6H6
Formula Weight	78.1
Boiling Point	80.1 C (176 F) at 760 mm Hg
Melting Point	5.5 C (42 F)
Specific Gravity	0.8790 g/ml at $\frac{20\text{ C }(68\text{ F})}{4\text{ C }(39.2\text{ F})}$
Solubility	0.06% in water, mixes freely with alcohol, ether and most organic solvents.
Explosive Range for Vapor	1.4 - 7.1% by volume in air
Flash Point	-12 to -10 C (10.4-14 F)
Ignition Temperature	490 C (914 F)
Vapor Density	2.7 (Air = 1.0)

Derived from references 7 and 8

TABLE XII-2

BENZENE REACTIONS OF COMMERCIAL IMPORTANCE

1. Halogenation and subsequent hydrolysis to produce phenol:

$C_6H_6 + Cl_2 \xrightarrow{\text{(Metallic Iron Catalyst)}} C_6H_5Cl + HCl$
chlorobenzene

$C_6H_5Cl + NaOH$ (6-8% aqueous solution) $\xrightarrow[\text{4500 lb/sq in}]{\text{360 C}}$

$C_6H_5ONa + HCl \xrightarrow{\qquad} C_6H_5OH + NaCl$
phenol

2. Hydrogenation of benzene to produce cyclohexane:

$C_6H_6 + 3H_2 \xrightarrow[\text{150-200 C, 25 atm}]{\text{(Metallic Nickel Catalyst)}} C_6H_{12}$
cyclohexane

3. Friedel-Crafts reaction of benzene and ethylene to produce ethyl benzene which is then dehydrogenated to yield styrene:

$C_6H_6 + C_2H_4 \xrightarrow{\text{(Phosphoric Acid Catalyst)}} C_6H_5C_2H_5$
ethyl benzene

$C_6H_5C_2H_5 \xrightarrow[\text{600 C}]{(Cr_2O_3\ .\ Al_2O_3\ \text{Catalyst})} C_6H_5CH{=}CH_2 + H_2$
styrene

From Chemical Economics Handbook [3]

TABLE XII-3

SUMMARY OF BLOOD FINDINGS ON EXAMINATION OF WORKERS EXPOSED TO BENZENE

Group	Room	Local ventilation	Average benzene in air, ppm		Blood findings	
			Summer	Winter	Number of persons examined	Number positive
I-A						
Small amount of benzene;	150B	-	100		9	2
no local ventilation;	60	-	150		1	0
low benzene content in air.	27A	-	110		2	1
I-B						
Small amount of benzene;	27B	-	700		2	0
no local ventilation; high	59	-	150	210	9	1
benzene content in air.	61A	-	130	210	12	6
	61B	-	1,360	580	1	1
II-A						
Large amount of benzene;	78A	+	70	90	0	
local ventilation; low	150A	+	90		1	1
benzene content in air.	75B	+	100		3	1
II-B						
Large amount of benzene;	91	+	180	400	5	*0
local ventilation; high	50B	+		430	3	1
benzene content in air.	50A	+		500	4	1
	75A	+	130	330	10	1
III						
Large amount of benzene; no	78B	-	340		1	0
local ventilation;high	23	-			6	2
benzene content in air.	83	-	620		9	6
	95	-	1,800		3	2
Total					81	26

*3 clinical cases, 1 fatal, since tests were made.
From Greenburg [19]

TABLE XII-4

DETAILED BLOOD COUNTS ON 13 WORKERS EXHIBITING THE PICTURE OF EARLY BENZOL POISONING

Plant Code No.	Hb	RBC	WBC	Poly %	Lymphocytes %	Large Mononuclears %	Eosin %	Trans %
23	65	4,376,000	5,300	58	36	3.5	1.5	0.5
23	75	4,400,000	5,200	55	39	3.5	2.0	0.5
23			4,100					
23			4,800					
27	55	4,304,000	4,667	55	36	5.0	1.0	2.0
59	70	5,424,000	6,140	47	47	3.5	0.5	1.0
61	85		4,450					
61	50		4,000					
	40	1,736,000	3,000					
61	75		2,850					
	80	1,736,000	4,200					
61	23	800,000	3,000					
83	27	1,055,000	1,450	58	36	5.0	1.0	0.0
	41							
	30	2,100,000	2,100					
	29	1,365,000	2,200	44	49	6.0	1.0	0.0
95	55	3,193,000	3,100	50	39	1.5	7.0	1.5
95	70	4,968,000	3,600	47	41	0.5	8.0	3.0
Normal male	90-110	5,000,000 5,500,000	7,500	65-70	30	1-2	1-2	2-4
Normal female	50-100	4,500,000 5,000,000	7,500	65-70	30	1-2	1-2	2-4

From Greenburg [19]

TABLE XII-5

INCIDENCE OF SIGNIFICANT ABNORMALITIES IN CASES COMPLETELY STUDIED, BY DIAGNOSIS

Test	Criteria of Abnormality	Severe Cases No.	Severe Cases %	Early Cases No.	Early Cases %	Negative Cases No.	Negative Cases %
RBC	Less than 4.5 million	15	68.2	31	72.1		
Mean corp volume	More than 94 cu μm	14	63.6	25	58.1	9	24.3
Platelets	Less than 100,000	18	81.3	14	32.6		
Hemoglobin	Less than 13.0 gm/100 cc	8	36.4	11	25.6		
WBC	Less than 5,000	19	86.5	13	30.2		
	Number of cases examined	22		43		37	

From Greenburg et al [17]

TABLE XII-6

COMBINATIONS OF TESTS WHICH WOULD REVEAL A HIGH PROPORTION OF INDIVIDUALS SHOWING THE BENZENE EFFECT, ACCORDING TO POSITIVE CASES WITH COMPLETE BLOOD STUDIES*

Combined Tests	Cases of Poisoning Revealed by Given Test Combinations No.	%
MCV + RBC	61	82.4
MCV + WBC	59	79.7
MCV + Hb	59	79.7
MCV + Platelets	57	77.0
RBC + Platelets	56	75.7
RBC + WBC	54	73.0
RBC + Hb	51	68.9
MCV + RBC + WBC + Platelets	72	97.3
MCV + RBC + WBC	69	93.2
MCV + RBC + Platelets	66	89.2
MCV + RBC + Hb	65	87.8
Single Tests		
MCV	48	64.9
RBC	47	63.5
Platelets	31	41.9
WBC	30	40.5
Hb	30	40.5
Total positive cases having complete blood studies	74	100.0

*Includes 9 cases with macrocytosis as the only blood abnormality.
From Greenburg et al [17]

TABLE XII-7

PRESUMPTIVE DURATION OF CONTACT AND INTERVAL
BETWEEN LAST CONTACT AND DEATH OR BIOPSY
IN CHRONIC BENZENE POISONING

Case	Sex	Age	Industry	Duration of Contact	Interval Since Last Contact
1	M	22	Rubber factory	6 months	9 months (N)
2	M	54	Artificial leather	7 years	1 month (N)
3	F	20	Rubber cement	8 months	1 month (N)
4	M	25	Artificial leather	3 years	1 month (N)
5	M	46	Cobbler*	years	1 month (N)
6	F	44	Rubber factory	4 years	6 months (N)
7	M	48	Artificial leather	12 years	5 months (B)
8	M	45	Artificial leather	1 1/2 years	4 months (N)
9	M	45	Artificial leather	3 years	1 1/2 years (N)
10	M	43	Artificial leather	years	? (N)
11	F	18	Rubber factory	7 months	1 month (N)
12	M	54	Artificial leather	3 years	3 months (N)
13	M	51	Cobbler*	2 years	? (N)
14	F	63	Telephone operator**	5 years	3 months (N)
15	M	28	Artificial leather	4 years	6 years (N)
16	M	57	Artificial leather	1 year	2 years (A) (B)
17	M	57	Artificial leather	5 years	5 months (A) (B)
18	M	41	Furniture finisher***	years	2 1/2 months (N)
19	M	12	Schoolboy***	?	2 months (A) (B)

(N) Necropsy, (B) Biopsy, (A) Alive.

*Used benzene as solvent for rubber cement.

**Used solvent containing 50% benzene for eradicating names on switchboard.

***Used paint remover containing benzene.

From Mallory et al [22]

TABLE XII-8

AIR ANALYSES AT A BENZENE COATING PLANT

	Benzene Vapor ppm			
Location	December 1938	July 1946**	August 1946	Average
Coating Room-Machine No. 1	60*	70*	50*	60*
Coating Room-Average	45	40	40	40
Coating Room-Maximum	60	70	55	60
Mixing Room-Average	80	80		80

*Exposure of deceased worker or successor.
**Analysis by an insurance company.
Derived from Hardy and Elkins [57]

TABLE XII-9

SUMMARY OF ENVIRONMENTAL BENZENE LEVELS AND URINARY PHENOL EXCRETIONS FOR WORKERS IN A RUBBER COATING PLANT USING NAPHTHA SOLVENTS (3-7.5% by Volume)

					5/25/60			7/14/60			1/13/61			9/6/61	
Wkr	Job	Date Empl Began	Age When Hired	Urine Phenol mg/l	Equiv Air Level ppm	Actl Air Anal ppm	Urine Phenol mg/l	Equiv Air Level ppm	Actl Air Anal ppm	Urine Phenol mg/l	Equiv Air Level ppm	Actl Air Anal ppm	Urine Phenol mg/l	Equiv Air Level ppm	Actl Air Anal ppm
A	Spreader	7/55	55	106	10	5,11,	158	19	7,25	250	29	20,25	-	-	19,36,
B		9/44	17	114	13	12,27	75	10	(16.0)	160	19	(22.5)	130	13	25
C		6/57	24	68	10	(13.8)*	-	-		250	29		162	19	(26.3)
D		8/51	47	111	13		-	-		330	38		200	25	
E		12/55	34	270	31		-	-		-	-		200	25	
F		2/46	34	-	-		-	-		350	41		260	31	
G		7/60	33	-	-		-	-		-	-		255	31	
H	Saturator	8/57	20	570	74	68	-	-	57	700	95**	90	295	35	22,23
I	Churner	9/47	38	-	-		190	22	12,17	360	44		152	19	14,16,
J		9/53	22	-	-		-	-	(14.5)	270	31		106	10	44
K		2/59	18	-	-		-	-		300	35		-	-	(24.7)
L		10/58	21	-	-		-	-		480	62		390	47	

* Mean

** Extrapolated

From Pagnotto (written communication, 1972)

TABLE XII-9

SUMMARY OF ENVIRONMENTAL BENZENE LEVELS AND URINARY PHENOL EXCRETIONS FOR WORKERS IN A RUBBER COATING PLANT USING NAPHTHA SOLVENTS (3-7.5% by Volume)
(Continued)

		8/16/62			4/10/63			12/12/63			
Worker	Job	Urine Phenol mg/l	Equiv Air Level ppm	Actual Air Analysis ppm	Urine Phenol mg/l	Equiv Air Level ppm	Actual Air Analysis ppm	Urine Phenol mg/l	Equiv Air Level ppm	Actual Air Analysis ppm	Years Expos
A	Spreader	-	-	12,20,	195	25	35,10,	133	16	17,23,	8
B		96	10	18,3,4	230	27	10,21,	193	25	17,30,	19
C		68	10	(11.4)*	145	16	14,17,	132	16	35,20	6
D		87	10		350	41	38,39,	232	29	(25.3)	12
E		85	10		280	33	25,29	152	19		8
F		268	31		370	44	(21.5)	119	13		17
G		130	13		435	56		165	19		3
H	Saturator	280	33	10,14 (12)	440	56	43,43, 33 (39.7)	260	31	38,82, 140 (86.7)	6
I	Churner	-	-		160	19	6	-	-		16
J		-	-		150	16		-	-		10
K		-	-		-	-		-	-		?
L		206	25		300	35		325	38		5

*Mean

From Pagnotto (written communication, 1972)

TABLE XII-10

URINARY PHENOL LEVELS WITH CORRESPONDING EQUIVALENT ENVIRONMENTAL BENZENE EXPOSURE LEVELS

Urine Phenol (mg/liter)	Approx. Av. Equiv. Benzene Air Level (ppm)
100	10
120	13
140	16
160	19
180	22
200	25
220	27
240	29
260	31
280	33
300	35
320	38
340	41
360	44
380	47
400	50
420	53
440	56
460	59
480	62
500	65
520	68
540	71
560	74
580	77
600	80

From Pagnotto (written communication, 1972)

TABLE XII-11

SUMMARY OF HEMOGLOBIN LEVELS FOR WORKERS IN A RUBBER COATING PLANT USING NAPHTHA SOLVENTS
(3-7% by Volume)

Worker	3/10/61	3/30/61	9/20/63	10/31/63
B		12.5		12.6
H		13.0	13.8	
J	13.4	12.8		
L	12.2	11.3	11.2	11.5
M	14.6			
N		12.7		
O		12.2		

From Pagnotto (written communication, 1972)

TABLE XII-12

COMPARISON OF BENZENE AIR LEVELS FROM URINE PHENOL AND AIR SAMPLE DATA

		Benzene in Air ppm	
Occupation	Urine Phenol* mg/liter	Estimated from Urine Phenols	Air Sampling Data (TWA)
Agitator operator	105	10	1.3
Agitator operator	107	10	10.7
Benzol loader	<65	<5	1.7
Benzol still operator	<65	<5	6.7
Benzol oil still operator	<65	<5	0.8
Naphthalene operator	115	12	8.5
Analyst	105	10	2.4
Chemical observer	68	5	12.0
Foreman	<65	<5	none
Repairman	<65	<5	2.6
Chemical observer	65	5	17.1
Chemical observer	112	11	12.2
Chemical observer	66	5	6.5
Control tester	66	5	14.6
Stillman	212	24	39.2
Chemist	157	17	8.8
Pumpman helper	302	36	55
Pumpman helper	84	7	9.5

From Bethlehem Steel data (written communication, 1972)

*Values less than 65 mg/liter were not considered to differ significantly from that of an unexposed normal adult.

TABLE XII-13

BENZENE PLANT AIR LEVELS
ppm

Occupation	Benzene in Air 8-Hour TWA	 Range
Agitator Operator	6.0	0.5 - 20
Benzol Loader & Loader Helper	4.0	0.5 - 15
Benzol Still Operator	4.0	1 - 15
Light Oil Still Operator	2.5	1 - 15
Naphthalene Operator	10	2 - 30
Analyst	10	2 - 30
Chemical Observer	10	4 - 50
Foreman	1.5	1 - 10

From Bethlehem Steel data (written communication, 1972)

TABLE XII-14

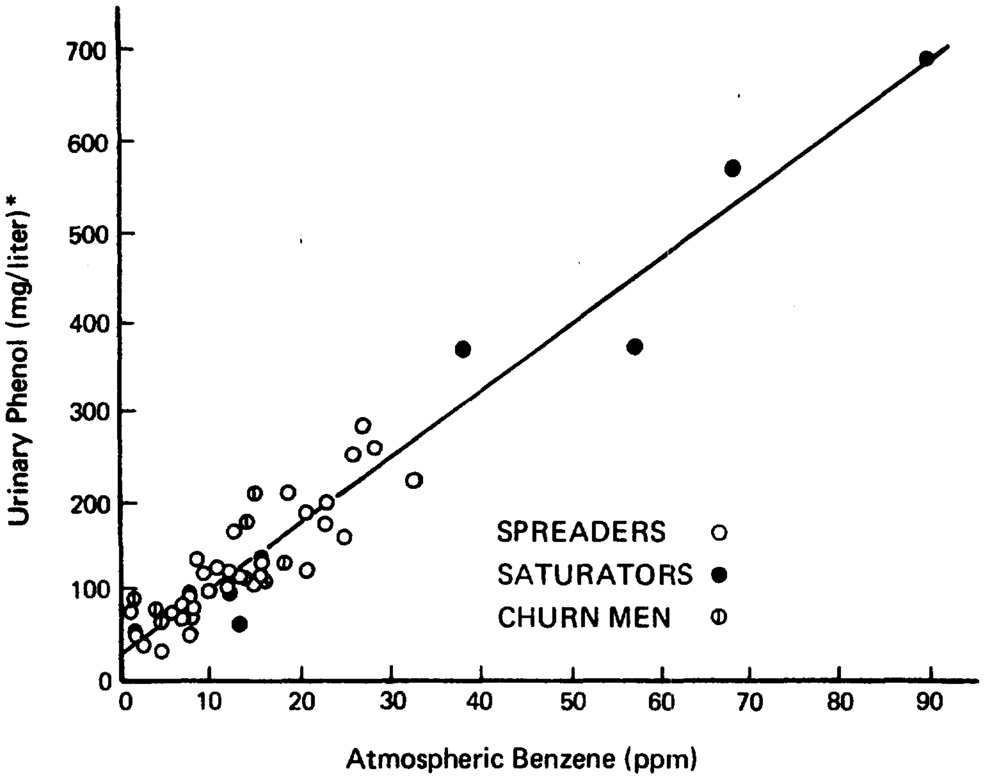
NORMAL HEMATOLOGIC VALUES

Cell Counts		
Erythrocytes	Male	4.6-6.2 million/cu mm
	Female	4.2-5.4 million/cu mm
Leukocytes	Total	5,000-10,000/cu mm
	Differential	
	Myelocytes	0%
	Immature polymorphonuclears	3-5%
	Segmented neutrophils	54-62%
	Lymphocytes	25-33%
	Monocytes	3-7%
	Eosinophils	1-3%
	Basophils	0-0.75%
Platelets		150,000-350,000/cu mm
Reticulocytes		0.5-1.5% of erythrocytes
Corpuscular Values for Erythrocytes		
Mean Corpuscular Hemoglobin		27-31 picograms
Mean Corpuscular Volume		82-92 cu micra
Mean Corpuscular Hemoglobin Concentration		32-36%
Hematocrit	Male	40-54%
	Female	37-47%
Hemoglobin	Male	14.0-18.0 g%
	Female	12.0-16.0 g%
Serum Bilirubin Concentration		
	Total	0.3-1.1 mg%
	Direct	0.1-0.4 mg%
	Indirect	0.2-0.7 mg%

From Conn [142]

FIGURE XII-1

COMPARISON OF PHENOL IN URINE WITH BENZENE IN AIR

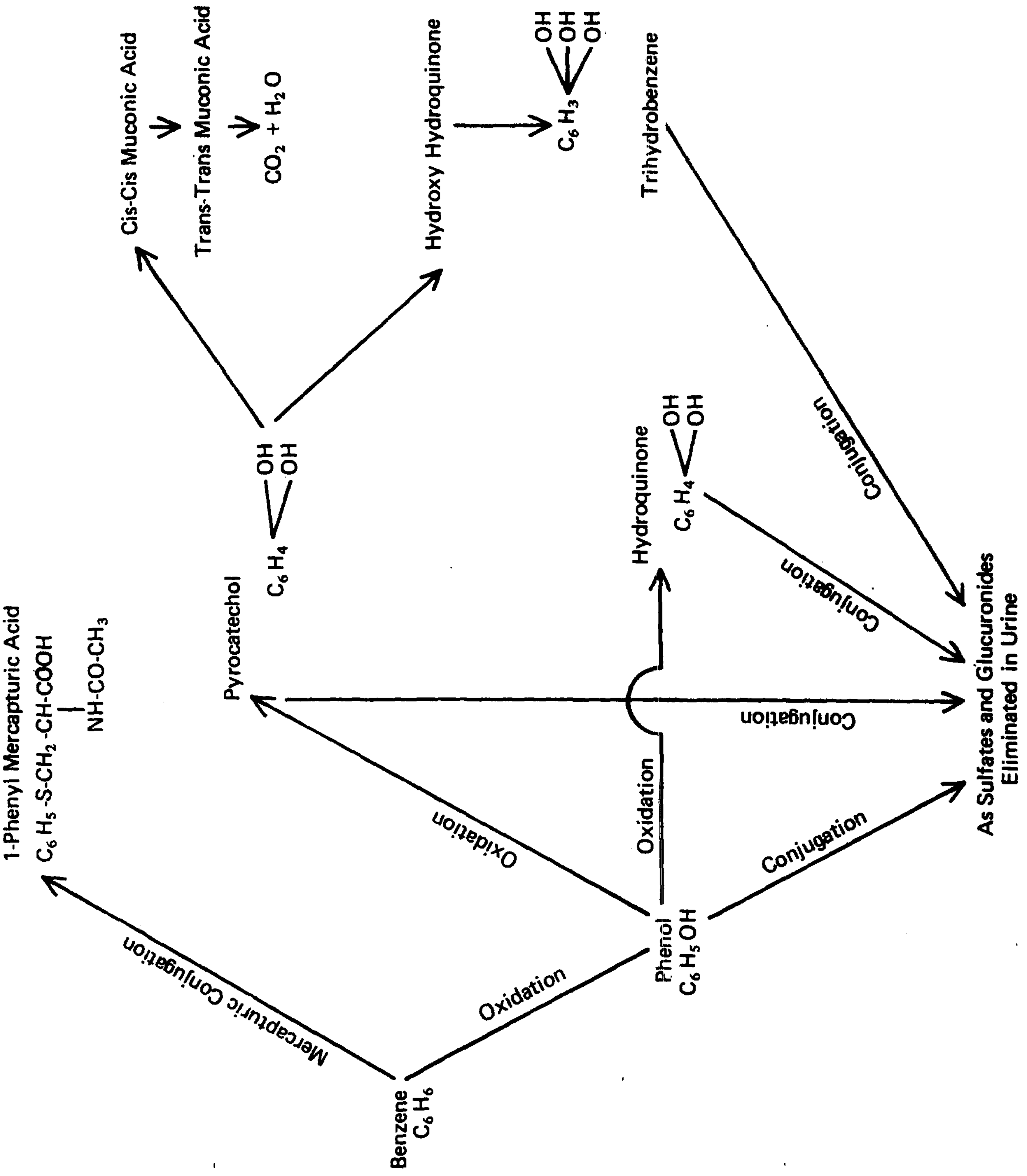


*Represents both phenol and paracresol. Phenol alone would result in values lower than indicated.

Derived from Pagnotto [12]

FIGURE XII-2

SUGGESTED METABOLIC TRANSFORMATION OF BENZENE IN MAN



From Truhaut [126]

☆U.S.Government Printing Office: 1974 — 758-520/2150

HEW Publication No. (NIOSH) 74-137