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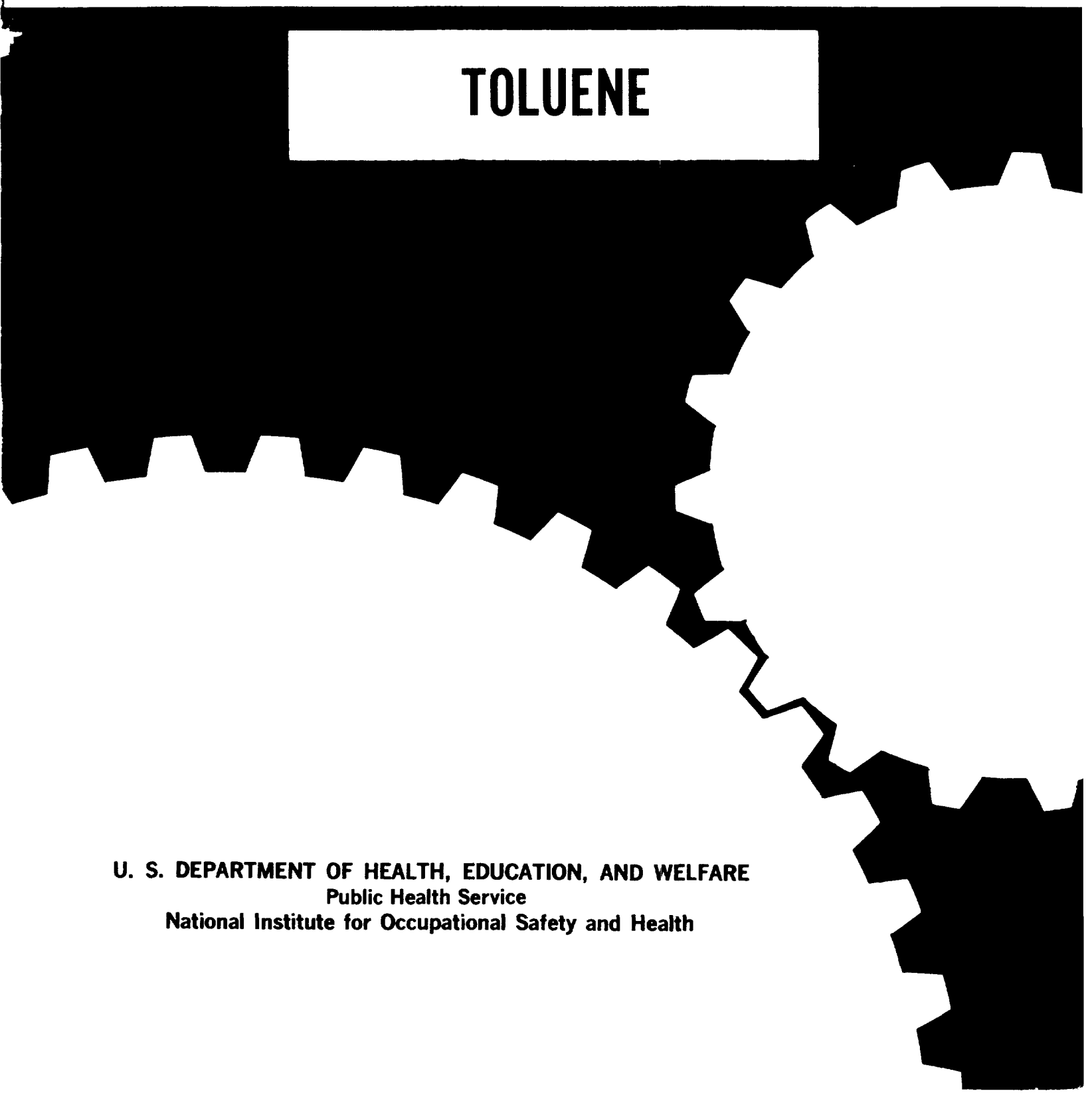
OCCUPATIONAL EXPOSURE TO

TOLUENE



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

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OCCUPATIONAL EXPOSURE TO TOLUENE

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1973

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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 toluene by members of my staff, the valuable and constructive comments presented by the Review Consultants on Toluene, the ad hoc committees of the American Academy of Industrial Hygiene and the Industrial Medical Association, by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, and by Edwin C. Hyatt 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 toluene. 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 toluene. George D. Clayton and Associates developed the basic information for consideration by NIOSH staff and consultants under contract No. HSM-99-72-118. 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 TOLUENE

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I. RECOMMENDATIONS FOR A TOLUENE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to toluene in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and safety of workers for an 8-hour day, 40-hour week over a working lifetime; compliance with the standard should therefore prevent adverse effects of toluene 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.

"Exposure to toluene" means exposure to a concentration of toluene equal to or above one-half the recommended workroom environmental standard. Exposures at lower environmental concentrations will not require adherence to the following sections.

If "exposure" to other chemicals also occurs, for example from contamination of toluene with benzene, provisions of any applicable standard for the other chemicals shall also be followed.

Section 1 - Environmental (Workplace air)

(a) Concentration

Occupational exposure to toluene shall be controlled so that workers shall not be exposed to toluene at a concentration greater

than 100 parts per million parts of air (375 milligrams per cubic meter of air) determined as a time-weighted average (TWA) exposure for an 8-hour workday with a ceiling of 200 parts per million parts of air (750 milligrams per cubic meter of air) as determined by a sampling time of 10 minutes.

(b) Sampling, Collection, and Analysis

Procedures for collection 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.

Section 2 - Medical

Comprehensive preplacement and biennial medical examinations should be provided for all workers subject to "exposure to toluene." The examination should be directed towards but not limited to the incidence of headaches, nausea, and dizziness; particular attention should be focused on complaints and evidence of eye, mucous membrane, and skin irritation. Laboratory tests recommended at the time of the biennial examination include complete blood count and urinalysis.

Section 3 - Labeling (Posting)

Areas where exposure to toluene is likely to occur shall be posted with signs reading:

TOLUENE

WARNING! FLAMMABLE

Keep away from heat, sparks, and open flame.

VAPOR HARMFUL

Keep containers closed.

Use only with adequate ventilation.

Avoid prolonged breathing of vapor.

Avoid prolonged or repeated contact with skin.

If environmental levels are at or greater than the environmental limit, or if a variance permitting use of respiratory controls has been granted, add to the label or placard the location of the respirators.

Section 4 - Personal Protective Equipment and Work Clothing

Subsection (a) shall apply whenever a variance from the standard recommended in Section 1 is granted under provisions of the Occupational Safety and Health Act, or in the interim period during the application for a variance. When the limits of exposure to toluene prescribed in subsection (a) of Section 1 cannot be met by limiting the concentration of toluene in the work environment, an employer must utilize, as provided in subsection (a) of this Section,

a program of respiratory protection to effect the required protection of every worker exposed.

(a) Respiratory Protection

Engineering controls shall be used wherever feasible to maintain toluene concentrations below the prescribed limits. Appropriate respirators shall be provided and used when a variance has been granted to allow respirators as a means of control of exposure to routine operations and while the application is pending. Administrative controls should also be used to reduce exposure. Respirators shall also be provided and used for nonroutine operations (occasional brief exposures above the TWA of 100 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 toluene 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 toluene concentration. The employer shall ensure that no worker is being exposed to toluene in excess of the standard either because of improper respirator selection or fit.

(2) Employees experiencing breathing difficulty while wearing respirators shall be medically examined to determine their ability to wear the respirator.

(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.

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

(5) Respiratory protective devices described in the following Table I-1 shall be either those approved under the following listed regulations or those approved under 30 CFR 11, published March 25, 1972 or future amendments.

(A) Gas masks----

30 CFR 13 (Bureau of Mines Schedule 14 F)

(B) Supplied-air respirators----

30 CFR 12 (Bureau of Mines Schedule 19 B)

(C) Self-contained breathing apparatus----

30 CFR 11 (Bureau of Mines Schedule 13 E)

(D) Chemical cartridge respirators----

30 CFR 14 (Bureau of Mines Schedule 23B)

(6) Usage of a respirator specified for use in higher concentrations of toluene is permitted in atmospheres of lower concentrations.

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

TABLE I-1

REQUIREMENTS FOR RESPIRATOR USAGE

AT MULTIPLES OF THE STANDARD

Multiples of TWA Limit	Respirator Type
Less than or equal to 10 times	(1) Chemical cartridge respirator with replaceable organic vapor cartridge(s) and half-mask or full facepiece.
	(2) Air line respirator, demand type (negative pressure), with half-mask facepiece.
Less than or equal to 50 times	(1) Full face gas mask, chin style, with organic vapor canister.

	(2) Supplied air respirator, demand type (negative pressure), with full facepiece.
	(3) Supplied air respirator, continuous flow type.
Less than or equal to 100 times	(1) Gas mask, full facepiece, with front or back mounted chest type organic vapor canister.
	(2) Combination supplied air respirator, demand type, full facepiece with auxiliary self-contained air supply.
Greater than 100 times	Self-contained breathing apparatus with positive pressure facepiece.

(b) Work Clothing

(1) If operations require continued exposure to liquid toluene, workers should wear impervious clothing, gloves, or coverings to protect the potentially exposed area of the body.

(2) Toluene-wetted clothing, unless impervious, shall be removed promptly.

(A) Workers wearing toluene-wetted clothing shall not go near heaters or open flames.

(B) Toluene-wetted clothing shall not be placed in proximity of flames, heaters, or spark-producing equipment.

(3) Work clothing should be changed at least twice a week or more frequently if required.

(4) Glasses having shatter-resistant glass or equivalent lenses and side shields shall be worn when there is a danger of liquid toluene splashing into the eye.

Section 5 - Apprisal of Employees of Hazards from Toluene

(a) Each employee exposed to toluene shall be apprised at the beginning of his employment in, or assignment to, a toluene area of the hazards, relevant symptoms, appropriate emergency procedures, and proper conditions and precautions for safe use of, or exposure to toluene and, during employment, shall be kept currently informed through posting (see Section 3) and instructed as to availability of such information. This information shall be kept on file, including that prescribed in (b) below, and shall be accessible to the worker at each place of employment where exposure to toluene may occur.

(b) Information as specified in Appendix III shall be recorded on U. S. Department of Labor Form OSHA-20, "Material Safety Data Sheet" or on a similar form approved by the Occupational Safety and Health Administration, U. S. Department of Labor.

Section 6 - Work Practices

(a) Smoking materials, including personal matches and lighters, shall be prohibited in all areas where there is toluene.

(b) Emergency Procedures

(1) Fire fighting procedures shall be established and implemented; these shall include procedures for emergencies involving release of toluene vapor.

(A) Drench-type showers, eye-wash fountains, and cleansing facilities should be installed and maintained to provide prompt, immediate access by the workers.

(2) Appropriate respirators shall be available for wear during evacuation.

(3) Appropriate extinguishants shall be available for use in toluene fires.

(c) Exhaust Systems

Where a local exhaust ventilation system is used, it shall be designed and maintained to prevent the accumulation or recirculation of toluene vapor into the workroom.

(d) General Housekeeping

Emphasis shall be placed upon cleanup of spills, inspection and repair of equipment and leaks, and proper storage of materials.

(e) Disposal

(1) The disposal of waste toluene and of materials contaminated with it shall be in accordance with applicable regulations.

(2) Toluene or toluene-containing materials should not be discharged into drains or sewers.

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 toluene exposure. Records of these surveys, including the basis for concluding that air levels are below one-half the environmental standard, shall be kept.

Requirements set forth below apply to toluene exposures.

(a) Employers shall monitor environmental levels of toluene at least semiannually, except as otherwise indicated by a professional industrial hygiene survey. If the time-weighted average or ceiling concentrations are at or above the standard, environmental levels shall be monitored monthly. This increased frequency of monitoring shall be continued until at least two 30-day monitoring periods have demonstrated environmental levels which are at or below the standard.

Air samples shall be collected in the breathing zone of workers to permit calculation of a time-weighted average exposure and ceiling concentration for every toluene exposure area. As a minimum, samples for determination of the following number of time-weighted average and ceiling concentrations shall be collected and analyzed, based on the

number of workers exposed in any toluene exposure area, or as otherwise indicated by a professional industrial hygiene survey.

Number of Employees Exposed	Number of Samples
1-20	5 samples or 50% of the total number of workers, whichever is greater
20-100	10 samples plus 25% of the excess over 20 workers
over 100	30 samples plus 5% of the excess over 100 workers

(b) Records shall be maintained for all sampling schedules to include the sampling methods, analytical methods, type of respiratory protection in use (if applicable), and the time-weighted average and ceiling concentrations of toluene in each work area. Records of results shall be maintained so that they can be classified by employee; they shall be made available to each employee.

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 toluene. 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 consultation 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 toluene are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the processing, manufacture, and use of toluene in

products as applicable under the Occupational Safety and Health Act of 1970.

These criteria were developed to ensure that the standard based thereon would (1) protect against development of acute and chronic toluene poisoning, (2) be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies, and (3) be attainable with existing technology.

For many years, toxicity to the blood and blood forming organs has been attributed to toluene, primarily because of the close structural similarity which exists between toluene and benzene and the established myelotoxicity of benzene. Toluene has been contaminated frequently with benzene. Current scientific evidence obtained from human and animal studies indicates that chemical alkylation of the benzene ring structure such as exists with toluene (methyl benzene) results in a loss of the myelotoxic activity. Benzene appears to be unique among the monocyclic aromatic hydrocarbons in its myelotoxic properties; therefore, the major problem of toluene toxicity concerns its narcotic effects on workers by causing symptoms and signs such as muscular weakness, incoordination, and mental confusion which may pose a risk to both the worker and others.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Toluene (toluol) is a clear, colorless, noncorrosive liquid with a sweet, pungent benzene-like odor. The more important physical properties of toluene are presented in Table X-1. [1,2]

Production of toluene as a by-product of the carbonization of coal was the major source of toluene during the latter part of the 19th century. Although fractional distillation of coal-tar oil accounted for 4% of the toluene production in 1966, the major source (96%) was from petroleum and petrochemical processes including the catalytic reforming reactions. [3] In the United States, the production of toluene [4,5] has increased steadily since 1940 when its production was approximately 31 million gallons; in 1970, production had increased to 694 million gallons.

Approximately 70% of all toluene that is produced is converted into benzene. [5] Another 15% is consumed in the production of chemicals such as toluene diisocyanate, phenol, benzyl and benzoyl derivatives, benzoic acid, toluene sulfonates, nitrotoluenes, vinyl toluene, and saccharin. The remainder is used as a solvent for paints and coatings or as a component of motor and aviation gasolines. [5]

Highly purified toluene (Reagent Grade and Nitration Grade) is presently used for many commercial purposes and contains less than 0.01% benzene as a contaminant [J. D. Hammond, oral communication,

June 1973]. Industrial Grade and 90/120 Grade toluene contain significant quantities of benzene with the 90/120 Grade containing as much as 25%. [1]

Toluene may be encountered as a relatively pure substance or as a constituent of solvent mixtures. When toluene is contained in enclosed systems, potential exposures may occur from transfer of liquid, spillage, or from leaking equipment. Exposures also may occur when toluene is present as a component of paints, thinners, lacquers, and solvents.

Using data obtained from a survey conducted by the U. S. Public Health Service, Bureau of Occupational Safety and Health in 1970, [6] NIOSH estimates that 100,000 persons in the work force could have potential exposure to toluene.

Historical Reports

Early reports on the health effects resulting from exposure to toluene described its toxicity as being similar to that of benzene. [7-9] Certain grades of toluene may contain as much as 25% benzene [1]; thus, its purity must be carefully considered. Because of the benzene content in toluene, conclusions made by the early investigators, [7-9] and even statements in some relatively recent reports, [10,11] have confused the problem of toluene toxicity on the hematopoietic system. Banfer [12] in 1961 reported that commercial toluene in Germany contained up to 15% benzene and other aromatics and

that pure toluene, containing only traces of benzene (up to 0.3%), had been available for only 6 years.

Effects on Humans

(a) Effects on Blood and Hematopoietic Tissue

(1) Bone Marrow

Although studies in experimental animals show rather convincingly that toluene is not myelotoxic, there has been some persistent controversy concerning the effects of toluene on human bone marrow. This is probably due to investigations of groups of industrial workers exposed to toluene derived from coal tar which was contaminated with considerable benzene, frequently as much as 15%. [12] The belief that toluene has myelotoxic properties led to its use in the treatment of leukemia. Francone and Braier [13] in 1954 mentioned the oral administration of toluene for this purpose. They found that leukemia patients tolerated daily doses of 10 g of toluene in olive oil for three weeks without complaints or clinical evidence of side effects. In 1926, however, Hultgren [14] had stated that the methyl derivatives of benzene (toluene, xylene, and mesitylene) should not be used to treat leukemia because they have no effect on the bone marrow. His opinion was based on his research in rabbits.

Parmeggiani and Sassi [15] reported in 1954 on their study of 11 paint and pharmaceutical industry workers who were exposed to toluene vapor ranging from 200 to 800 ppm. Irritation of the conjunctiva and

of the upper respiratory tract mucosa was found in one worker, and nervous excitability in six others. From laboratory investigations and physical examinations, the authors concluded that toluene has no particular action on the bone marrow or on other organs and expressed the opinion that workers can tolerate 300 ppm toluene without hazard to health.

Cieslinska et al [10] in 1969 studied the serum levels of iron and copper and the urinary excretion of porphyrins in 51 female workers with an occupational history of exposure to toluene. These authors interpreted their findings of altered levels of iron or copper in three different groups of these subjects to suggest that toluene, as well as benzene, has a harmful action on the hematopoietic tissue although there were no clinical changes observed in these workers. These investigators emphasized the similarity of the toxic responses evoked by benzene and toluene, but, in actuality, the workers had mixed exposures to these substances.

Capellini and Allessio [16] in 1971 reported results of 17 workers who had been exposed for "several" years to mean atmospheric concentrations of toluene of 125 ppm (range, 80-160 ppm) in a plant manufacturing V-belts for industrial machinery. With regular medical supervision, no changes in the blood picture or liver function were detected in any case. Examinations included hemoglobin values, red cell counts, white cell counts, and platelet counts, all of which were within the same limits as 19 control subjects employed in the same

plant who had never been exposed to toluene vapor inhalation during their occupational activity. Also, blood findings were within normal limits in one worker employed in a different department who was exposed to mean toluene concentrations of 250 ppm (range, 210-300 ppm) and who demonstrated symptoms of central nervous system toxicity [see part (c) of this section].

The preponderance of the reported clinical evidence indicates that toluene does not possess the myelotoxic properties of benzene. In Browning's experience [17] based on a large number of blood examinations of many persons exposed to toluene, no effect similar to that of benzene on the blood picture had been observed except where the toluene was found to contain some benzene.

(2) Blood Coagulation

An increase in the prothrombin time was found in 191 printers exposed to 170-340 ppm toluene as reported by Pacseri and Emszt [18] in 1970. Only two subjects showed a reduced number of red blood cells. No other hematologic abnormalities were found in these workers. The benzene content of the toluene was not reported.

(3) Phagocytic Activity of Leukocytes

Bansagi [19] found a decreased phagocytic activity of the polymorphonuclear leukocytes of workers exposed to toluene vapor in the printing industry. However, there was no relationship between the decrease of phagocytic activity and the degree of exposure to toluene. Again, the benzene content of the toluene is not known.

(b) Effects on Menstruation

Michon [20] in 1965 reported the effects of aromatic hydrocarbon exposure on the menstrual cycles of 500 women, aged 20 to 40, working in a factory producing leather and rubber shoes. These workers were exposed to a mixture of benzene, toluene, and xylene at unspecified concentrations, but which were claimed to be within permissible limits established at the time in Poland [100 mg/cu m (31 ppm) for benzene, 250 mg/cu m (67 ppm) for toluene, and 250 mg/cu m (58 ppm) for xylene]. The menstrual cycles of these workers were compared with those of 100 women in the same plant not exposed to these hydrocarbons. The author reported that the women exposed to the aromatic hydrocarbon vapors had a prolonged and more intense bleeding than the control group. It seems more likely that the effects noted were related more to exposure to benzene rather than to toluene. The regularity of the menstrual cycle was not affected.

(c) Effects on Central Nervous System

The controlled 8-hour exposures of three human beings twice weekly for a period of three months by von Oettingen et al [21,22] to concentrations of 50 to 800 ppm of toluene are listed as follows:

0 ppm (control) - occasional moderate tiredness explained by lack of physical exercise, unfavorable illumination, and monotonous noise from fans.

50 ppm - no subjective complaints from one subject and drowsiness with very mild headache in the second subject. No after-effects.

100 ppm - moderate fatigue and slight headache on one occasion. No after-effects.

200 ppm - muscular weakness, confusion, paresthesias of the skin, impaired coordination, dilation of pupils, impaired light accommodation, repeated headache, and nausea at the end of exposure. After-effects included fatigue, general confusion, moderate insomnia, and restless sleep.

300 ppm - severe fatigue, headache, muscular weakness, incoordination, slight pallor. After-effects were fatigue, headache, skin paresthesias, and insomnia.

400 ppm - fatigue, mental confusion, headache, skin paresthesias, muscular weakness, dilated pupils. After-effects were fatigue, headache, skin paresthesias, and insomnia.

600 ppm - extreme fatigue, mental confusion, exhilaration, nausea, severe headache, and dizziness after 3 hours exposure. Eight-hour exposures showed incoordination and staggering gait. After-effects included nervousness and some confusion.

800 ppm - severe fatigue, extreme nausea, confusion, lack of self-control, considerable incoordination, and staggering

gait after 3-hours exposure. After-effects included moderate to severe insomnia lasting several days.

It should be noted that the investigators, three in number, were the experimental subjects in these experiments.

Wilson [23] in 1943 reported on the effects of exposure of 100 workers out of a total of 1,000 employees exposed to vapor of commercial toluene who presented themselves to the hospital for examination. The patients were classified into 3 groups: group 1, those patients exposed to toluene vapor from 50 up to 200 ppm; group 2, those persons exposed to vapor from 200 to 500 ppm; and group 3, those workers exposed to vapor from 500 to 1,500 ppm. Exposures were from 6 to 8 hours daily for periods of 1 to 3 weeks.

The following effects were reported at:

50 to 200 ppm (approximately 60% of the patients) - headache, lassitude, and loss of appetite.

200 to 500 ppm (approximately 30% of the patients) - headache, nausea, bad taste in the mouth, anorexia, lassitude, slight but definite impairment of coordination and reaction time, and momentary loss of memory. Complaints were more numerous and more pronounced than at lower exposure levels.

500 to 1,500 ppm (approximately 10% of the patients) - headache, nausea, dizziness, anorexia, palpitation and extreme

weakness. Loss of coordination was pronounced and reaction time was definitely impaired.

The symptoms from 50 to 200 ppm were considered by the author to be due chiefly to "psychogenic" factors rather than to toluene vapor. The author recommended that the vapor concentration of toluene should never exceed 200 ppm. In addition, changes in the blood and bone marrow were noted and exposures to concentrations of toluene over 500 ppm were considered to pose a risk of depression of the bone marrow. The benzene content of the toluene was not reported.

Carpenter et al [24] exposed 2 male subjects to known concentrations of toluene in a 4000-cubic foot room for 7- to 8-hour periods.

The following responses were reported at:

200 ppm - transitory, mild throat and eye irritation and slight exhilaration.

400 ppm - mild eye irritation, lacrimation, lassitude, nausea, and hilarity.

600 ppm - lassitude, hilarity, verbosity, boisterousness. After termination of the exposure, anorexia, and listlessness.

800 ppm - metallic taste, transitory headaches, extreme lassitude, areas of dimmed vision (scotomata), verbosity, "inebriation", and slight nausea.

Capellini and Alessio [16] in 1971 reported complaints from one worker employed in preparing a toluene-containing mixture for use in

the manufacture of V-belts. The mean atmospheric concentration of toluene in the mixing department was 250 ppm with extremes of 210 ppm and 300 ppm. The worker had irritation of the conjunctiva and an occasional feeling of stupor during work, and often reported insomnia and nervousness. No findings of central nervous system changes were reported in 17 other workers in another department [see part (a) (1) of this section] who had mean exposures over several years to 125 ppm of toluene with extremes of 80 ppm and 160 ppm.

Longley et al [25] in 1967 described an episode of acute toluene exposure involving 29 men. Toluene concentrations were estimated to have ranged from 10,000 ppm at waist level to 30,000 ppm at floor level. The effects at these concentrations for unspecified exposure periods were dizziness, "drunkenness", collapse, and loss of consciousness. They recovered spontaneously after removal from the contaminated atmosphere without any after-effects, two months after the acute exposure.

A case of habituation to toluene extending over a ten-year period was reported by Satran and Dodson. [26] Acute intoxications were characterized by headache, "inappropriate" speech, and brief episodes of memory loss. Despite the long period of toluene exposure, which caused many episodes of loss of consciousness, none of the clinical or laboratory studies indicated systemic pathological abnormalities. Electroencephalographic abnormalities were found, consisting of excessive episodic slow activity and occasional sharp,

nonfocal discharges. These findings were regarded as being consistent with diffuse encephalopathy but the features of the record were nonspecific.

The first case in man of permanent encephalopathy from repeated, prolonged exposure to toluene vapor was reported by Knox and Nelson [27] in 1966. A 33-year old man purchased a gallon of pure toluene from a paint store every four to six weeks for 14 years to satisfy his addiction to toluene vapor. The inhalation technique consisted of several breaths of toluene vapor taken by mouth from a soaked rag until he noted reddening of vision and had lightheadedness. A typical day started with inhalation of several breaths of toluene vapor at the bedside soon after awakening. This went on all day at frequent intervals. He carried a small vial of toluene and a rag in his pocket so that he could take a whiff in public without arousing any suspicion. The result of this bizarre addiction was permanent cerebral atrophy. The clinical signs were ataxia, tremulousness, emotional lability, marked snout reflex (distorted nostrils on subjection to sniff test), and positive Babinski toe reflex on the right side. The brain damage was confirmed by electroencephalography and pneumoencephalography. This same individual was the subject of a paper published by Grabski in 1961 [28] when he reported cerebellar degeneration after six years of toluene vapor inhalation.

Gusev [29] in 1965 reported his USSR study on the relationship of inhalation of toluene vapor with changes in the

electroencephalogram of human subjects. Toluene concentrations of 1 mg/cu m (0.27 ppm) caused a distinct, statistically significant intensification of the electric potentials from the left temporal-occipital leads in all four subjects tested. A concentration of 0.6 mg/cu m (0.16 ppm) of toluene was subliminal with respect to its effect on the electrical activity of the cerebral cortex and imperceptible to the subjects with respect to odor. The author recommended this concentration as the maximum permissible one-time concentration of toluene. Further investigations are necessary to validate these findings.

Toluene has been found in the atmosphere of nuclear submarines at a concentration of 0.18 ppm, according to Chiantella et al [30] in 1966. The toluene originated from the paint solvents, mineral spirits, and diesel fuel used in the submarine.

Kowal-Gierczak et al [11] in 1969 reported on changes in the production of serum glycoproteins, seromucoid, and haptoglobulins in 53 women exposed during the workday to toluene vapor at average workroom concentrations of 0.25 mg/liter (67 ppm). In all the women the production of at least one of these substances was abnormal, the most frequent of which was shown by the glycoproteins (expressed by the concentration of sialic acid) followed by seromucoid and haptoglobulin levels. No clinical or laboratory evidence of liver changes or altered liver function was observed by the authors. They speculated that glycoprotein changes (expressed by the changes in the

concentration of blood sialic acid) might have reflected early changes in liver function. Exact environmental levels of toluene were not reported.

(c) Effects on Skin

(1) Local Effects

Toluene is an excellent fat solvent. Repeated or prolonged skin contact with liquid toluene will remove the natural lipids from the skin, causing drying, fissuring, and dermatitis. [31]

(2) Percutaneous Absorption

Dutkiewicz and Tyras [32] in 1968 reported the rate of absorption of liquid toluene and aqueous solutions of toluene through the skin of the hand and forearm of nine human volunteers. The quantity of toluene absorbed was the difference between the volume applied to the skin and the volume remaining 10 or 15 minutes after contact with the skin. For liquid toluene, the amounts absorbed ranged from 41 to 100 mg and the rates of absorption ranged from 14 to 23 mg/sq cm/hour. The concentration of toluene in the aqueous solutions used ranged from 189 to 607 mg/liter. The amounts of toluene absorbed percutaneously ranged from 52 to 206 mg, which corresponded to absorption rates of 160 to 600 µg/sq cm/hour, respectively. The quantity of toluene absorbed increased with increasing concentration of the hydrocarbon in the aqueous solution. The investigators used a measured quantity of toluene put in a watchglass, which was placed on the arm. After 10 minutes, they

washed the arm and measured chemically the residual toluene. The difference was attributed to percutaneous absorption. The authors believed that skin absorption from contact with liquid toluene should be taken into account in the evaluation of toluene exposure.

Piotrowski [33] in 1967 reported the skin absorption of toluene vapor in three male subjects exposed unclothed in a chamber to a toluene vapor concentration of 1,600 mg/cu m (427 ppm) for 8 hrs. The subjects were protected from inhalation of the toluene vapor by breathing uncontaminated air from outside the chamber through a respirator. Analysis of the urine samples collected at the end of the exposure period showed no increase in the excretion level of benzoic acid. The author concluded that "one can assume that the possibility of toluene vapor absorption through the skin will not exceed 5% of the amount absorbed in the same period of time through the respiratory tract." Gerarde [31] in 1960 stated that liquid toluene is poorly absorbed through the intact skin so that systemic intoxication by percutaneous absorption is highly improbable.

(d) Effects on the Eye

McLaughlin [34] in 1946 reported that two workers accidentally splashed with toluene suffered transient disturbances of the eyes, consisting of corneal damage and conjunctival irritation. Complete recovery resulted within 48 hours with no loss of vision.

Grant [35] reported on another worker splashed with a solution of stearic acid in toluene who experienced only transient epithelial

injury. He felt immediate, severe, burning pain and had involuntary blepharospasm. Although the eyes were not irrigated until 4-5 minutes after the accident, only moderate conjunctival hyperemia and corneal epithelial edema resulted, with complete return to normal in 2 days.

Carpenter et al [24] in 1944 reported mild eye irritation in volunteers exposed for 8 hours to 200 ppm toluene vapor.

A burning sensation in the eyes of one worker exposed to an average of 250 ppm toluene vapor (range, 210-300 ppm) was reported in 1971 by Capellini and Alessio. [16] The length of the exposure was not stated.

(e) Effects on Kidneys, Liver, and Lungs

O'Brien et al [36] in 1971 described a case of hepatorenal damage from chronic toluene vapor exposure in a 19-year-old male glue sniffer. Toluene caused serious but apparently reversible injury to the kidneys and liver after three years of glue sniffing. The principal component of the inhaled solvent was toluene (80% v/v), while other constituents were not mentioned. During the patient's hospitalization following a severe episode of toluene exposure, the concentration of toluene in the serum was found to be 180 ppm.

Greenburg et al [37] in 1942 found enlarged livers in 13 out of 61 painters (21%) exposed to toluene concentrations ranging from 100 to 1,100 ppm. Careful breathing zone sampling was performed and environmental levels were subgrouped into increments of approximately 100 ppm; however, only the number of workers exposed at each level of

toluene was presented and no comparison could be made between the incidence of liver enlargement and the degree of toluene exposure. The hepatomegaly was 3 times the frequency observed in the control group of 430 fur workers having no exposure to toluene.

Epidemiologic Studies

Banfer [12] reported in 1961 on his study of the effect of toluene containing 0.3% benzene on the peripheral blood elements (RBC, Hgb, WBC, and granulocytes) of 889 rotogravure printers and helpers employed for more than three years and compared the findings with those from 478 nonexposed subjects in the industry. Studies were made at 6-month intervals (3 months by law for workers under 18 years of age) for "several" years. The only environmental air levels reported consisted of samples taken on a single day from 5 different places in the machine room. Three samples showed the toluene concentration below 200 ppm, one value reached 200 ppm, and the fifth sample indicated 400 ppm. No effects on the formed elements of the blood were seen which were different from the controls. Also, 6 sternal biopsies were reported and no pathological changes of the bone marrow were found.

In 1942 von Oettingen et al [21,22] reported on the results of the exposure of three human subjects repeated 15 times over a three-month period to concentrations of toluene ranging from 50 to 800 ppm.

No abnormal changes were found in the peripheral blood leukocyte count.

In the same year Greenburg et al [37] studied a group of 61 workers who had been exposed to toluene and to no other toxic volatile solvents, so far as was known, for periods extending from 2 weeks to 5 years. The reported atmospheric concentrations ranged from 100 ppm to 1,100 ppm in increments of approximately 100 ppm (see Effects on Humans (e) above). As previously stated, comparisons could not be made between the observed toxic effects and the degree of toluene exposure. Although there was no record of severe illness, Greenburg et al found evidences of mild intoxication, enlarged livers, macrocytosis, mild depression of the erythrocyte level, absolute lymphocytosis, and elevation of the hemoglobin level and the mean corpuscular hemoglobin concentration. These investigators concluded that early chronic toluene intoxication in man is "best evidenced by hepatomegaly" (enlargement of the liver) "and macrocytosis" (enlarged red blood cells).

Forni et al [38] in 1971 investigated the changes in the chromosomes of peripheral blood lymphocytes in rotogravure plant workers exposed to toluene concentrations of 200 ppm throughout most of the work shift and to concentrations well above 200 ppm for very short periods. The group of workers exposed only to toluene for periods of 3 to 15 years showed a somewhat higher rate (0.8%) of unstable chromosome changes and of calculated breaks (0.83%) compared

with the controls (0.61 and 0.67%, respectively) but the differences were not statistically significant. The authors concluded that chronic inhalation of toluene vapor at concentrations in the order of 200 ppm did not significantly affect the rate of chromosome changes in peripheral blood lymphocytes but cautioned that it would not be appropriate to conclude from this study that prolonged exposure to toluene concentrations of about 200 ppm lacks toxic effects on chromosomes. The comparisons were made with a group of controls whose frequencies of chromosome changes were somewhat dispersed, suggesting to the authors that a different individual susceptibility to chromosome damage might exist from unknown environmental agents.

Animal Toxicity

Because of the close chemical similarities which exist between toluene and benzene, early animal investigations emphasized the comparative toxicity of these two hydrocarbons. [7,8,39-44] In general, toluene was considered to be more toxic than benzene in the production of narcosis. In 1903, Chassevant and Garnier [39] reported toluene to be more toxic in guinea pigs than benzene when the toluene was administered in single doses. The effects of toluene were reported to resemble those of benzene poisoning but were more delayed in onset. Lehmann [40] found that at equal atmospheric concentrations the order of increasing narcosis was benzene, xylene, and toluene. In contrast, Rambousek [42] in 1913 considered toluene to be less toxic

than benzene in dogs, cats, and rabbits. Toluene produced narcosis more slowly and recovery was not as rapid as with benzene. Also, convulsions or spasms were not observed in animals dosed with toluene.

Toluene has also been reported to exert toxic effects on the blood and blood-forming organs. [7-9] Selling [7] in 1911 reported that toluene produced an initial destruction of the white blood cells, but, compared with benzene, its action was feeble. The bone marrow readily compensated for any destructive effect on the blood cells. Ferguson et al [8] in 1933 concluded from their animal experiments and a review of the literature that the actions of benzene and toluene on the blood were very similar.

It is interesting that the toxicity of toluene was recognized as early as 1903 [39]; however, animal data from the earlier studies is of doubtful validity because prior to the 1940's in the United States, and even up to the mid-1950's in some other countries, the possibility of separate toxic effects for toluene and benzene was generally not recognized. Toluene was considered to possess myelotoxic properties similar to benzene, the difference being only one of degree. As previously pointed out (see Historical Reports), toluene frequently contained benzene in significant quantities [12,23] but its presence was seldom mentioned and attempts were rarely made to identify the benzene either qualitatively or quantitatively. Twenty-five years ago, commercial grades of toluene contained up to 15% benzene. [45] Thus, in any evaluation of reported myelotoxicity for toluene, the

benzene content, if known, is an important factor for consideration. More recent animal studies discussed below [46-49] have reported the lack of toluene toxicity on the blood and bone marrow.

(a) Inhalation

Batchelor [9] in 1927 reported exposing rats to toluene vapor ranging from 620 to 1,600 ppm daily for total exposure times of 18 to 120 hours. The reported effects indicate the toluene probably contained benzene but any quantity is unknown. With exposures to 1,600 ppm, the animals first developed instability and incoordination with evidence of mucous membrane irritation and light narcosis. By the third day, a mild twitching became evident, a general hypertonicity of the body musculature developed, the body temperature fell as much as 7 C; the animals became weak and died. With concentrations of 1,250 ppm, slight instability and incoordination appeared with signs of mucous membrane irritation. At concentrations of 1,100 ppm and 620 ppm the animals showed no signs of toxicity. In a little under half of the cases, even at the lowest concentration of 620 ppm, increases of from 4 to 13% appeared in the red cell count, and in five of the cases a reduction of 28% to 56% was found in the white cell count. With these findings, definite evidence of hyperplasia in the bone marrow was noted in the majority of cases.

In 1928, Smyth and Smyth [50] reported that guinea pigs were severely prostrated, but no deaths resulted after 18 daily 4-hour exposures to 1,250 ppm of toluene purified by repeated distillation to

produce a benzene-free product. Daily 4-hour exposures to 4,000 ppm caused fatalities in the exposed animals. Exposures to 1,000 ppm for 35 days resulted in no untoward effects. No mention was made of any blood changes.

In 1943 Svirbely et al [44] reported the acute toxicity of toluene vapor in mice. The toluene contained not more than 0.01% benzene. They found the minimum lethal concentration (MLC) to be 20 mg/liter (5,300 ppm) for an 8-hour exposure. They concluded that toluene has a greater acute toxicity and stronger narcotic action than benzene by inhalation and by other routes of administration. The principal pathological findings were pulmonary irritation, renal irritation, and evidence of cellular damage in the spleen. No evidence of blood damage was found. The authors stated that the short duration of exposures and early sacrificing of animals probably prevented the appearance of pathological changes, if any were to appear.

In 1955, Fabre et al [46] reported on two dogs exposed 8 hours/day, 6 days/week for 4 months to 7.5 mg/liter (2,000 ppm) of toluene vapor then to 10 mg/liter (2,660 ppm) for 2 additional months. During the last 2 months of the exposures, the animals manifested signs of central nervous system intoxication, incoordination, and paralysis of the hind legs. No hematological abnormalities (blood or bone marrow) were found in these animals. Microscopic examination of

the lungs, liver, kidney, heart, and spleen showed congestive changes. The toluene used was analyzed and contained less than 0.1% benzene.

Takeuchi [47] in 1969 described results of rats exposed to 200, 1,000, and 2,000 ppm toluene vapor 8 hours/day for 32 weeks. At the end of the exposure period no significant changes were found in body weight, leukocyte count, erythrocyte count, eosinophil count, and hemoglobin levels of the exposed animals as compared with the controls. The toluene used was analyzed at 99.9% purity with less than 0.2 ppm of benzene being present in the 2,000 ppm toluene concentration.

Taylor and Harris [51] in 1970 studied effects in mice exposed for 10 minutes to unspecified high concentrations of toluene-containing glue and toluene vapor and found evidence of cardiotoxicity. This was manifested as a slowing of the sinoatrial rate and prolongation of the P-R interval of the electrocardiogram. Neither the total composition of the glue nor the purity of the toluene was specified.

Furnas and Hine [52] in 1958 reported the effects of exposure to 5000, 10,000, and 20,000 ppm of chemically pure toluene vapor on the electroencephalogram (EEG) of rats having cortically implanted electrodes. The investigators failed to detect any abnormal EEG changes at 5,000 ppm for 20 minutes or 10,000 ppm for 40 minutes. At 20,000 ppm for an unspecified period of time, they found a spikelike

EEG activity which was assumed to be a manifestation of a convulsant effect.

(b) Subcutaneous Administration

In 1956, Gerarde [48] reported the effects on the blood, thymus, spleen, and bone marrow of albino rats of repeated subcutaneous doses of chemically pure (analyzed) toluene and other alkylbenzenes in 1.0 mg/kg doses. No abnormalities were found in the leukocyte count of the peripheral blood or in the total number of nucleated cells in the femoral bone marrow or the weight of the thymus glands or spleen of the animals dosed with toluene.

Speck and Moeschlin [49] in 1968 investigated the influence of "pure" toluene and xylene injected subcutaneously in rabbits on the synthesis of deoxyribonucleic acid (DNA) in bone marrow cells and the resulting peripheral blood cell count. No depression of bone marrow function was found as measured by the uptake of tritium-labeled thymidine. No decrease in the number of peripheral blood elements or variation in the differential counts was found. The doses of toluene administered were 300 mg/kg/day for 6 weeks or 700 mg/kg/day for up to 9 weeks. Rats given the same amounts of benzene developed aplastic anemia and autoradiography of the bone marrow revealed marked inhibition of DNA synthesis. The authors stated that their results "present a substantial argument for the lack of myelotoxicity of toluene and xylene."

(c) Effects on the Eye

Wolf et al [53] instilled 0.1 ml of undiluted toluene directly onto the right eye of rabbits. A barely perceptible irritation of the conjunctival membranes was noted within 1 to 4 hours in 3 of the 6 animals tested at 24, 48, and 72 hours after treatment. Examination of the cornea with sodium fluorescein solution revealed no evidence of even superficial necrosis in any of the treated eyes.

(d) Metabolism

In man and rabbits, about 20% of absorbed toluene is excreted unchanged by the lungs while about 80% is converted to benzoic acid and excreted in the urine as hippuric acid, the glycine conjugate. Bakke and Scheline [54] reported in 1970 that about 0.4 - 1.1% of the dose of toluene is hydroxylated to ortho- and para-cresol. Furthermore, small amounts of benzyl alcohol were detected in the hydrolyzed urine extracts. This suggested that benzyl alcohol may be formed as an intermediate step in the production of benzoic acid. Gerarde [31] found an increased urinary excretion of organic sulfate after dosing rats with large amounts of toluene subcutaneously. This indicated that an additional metabolic pathway was used to detoxify toluene if the concentrations in the blood were elevated.

Ikeda and Ohtsuji [55] reported in 1971 that following treatment of rats with phenobarbital, there was an increase in the rate of disappearance of toluene from the blood, a reduced sensitivity of the central nervous system, and a shortened sleeping time after injection

of toluene. These phenomena were explained by an enhanced hepatic metabolism induced by phenobarbital.

Abou-el-Makarem and co-workers [56] noted in 1967 that toluene metabolites are poorly excreted in the bile of rats. Less than 2% of a dose of toluene was found in the bile 24 hours after dosing.

Smith et al [57] reported in 1954 that about 18% of an oral dose of toluene was eliminated unchanged in the expired air.

Van Rees [58] in 1967 reported the influence of toluene on the metabolism of benzene in rats by measuring urinary phenol excretion after dosing the animals with toluene and benzene simultaneously. He found that toluene diminished the amount of phenol excreted during the first 8 hours after the administration of benzene. It appears that toluene inhibits the metabolism of benzene when the two compounds are administered simultaneously.

In summary, animal experiments indicate the main toxic effects of toluene to be upon the central nervous system. In general, daily 4- to 8-hour exposures of up to about 1,000 ppm of toluene produce little or no effect in different species of animals. At concentrations from 1,000 to about 2,000 ppm, the effects vary from those of instability, incoordination, and light narcosis to tremors, muscular hypertonicity, and general weakness. At high exposure levels, prostration and death occur. Regarding toluene effects on the blood and blood-forming organs by either inhalation or parenteral administration, purified toluene has been shown to produce no blood

abnormalities nor alteration of bone marrow function in various animal species, even at dose levels which produce marked central nervous system effects. When instilled onto the eye, undiluted toluene produces irritation of the conjunctiva; the effects are transient and no reports of corneal damage in animals have been found. Approximately 80% of absorbed toluene is metabolized to benzoic acid, conjugated, and excreted in the urine as hippuric acid. About 20% of absorbed toluene is excreted unchanged by the lungs.

Correlation of Exposure and Effect

In evaluating the effects of toluene exposures, care must be taken to assess the purity of the compound used in a given study. Benzene is a common contaminant of toluene [1,12,17] and, considering the unique effects of benzene on the hematopoietic system, investigators have frequently attributed effects to toluene which more correctly reflect the myelotoxic property of the benzene contaminant. [8,9]

A critical evaluation of the reports of experimental and occupational inhalation exposures to toluene has shown that the only documented exposures of human subjects to essentially pure toluene were those reported by von Oettingen et al. [21,22] These investigations used toluene which, on spectrophotometric analysis, was shown to contain not more than 0.01% benzene. This same high purity

source of toluene was used by Svirbely et al [44] in their studies of the toxicity of toluene in experimental animals.

The study of von Oettingen et al [21,22] involving the controlled 8-hour exposures of subjects to purified toluene produced mild fatigue, muscular weakness, impaired coordination, moderate dilation of the pupils, and paresthesias of the skin at the 200 ppm level. These same symptoms were intensified at 300 ppm whereas mental confusion was also noted as a result of exposure at 400 ppm. The narcotic effects became more severe at higher exposure levels. At 50 and 100 ppm, only mild to moderate fatigue and drowsiness were experienced by all 3 of the subjects toward the end of exposure periods. This same degree of tiredness was reported during exposure to a zero concentration of toluene. Observed variations in the pulse rate, diastolic blood pressure, and pulse pressure, respiratory rate and minute volume were within control limits. Thus, a 100 ppm concentration of toluene or below constituted a level of exposure which did not produce deleterious effects, whereas exposure to 200 ppm evoked the initial effects of narcosis. The experimental findings reported by von Oettingen et al [21,22] were supported by those of Wilson [23] in that exposures to concentrations less than 200 ppm were considered to be due chiefly to factors other than the toluene vapor. Exposures to toluene concentrations of 200 ppm and higher showed impairment of coordination and reaction time and momentary loss of

memory. Wilson [23] believed that the vapor concentration of toluene should never exceed 200 ppm.

In considering most reports of occupational exposures to toluene, a lack of information has been apparent about either the purity of the toluene or the accurate atmospheric concentrations of toluene with other solvent vapors at work sites. The following studies, [12,15,16,18] as relatively recent investigations, indicate the absence of the myelotoxic effects ascribed by earlier investigators to toluene. [8,9,23]

Parmeggiani and Sassi [15] in 1954 reported on their study of 11 paint and pharmaceutical workers exposed to atmospheric concentrations of toluene ranging from 200 to 800 ppm. From the results of their clinical study they concluded that toluene had no particular action on the bone marrow or on the other organs. The purity of the toluene was not reported.

In 1961 Banfer [12] stated that sufficient quantities of toluene containing up to 0.3% benzene had been available in Germany for industrial uses for only about 6 years. He made reference to a 1954 statement of Humperdinck in a trade union report that in Germany so-called purified toluene contained 15% benzene and 10% xylene. In the study of rotogravure printers and helpers exposed for more than 3 years to the vapors arising from printing inks containing toluene but no benzene detectable by chemical analysis of the inks and thinners, extensive blood studies and some bone marrow tests were performed

which failed to indicate any significant changes. Only 3 out of 889 blood tests (0.33%) were found with total white cell counts of less than 4,000/cu mm as compared with 1 out of 155 control subjects (0.64%) from other departments in the plant. The absolute lymphocyte count never exceeded 5,000 in either the printers or in the controls. The absolute number of granulocytes was not observed below a lower limit of 2,000 in any case. During the first 6 months of the study (in 1957), 5 sternal punctates from printers with white cell counts of less than 5,000 were evaluated at two hospital medical clinics and no pathological bone marrow changes were detected in any case. There were no evidences of damage to any of the blood cell elements of the printers and helpers throughout this study. Analysis of the atmosphere was limited to samples collected at 5 sites in the machine room on a particular day; the atmospheric toluene concentration was unspecified but below 200 ppm in 3 of the samples, at 200 ppm in the fourth, and 400 ppm in the fifth sample. Benzene and xylene were not detected in any of these samples by infrared spectrophotometry.

The finding of liver enlargement in painters exposed to toluene concentrations reported by Greenburg et al [37] in 1942 was considered important because liver enlargement had not been previously described. Neither clinical nor laboratory evidence of hepatic disease could be correlated with the hepatomegaly. The possibility was suggested that the liver enlargement might be compensatory in character rather than an indication of hepatic disease; however, the data were considered

insufficient to answer the question. Because of the incidence of enlarged livers and elevated mean corpuscular volume of the blood noted from the study, these 2 indexes were suggested to most likely reveal the early presence or absence of toluene toxicity. In addition to the elevated mean corpuscular volume, findings included mild depression of the erythrocyte level, elevation of the hemoglobin value, and lymphocytosis. Although the study had eliminated painters having known prior benzene exposure, the blood findings were so consistent with that of benzene poisoning that benzene contamination of the toluene vehicle in the paints cannot be overruled. Also, the liver enlargement could have been due to paint ingredients other than toluene. Volatile components such as ethyl alcohol, ethyl acetate, butyl alcohol, and petroleum naphtha were present in quantity in the lacquers, dopes, and brush washes used.

From the study of Pacseri and Emszt [18] in 1970, a decrease in the prothrombin level was reported but no other hematologic abnormalities were noted in printers exposed to atmospheric toluene concentrations ranging from 170 to 340 ppm.

Capellini and Alessio [16] in 1971 reported no changes in Hgb values, RBC, WBC, and platelet counts, or changes in liver function of workers exposed for several years to toluene vapor which ranged from 80 ppm to 300 ppm although findings of central nervous system toxicity were found from exposures to concentrations of 210 to 300 ppm. The benzene content of the toluene was not reported.

From the data of Gerarde [31] and Piotrowski and Tyras [33] it may be concluded that systemic intoxication by percutaneous absorption of toluene in the vapor phase is improbable. If skin contact with liquid toluene is experienced, probably by immersion of hands and arms, sufficient quantitites might be absorbed such that the percutaneous route may be important. [32]

Animal toxicity studies by von Oettingen et al [21,22] on the effects of inhaled toluene indicated that exposures up to 600 ppm produced increased hippuric acid excretion (up to 27%) in dogs and rats. At concentrations above 1,000 ppm, slight but statistically insignificant decreases in total leukocyte counts were reported in rats and guinea pigs after 30 exposures for 8 hours/day, 5 days/week. At 2,500 ppm, rats showed muscular incoordination, and complete narcosis at 5,000 ppm for 2 to 3 hours.

Furnas and Hine [52] reported in 1958 on the neurotoxicity of toluene to rats whose initial exposures to 5,000 ppm proved to be ineffective in producing central nervous system changes. Exposures were increased to 10,000 ppm for 20 minutes and then to 20,000 ppm for 1 hour. At the highest level, there was decreased mobility but no quivering or twitching and no hyperresponse to auditory stimuli. The source of the toluene was a chemically pure product provided by one of the petroleum companies.

Gerarde [48] in 1956 reported no abnormalities in the leukocyte count of the peripheral blood, in the total number of nucleated cells

in the femoral bone marrow, or in the weight of the thymus glands and spleens of rats given daily subcutaneous injections of 1 ml/kg of toluene in olive oil for 2 weeks. It was concluded that the attachment of an alkyl group to the aromatic ring, as in toluene, resulted in a loss of myelotoxicity which is characteristic of benzene.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Environmental Concentrations

Historically, high atmospheric concentrations of organic solvents existed in the working environment principally due to the lack of knowledge of solvent toxicity, of hazards associated with solvent use, and the lack of enforcement of proper engineering controls. The problem was most serious during the winter months when doors and windows of plants were closed, thus preventing adequate ventilation. Although improvements in conditions have been made through substitution of solvents and incorporation of adequate ventilation design, the problem still exists in varying degrees. As recently as 1967, Longley et al [25] reported an incident involving a total of 29 men being exposed to high concentrations of toluene. Due to inadequate ventilation, levels of toluene rose to an estimated 10,000 to 30,000 ppm rendering 2 men unconscious while spraying a toluene-containing insecticide inside the hold of a merchant ship. Two hours after the incident, the toluene concentration was measured and indicated a range of 5,000-10,000 ppm. When one considers that the lower flammable limit of toluene is 12,000 ppm, the hazard encountered was not only a health hazard but also one of fire or an explosion.

In 1971, Forni et al [38] reported results of a study initiated in 1953 in a rotogravure plant. Toluene was substituted for benzene

in that year following an epidemic of benzene poisoning in the plant. From 1954 to 1956, the concentration of toluene ranged from 0 to 240 ppm in different parts of the work areas. Tabulated results of toluene concentrations from 1957 to 1965 indicated an annual mean value of 203 ppm (range, 140-239 ppm) at the center of the room, 203 ppm (range, 56-277 ppm) near one of the folding machines, and 431 ppm (range, 306-824 ppm) between the machine elements. In 1966, the plant was moved and improved ventilation was installed such that in 1967, the annual mean concentration of toluene was 156 ppm near the folding machines and 265 ppm between the machine elements.

Ikeda and Ohtsuji [59] in 1969, during a study of hippuric acid excretion in the urine of workers, reported on toluene concentrations in 11 workshops in 8 factories operating polychromic rotary processes for photogravure printing. Concentrations of toluene ranged from 4 to 240 ppm in the 11 workshops.

Pagnotto and Lieberman [60] in 1967 reported the results of their study of exposures to toluene in 11 leather finishing and rubber coating plants. In leather finishing, toluene was an ingredient in thinners used to prepare lacquers and stains that were automatically sprayed on leather with mechanical exhaust ventilation in operation. Toluene concentrations ranged from 19-85 ppm, averaging 53 ppm, in the finishing area. The highest exposures were found in washing and topping operations where leather was washed with a thinner and the finish applications were performed by hand with a gauze sponge. At

the washing and topping operation, an average value of 112 ppm was found (range, 29-195 ppm). In the rubber coating plants, toluene exposure occurred when rubber, prepared with petroleum naphtha (less than 1% benzene and 8% toluene), was applied to fabric as it was unrolled on a spreading machine. Some plants used pure toluene in the rubber preparation. Concentrations of toluene averaged 73 ppm at the spreading machines (range 34-120 ppm) at the 11 plants.

The aircraft industry has used large amounts of toluene as a component in paints. In 1942 Greenburg et al [37] reported ineffective local exhaust systems in paint-dip rooms during his study of 106 painters in which the average exposure ranged from 100 to 1,100 ppm.

Atmospheric levels such as those cited above can reflect only the conditions prevailing at the time of an investigation. They do not represent the peak exposures to which workers may be subjected during such incidents as breakdown or leakage of process equipment, transfer operations, etc. In addition, the levels reported during early studies may be inaccurate due to the type of sampling and analytical methods used at that time. These are rarely defined. Also, published reports indicate overexposure almost exclusively and conditions that are within acceptable limits must be deduced by inference.

Environmental Sampling and Analytical Method

Many methods have been used to determine the concentration of toluene vapor in air. Methods of collection have included the use of plastic bags, [61] absorption in scrubbers by nitrating solutions [62,63] or organic solvents, [64,65] and adsorption on silica gel [66] or activated charcoal. [67-69] Analytical methods have included colorimetry, involving nitration followed by reaction with various ketones, [62,63] spectrophotometry, [64,65] direct estimation by means of colorimetric indicator tubes, [70,71] and gas chromatography. [66,67,72]

Of the various methods of collection, adsorption on activated charcoal provides the greatest efficiency and ease of collection. [67,68] The use of absorbing liquids requires additional field sampling equipment and is inconvenient in obtaining personal breathing-zone samples, especially when 2 or more scrubbers must be connected in series to assure a high collection efficiency. [60,67] Activated charcoal is preferable to silica gel because aromatic hydrocarbons, such as toluene, are easily displaced from silica gel by water vapor, resulting in possible losses of the sample when silica gel is used as an adsorbent in humid atmospheres. [66] The design of activated charcoal tubes for the sampling of toluene vapor in industrial atmospheres and the conditions of sampling and desorption have been defined by White et al. [68] They reported average desorption efficiencies of 100% (range, 97-102%) and 95% (range, 93-

96%) for 100 ppm concentrations of toluene sampled alone and in the presence of 6 other organic vapors, respectively.

Gas chromatography offers the greatest specificity and sensitivity of the numerous methods of analysis. [66-68] 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. [62]

Other sampling and analytical methods can be useful adjuncts to the compliance method outlined in Appendix I, especially for the determination of "exposure to toluene" as originally defined and for special purposes for identification of hazardous conditions. Descriptions of additional methods utilizing detector tubes and portable instruments are given in Appendix II.

Sorbability of Toluene on Charcoal

Concentrations of 200 ppm of toluene were dynamically generated in a NIOSH laboratory to test the sorbability of toluene 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 toluene from the air. The 200 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 toluene 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 19 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 200 ppm of toluene at a flowrate of 1 liter/minute and for various lengths of time ranging from 10-20 minutes. Breakthrough was defined as the point in sampling at which 0.1 mg of toluene was collected on the 50-mg (backup) section of charcoal. The data points are listed in Table IV-1.

TABLE IV-1

Tube No.	Volume sampled (liters)	Toluene Concentration: Front section (mg)	Toluene Concentration: Backup section (mg)
1	17	12.46	0.015
2	17	12.75	0.064
3	18	13.47	0.056
4	18	13.27	0.037
5	19	13.57	0.039
6	19	13.56	0.143
7	20	13.61	0.119
8	20	14.33	0.041

A plot was made of total volume sampled vs weight of toluene 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 toluene on the backup section was selected as the point of breakthrough and was determined to be 19 liters. 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 toluene. At this sampled volume of 10 liters, no appreciable amount of toluene will pass to the backup filter.

Accuracy and Precision Data

(a) Analytical Method, Not Including Sampling Error

Eight samples from the breakthrough tests were used to determine the accuracy and precision of the analytical method alone (not including sampling error) as listed in Table IV-2. The 200 ppm toluene concentration was prepared by continuously injecting toluene 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.

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.

TABLE IV-2

Tube No.	Total toluene collected (mg)	Volume sampled (liters)	Measured conc. (ppm)
1	12.5	17	195
2	12.8	17	200
3	13.5	18	199
4	13.3	18	196
5	13.6	19	190
6	13.7	19	191
7	13.7	20	182
8	14.4	20	191

Mean ($\bar{X}$) of the 8 measured values = 193.0 ppm

Standard deviation(s) = 5.4 ppm

Accuracy: (1) Systematic error = $\frac{200-193}{200} \times 100 = 3.5\%$

(2) Precision (relative standard deviation) =

$$\frac{s}{\bar{X}} \times 100 = 2.8\%$$

(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 (2 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 three-foot length of Tygon tubing. With pump operation, the rotameter ball was set for the desired flow rate (1 liter/minute), and the toluene-containing air (200 ppm) was sampled for 10 minutes.

TABLE IV-3

Tube No.	Total toluene collected (mg)	Measured conc. (ppm)
1	5.62	149.1
2	5.55	147.2
3	5.03	133.4
4	4.79	127.1
5	5.81	154.1
6	6.35	168.5
7	6.37	168.9
8	6.37	169.1
9	6.05	160.7
10	6.16	163.5

Mean ($\bar{X}$) = 154.2 ppm

Standard Deviation(s) = 150.0 ppm

Accuracy: Systematic error = $\frac{200-\bar{X}}{200} \times 100 = 22.9\%$

Precision (relative standard deviation) =

$$\frac{s}{\bar{X}} \times 100 = 9.7\%$$

Theoretical sampling volume = 10 liters/tube

Generated concentration = 25 ppm

Temperature of sampling = approximately 25 C

Pressure = approximately 745 mm Hg

(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

Tube No.	Total toluene collected (mg)	Measured conc. (ppm)
11	7.86	208.7
12	7.88	209.0
13	8.70	231.0
14	8.54	226.9
15	8.01	212.6
16	8.37	222.0
17	7.89	209.3
18	7.79	206.6
19	8.27	219.5
20	7.58	201.1

Mean ($\bar{X}$) = 214.7 ppm

Standard Deviation(s) = 9.7 ppm

Accuracy: (1) Systematic error = $\frac{\bar{X}-200}{200} \times 100 = 7.4\%$

(2) Precision (relative standard deviation) =

$$\frac{s}{\bar{X}} \times 100 = 4.5\%$$

The accuracy of the tests with in-line calibration was approximately 16% better than that in (1) above which lacked the in-line calibration.

Biologic Evaluation

The metabolism of toluene involves oxidation and conjugation prior to excretion. Teisinger and Srbova [73] stated that it is oxidized to benzoic acid, the major portion of which is conjugated with glycine in the liver, and excreted mainly as hippuric acid, a water-soluble urinary metabolite. About 20% of the benzoic acid intermediate is conjugated with glucuronic acid with formation of benzoylglucuronic acid.

Ogata et al [74] reporting in 1970 on the excretion of toluene and xylene metabolites showed that during the 18-hour period following the initiation of controlled human exposures to 100 and 200 ppm concentrations the amount of excreted hippuric acid was equivalent to 68% of the toluene absorbed. The excretion of this metabolite, therefore, was relatively rapid.

In their studies, Teisinger and Srbova [73] measured benzoic acid instead of hippuric acid in the urine to take into account the minor portion of the intermediate which is conjugated with glucuronic acid. These investigators reported a mean daily benzoic acid excretion of 0.746 g/day (equivalent to approximately 1 g of hippuric acid). On the basis of their experimental absorption data for

toluene, they estimated that a worker exposed to 200 ppm of toluene in air excretes approximately 3 to 5 times more benzoic acid than the normal average.

Arato [75] in 1968 reported that although the amount of benzoic acid excreted in the urine of workers exposed to toluene vapor was elevated in all cases, individual variations made it difficult to correlate the urine levels with the air concentrations. Airborne toluene concentrations reportedly varied from 150 mg/cu m to more than 2,000 mg/cu m (40 to 533 ppm). During each workday, the air levels of toluene appeared to undergo wide fluctuations which probably accounts for the difficulty in individual comparisons with environmental levels.

Capellini and Alessio [16] in 1971 reported the urinary excretion of hippuric acid in 17 workers who had been exposed for several years to mean atmospheric concentrations of toluene of 125 ppm (range, 80-160 ppm) measured at the working stations. The control subjects were 19 co-workers who had never been exposed to toluene and whose main meal at the canteen was similar to that of the toluene-exposed workers. The mean urinary hippuric acid value for the controls was 0.95 ±0.33 g/liter (range, 0.55-1.6 g/liter); that measured in samples from the workers was 2.1 ±0.83 g/liter. The difference from the control value was statistically significant (p less than 0.01). All samples were collected at the end of the working day and were analyzed, after solvent extraction, by the ultraviolet

spectrophotometric method of Pagnotto and Lieberman. [60] The urinary results were adjusted to a specific gravity of 1.016. If an adjustment to a specific gravity of 1.024 had been made, the hippuric acid means for the control and for the toluene-exposed (mean, 125 ppm) workers would have been 1.43 and 3.15 g/liter, respectively.

Pagnotto and Lieberman [60] reported in 1967 that their study had shown that exposures of workers to 200 ppm of toluene produced 7 g of hippuric acid/liter of urine as compared with 0.8 g/liter (range, 0.4-1.4 g/liter) for unexposed subjects. The samples were collected at the end of the work shift. Following an extraction with a mixture of isopropyl alcohol and diethyl ether, the hippuric acid was measured at 230 nm in a spectrophotometer. The higher hippuric acid values obtained by these investigators may well have been due to the presence of methylhippuric acid, a metabolite resulting from the mixed exposure of the workers to xylene and toluene in the leather-finishing and rubber-coating plants. Methylhippuric acid also contributes to spectrophotometric absorbance in the 230 nm region.

There is a relatively wide range of hippuric acid excretion levels reported for groups of workers exposed to toluene at given operations. For example, Pagnotto and Lieberman [60] found a range of 2.75 to 6.80 g/liter (mean, 3.66 g/liter) for spreaders in the rubber-coating industry exposed to 34-120 ppm (mean, 73 ppm) of toluene; a 1.024 specific gravity correction was applied in developing these values. In 1969, Ikeda and Ohtsuji, [59] using a specific gravity

correction of 1.016 for groups of Japanese workers in photogravure printing factories, reported hippuric acid excretion values of 8 workers exposed to a 125 ppm average concentration of toluene to range from 2.28 to 3.54 g/liter (mean, 2.84 g/liter).

Ogata et al [76] in 1969 applied paper chromatography to separate hippuric acid from methylhippuric acid and other urinary constituents to improve the specificity of the analysis. With this method and a 1.024 specific gravity correction, these investigators reported hippuric acid excretion levels of 2.55 ±0.55 and 5.99 ±1.20 g/liter of hippuric acid for 23 male volunteers exposed to 100 and 200 ppm toluene, respectively, for 3 hours in the morning and 4 hours after the noon lunch period. The samples were collected at the end of the afternoon exposure period.

The dietary habits of workers provide a potential variable affecting hippuric acid excretion levels. Gerarde [31] has pointed out that hippuric acid is a normal urinary constituent originating in foods containing benzoic acid or benzoates.

It is on the basis of these studies that a recommended level of 5 g/liter of hippuric acid in urine has been selected to correlate with the time-weighted average of 200 ppm of toluene vapor. This level of urinary hippuric acid represents an unacceptable absorption of toluene posing a possible risk of toluene intoxication. The measurement of urinary hippuric acid is more of a diagnostic practice than one of compliance. It is not a mandatory procedure but is left

to the discretion of the medical supervisor to be included in the medical program. Biologic monitoring, therefore, provides a valuable measurement technique to verify toluene exposure in the individual worker.

Ellman et al [77] have reviewed the early methods of hippuric acid analysis. The methods involved crystallization, ether extraction, and determination of hippuric acid by weighing, titration, or Kjeldahl analysis. The methods are seldom used today because they are tedious and do not always produce quantitative results. More acceptable procedures have been based on colorimetry, [59,60,74,76,78,79] fluorimetry, [77] and ultraviolet spectrophotometry. [80,81] Improved specificity has been achieved with some of the methods by preliminary sample treatment with ion-exchange resin, [81] paper chromatography, [59,76,78] or alcohol-ether extraction. [60]

Colorimetric methods are used most frequently for the determination of hippuric acid in urine. The method used by Pagnotto and Lieberman [60] successfully detected urinary hippuric acid in unexposed and toluene exposed workers. The average values were reported to be 0.8 g/liter for unexposed subjects and 7.0 g/liter for workers exposed to 200 ppm of toluene (adjusted to a specific gravity of 1.024). However, their spectrophotometric method was not specific for hippuric acid but measured hippuric, methylhippuric, and uric acids at the same wavelength. Other investigators [59,76] have

developed methods which are more specific for hippuric acid, and thus, urine levels reported for the same toluene concentration are slightly lower than those reported by Pagnotto and Lieberman. Ikeda and Ohtsuji, [59] using paper chromatography, reported 3.5 g/liter in workers exposed to 200 ppm of toluene. Their value was adjusted to a specific gravity of 1.016; if adjusted to 1.024, the value would have been 5.3 g/liter. Ogata et al, [76] in order to improve specificity, formed an azlactone derivative of the urinary hippuric acid. This improved method is particularly advantageous in monitoring workers exposed to mixed vapors of toluene and m- or p-xylene since it provides for the separation of the respective xylene metabolites, namely m- or p-methylhippuric acids.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1943, the U.S. Public Health Service [82] published a table of toxic limits in which toluene was given a value of 200 ppm based on the 1942 reports of von Oettingen et al [21] and Greenburg et al. [37]

The Z.37 Committee of the American Standards Association, now known as the American National Standards Institute (ANSI), in 1943, published a standard of 200 ppm for an 8-hour daily exposure to toluene based likewise on the reports of von Oettingen and Greenburg. ANSI has periodically reaffirmed this standard and in 1969, a time-weighted average of 200 ppm was approved. [83] A ceiling of 300 ppm was also recommended along with an acceptable maximum excursion of 500 ppm for a duration of not more than 10 minutes, provided such an exposure is encountered not more than once a day. The acceptable excursion level and duration were based purely on judgment by the Committee (WA Cook, written communication, 1973). Examination of the literature by NIOSH has failed to find data to support such an excursion above a ceiling or any other level relating concentration and time.

In 1947, the American Conference of Governmental Industrial Hygienists (ACGIH) [84] established a Threshold Limit Value (TLV) for toluene of 200 ppm, based on the report of Wilson [23] that physical findings among workers exposed to toluene concentrations below 200 ppm

were essentially negative. In 1971, the ACGIH [85] lowered the threshold limit for toluene to 100 ppm on the basis of irritative effects on the eyes, mucous membranes, and upper respiratory tract of individual subjects exposed variously to 200 to 500 ppm.

In 1957, the Hygienic Guides Committee of the American Industrial Hygiene Association [86] recommended a Maximum Atmospheric Concentration (MAC) of 200 ppm of toluene vapor by volume for 8 hours. This MAC was based on human experience in industry and toxicologic observations in animals.

The present Federal Standard for toluene is an 8-hour time-weighted average of 200 ppm with a ceiling concentration of 300 ppm not to be exceeded during any 8-hour shift. In addition, a maximum peak of 500 ppm for a maximum duration of 10 minutes is acceptable during the 8-hour work shift (29 CFR Part 1910.93 published in the Federal Register, volume 37, page 22139, dated October 18, 1972). This Federal Standard is based on ANSI Z37.12-1967. [83]

Basis for Recommended Environmental Standard

Von Oettingen et al [21,22] have provided the most complete description of the effects of pure toluene on the central nervous system. In this controlled series of exposures of 3 human subjects, no distinct symptoms or after-effects were reported for the 50- and 100-ppm exposures other than drowsiness and mild-to-moderate fatigue as well as a very mild headache by one of the subjects toward the end

of the 8-hour exposure. Moderate tiredness was experienced by these same subjects toward the end of an 8-hour exposure to a zero concentration of toluene in the exposure chamber probably because of a lack of physical exercise, unfavorable illumination, and monotonous noise (fans) where they were occupied during all experimental exposures with their usual routine work to minimize monotony and lack of occupation. At a 200-ppm exposure level, however, two of the subjects experienced muscular weakness, impaired coordination, confusion, and paresthesias of the skin. At the higher exposure levels the symptoms became more pronounced. At 400 ppm all 3 subjects showed signs of mental confusion, fatigue, exhilaration, headache, nausea, and dizziness at the end of 3 hours and, at the end of 8 hours, they showed marked incoordination and a staggering gait. Finally, at 800 ppm all subjects were very confused and showed a lack of self-control and a staggering gait at the end of three hours. Observed variations in the leukocyte count, pulse rate, diastolic blood pressure, pulse pressure, respiratory rate, and minute volume to exposures from 50 to 800 ppm were within control limits.

Carpenter et al [24] reported transitory mild throat and eye irritation and slight exhilaration experienced by 2 male subjects given one-time exposures to 200 ppm of toluene for 7 or 8-hour periods. This was the lowest concentration which was studied. The possibility of benzene contamination was not mentioned in the report.

More recently, Ogata et al [74] in 1970 reported that Japanese subjects given single exposures to 200 ppm of toluene for a period of 7 hours showed a prolongation of eye-to-hand reaction time, a decrease in pulse rate, and a statistically insignificant decrease in systolic blood pressure. No physiological changes were reported at exposures to 100 ppm. They did not consider that 200 ppm of toluene was safe on the basis of their observations.

Capellini and Alessio [16] in 1971 reported that 17 workers who had been exposed for "several" years to mean atmospheric concentrations of toluene of 125 ppm (range 80-160 ppm) and one worker who had mean exposures of 250 ppm (range 210-300 ppm) showed no changes in the blood picture which included Hgb values, RBC, WBC, and platelet counts, or changes in liver function as compared with 19 control subjects. Although no blood abnormalities were detected in any case, the worker whose job activity entailed mean toluene exposures of 250 ppm had irritation of the conjunctiva and central nervous system effects described as a feeling of stupor during work, followed by insomnia and nervousness. Although not reported, the toluene is assumed to have been relatively free of benzene contamination since members of the Italian clinic from which this report originated have published extensively in recent years on the toxicity of benzene in industrial workers.

In summary, changes in muscular coordination, reaction time, and production of mental confusion and irritation of mucous membranes have

been observed for toluene exposures to 200 ppm. These adverse effects have not been reported for toluene exposures of 100 ppm or less in industrial workers or experimental subjects. Although only 3 subjects were employed in the study of von Oettingen et al, [21,22] the findings reported by Carpenter et al, [24] Ogata et al, [74] and Capellini and Alessio [16] help to corroborate the report of von Oettingen et al as being valid for setting a standard. It is recommended, therefore, that the 8-hour time-weighted exposure to toluene be established at 100 ppm.

Of further importance is the current evidence from studies using purified toluene that the chemical lacks toxic effects on the blood or on blood-forming organs. [15,17,33,38,46,47,49] The myelotoxic effects previously attributed to toluene from early studies are presently judged by updated investigations to be the result of concurrent exposure to benzene present as a contaminant. Evidence in the literature [21,22,24,74] that the fatigue, dizziness, exhilaration, and mental confusion resulting from exposures of subjects to concentrations of toluene above 200 ppm for several hours, argues for a ceiling limit of 200 ppm as part of the environmental standard. A ceiling of 200 ppm will limit the range of exposure in the work environment in a manner consistent with the 8-hour time-weighted average recommendation of 100 ppm so as to preclude acute narcotic effects from exposure to toluene.

Liver injury has been reported after continued exposure to apparently high toluene concentrations [36] with resultant recovery following treatment. The findings of liver enlargement in painters reported by Greenburg et al [37] in 1942 indicated toluene exposures up to 1,100 ppm but no correlations could be made between the hepatomegaly and the concentrations of toluene which were encountered. Investigations of the literature by NIOSH have failed to show any reports of permanent liver damage as a result of exposure to toluene even in the few reports where liver enlargement has been mentioned. Apparently any alterations in the liver, even to high toluene concentrations, are reversible. Workers exposed for many years to toluene concentrations in the range of 80 to 300 ppm have failed to show any clinical or laboratory evidence of altered liver function [16]; therefore, it is considered that the recommended standard will prevent adverse effects of toluene on the liver.

VI. REFERENCES

1. Manufacturing Chemists' Association: Chemical Safety Data Sheet SD-63 Toluene. Washington, DC, Manufacturing Chemists Assoc, 1956, pp 18

2. Weast RC (ed.): Handbook of Chemistry and Physics, ed 52, Cleveland, The Chemical Rubber Co, 1971

3. Cier HE: Toluene, in Kirk RE, Othmer DF (eds.): Encyclopedia of Chemical Technology, ed 2. New York, Interscience Publishers, 1969, vol 20, pp 527-65

4. 1970 chemical production data. Chem Eng News 49:12A, 1971

5. Erskine MG: Chemical Economics Handbook, Organic Chemicals P-Z, 696.503D. Menlo Park, California, Stanford Research Institute, 1967

6. Occupational Health Survey of the Chicago Metropolitan Area. Cincinnati, U.S. Department of Health, Education, and Welfare, Public Health Service, Bureau of Occupational Safety and Health, 1970

7. Selling L: [XX. Benzol as a leucotoxin--Studies on the degeneration and regeneration of the blood and the hemopoietic system.] Beitr Pathol Anat 54:576-79, 1911 (Ger)

8. Ferguson T, Harvey WF, Hamilton TD: An enquiry into the relative toxicity of benzene and toluene. J Hyg 33:547-75, 1933

9. Batchelor JJ: The relative toxicity of benzol and its higher homologues. Am J Hyg 7:276-98, 1927

10. Cieslinska A, Kowal-Gierczak B, Kuczynska-Sekieta K, Malolepszy J, Wrzyszcz M: [Serum iron and copper levels in subjects with chronic toluene exposure.] Pol Tyg Lek 24:1848-50, 1969 (Pol)

11. Kowal-Gierczak B, Kuczynska-Sekieta K, Cieslinska A, Wrzyszcz M, Malolepszy J: [Some biochemical tests in subjects occupationally exposed to toluene.] Pol Tyg Lek 24: 1682-85, 1969 (Pol)

12. Banfer W: [Studies on the effect of pure toluene on the blood picture of photogravure printers and helper workers.] Zentralbl Arbeitsmed 11:35-40, 1961 (Ger)

13. Francone MP, Braier L: [The basis for the substitution of benzene by the higher homologues in industry.] Med Lavoro 45:29-32, 1954 (It)

14. Hultgren G: [The effect of different methylated benzene derivatives on the composition of the blood of rabbits.] C R Soc Biol 95:1066-68, 1926 (Fr)

15. Parmeggiani L, Sassi C: [Occupational risk of toluene: Environmental studies and clinical investigations of chronic intoxication.] Med Lavoro 45:574-83, 1954 (It)

16. Capellini A, Alessio L: [The urinary excretion of hippuric acid in workers exposed to toluene.] Med Lavoro 62:196-201, 1971 (It)

17. Browning E: Toxicity and Metabolism of Industrial Solvents. New York, Elsevier Publishing Co, 1965, p 66-76

18. Pacseri I, Emszt G: [Medical aspects of the exposure to toluol.] Munkavedelem 16:41-46, 1970 (Hun)

19. Bansagi J: [Effect of toluene on the phagocytic activity of white blood cells in printers.] Munkavedelem 14:26-28, 1968 (Hun)

20. Michon S: [Disturbance of menstruation in women working in an atmosphere polluted with aromatic hydrocarbons.] Pol Tyg Lek 20:1648-49, 1965 (Pol)

21. Oettingen WF von, Neal PA, Donahue DD: The toxicity and potential dangers of toluene--Preliminary report. JAMA 118:579-84, 1942

22. Oettingen WF von, Neal PA, Donahue DD, Svirbely JL, Baernstein HD, Monaco AR, Valaer PJ, Mitchell JL: The toxicity and potential dangers of toluene with special reference to its maximal permissible concentration, bulletin 279. Public Health Service, 1942, pp 50

23. Wilson RH: Toluene poisoning. JAMA 123:1106-08, 1943

24. 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

25. Longley EO, Jones AT, Welch R, Lomaev O: Two acute toluene episodes in merchant ships. Arch Environ Health 14:48187, 1967

26. Satran R, Dodson VN: Toluene habituation--Report of a case. N Engl J Med 268:719-21, 1963

27. Knox JW, Nelson JR: Permanent encephalopathy from toluene inhalation. N Engl J Med 275:1494-96, 1966

28. Grabski DA: Toluene sniffing producing cerebellar degeneration. Am J Psychiatry 118:461-62, 1961

29. Gusev IS: Reflective effects of microconcentrations of benzene, toluene, xylene and their comparative assessment. Hyg Sanit 30:331-35, 1965

30. Chiantella AJ, Smith WD, Umstead ME, Johnson JE: Aromatic hydrocarbons in nuclear submarine atmospheres. Am Ind Hyg Assoc J 27:186-92, 1966

31. Gerarde HW: Toxicology and Biochemistry of Aromatic Hydrocarbons. New York, Elsevier Publishing Co, 1960, pp 141-50

32. Dutkiewicz T, Tyras H: The quantitative estimation of toluene skin absorption in man. Arch Gewerbepath Gewerbehyg 24:253-57, 1968

33. Piotrowski J: [Quantitative estimate of the absorption of toluene in people.] Med Pracy 18:213-23, 1967 (Pol)

34. McLaughlin, RS: Chemical burns of the human cornea. Am J Ophthalmol 29:1355-62, 1946

35. Grant WM: Toxicology of the Eye. Springfield, Ill, Charles C Thomas, 1962, pp 544-45

36. O'Brien ET, Yeoman WB, Hobby JAE: Hepatorenal damage from toluene in a "glue sniffer." Br Med J 2:29-30, 1971

37. Greenburg L, Mayers MR, Heimann H, Moskowitz S: The effects of exposure to toluene in industry. JAMA 118:57378, 1942

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

39. Chassevant A, Garnier M: [The toxicity of benzene and some aromatic hydrocarbon homologs.] CR Soc Biol 55: 1255-57, 1903 (Fr)

40. Lehmann KB: [Experimental studies on the influence of technically and hygienically important gases and vapors on organisms (XXIV-XXIX)--The hydrocarbons: Benzene, toluene, xylene, light benzine, and heavy benzine.] Arch Hyg 75: 1,36-41,67,116-119, 1911-12 (Ger)

41. 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

42. Rambousek J: Industrial Poisons. London, Edward Arnold, 1913, pp 206-07

43. Hektoen L: The effect of toluene on the production of antibodies. J Infect Dis 19:737-45, 1916

44. Svirbely JL, Dunn RC, von Oettingen WF: The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. J Ind Hyg Toxicol 25:36673, 1943

45. Fairhall LT: Industrial Toxicology. Baltimore, Williams & Wilkins Co, 1949, p 447

46. Fabre R, Truhaut R, Laham S, Peron M: [Toxicological research on substitute solvents for benzene--II. Study of toluene.] Arch Mal Prof 16:197-215, 1955 (Fr)

47. Takeuchi Y: Experimental studies on the toluene poisoning--chiefly on the findings of peripheral blood and adrenal gland. Ind Health 7:31-45, 1969

48. Gerarde HW: Toxicological studies on hydrocarbons--II. A comparative study of the effects of benzene and certain mono-n-alkylbenzenes on hemopoiesis and bone marrow metabolism in rats. AMA Arch Ind Health 13:468-74, 1956

49. Speck B, Moeschlin S: [Effects of toluene, xylene, chloramphenicol, and thiouracil on bone marrow.] Schweiz Med Wochenschr 98:1684-86, 1968 (Ger)

50. Smyth HF, Smyth HF Jr: Inhalation experiments with certain lacquer solvents. J Ind Hyg 10:261-71, 1928

51. Taylor GJ, Harris WS: Glue sniffing causes heart block in mice. Science 170:866-67, 1970

52. Furnas DW, Hine CH: Neurotoxicity of some selected hydrocarbons. AMA Arch Ind Health 18:9-15, 1958

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

54. Bakke OM, Scheline RR: Hydroxylation of aromatic hydrocarbons in the rat. Toxicol Appl Pharmacol 16:691-700, 1970

55. Ikeda M, Ohtsuji H: Phenobarbital-induced protection against toxicity of toluene and benzene in the rat. Toxicol Appl Pharmacol 20:30-43, 1971

56. Abou-el-Makarem MM, Millburn P, Smith RL, Williams RT: Biliary excretion of foreign compounds--Benzene and its derivatives in the rat. Biochem J 105:1269-74, 1967

57. Smith JN, Smithies RH, Williams RT: Studies in detoxication--55 The metabolism of alkylbenzenes. (a) Glucuronic acid excretion following the administration of alkylbenzenes. (b) Elimination of toluene in the expired air in rabbits. Biochem J 56:317-20, 1954

58. Rees H van: The influene of toluene on the metabolism of benzene in rats. Netherlands Society for Physiology and Pharmacology. Abstracts of meeting, Groningen, April 6-7, 1967, pp 64-65

59. Ikeda M, Ohtsuji H: Significance of urinary hippuric acid determination as an index of toluene exposure. Br J Ind Med 26:244-46, 1969

60. Pagnotto LD, Lieberman LM: Urinary hippuric acid excretion as an index of toluene exposure. Am Ind Hyg Assoc J 28:129-34, 1967

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

62. Yant WP, Pearce SJ, Schrenk HH: A microcolorimetric method for the determination of toluene, Report Investigations 3323. US Dept of the Interior, Bureau of Mines, 1936, pp 12

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

64. 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 Q 17:186-88, 1956

65. Dambrauskas T, Cook WA: Methanol as the absorbing reagent in the determination of benzene, toluene, xylene and their mixtures in air. Am Ind Hyg Assoc J 24:568-75, 1963

66. 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

67. 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

68. 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 31:22532, 1970

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

70. Hubbard BR, Silverman L: Rapid method for the determination of aromatic hydrocarbons in air. AMA Arch Ind Hyg Occup Med 2:49-55, 1950

71. Kol'kovsky P: [A new color reaction for the vapor of some aromatic hydrocarbons.] Russian J Anal Chem 22:403-04, 1967 (Rus)

72. Williams NH: Gas chromatographic techniques for the identification of low concentrations of atmospheric pollutants. Anal Chem 37:1723-32, 1965

73. Teisinger J, Srbova J: [Elimination of benzoic acid with the urine and its relation to the maximum tolerable toluene concentration in the air.] Arch Mal Prof 16:216-20, 1955 (Fr)

74. Ogata M, Tomokuni K, Takatsuka Y: Urinary excretion of hippuric acid and m- or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. Br J Ind Med 27:43-50, 1970

75. Arato ES: [Toluene concentration of expired air and urinary benzoic acid concentration in subjects exposed to toluene.] Egeszsegtudomany 12:247-52, 1968 (Hun)

76. Ogata M, Tomokuni K, Takatsuka Y: Quantitative determination in urine of hippuric acid and m- or p-methylhippuric acid metabolites of toluene and m- or p-xylene. Br J Ind Med 26:330-34, 1969

77. Ellman GL, Burkhalter A, Ladou J: A fluorometric method for the determination of hippuric acid. J Lab Clin Med 57:813-18, 1961

78. Gaffney GW, Schreier K, Di-Ferrante N, Altman KI: The quantitative determination of hippuric acid. J Biol Chem 206:695-8, 1954

79. Umberger CJ, Fiorese FF: Colorimetric method for hippuric acid. Clin Chem 9:91-6, 1963

80. Rieder HP: Bestimmung von Benzosaure neben Hippursaure mit Hilfe einer Differential-spektrophotometrischen Methode. Clin Chim Acta 2:497-501, 1957

81. Elliott HC Jr: Microdetermination of hippuric acid in urine. Anal Chem 29:1712-15, 1957

82. Gafafer WM (ed.): Acceptable concentrations of contaminants in workroom atmospheres, in Manual of Industrial Hygiene, USPHS. Philadelphia, WB Saunders Co, 1943

83. American National Standards Institute: Acceptable Concentration of Toluene Z37.12-1967, New York, 1969, 8 pp

84. Transactions of the Ninth Annual Meeting of the American Conference of Governmental Industrial Hygienists, Cincinnati, 1947, p 44

85. Threshold Limit Values of Airborne Contaminants and Physical Agents with Intended Changes Adopted by ACGIH for 1971. American Conference of Governmental Industrial Hygienists, Cincinnati, 1971

86. Hygienic Guide Series, Toluene. American Industrial Hygiene Association, Hygienic Guide Committee, 1957

87. 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, Pa., American Society of Testing and Materials, 1971, pp 18

VII. APPENDIX I

COMPLIANCE METHOD

SAMPLING AND ANALYTICAL PROCEDURES

FOR DETERMINATION OF TOLUENE

The following sampling and analytical method for analysis of toluene in air employs adsorption on charcoal, followed by desorption and gas chromatographic measurement. This is a modified method that is derived from White et al [68] and Kupel and White. [69] Additional data are contained in Part IV under 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 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) Procedure

(i) 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.

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

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

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

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

(vi) 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.

(vii) 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 person performing the calibration; and the date.

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

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

(x) 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 and 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 toluene with instrument attenuation and splitter techniques is 0.01 mg/sample. This value can be lowered by reducing the attenuation or by eliminating the splitter. The upper limit value for toluene is 12.5 mg/sample. This value is the number of milligrams of toluene 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 to avoid exceeding the adsorbent capacity of the charcoal in the tube.

(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. Water present as a mist is a problem, not water vapor.

(2) Any compound which has the same retention time in the gas chromatograph as toluene 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 toluene (see also Accuracy and Precision Data in Part IV) was found to be:

	Accuracy	Precision
Motor driven laboratory pump	3.5%	2.8%
Approved coal mine personal sampling pump (calibrated with no in-line resistance)	22.9%	9.7%
Approved coal mine personal sampling pump (calibrated with charcoal tube in line)	7.4%	4.5%

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. [87]

(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 toluene which the tube will hold before overloading as indicated by toluene 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 2 sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The adsorbing 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 backup section. A plug of glass wool is placed in front of the adsorbing 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 µl, and convenient sizes for preparation of standards.

(g) Reagents

(1) Spectroquality carbon disulfide.

(2) Toluene, 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 the tubing shall not 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 recharging 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 toluene 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 are 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 toluene desorption from the charcoal. To prepare a 0.3 mg/ 0.5 ml standard, 6.0 mg of toluene (converted to microliters for easy measurement) is injected into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The excess quantity of toluene 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 is determined for each batch of charcoal being 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 toluene, 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 toluene 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 toluene 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 toluene 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 toluene 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 toluene:

$$\text{ppm} = \frac{24{,}450 \text{ ml/mole} \times \text{mg in sample}/10 \text{ liters}}{92.13 \text{ g/mole}}$$

$$\text{ppm} = 26.54 \times \text{mg in sample}$$

VIII. APPENDIX II

METHODS FOR DETERMINATION OF EXPOSURE AREAS TO TOLUENE

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 toluene in air and correlating concentration with stain length or color intensity.

The use of detector tubes with their respective pumps for compliance purposes is inappropriate because sampling times are necessarily very brief; thus, an excessive number of sampling periods would be required to permit calculation of a time-weighted average. In addition, the accuracy of detector tubes is limited [see (e) below].

(c) Range and Sensitivity

Certification standards require that certified tubes have a range from 1/2 to 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 under the provisions of 42 CFR Part 84 (37 FR 19643) specify reliability to within ±25% of the actual concentration in the range 0.75 to 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 toluene 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 toluene 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 toluene identification using combustible gas meters. Mixtures of any carbon-containing compounds, other than toluene, 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

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material containing toluene 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) The product designation in the upper left-hand corner of both front and back to facilitate filing and retrieval. Print in upper case letters in as large a print as possible.

(b) 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.

(c) 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 of maximum amount, ie, 10-20% by volume; 10% maximum by weight.

(3) Basis for toxicity for each hazardous material such as established OSHA standard in appropriate units and/or LD50, showing amount and mode of exposure and species, or LC50 showing concentration and species.

(d) Section III. Physical Data.

(1) 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.

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

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

(f) Section V. Health Hazard Data.

(1) Toxic level for total compound or mixture, relevant symptoms of exposure, skin and eye irritation properties,

principal routes of absorption, effects of chronic (long-term) exposure, and emergency and first aid procedures.

(g) Section VI. Reactivity Data.

(1) Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

(h) Section VII. Spill or Leak Procedures.

(1) 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.

(i) Section VIII. Special Protection Information.

(1) 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.

(j) Section IX. Special Precautions.

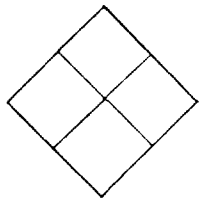
(1) Any other general precautionary information such as personal protective equipment for exposure to the thermal decomposition products listed in Section VI, and to particulates formed by abrading a dry coating, such as by a power sanding disc.

(k) The signature of the responsible person filling out the data sheet, his address, and the date on which it is filled out.

PRODUCT DESIGNATION

MATERIAL SAFETY DATA SHEET

Form Approved
Budget Bureau No.
Approval Expires
Form No. OSHA



SECTION I SOURCE AND NOMENCLATURE

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

SECTION II HAZARDOUS INGREDIENTS

BASIC MATERIAL	APPROXIMATE OR MAXIMUM % WT. OR VOL.	ESTABLISHED OSHA STANDARD	LD 50		LC 50	
			ORAL	PERCUT.	SPECIES	CONC.

SECTION III PHYSICAL DATA

BOILING POINT °F.	VAPOR PRESSURE mm Hg.
MELTING POINT °F.	VAPOR DENSITY (Air=1)
SPECIFIC GRAVITY (H_2O=1)	EVAPORATION RATE (=1)
SOLUBILITY IN WATER Pts/100 pts H_2O	VOLATILE % Vol. % Wt.
APPEARANCE AND ODOR	

SECTION IV FIRE AND EXPLOSION HAZARD DATA

FLASH POINT	FLAMMABLE (EXPLOSIVE) LIMITS	UPPER
METHOD USED		LOWER
EXTINGUISHING MEDIA		
SPECIAL FIRE FIGHTING PROCEDURES		
UNUSUAL FIRE AND EXPLOSION HAZARDS		

PRODUCT DESIGNATION

SECTION V HEALTH HAZARD DATA	
TOXIC LEVEL	CARCINOGENIC
PRINCIPAL ROUTES OF ABSORPTION	SKIN AND EYE IRRITATION
RELEVANT SYMPTOMS OF EXPOSURE	
EFFECTS OF CHRONIC EXPOSURE	
EMERGENCY AND FIRST AID PROCEDURES	

SECTION VI REACTIVITY DATA
CONDITIONS CONTRIBUTING TO INSTABILITY
CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION
INCOMPATIBILITY (Materials to Avoid)
HAZARDOUS DECOMPOSITION PRODUCTS

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	
VENTILATION REQUIREMENTS LOCAL EXHAUST	PROTECTIVE EQUIPMENT (Specify Types) EYE
MECHANICAL (General)	GLOVES
SPECIAL	RESPIRATOR
OTHER PROTECTIVE EQUIPMENT	

SECTION IX SPECIAL PRECAUTIONS
PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE
OTHER PRECAUTIONS

Signature _____ Address

Date

TABLE X-1

PHYSICAL PROPERTIES OF TOLUENE

Molecular Formula	C6H5CH3
Molecular Weight	92.13
Boiling Point	110.6 C (231 F)
Melting Point (Freezing Point)	-95 C (-139 F)
Vapor Pressure at 25 C (77 F)	28mm Hg
Specific Gravity (20 C/4 C)	0.866
Solubility	Insoluble in water; soluble in acetone; miscible with alcohol, ether, and benzene
Explosive Limits (by volume in air)	1.27 - 7.0%
Flash Point (closed cup)	4.4 C (40 F)
Autoignition temperature	552 C (1026 F)
Vapor Density (relative to air)	3.14

Derived from [1,2]

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