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FROM: T. G. Grumbles

DATE: July 27, 1990

SUBJ: ACGIH RECOMMENDED CHANGE FOR BENZENE TLV

VISTA

The ACGIH TLV committee is proposing to revise the Benzene TLV from 10 ppm to 0.1 ppm, 8-hour TWA, with no STEL recommended.

This change is recommended based on revised risk assessments of the available animal and epidemiological data. It is an unprecedented recommendation for ACGIH in that they are recommending a "no residual risk" exposure limit. Also, ACGIH generally does not consider feasibility issues in their determinations.

The TLV process will put this 0.1 ppm limit on a "notice of intended changes" list for 2 years, during which interested parties can comment. No final decision will be made until then.

The impact of this recommendation is undefinable at this time. TLV's have some regulatory significance but are not binding in occupational settings per se. Some states use them as air toxics guidelines, and plaintiff's lawyers certainly will utilize the recommendation.

The documentation for the recommended change is attached.

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Attachment

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VVV 000013383

Notice of Intended Changes—Benzene

Editor's Note: In anticipation of significant interest and to ensure reader awareness of the proposed revision of the Threshold Limit Value (TLV) for benzene, publication of this revised documentation is issued at this time and in advance of the publication of the *Threshold Limit Values and Biological Exposure Indices for 1990–1991* booklet. The recommendation of the Chemical Substances TLV Committee received approval from the ACGIH Board of Directors and members in attendance at the annual ACGIH business meeting on May 16, 1990. The recommendation is that benzene be listed on the Chemical Substances TLV Notice of Intended Changes for 1990–91 at 0.1 ppm as a time-weighted average (TWA) with a Skin notation and designation as an A1 carcinogen (confirmed human carcinogen).

This proposed reduction for the adopted benzene TLV—TWA of 10 ppm and A2 carcinogen designation (suspected human carcinogen) will undoubtedly prompt speculation as to the basis for the proposed revision. An estimated exposure to benzene of 238,000 U.S. workers and usage of more than 11 billion gallons of benzene per year are added incentives to publish the revised documentation at this time. The proposed revision will remain on the Notice of Intended Changes for a period of at least two years during which comment and substantive evidence for or against the appropriateness of the revised TLV is solicited by the TLV Committee.

This publication of the documentation in *Applied* provides an additional opportunity for comment.

Benzene

CAS: 71-43-2

Benzol; phenyl hydride; cyclohexatriene; coal naphtha C_6H_6

Skin

TLV—TWA, 0.1 ppm (0.3 mg/m³)

A1—Confirmed Human Carcinogen

TLV—TWA, 100 ppm, 1946

TLV—TWA, 50 ppm, 1947

TLV—TWA, 35 ppm, 1948–1956

TLV—TWA, 25 ppm, 1957–1962

TLV—Ceiling, 25 ppm, Skin, 1963–1976

TLV—TWA, 10 ppm, A2, Skin, 1977–present; Skin notation deleted 1978

TLV—STEL, 25 ppm, A2, 1980–1987

TLV—TWA, 0.1 ppm, A1, Skin: proposed 1990

Documentation revised, 1990

Chemical and Physical Properties

Benzene is a colorless, highly flammable, nonpolar liquid with an odor that is characteristic of aromatic hydrocarbons. Benzene can be supplied as industrial grade, ni-

tration grade, or refined. Physicochemical properties of reagent grade benzene include:

Molecular weight: 78.11

Specific gravity: 0.87865 at 20°C

Melting point: 5.5°C

Boiling point: 80.1°C

Vapor pressure: 75 torr at 20°C

Closed cup flash point: –11.1°C

Autoignition temperature: 562°C

Flammability limit in air: 1.5–8.0 vol%

Odor threshold: 12 ppm

Saturated air at 25°C contains 120,000 ppm

Solubility: 0.180 g/100 ml water at 25°C; miscible in all proportions with carbon tetrachloride, ethanol, chloroform, diethyl ether, carbon disulfide, acetone, glacial acetic acid, and oils.

Major Uses and Sources of Occupational Exposure

At one time, benzene was an important solvent, especially for inks, rubber, lacquers, and paint removers. At present, such uses are minimal; most benzene is consumed in the chemical industry as a raw material for numerous organic chemicals and in plastics manufacture. It is found in gasoline from trace amounts to as much as 30 percent in some countries (U.S. average, 1–3%). Total benzene usage exceeds 11 billion gallons per year,⁽¹⁾ and it is estimated that 238,000 employees in U.S. petrochemical plants, petroleum refineries, coke and coal operations, tire manufacturers, bulk terminals and plants, and in truck transport are exposed to benzene.⁽²⁾

Benzene is a myelotoxicant, known to suppress bone marrow cell proliferation and to induce hematologic disorders in humans and in animals. Signs of benzene-induced aplastic anemia include suppression of leukocytes (leukopenia), red cells (anemia), platelets (thrombocytopenia), or all three cell types (pancytopenia). Classic symptoms include weakness, purpura, hemorrhage, pancytopenia, and aplastic anemia.

Animal Studies

VVV 000013384

Subchronic

When Sprague–Dawley rats and CD-1 mice of either sex were exposed by inhalation to benzene at 1, 10, 30, or 300 ppm, 6 hours per day, 5 days per week for 13 weeks, treatment-related pathology was observed in the high dose (300 ppm) groups of both species.⁽³⁾ In mice, hematologic changes included decreased hematocrit, total hemoglobin, erythrocyte/leukocyte count, platelet count, and myeloid:erythroid ratio. In rats, decreased lymphocyte count and a relative increase in neutrophil count were the only exposure-related clinical change. Histopathological changes

were observed in the testes and ovaries at concentrations below 300 ppm, and lesions were observed in the thymus, bone marrow, lymph nodes, spleen, ovaries, and testes in mice inhaling 300 ppm. The alterations were more severe in the males than in the females. In rats, the only exposure-related pathology was a slight reduction in femoral marrow cellularity at 300 ppm.⁽³⁾

Studies to identify the target cells for benzene hematopoietic toxicity indicated that benzene exposure damaged mouse pluripotent stem cells, the colony-forming cell units in the spleen, and the progenitor cells for granulocytes and macrophages.⁽⁴⁻⁶⁾ Hematopoietic depression in rodents was observed at benzene concentrations as low as 103 ppm after a 5-day exposure.⁽⁷⁾ Cronkite *et al.*^(8,9) reported a series of studies where CBA/CA mice were exposed to benzene at 10, 25, 100, 300, or 400 ppm, 6 hours per day, 5 days per week for 2, 4, 8, and 16 weeks. Exposure to 100 ppm or greater for two weeks reduced bone marrow cellularity.⁽⁸⁾ When C57BL/6J mice inhaled 300 ppm benzene 6 hours per day, 5 days per week for a total of 115 exposures, the numbers of B-lymphocytes in bone marrow and spleen and the numbers of T-lymphocytes in thymus and spleen were reduced.⁽¹⁰⁾ When BALB/C mice were exposed at 50 or 200 ppm benzene 6 hours per day for 7 or 14 days, the ratios and the absolute numbers of T- and B-lymphocytes in blood and spleen were depressed.⁽¹¹⁾ Depression of B-lymphocytes was dose-dependent, and it was more severe than that of the T-cells.⁽¹¹⁾ When male C57BL mice inhaled 10 ppm, 6 hours per day for 6 days, a significant depression in colony-forming units in B-lymphocytes was observed; similar inhalation of 31 ppm resulted in depressed blastogenesis of T-lymphocytes.⁽¹²⁾

Chronic/Carcinogenicity

When groups of 40 CD-1 mice were exposed to benzene in air at 100 or 300 ppm, 6 hours per day, 5 days per week for life, two mice in the high dose group developed myelogenous leukemia. No leukemia was observed in the 100-ppm dose group.⁽¹³⁾ Snyder *et al.*⁽¹⁴⁾ found that after groups of 40 C57BL mice inhaled 300 ppm benzene for 6 hours per day, 5 days per week for 2 years, eight cases of lymphoreticular neoplasia (six thymic lymphocytic lymphomas, one plasmacytoma, and one hemocytoblastic leukemia) occurred; two mice in the control group developed lymphocytic lymphomas. The incidence of tumors in the benzene-treated mice was significantly greater ($p = 0.005$) than that in the control.⁽¹⁴⁾ In a lifetime carcinogenicity bioassay in which oral doses of benzene were administered at 50 and 250 mg/kg-day, 4-5 days per week for 52 weeks, there was a dose-dependent increase in total cancers.⁽¹⁵⁾ The most prominent rat tumors observed were Zymbal gland carcinomas, mammary carcinomas, and leukemia. When Wistar rats and Swiss mice were given benzene at 500 mg/kg-day, 4 or 5 days per week for 104 or 78 weeks, respectively, the numbers of Zymbal gland carcinomas, hemolymphoreticular neoplasias, and total malignant tumors were increased in the rats; increases in mouse Zymbal gland dysplasia and carcinomas, mammary

carcinomas, pulmonary tumors, and total malignant tumors were observed.⁽¹⁶⁾

In the National Toxicology Program lifetime bioassay,⁽¹⁷⁾ 50 F344/N rats of each sex per dose group were treated with benzene by oral gavage at doses of 50, 100, or 200 mg/kg-day for the males and at 25, 50, or 100 mg/kg-day for the females for two years. Similar groups of B6C3F1 mice of both sexes were treated with 25, 50, or 100 mg/kg-day. For the male and female rats, increases of Zymbal gland carcinoma, squamous cell papilloma, and squamous cell carcinoma of the mouth were observed. In the male rats, squamous papilloma and squamous cell carcinoma of the skin were also increased. For male mice, increased numbers of animals with Zymbal gland carcinoma, malignant lymphoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined), Harderian gland adenoma, and squamous carcinoma of the preputial gland were observed. For female mice, increased numbers of animals compared to the control were afflicted with malignant lymphoma, ovarian granular cell carcinoma, carcinosarcoma of the mammary gland, alveolar/bronchiolar adenoma, and alveolar/bronchiolar carcinoma were reported.⁽¹⁷⁾

Cronkite⁽¹⁸⁾ conducted a carcinogenicity bioassay wherein male and female C57BL/6 and CBA/Ca mice inhaled 100-300 ppm benzene, 6 hours per day, 5 days per week for 16 weeks and found benzene-induced leukemia in the males. When mice inhaled 25 ppm benzene for as few as ten such exposures, lymphopenia resulted.⁽¹⁸⁾

Reproductive/Developmental

Studies on the potential developmental toxicity of benzene administered by subcutaneous injections, ingestion, or inhalation have generally failed to show significant adverse effects in mice, rats, or rabbits (for review, see Schwetz⁽¹⁹⁾). Adverse developmental effects have been described in an unpublished rat bioassay performed by Litton Bionetics⁽²⁰⁾ wherein Sprague-Dawley rats inhaled 10-40 ppm benzene, 6 hours per day on days 6-15 of gestation. Embryonic death increased from the control (6.2%) to 8.1 and 9.5 percent for rats exposed to 10 and 40 ppm benzene, respectively. However, the Litton study⁽²⁰⁾ was confounded by the high ambient temperature in one of the exposure chambers during the study; maternal hyperthermia is a known rodent teratogen.

Kuna and Kapp⁽²¹⁾ conducted an inhalation study in which pregnant Sprague-Dawley rats were exposed to benzene at 10, 50, or 500 ppm 7 hours per day on days 6-15 of gestation. Significant reductions in mean maternal body weight gain occurred. Mean fetal body weight was reduced. Fetal crown-rump distance was decreased significantly at 500 ppm, and developmental delay was evident upon examination of the fetal skeletons. Benzene was judged by these authors⁽²¹⁾ to be fetotoxic in rats at 50 and 500 ppm and to manifest teratogenicity at 500 ppm. Coate *et al.*⁽²²⁾ found that when pregnant Sprague-Dawley rats inhaled 1, 10, 40, or 100 ppm benzene 6 hours per day on days 6-15 of gestation, no maternal toxicity was noted; however,

a reduction in mean fetal body weight at 100 ppm was observed. No teratogenic effects were found.⁽²²⁾ When pregnant Swiss-Webster mice were exposed to 5, 10, or 20 ppm benzene in air on days 6–15 of gestation for 6 hours per day, alterations in the numbers of hematopoietic colony-forming cells in the progeny were recorded.⁽²³⁾ Marked reductions in erythroid colony-forming cells were observed at all benzene concentrations studied, and inhalation of 10 or 20 ppm also decreased the numbers of granulocytic colony-forming cells. When mice, previously exposed *in utero* to 10 ppm benzene, were re-exposed to 10 ppm for 6 hours per day for 2 weeks, a marked reduction in the numbers of bone marrow differentiated erythroid colony-forming cells occurred.⁽²³⁾ Keller and Snyder⁽²³⁾ interpreted these data as an indication that alterations of the murine hematopoietic system induced by neonatal benzene exposure could persist into adulthood.

Ungvary and Tatrai⁽²⁴⁾ exposed CFP mice and NZ rabbits to benzene at 154 or 308 ppm, 24 hours per day, throughout days 6–15 of gestation. Benzene was detected in fetal blood and in amniotic fluid. At 308 ppm, retarded skeletal development and reduced fetal body weight were observed in mouse fetuses, and spontaneous abortions were reported in rabbits.⁽²⁴⁾

Genotoxicity Studies

Benzene exposure can cause chromosomal aberrations in animals and in humans. Benzene exposure induces clastogenesis, sister chromatid exchange, and micronuclei both *in vivo* and *in vitro*.⁽²⁵⁾ Benzene exposure has been shown to induce aneuploidy in dividing cells, presumably through inhibition of tubulin assembly during mitosis. However, benzene exposure has failed consistently to induce point mutations in genotoxicity test systems.

Point Mutation

In the *Salmonella typhimurium* gene mutation assay, benzene proved consistently negative for mutagenesis in plate-incorporation assays with or without microsomal enzyme activation.^(26–29) McCarroll *et al.*⁽³⁰⁾ published the only positive result using a microsuspension assay with hepatic microsomal activation such that an increase in the numbers of revertants in *Salmonella* strain TA100 was observed.

Benzene exposure inhibited the growth of DNA repair deficient *Escherichia coli* strain WP100 (*uvrA*[–], *recA*[–], but no such effect was observed in repair proficient strains.⁽³¹⁾ Growth inhibition was also observed in DNA repair deficient *Bacillus subtilis* strain M45 (*rec*[–])⁽³²⁾ but benzene was considered without mutagenic activity in the *E. coli* PolA assay, an indication that the DNA polymerase activity was not critical for repair of benzene-induced damage to nucleic acid.⁽³³⁾ Benzene was reported negative in *Saccharomyces cerevisiae* gene conversion and mitotic crossing-over assays,⁽³⁴⁾ however, it was considered mutagenic for *S. cerevisiae* strains D61-M and D6.⁽³⁵⁾

When benzene was fed to *Drosophila melanogaster* at

up to 2.5 percent in the diet, no evidence for a mutagenic response using the eye pigmentation as a genetic marker was found.⁽³⁶⁾ When *Drosophila* were placed in air containing 27,000 ppm for 60 minutes (20% survival), a significant increase in spermatogonial crossing-over was observed and mutation frequency and translocation frequency were increased. These data were considered indicative of the stage-specific nature of benzene-induced spermatogonial mutagenesis in *Drosophila*.⁽³⁷⁾ Benzene exposure altered gene expression as measured in the *Drosophila* wing morphology assay,⁽³⁸⁾ but results using the *Drosophila* eye spot assay were judged negative⁽³⁹⁾ or at most equivocal.⁽⁴⁰⁾ In grasshopper embryos, benzene exposure was associated with mitotic arrest, multipolar division, and chromosome lags.⁽⁴¹⁾

Benzene was tested in a collaborative study of 12 laboratories using a variety of cell lines and genetic markers.⁽⁴²⁾ Benzene was mutagenic without hepatic enzyme (S9) activation in the mouse lymphoma L5178Y (TK + / +) assay in one laboratory, it was mutagenic in the Chinese hamster V79 cell assay at the ouabain-resistant locus (NaK-ATPase defective) in one laboratory, and it was mutagenic at the 6-thioguanine resistance locus (HGPRT[–]) in one laboratory. Mutagenic activity was observed with S9 activation in the mouse lymphoma L5178Y (TK + / +) assay for trifluorothymine resistance (TK[–]) in two of the laboratories, and mutagenicity was observed in the mouse lymphoma L5178Y (TK + / +) assay for ouabain-resistance in one of the laboratories. Benzene was considered mutagenic without exogenous activation for 6-thioguanine resistance in human AHH-1 lymphoblasts. Except for the human lymphoblast and Chinese hamster V79 studies (which were not repeated in other laboratories), the findings for benzene point mutation could not be confirmed by other laboratories involved in the collaborative study.⁽⁴²⁾ Therefore, potential point mutation associated with benzene exposure in cultured mammalian cells is considered inconclusive based on the studies published to date.

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Chromosomal Aberration

Benzene treatment induces chromosomal structural changes and aneuploidy in cultured mammalian cells. In cultured human lymphocytes, chromosomal aberrations were observed after three hours of incubation with 9–88 µg benzene/ml with or without S9 activation.⁽⁴³⁾ Aberrations were also observed in Chinese hamster lung fibroblasts after treatment with 1100 µg benzene/ml and in Chinese hamster ovary (CHO) cells at 100 µg benzene/ml with S9 activation. Aneuploidy was reported in Chinese hamster primary hepatocytes treated with benzene at 62.5 µg/ml.⁽⁴⁴⁾

Benzene itself failed to induce sister chromatid exchange (SCE) in cultured human lymphocytes without exogenous metabolic activation (S9), but benzene metabolites increased SCE in a dose-dependent fashion.⁽⁴⁵⁾ The primary benzene metabolites (phenol, catechol, hydroquinone) are transformed to benzo(semi)quinones, which presumably act as the ultimate genotoxic agents.⁽⁴⁵⁾ Ca-

catechol and hydroquinone were potent SCE inducers at 4.4 $\mu\text{g}/\text{mL}$.⁽⁴⁶⁾ Glutathione (GSH) inhibited benzene-induced SCE formation, and it was hypothesized that GSH conjugation to benzene metabolites prevented DNA damage.⁽⁴⁷⁾ Benzene and its metabolites were reported to decrease mitotic index, to inhibit cell cycle transverse, and to increase SCE frequency in cultured human T-lymphocytes. The relative potency of benzene metabolites for SCE induction were catechol > 1,4-benzoquinone > hydroquinone > 1,2,4-benzenetriol > phenol > benzene.⁽⁴⁸⁾

Tice *et al.*⁽⁴⁹⁾ found a concentration-dependent increase in DBA/2 mouse bone marrow lymphocytes after a single, 4-hour inhalation study of benzene at 28–3000 ppm; an increase in SCE was detected at 28 ppm. This response was strain-dependent as DBA/2 mice were more sensitive than C57BL/6 mice, young DBA/2 mice (three months) were more sensitive than older mice (10 months), and male mice were more sensitive than female mice. Following intraperitoneal injection, a linear dose-dependent increase in SCE was observed in DBA/2 mice.⁽⁴⁹⁾

DNA Damage

Benzene failed repeatedly to exhibit genotoxicity in tests for unscheduled DNA synthesis (UDS) in cultured primary rat hepatocytes. Benzene is consistently negative in HeLa cells with or without metabolic activation. Glauert *et al.*⁽⁵⁰⁾ published the single positive report for increased UDS in cultured primary rat hepatocytes associated with benzene exposure.

In a study of *in vitro* DNA damage, mouse L5178 YS lymphoma cells failed to show single strand breaks after exposure to 1.0 mM benzene, phenol, or catechol or to 0.1 mM hydroquinone; however, a dose-dependent increase in DNA damage was observed after treatment with para-benzoquinone or 1,2,4-benzenetriol.⁽⁵¹⁾ Para-benzoquinone at 6 μM induced 70 percent single strand DNA breaks within 3 minutes of exposure; the same damage was achieved by benzenetriol within 60 minutes.⁽⁵¹⁾

A concentration-dependent increase in mouse peripheral blood micronuclei was observed after C57BL/6 mice inhaled 10, 25, 100, or 400 ppm, 6 hours per day, for 9 days.⁽⁵²⁾ When C57BL/6 mice inhaled 300 ppm benzene for 16 weeks under a similar protocol and the patterns for micronucleus induction monitored, the initial increase was followed by a gradual decrease.⁽⁵³⁾ When the peripheral blood of B6C3F1 mice given oral benzene⁽¹⁷⁾ was studied, a dose-dependent increase in the numbers of circulating erythrocyte micronuclei occurred. A significant increase was observed in male mice given a dose as low as 25 mg/kg-day for 120 days.⁽⁵⁴⁾ Pretreatment of male and female CD-1 mice with metabolic enzyme-inducing agents (phenobarbital, SKF-525A, Arochlor 1254) failed to protect against the clastogenic effect of benzene exposure, but pretreatment with 3-methylcholanthrene potentiated benzene myeloclastogenicity.⁽⁵⁵⁾ Male mice were more sensitive than female mice and chromosomal damage was greater after oral than after intraperitoneal administration.⁽⁵⁵⁾

Chromosome aberrations were induced in Wistar rats

after inhalation of 100 or 1000 ppm benzene.⁽⁵⁶⁾ Wh male DBA/2 mice inhaled benzene at 0, 10, 100, or 1000 ppm or male Sprague-Dawley rats inhaled benzene at 0, 0.3, 1, 3, 10, or 30 ppm for 6 hours, significant (dose dependent) increases in SCE and micronuclei were observed in mice at ≥ 10 ppm, and increased SCE and micronuclei were observed in rats inhaling ≥ 3 ppm and 1 ppm, respectively.⁽⁵⁷⁾ The Erexson data⁽⁵⁷⁾ are the lowest concentrations of inhaled benzene that have been reported to induce genotoxicity.

Neoplastic Transformation

Using morphologically transformed colonies as a marker benzene was considered mutagenic in Syrian hamster embryo (SHE) cells, but it was not considered mutagenic in cultured Balb/C 3T3 mouse fibroblasts, in Simian adenovirus-transformed SHE cells, and in Chinese hamster ovary (CHO) cells.⁽⁵⁸⁾ Benzene, hydroquinone, and para-benzoquinone were reported to alter gene expression in cultured Swiss mouse spleen lymphocytes, where hydroquinone and para-benzoquinone at 10–20 μM inhibited RNA synthesis 50 percent.⁽⁵⁹⁾ Inhibition of T-cell proliferation and reduced production of interleukin-2 (a T-cell growth factor) by 5 μM para-benzoquinone was suggested to account, in part, for benzene-induced aplastic anemia.⁽⁵⁹⁾

Human Cytogenicity

Forni *et al.*⁽⁶⁰⁾ found a significant increase in lymphocyte chromosome aberrations in two groups of workers with overt benzene intoxication as compared to age-matched controls. One group consisted of 25 individuals recovered from benzene hemopathy 1–18 years previous along with 4 additional workers currently suffering from acute benzene poisoning. The second group consisted of 34 workers in a rotogravure plant exposed at 125–532 ppm benzene in air from 1952 to 1953. Tough *et al.*^(61,62) found an increased incidence of chromosome aberrations in 38 workers inhaling 25–150 ppm benzene for 1–25 years compared to the incidence in the general human population. These individuals had been exposed to benzene until two to four years prior to the study.^(61,62) Watanabe *et al.*⁽⁶³⁾ found an increase in the frequency of SCE among nine females at six months after cessation of benzene exposure at 1–9 ppm for 1–20 years and among seven females exposed to benzene at 3–50 ppm for 2–12 years. Killian and Daniel⁽⁶⁴⁾ found a significant increase in chromosomal aberrations among workers exposed to average benzene levels below 10 ppm. Workers exposed to benzene (average, 56.6 months) had a doubling of chromosomal breaks and a threefold increase in rings and dicentric chromosomes. Almost twice as many benzene-exposed workers as controls exhibited both chromosome breaks and rings and dicentric chromosomes.⁽⁶⁴⁾

Picciano^(65,66) examined the Killian and Daniel⁽⁶⁴⁾ data and reported that 38 (73.1%) of 52 workers exposed to mean ambient benzene at less than 10 ppm had chromosome breaks as compared with 18 (40.9%) of 44 matched (unexposed) controls. When individuals with both chro-

mosome breaks and chromosome markers (rings, dicentric chromosomes) were compared, less than 3 percent of the nonexposed group showed genetic damage where 27 percent of the exposed workers were afflicted with chromosome aberrations ($p < 0.001$).

A number of reports suggests that benzene-induced human chromosome damage is site-specific. Ding *et al.*⁽⁶⁷⁾ reported a cytogenetic study of 21 patients (8 male and 13 female) with chronic benzene poisoning who had been exposed to unspecified benzene concentrations for 1–28 years (average, 6 years). At the time of cytogenetic analyses, all individuals had not been exposed for 5–20 years (average, 10 years), and all but one had recovered from clinical signs of benzene poisoning. Hypodiploid and hyperdiploid cells were increased significantly in the benzene-exposed patients, and chromosome deletions in the hypodiploid cells involved groups C, E, and G chromosomes and chromosome gains in the hyperdiploid cells involved groups C and E. Similar findings were also reported by Sasiadek and Jagielski⁽⁶⁸⁾ where chromosomal aberrations were detected more frequently in chromosomes 2 (Group A), 4 (Group B), and 6 and 9 (both are Group C). Sarto and associates⁽⁶⁹⁾ found an increase in chromosome aberrations among 22 workers inhaling 0.2–12.4 ppm benzene for 11.4 ± 7.0 years; a control population was matched for sex, age, smoking habits, and site of residence.

Pharmacokinetic/Metabolism Studies

Rusch *et al.*⁽⁷⁾ concluded that humans absorb approximately 46 percent of the benzene that is inhaled. Assuming a respiratory rate of 16 per minute and a tidal volume of 0.5 liters, approximately 7.5 μL benzene can be expected to be absorbed each hour through the lungs of a person inhaling air containing 10 ppm benzene.⁽⁷⁾

Benzene dermal absorption was 0.05 percent when neat liquid benzene was applied directly to a human forearm

at 0.0022 mg/cm² and allowed to dry,⁽⁷⁰⁾ and the flux of benzene through cultured human abdominal skin from air saturated with benzene at 31°C was 1.0 $\mu\text{L cm}^{-2}\text{hr}^{-1}$.⁽⁷¹⁾ Susten *et al.*⁽⁷²⁾ found that after dermal application of 5 $\mu\text{L}^{14}\text{C}$ -labeled benzene to intact skin of hairless mice, maximal skin radioactivity occurred at 1.5 min, and it remained "essentially unchanged for at least 2.5 hr." Permeability is, however, dependent upon presence of solvents. Blank and McAuliffe⁽⁷¹⁾ found the constants to be 111, 3.73, 2.4, and 1.4×10^{-3} $\mu\text{L cm}^{-2}\text{hr}^{-1}$, respectively, for water, hexadecane, isooctane, hexane, and gasoline. Based on *in vitro* percutaneous absorption and *in vivo* inhalation data, one example of calculated total benzene exposure used an adult working in ambient air containing 10 ppm benzene with 100 cm² skin surface in direct contact with gasoline containing 5 percent benzene. It was estimated that if the worker's entire skin surface was in contact with ambient air, the individual would absorb 7.5 μL benzene via inhalation in one hour, 7.0 μL from direct dermal contact with gasoline, and 1.5 μL from body surface exposure to ambient air.⁽⁷¹⁾

Sabourin *et al.*⁽⁷³⁾ investigated the absorption and elimination of benzene in F344/N rats, Sprague-Dawley rats, and B6C3F1 mice after an oral or intraperitoneal dose of 0.5–150 mg/kg. They reported that gastrointestinal absorption was essentially complete.

The toxicity of benzene has been attributed to its metabolites.⁽⁷⁴⁾ A major metabolite is phenol (Figure 1), generated by oxidation of benzene by the liver cytochrome microsomal system⁽⁷⁵⁾ via the reactive epoxide intermediate, benzene oxide. Results of physiologically based pharmacokinetic modeling of benzene metabolism found that mice metabolized a greater proportion of absorbed benzene to the hydroquinone conjugates and muconic acid than did rats.⁽⁷⁶⁾ Rats metabolized benzene primarily to the phenyl conjugates and to the phenyl mercapturic

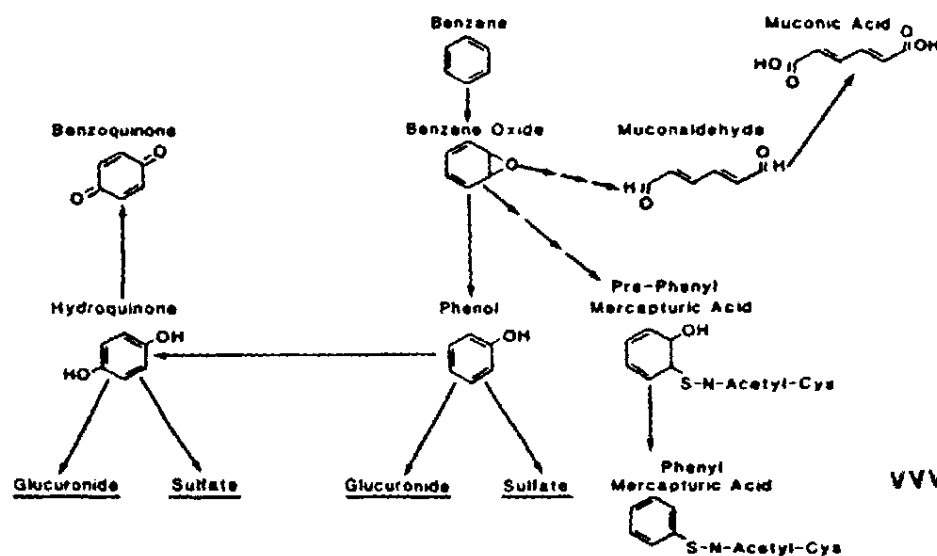


FIGURE 1. Major pathways of benzene metabolism. (Reproduced with permission from reference 76.)

acids.⁽⁷⁶⁾ Although bone marrow enzymes are not efficient for benzene metabolism, phenol can be metabolized in marrow via myeloperoxidase.⁽⁷⁷⁾ Benzene metabolism to phenol, formation of water-soluble phenyl glucuronide and sulfate conjugates, and conjugation with glutathione and urinary elimination of benzene as the phenylmercapturic acid are considered detoxication pathways. Microsome ring-opening reactions giving rise to the reactive muconialdehyde yield muconic acid, a pathway considered responsible for at least some aspects of benzene toxicity. Hydroxylation of phenol generates hydroquinone; dehydrogenation of benzene dihydrodiol generates catechol.^(78,79) Hydroquinone and catechol can accumulate in bone marrow and lymphoid tissues,⁽⁸⁰⁾ hydroquinone can oxidize spontaneously *in vitro* to para-benzoquinone under physiologic conditions.^(81,82) Catechol does not oxidize spontaneously under these conditions; however, it can be metabolized (presumably the cytochrome P-450 system) to 1,2,4-benzenetriol.⁽⁸³⁾ The toxicity of hydroquinone and 1,2,4-benzenetriol involves free radical formation via superoxides; covalent binding of the semiquinones to DNA, RNA, and other cellular components; and direct alkylation of sulfhydryl groups by para-benzoquinone or its derivatives. Hydroquinone and benzoquinone were the most toxic metabolites to cultured bone marrow stromal cells, where catechol and benzenetriol inhibited colony growth only at very high benzene doses to male B6C3F1 mice.⁽⁸⁰⁾ Injury to bone marrow stromal cells has been implicated as a precursor step to benzene hematotoxicity.⁽⁸⁰⁾ A recent symposium on benzene metabolism, toxicity, and carcinogenesis⁽⁸⁴⁾ provides an authoritative summary on benzene biotransformation and the implication for human health risk assessment.

Human Studies

As an acute poison, benzene produces narcotic effects comparable to those of toluene. Benzene is considered very toxic; probable human oral lethal dose would be between 50–500 mg/kg (1 tsp to 1 oz).⁽⁸⁵⁾ Human inhalation of approximately 20,000 ppm (2% in air) was fatal in 5–10 minutes.⁽⁸⁶⁾

Aksoy *et al.*^(87–89) studied 28,500 Turkish shoe and handbag production workers who inhaled an average of 150–210 ppm when benzene-containing adhesives were used and 15–30 ppm at other times. Peak benzene exposures varied between 210 and 640 ppm, and the duration of exposure was estimated to average 9.7 years. Of the 44 cases of pancytopenia, 23 (52%) experienced remission of the aplastic anemia, 14 (32%) died from complications of aplastic anemia or pancytopenia, and 6 (14%) later died from leukemia. Of 42 leukemia cases, 26 percent were preceded by a 6-month to 6-year period of pancytopenia prior to the onset of leukemia. Aksoy^(90,91) reported an update to the above cohort to the year 1983, wherein a total of 73 patients chronically exposed to benzene were examined. Fifty-one of the 73 had leukemia, 12 had malignant lymphoma, 4 had multiple myeloma, and 6 had

lung cancer. Among the 51 leukemic patients, 20 were afflicted with acute myeloblastic leukemia, 7 were considered preleukemic, 20 were diagnosed with acute erythroleukemia, 5 had acute myelomonocytic leukemia, and 1 was diagnosed as an acute undifferentiated leukemia. Thirteen of the 51 leukemic patients had suffered pancytopenia; the average duration of benzene exposure was 9.93 years.

Vigliani⁽⁹²⁾ studied groups of workers employed in rotogravure plants, shoe factories, and other industries where benzene was used as a solvent. Benzene concentrations in air near the rotogravure machines were 200–400 ppm, with peak values as high as 1500 ppm. Sixty-six cases of benzene hemopathy were observed, and of the 18 deaths in this group, 7 died of aplastic anemia and 11 died of leukemia. In a second group of workers where ambient benzene ranged from 25–600 ppm, 135 workers with benzene hemopathy were studied. Of the 135, 16 died (3 from aplastic anemia and 13 from leukemia).

Infante *et al.*⁽⁹³⁾ reviewed death certificates for a cohort of 748 white male workers who had been occupationally exposed to benzene from 1940–1949; exposures are not known precisely but ranged up to 100 ppm.⁽⁹⁴⁾ Others⁽⁹⁵⁾ cite reports that peak exposures may have been as high as 200–350 ppm. Vital status was followed up to 1973. A fivefold excess risk of all leukemias was reported, and a tenfold excess of deaths from myelogenous and monocytic leukemias was observed. In a follow-up through June 30, 1975, Rinsky *et al.*⁽⁹⁶⁾ reported 7 deaths from leukemia versus 1.25 expected (standardized mortality ratio [SMR] = observed no. deaths/expected no. deaths = 560). When compared by length of employment, there was a significant excess of leukemia observed among workers employed five or more years, but not among those employed less than five years. Two workers died from leukemia among the group employed less than five years compared to 1.02 expected (not statistically significant). Among those employed for five or more years, five died from leukemia compared to 0.23 expected (SMR = 2100). Short-term area samples measured between 1946 and 1976 indicated that most benzene levels were below 100 ppm and some were above 100 ppm.^(95,96) Rinsky *et al.*⁽⁹⁶⁾ cite documents indicating that these workers were required to wear respirators (efficiency not stated) when exposed (even momentarily) to concentrations greater than the TWA (ranging to a maximum allowable concentration of 100 ppm in 1941 to an 8-hour TWA of 10 ppm from 1969 on). For those individuals with more than ten years of employment, three leukemia deaths were observed as compared to 0.09 expected (SMR = 3300). Cumulative benzene exposure was calculated for each member of the benzene cohort in ppm-years, and the cohort follow-up was extended to 1982.⁽⁹⁷⁾ A total of 1165 white males with at least one ppm-day of cumulative benzene exposure (to December 31, 1965) were included in the cohort for a total of 31,612 person-years at risk. Fifteen deaths in this cohort were observed from lymphatic and hemopoietic cancers versus 6.6 expected (SMR = 227). Nine cases of leukemia were observed com-

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pared to 2.7 expected (SMR = 337), and four cases of multiple myeloma were observed compared to one expected (SMR = 409) [all cases statistically significant]. Rinsky *et al.*⁽⁹⁷⁾ determined that cumulative exposure to benzene (measured as ppm-years) was the most reliable predictor of death from benzene-induced leukemia. Increases in cumulative exposure were associated with marked progressive increases in the SMR for leukemia: among workers with less than 40 ppm-years cumulative exposure, the SMR = 109; with 40 to 199.99 ppm-years cumulative exposure, the SMR = 322; with 200 to 399.99 ppm-years cumulative exposure, the SMR = 1186; and with 400 or more ppm-years, the SMR = 6637. (The ppm-years were calculated as 40 years at 10 ppm average exposure/year = 400 ppm-years.) Seven of the nine leukemia deaths with multiple myeloma had less than 40 ppm-years of benzene exposure. Rinsky *et al.*⁽⁹⁷⁾ concluded that protection from benzene-induced leukemia increased exponentially with reductions in exposure time.

Yin *et al.*⁽⁹⁸⁾ conducted a retrospective cohort study of 28,460 workers exposed to 3–308 ppm benzene (with the majority exposed to 15–150 ppm) compared to a control cohort of 28,257 workers not known to be exposed to benzene. Thirty cases of leukemia were found in the exposed population compared to four such cases in the control. The benzene cohort experienced a leukemia mortality rate of 14 per 100,000 person-years, and the control population experienced a leukemia mortality rate of 2 per 100,000 person years (SMR = 5.74). In an additional study authored by Yin and associates,⁽⁹⁹⁾ ambient benzene concentrations for 508,818 workers averaged 5.6 ppm with 65 percent of the workplaces having less than 12 ppm and 1.3 percent having benzene levels greater than 308 ppm. Aplastic anemia occurred at 12.1 per 100,000 persons in this cohort and represented a 5.8-fold increase over that of the general population.

Ott *et al.*⁽¹⁰⁰⁾ carried out a mortality study of 594 white male workers exposed to benzene from 1940–1970. The Occupational Safety and Health Administration (OSHA)⁽¹⁰¹⁾ concluded that the Ott cohort was exposed to an average of 5 ppm for an average of nine years. Three cases of myelocytic leukemia (2 classified as acute) were found compared to 0.8 cases expected ($p < 0.047$). Bond *et al.*⁽¹⁰²⁾ extended the cohort definition for the Ott study to include those employees who worked for at least one month (1938–1978) and increased the observation follow-up to 1982, bringing the total persons studied to 956. Four deaths due to myelogenous leukemia were observed with 0.9 expected (SMR = 444).

Decoufle *et al.*⁽¹⁰³⁾ found a fourfold excess risk for lymphatic and hematopoietic cancers among oil refinery and chemical plant workers exposed to benzene. The exposures were very poorly documented, but they resulted primarily from plant fugitive emissions and perhaps accompanied by gross exposures from cleaning tools, hands, and clothing with liquid benzene. The historical cohort mortality study of 259 male employees found four deaths from lymphoreticular cancers compared to 1.1 expected

(SMR = 364), and three deaths due to leukemia where 0.4 were expected. The multiple myelomas observed here, taken together with previous reports of benzene-associated myeloma, prompted the suggestion that the pathogenesis of human multiple myeloma and chronic lymphatic leukemia may arise from damage to B-cell lineage.⁽¹⁰³⁾ Wong^(104,105) divided the benzene exposure for 4602 workers (minimum time of 6 months) into four categories: < 1 ppm; 1–10 ppm; 11–50 ppm; and 50 ppm, with peak exposures of < 25 ppm, 25–100 ppm, and > 100 ppm. He compared their mortality with that of 3074 employees from the same or similar plants who had no known occupational benzene exposure. When all lymphatic and hemopoietic cancers were considered, there was a significantly elevated risk ($p = 0.03$) for benzene-exposed white males when compared to unexposed workers. There was a significant concentration-dependent increase for all lymphohematopoietic cancers ($p = 0.02$), for leukemia ($p = 0.01$), with borderline significance ($p = 0.057$) for non-Hodgkin's lymphopoietic cancers. Prolonged cumulative exposures were judged more important for human benzene carcinogenicity than maximum peak exposures, and the authors^(104,105) concluded that there was a significant association between occupational benzene exposure and the occurrence of leukemia, all lymphopoietic cancers, and non-Hodgkin's lymphopoietic cancers.

A number of epidemiologic studies^(106,117) have considered the mortality and cancer incidence among petroleum and rubber workers. Most of these studies, however, failed to quantify the benzene exposures adequately, failed to determine whether the toxicity reported was indeed associated with benzene exposures, and were confounded by difficulties in confirming the validity of the diagnoses upon which the SMR and other risk estimates were made.

The latency period for benzene induction of human leukemia varies from 2 to 50 years. Aksoy *et al.*^(87–91) found that the induction period ranged from 6 to 14 years (median, 11 years). Vigliani⁽⁹²⁾ reported an induction period of 3 to 23 years (median, 9 years), and Rinsky⁽⁹⁶⁾ indicated a median latency of 12 years (2–22 years). The Shell Oil study⁽¹¹³⁾ indicated a latency of 17–54 years between the date of hire and date of death from leukemia. Yin⁽⁹⁸⁾ estimated the average latency time for benzene-induced leukemia as 11.4 years. The 1985 OSHA report⁽¹⁰¹⁾ concluded that 11 years was a reasonable estimate for the average duration of leukemia induction associated with occupational benzene exposure.

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Basis of the TLV

Although benzene has long been recognized as a myelotoxicant (e.g., more than 140 fatalities due to benzene poisoning were recorded in the open scientific literature prior to 1959), the carcinogenic activity of chronic exposure to relatively low ambient concentrations of benzene in workplace air was not recognized until the last ten years. Benzene is a human and rodent clastogen and carcinogen. Adverse health effects in animals exposed to benzene mir-

for those reported in humans, with exposure at 1 ppm benzene and above inducing measurable cytogenetic damage.⁽⁵⁷⁾ Women inhaling 1–9 ppm exhibited increased lymphocyte chromosome aberrations,⁽⁶³⁾ and significant elevations in chromosomal aberrations have been corroborated among workers inhaling benzene at mean concentrations less than 10 ppm.^(64–66)

Several quantitative human health risk assessments have been carried out in an attempt to define the concentrations of benzene in air that are associated with lifetime excess cancer risk,⁽²⁾ but these methods are problematic, particularly when attempting to extrapolate quantitative animal data to the human. Notable has been their failure to incorporate the differential metabolic disposition and known pharmacokinetic parameters for rodents⁽⁷⁶⁾ compared to human beings. The rodent carcinogenicity data support the designation of benzene as a known human carcinogen.

Theoretical estimates of excess cancer risk can be calculated using any of a variety of statistical models, including the linearized "multistage" (which does *not* describe biologic initiation/promotion phenomena), the one-hit, Weibull, logit, or probit models; however, there is no current understanding of the biochemical mechanisms involved in benzene-induced leukemia and other cancers to show that any one of these methods is any more accurate than another. Because of the different assumptions that must be made for use of the different models, the theoretical estimates of excess cancer risk that result can differ by orders of magnitude. White *et al.*⁽¹¹⁸⁾ used a linear, nonthreshold model to describe the benzene dose-response human carcinogenicity data and calculated that at 10 ppm benzene, 44–152 excess cases of leukemia per 1000 exposed workers would occur, and that at 1 ppm benzene, 5–16 such excess case would occur. The International Agency for Research on Cancer (IARC)⁽¹¹⁵⁾ used a similar approach and published theoretical excess cancer risk estimates of 14–140 excess cases per 1000 individuals exposed at 10 ppm, and 1.4–14 excess cases among 1000 individuals exposed at 1 ppm. Crump and Allen^(2,119) carried out quantitative analyses of the epidemiologic data gathered by Rinsky *et al.*^(96,97) Ott *et al.*⁽¹⁰⁰⁾ and Wong *et al.*^(104,105) After 45 years (working lifetime) exposure at 10 ppm benzene, Crump and Allen⁽¹¹⁹⁾ calculated 95 theoretical excess leukemia deaths per 1000 workers. Exposure at 1 ppm was calculated as associated with 10 theoretical excess leukemia deaths per 1000 workers. Although such estimates have been preferred in the legal arena,⁽²⁾ these methods remain the subjects of severe criticism.^(2,120,121)

Because of the acknowledged high quality of the epidemiologic data,⁽²⁾ direct inspection of these data can provide the basis for the benzene TLV. The Dow Chemical Company study⁽¹⁰⁰⁾ "demonstrates a significant fourfold increase in myelogenous leukemia for workers who had been exposed to average benzene concentrations of about 5 ppm for an average of about nine years" and "two out of the four individuals in the study who died from leukemia were characterized as having been exposed to average benzene levels below 2 ppm."⁽²⁾

The risk assessment for benzene and leukemia is based on the human data. Rinsky *et al.*⁽⁹⁷⁾ provided the most authoritative examination of the known odds of death from benzene-induced leukemia. For a worker exposed at an average daily benzene concentrations of 10 ppm for 45 years the odds of death from leukemia were 290 times that of an unexposed worker. For an individual inhaling 1 ppm for 45 years, the odds of benzene-induced leukemic death were 1.7 times that of an unexposed worker. For an individual inhaling 0.5 ppm for 45 years, the odds of benzene-induced leukemic death were 1.3 times that of an unexposed worker. Using these data, the odds of benzene-induced leukemic death at 0.1 ppm approach very nearly the odds of leukemic death for a worker who is not exposed to benzene. Accordingly, a TLV-TWA of 0.1 ppm benzene is recommended. A STEL is not recommended. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV-TWA even when the 8-hour TWA is within recommended limits. The recommended TLV of 0.1 ppm is less than the concentration associated with genetic damage in animals,⁽⁵⁷⁾ and it is less than the concentrations associated with genetic damage in human beings.⁽⁶³⁾ As calculations show that benzene dermal absorption can contribute substantially to the total absorbed benzene dose,⁽⁷¹⁾ the *skin* designation is appropriate.

BEI Indication

Biological monitoring for human benzene exposure at ambient concentrations less than 1 ppm can be most readily documented by determination of urinary S-phenylmercapturic acid (Figure 1).⁽¹²²⁾ The mercapturic acid conjugate is formed and excreted together with phenol, catechol, hydroquinone, and hydroxy hydroquinone. It is a urinary metabolite of high specificity for occupational benzene exposure giving reliable indication of exposures at the 0.1–0.15 ppm range, whereas urinary phenol is not reliable unless gross benzene exposure has occurred.⁽¹²²⁾

The lowest practical detection limit, in the absence of interfering substances, has been reported at concentrations at least as low as 0.1 ppm. In the presence of interfering vapors, the accuracy and reliability of workplace air monitoring at ambient benzene concentrations even above 1.0 ppm can be questioned.

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