
Critical Issues in Benzene Toxicity and Metabolism: the Effect of Interactions with Other Organic Chemicals on Risk Assessment

Michele A. Medinsky, Paul M. Schlosser, James A. Bond

Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina

Benzene, an important industrial solvent, is also present in unleaded gasoline and cigarette smoke. The hematotoxic effects of benzene are well documented and include aplastic anemia and pancytopenia. Some individuals exposed repeatedly to cytotoxic concentrations of benzene develop acute myeloblastic anemia. It has been hypothesized that metabolism of benzene is required for its toxicity, although administration of no single benzene metabolite duplicates the toxicity of benzene. Several investigators have demonstrated that a combination of metabolites (hydroquinone and phenol, for example) is necessary to duplicate the hematotoxic effect of benzene. Enzymes implicated in the metabolic activation of benzene and its metabolites include the cytochrome P450 monooxygenases and myeloperoxidase. Since benzene and its hydroxylated metabolites (phenol, hydroquinone, and catechol) are substrates for the same cytochrome P450 enzymes, competitive interactions among the metabolites are possible. *In vivo* data on metabolite formation by mice exposed to various benzene concentrations are consistent with competitive inhibition of phenol oxidation by benzene. Other organic molecules that are substrates for cytochrome P450 can inhibit the metabolism of benzene. For example, toluene has been shown to inhibit the oxidation of benzene in a noncompetitive manner. Enzyme inducers, such as ethanol, can alter the target tissue dosimetry of benzene metabolites by inducing enzymes responsible for oxidation reactions involved in benzene metabolism. The dosimetry of benzene and its metabolites in the target tissue, bone marrow, depends on the balance of activation processes, such as enzymatic oxidation, and deactivation processes, like conjugation and excretion. Biologically based dosimetry models that incorporate the important determinants of benzene flux, including interactions with other chemicals, will enable prediction of target tissue doses of benzene and metabolites at low exposure concentrations relevant for humans. —*Environ Health Perspect* 102(Suppl 9):119–124 (1994)

Key words: benzene, benzene-toluene interactions, benzene-ethanol interactions, phenol, hydroquinone, competitive inhibition

Introduction

Benzene is a ubiquitous industrial and environmental pollutant (1). It is present in automobile emissions, both evaporative and combusive, and has been detected in cigarette smoke (2,3). Benzene is also commonly used as an industrial solvent in the workplace. Because of its uses in industry and its presence in common human environments, exposure to benzene is most likely associated with co exposure to other volatile organic chemicals normally present in these environments.

Benzene is hematotoxic and carcinogenic at high concentrations. Epidemiology studies have shown that people develop blood dyscrasias, such as pancytopenia, aplastic anemia, and acute myelogenous leukemia following repeated exposure to high concentrations of benzene (4,5). In 2-

year carcinogenicity studies, rats and mice developed hematotoxicity and tumors in multiple organs, including preputial, Zymbal and Harderian glands, liver, and lymphomas (6). Benzene also induces chromosomal aberrations and aneuploidy in laboratory animals (7,8).

A number of studies have suggested that metabolism of benzene is a key in benzene-induced toxicity (9–11). The metabolism of benzene involves a series of oxidations of the benzene ring by the cytochrome P450 monooxygenases. One current hypothesis regarding the role of benzene metabolites in hematotoxicity suggests that following absorption into the blood and translocation to the liver, benzene is metabolized by cytochrome P4502E1 to its major metabolite, phenol (Figure 1) (12). Phenol can be further oxidized, most likely by the same cytochrome P450, to the polyhydroxylated metabolite, hydroquinone. Alternatively, phenol is sufficiently stable that it can directly partition into the blood and be distributed to other tissues. Similarly, hydroquinone produced from the oxidation of phenol can also partition into the blood. Both phenol and hydroquinone are substrates for phase 2 conjugating enzymes, such as the sulfotransferases and glucuronyl transferases.

Phenyl and hydroquinone sulfates and glucuronides are major metabolites excreted in the urine of animals exposed to benzene (13). Once in the blood, both phenol and hydroquinone can partition into the bone marrow. Eastmond et al. (10) demonstrated that the myeloperoxidase-dependent metabolism of hydroquinone to the reactive metabolite, benzoquinone, is stimulated by the presence of phenol. Benzoquinone is myelotoxic and clastogenic (14,15) and may be responsible for some of benzene's toxic effects.

The multiplicity of benzene's metabolic pathways provides opportunities for modulation of benzene metabolism, either by competition with other organic chemicals for the available enzyme sites, by induction or inhibition of the oxidation or conjugation enzymes, or by direct competition between benzene and its metabolites. Specific examples of these interactions and the net effect on the formation of benzene metabolites and resultant hematotoxicity or genotoxicity are discussed below.

Effect of Coexposure to Benzene and Toluene on Genotoxicity

Exposure to benzene causes genetic damage to bone marrow cells. Analysis of micronuclei in polychromatic erythro-

This article was presented at the IV European ISSX Meeting on Toxicological Evaluation of Chemical Interactions: Relevance of Social, Environmental, and Occupational Factors held 3–6 July 1992 in Bologna, Italy.

The authors gratefully acknowledge financial support, in part, through a grant from the American Petroleum Institute.

Address correspondence to Michele Medinsky, Chemical Industry Institute of Toxicology, P.O. Box 12137, Research Triangle Park, NC 27709. Telephone (919) 558-1250.

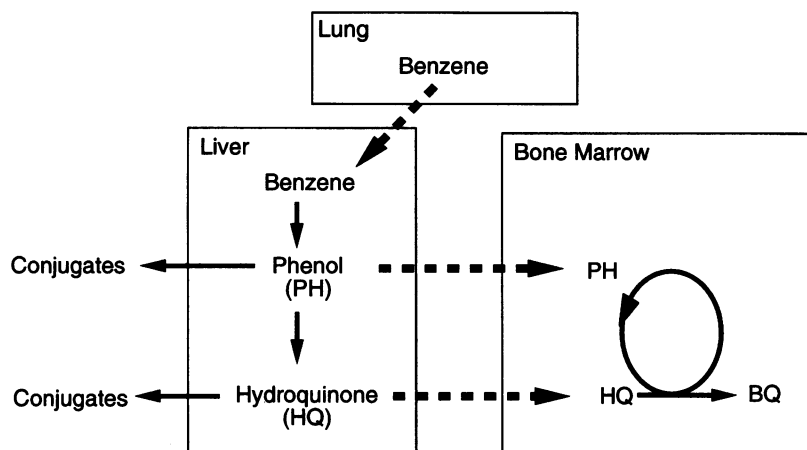


Figure 1. Proposed mechanisms for benzene-induced myelotoxicity. BQ, benzoquinone. Solid lines represent biochemical pathways for metabolism of benzene or its hydroxylated products (PH and HQ). Dashed lines represent transport of benzene or its metabolites in blood. From Smith et al. (12); reproduced with permission of *Environmental Health Perspectives*.

cytes provides information about recent bone marrow clastogenic or aneugenic damage (7). Micronuclei occur as a result of the exclusion of acentric chromosomal fragments or lagging chromosomes from daughter nuclei during cytokinesis. Gad-El-Karim et al. (16) investigated the genotoxicity of benzene in male and female CD-1 mice treated with two oral doses of benzene, or combinations of benzene and toluene, administered 24 hr apart. At 6 hr after the second dose, bone marrow from each femur was analyzed for micronuclei or metaphase chromosomes.

The toluene used in these studies was redistilled prior to use and was demonstrated to be entirely devoid of detectable clastogenic activity at a dose of 1720 mg/kg (Table 1). Benzene, however, was clastogenic to bone marrow cells and elevated numbers of micronucleated poly-

chromatic erythrocytes were detected in both male and female mice receiving 440 mg benzene/kg, compared to controls receiving only olive oil (Table 1). When both benzene (440 mg/kg) and toluene (1720 mg/kg) were coadministered, the clastogenic effect of benzene was reduced (Table 1). The protective effect of toluene was also seen following lower administered doses of toluene (860 mg/kg). The clastogenic effect of benzene did not seem to be as great for female mice compared to male mice. Because of the decreased response observed in females, Gad-El-Karim et al. were not able to demonstrate a statistically significant protective effect of coexposure to toluene.

Gad-El-Karim et al. (16) also examined the frequency of chromosomal aberrations in metaphase chromosomes after coexposure to benzene and toluene. Following benzene administration, various

types of chromosomal lesions were noted, including cells with at least one gap or break (damaged cells), cells with >10 aberrations/cell (severely damaged cells), and pulverized cells (those with >20 aberrations). As noted with the micronuclei, coadministration of toluene both at 1720 and at 860 mg/kg dose protected against the formation of chromosomal aberrations following benzene exposure in male mice. The investigators hypothesized that toluene inhibited the metabolism of benzene and that one or more metabolites of benzene were responsible for the myeloclastogenic effects.

Effect of Toluene Coexposure on Benzene Hematotoxicity

Exposure to benzene causes a decrease in the production of erythrocytes, leukocytes, and thrombocytes in bone marrow. The incorporation of ⁵⁹Fe into maturing red blood cells is used as a measure of erythropoiesis by many investigators. Toxic effects on the developing bone marrow cells reduces the percentage of iron that is incorporated into the cells compared to controls. Benzene inhibits the incorporation of ⁵⁹Fe into developing erythrocytes in a dose-dependent manner and inhibition becomes maximal 48 hours after the administration of a single dose of benzene. Andrews et al. (17) used radio-iron uptake to evaluate the effects of benzene on the hematopoietic system of mice. Intraperitoneal injections of benzene, toluene, or mixtures of benzene and toluene in corn oil were given to male Swiss albino (ICR) mice. The mice were injected with ⁵⁹Fe 48 hr later and, after an additional 24 hr, blood samples were assayed for ⁵⁹Fe. The percentage of iron taken up by the erythrocytes of treated mice was compared to control animals given only corn oil injections. Additional groups of mice were also given doses of benzene containing [³H]benzene to determine the extent of benzene metabolism with and without toluene coexposure.

When the ³H-benzene was administered to mice at two dose levels (440 and 880 mg/kg), a larger percentage of the dose appeared as benzene metabolites in the urine following the smaller dose compared to the larger dose (Table 2). Coadministration of toluene (1720 mg/kg) with either dose of benzene resulted in a reduction in the quantity of benzene metabolites measured in the urine to 30 or 40% of the response in the benzene-exposed group for the low and high doses, respectively. Coexposure to toluene also counteracted the benzene-induced reduction of red cell

Table 1. Effect of benzene or benzene-toluene mixtures on the formation of micronucleated-polychromatic erythrocytes in bone marrow of mice.^a

Chemical, mg/kg ^b	Sex	MPCE/1000 PCE ^c		
		Mean	σ_g	Range
Control (olive oil)	M	2.4	1.3	2-4
	F	1.4	1.7	0-3
Benzene (440)	M	16.7	2.4	7-74
	F	5.8	2.5	2-22
Toluene (1720)	M	1.9	1.4	1-3
	F	2.9	1.3	2-4
Benzene (440) + toluene (1720)	M	7.2	1.8	4-13
	F	4.2	1.2	3-5

^aFrom Gad-El-Karim et al. (16); reproduced with permission of *Mutation Research*. ^bChemical or control vehicle administered by oral gavage once followed by a second dose 24 hr later. ^cMicronucleated polychromatic erythrocytes per 1000 polychromatic erythrocytes in bone marrow of femurs taken from mice 6 hr after second oral dosing; data are sample geometric mean, geometric standard deviation, and range of four to five mice per group.

^{59}Fe uptake seen in mice given 440 or 880 mg/kg benzene alone (Table 2). While toluene itself did not affect radio-iron uptake, it completely prevented the depression in ^{59}Fe uptake produced by 440 mg/kg benzene and partially offset the greater depression induced by 880 mg/kg benzene. Thus, toluene both reduced benzene metabolism and protected against benzene-induced depression of ^{59}Fe utilization by red cells.

In separate studies Andrews et al. (17) also determined the effect of simultaneous exposure to benzene and toluene on the disposition of ^3H -benzene and its metabolites in target and nontarget tissues. Mice were injected subcutaneously with ^3H -benzene alone in olive oil or ^3H -benzene/toluene mixtures (880 mg/kg and 1720 mg/kg, respectively). Concentrations of benzene in various tissues (fat, liver, spleen, blood, or bone marrow) from mice given only benzene were very similar to those in which benzene was combined with toluene. A representative time course is shown in Figure 2 for benzene concentrations in blood and bone marrow. The similar benzene concentrations for the benzene-alone and benzene-toluene groups suggested that coadministration of toluene did not alter the disposition of benzene itself (Figure 2A,B). In contrast, the concentration of benzene metabolites in tissues of mice given benzene alone were much higher than those found when benzene was coadministered with toluene (Figure 2C,D). Coadministration of toluene did not delay the appearance of benzene metabolites in tissues but markedly reduced the concentration of metabolites found in each tissue for all time periods.

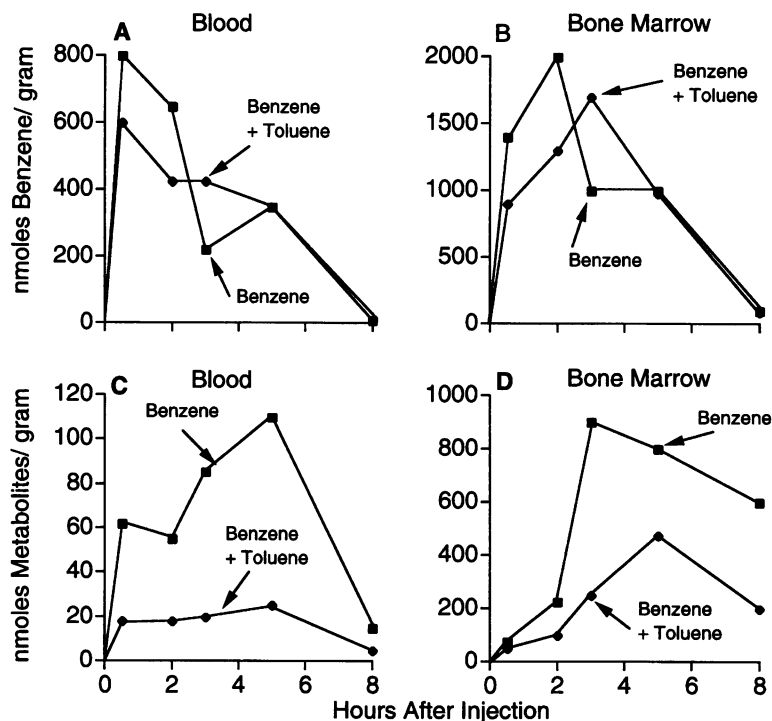


Figure 2. Effect of coadministration of toluene on the accumulation of $[^3\text{H}]$ benzene in blood (A) and bone marrow (B) or $[^3\text{H}]$ benzene metabolites in blood (C) bone marrow (D) of mice given subcutaneous injections of benzene (880 mg/kg) or benzene plus toluene (1720 mg/kg). From Andrews et al. (17); reproduced with permission of *Biochemical Pharmacology*.

In summary, the observations made in this study, that toluene reduced the level of urinary metabolites of benzene and also reduced the benzene-induced inhibition of erythrocyte ^{59}Fe uptake, suggest that metabolism of benzene is closely related to its hematotoxicity. Inhibition of benzene metabolism by toluene is supported by observations that toluene coexposure markedly reduced bone marrow concentrations of benzene metabolites but had no significant effect on the concentration of benzene in bone marrow. Thus, it seems

likely that toluene protects against benzene-induced inhibition of erythrocyte ^{59}Fe uptake by reducing the level of benzene metabolites in the bone marrow through suppression of benzene metabolism.

Effect of Coexposure to Benzene and Toluene on Benzene Metabolism in Humans

The previous study suggested that coexposure to large bolus doses of benzene and toluene can reduce both the amount of benzene that is metabolized and the resulting benzene-induced toxicity in animals. The direct relevance of these exposures in predicting risk for humans is uncertain since human exposures are typically by inhalation at much lower exposure concentrations for longer durations. However, there is some evidence to suggest that mutual metabolic suppression between benzene and toluene does occur in people exposed to concentrations of benzene and toluene in certain workplace environments.

Inoue et al. (18) examined both the exposure concentration during a workshift and the benzene metabolite concentrations in the shift-end urine of male Chinese workers exposed to either benzene, toluene, or a mixture of both chemicals. Additionally, these investigators looked at nonex-

Table 2. Effects of co exposure to toluene on benzene metabolism and red blood cell ^{59}Fe utilization in mice.^a

Chemical (mg/kg)	% Metabolized ^b	% ^{59}Fe Utilization ^c
Control (olive oil)	—	24.2 ± 4.7
Benzene (440)	35.8 ± 1.1	15.7 ± 4.8
Toluene (1720)	—	23.3 ± 4.6
Benzene (440) + toluene (860)	10.9 ± 7.5	22.0 ± 5.9
Control (olive oil)	—	18.4 ± 6.2
Benzene (880)	22.6 ± 5.7	4.9 ± 3.4
Toluene (1720)	—	15.8 ± 5.5
Benzene (880) + toluene (860)	9.9 ± 3.9	9.9 ± 4.5

^aFrom Andrews et al. (17); reproduced with permission of *Biochemical Pharmacology*. ^bPercent of the administered benzene excreted in the urine as benzene metabolites. Data expressed as mean percent ± standard deviation of 6 to 17 mice per group. ^cPercent uptake of a single injected dose of ^{59}Fe into circulating red blood cells. Data expressed as mean percent ± standard deviation of 17 to 28 mice per group.

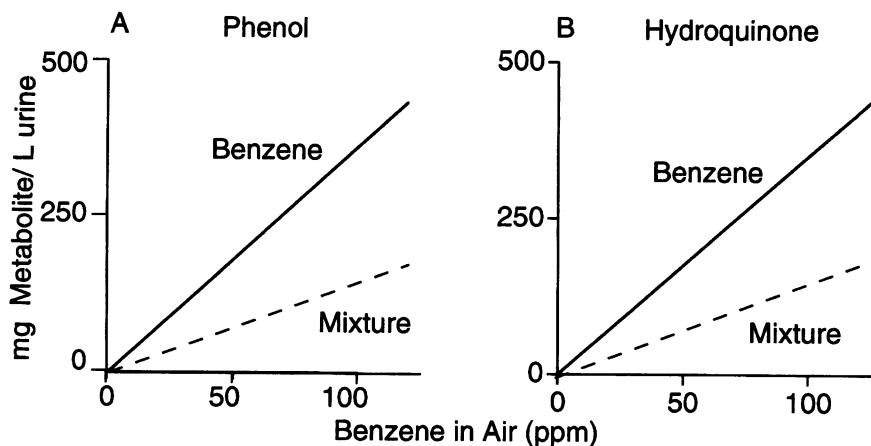


Figure 3. Comparison of urinary excretion of two benzene metabolites, phenol (A) and hydroquinone (B) in workers exposed to benzene alone or mixtures of benzene and toluene. The regression lines describe the relationship between benzene exposure (time-weighted average ppm) and metabolite excretion (mg metabolite/l urine) for benzene exposed (solid line) or toluene/benzene exposed (dashed line) groups. From Inoue et al. (18); reproduced with permission of *International Archives of Occupational and Environmental Health*.

posed male workers (control group). The time-weighted average (TWA) vapor concentration in the breathing zone of each worker was determined using a diffusive sampler that was placed on the lapel of the worker from the beginning of the workshift until the time of urine collection, which was at the end of the workday. The relationship between the TWA benzene concentration and the concentration of the individual metabolites (i.e., phenol, catechol, and hydroquinone from benzene, and hippuric acid and *o*-cresol from toluene) in urine was analyzed for each group by regression analysis. Comparison of the regression lines describing the relationship between exposure and metabolite levels indicated that urinary levels of phenol and

hydroquinone were lower in the group exposed to both toluene and benzene compared to the group exposed to benzene alone (Figure 3). The investigators hypothesized that biotransformation of benzene to its hydroxylated metabolites in people is suppressed by coexposure to toluene. These findings suggest that when workers are exposed to toluene in addition to benzene, the amounts of phenol and hydroquinone excreted in urine will be lower than those expected for exposure to only benzene at similar concentrations. These investigators also noted that the formation of hippuric acid and *o*-cresol from toluene were also reduced by coexposure to benzene; however, the extent of this reduction was not as

dramatic as the effect of toluene on benzene metabolism.

Sato and Nakajima (19) determined the concentrations of benzene and toluene in the blood of humans who inhaled either 25 ppm benzene or 100 ppm toluene or a mixture of benzene and toluene in controlled laboratory experiments for 2 hr (Figure 4). Their data indicated no difference in the disappearance rate of benzene or toluene from the blood after the end of exposure between the single or combination exposures. These studies with humans exposed to benzene or toluene by inhalation are consistent with the results of Andrews et al. (17) using experimental animals and bolus doses (Figure 2A). Both studies suggest that while the kinetics of benzene in the blood may be unchanged by coexposure to toluene the formation of the metabolites may be significantly altered by coexposure. The results of both human and animal studies suggest that analysis of metabolite levels may be a more sensitive indicator of interactive effects of benzene and other solvents than analysis of blood or tissue levels of benzene alone.

Alcohol/Benzene Interactions

Consumption of ethanol is an important social factor that might have a considerable impact on the pharmacokinetics and metabolism of benzene. Ethanol is known to induce CYP1B1, one of the cytochrome P450 enzymes responsible for benzene and phenol metabolism (20,21). Studies conducted by Nakajima et al. (22) have shown that pretreatment of rats with ethanol altered the *in vitro* metabolism of benzene and its major metabolite, phenol. Male Wistar rats were maintained for 3 weeks on a nutritionally adequate liquid diet (basal diet) or an ethanol diet (2 g of ethanol added to 80 ml of basal diet with a reduced sucrose content). At the end of the 3-week period, the animals were either sacrificed to obtain hepatic microsomes for assay of *in vitro* metabolic activity or were exposed to 500 ppm benzene for 2 hr to determine the clearance of benzene from blood. The *in vitro* experiments indicated that preexposure to ethanol increased the rate of metabolism of benzene by hepatic microsomes 6-fold and phenol metabolism by 4-fold. Clearance of benzene from the blood following a 2-hr exposure to 500 ppm was significantly faster in the ethanol-treated rats (Figure 5), indicating that for benzene the increased rates of metabolism noted *in vitro* were reflected in increased rates of benzene clearance *in vivo*.

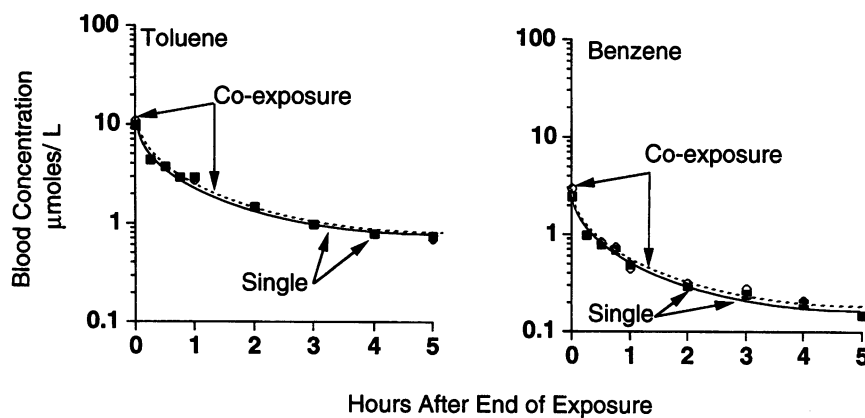


Figure 4. Clearance of benzene and toluene from blood of humans; concentrations of toluene (left) or benzene (right) measured in the blood from human volunteers exposed to 25 ppm benzene and 100 ppm toluene for 2 hr. Squares and solid lines represent blood concentrations of benzene or toluene determined when volunteers were exposed to the single chemical. Circles and dashed lines represent blood concentrations when volunteers were exposed to a mixture. Sato and Nakajima (19); reproduced with permission of *Toxicology and Applied Pharmacology*.

Presumably, the more rapid clearance of benzene from the blood in the pretreated animals was due to increased metabolism. Previously, Baarson et al. (23) determined that treatment of C57Bl/6J male mice with 5 or 15% ethanol in drinking water increased the hematotoxic effects following 13 weeks of exposure to 300 ppm benzene for 6 hr/day, 5 days/week. Anemia and lymphocytopenia in the peripheral blood and hypocellularity of the bone marrow and spleen were observed in both benzene and ethanol-benzene exposed groups, but were more severe in the ethanol-benzene-exposed groups. These studies are consistent with the results of Nakijima et al. (22) and suggest that ethanol administration, by inducing benzene and phenol metabolism in liver, results in a faster clearance of benzene from blood, and presumably higher concentrations of active metabolites in target tissues. These metabolites, in turn, result in an increased hematotoxicity.

Interactive Effects of Benzene and Its Metabolites

Previous studies in laboratory animals exposed to benzene by various routes of administration have demonstrated the dose-dependent metabolism of benzene (13). For example, in mice exposed to benzene by gavage, there is a decrease in the percent of the total amount of urinary metabolites eliminated as hydroquinone

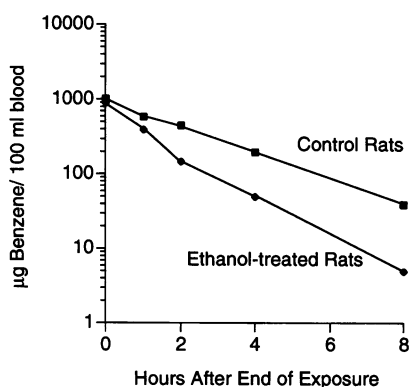


Figure 5. Decline in concentration of benzene in blood of rats after a 2-hr inhalation exposure to 500 ppm benzene. Rats were exposed to a basal diet or an ethanol diet (2 g of ethanol added to 80 ml of basal diet with a reduced sucrose content) for 3 weeks prior to exposure. From Nakijima et al. (22).

glucuronide and muconic acid as the benzene dose is increased from 1 mg/kg to 200 mg/kg (Figure 6). In contrast, the glucuronide, sulfate and glutathione conjugates of phenol represent an increasing percent of the total metabolites eliminated in urine with increasing dose. This dose-dependent metabolism of benzene can be explained in part by the interactive effects of benzene and its major metabolites. For example, it has been demonstrated that both benzene and phenol are substrates for the same cytochrome P450 enzyme, CYP1E1 (20). Thus, at high exposure concentrations benzene could competitively inhibit the further metabolism of phenol to hydroquinone. Presumably, concentrations of phenol in liver would be much less than concentrations of benzene. Studies by Rickert et al. (24) demonstrated that blood concentrations of benzene in male F-344 rats at the end of a 6-hr inhalation exposure to 500 ppm benzene were 10-fold higher than those of phenol. As indicated in Figure 1, benzene-derived phenol is also metabolized by the phase 2 conjugation enzymes. Therefore, it is likely that during exposures to high concentrations of benzene, the subsequent oxidation of phenol is inhibited by the higher hepatic concentrations of benzene. The free phenol formed would be removed by enzymatic

conjugation with UDP-glucuronic acid or phosphoadenosine-phosphosulfate (PAPS). This mechanism is consistent with the decrease in total hydroquinone conjugates and the increase in phenyl conjugates formed with exposure to increasing doses of benzene.

Conclusion

There have been a number of reports suggesting that in both laboratory animals and humans, benzene metabolism is modulated by coexposure or prior exposure to other organic chemicals. In addition, the metabolism of benzene itself appears to exhibit dose-dependent behavior, with the proportion of the metabolites formed changing considerably depending upon the dose of benzene administered. As a result, the net effect of inhibition of metabolism by coexposure or stimulation of metabolism by previous exposure to volatile organic chemicals can be quite complex. The use of biologically based mathematical models to quantitatively describe the disposition of benzene, its hydroxylated metabolites, and the ultimate concentrations of the active metabolites in the target tissue is probably the most fruitful approach for quantitatively assessing the risks of benzene exposure as a consequence of these numerous interactions.

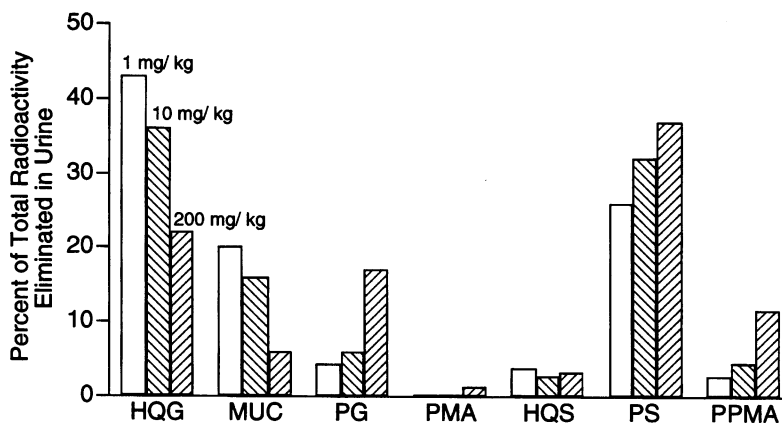


Figure 6. Urinary metabolites expressed as percent of the total metabolite eliminated in urine; Male B6C3F1 mice were given 1, 10, or 200 mg of ^{14}C benzene per kg of body weight by oral exposure. After exposure, animals were placed in metabolism cages. The urine was collected for 24 hr and the amount of each metabolite was determined by injecting a sample of the urine onto a high pressure liquid chromatograph and quantitating the radioactivity using liquid scintillation spectrometry. HQG, hydroquinone glucuronide; MUC, muconic acid; PG, phenyl glucuronide; PMA, phenyl mercapturic acid; HQS, hydroquinone sulfate; PS, phenyl sulfate; PPMA, prephenyl mercapturic acid. Sabourin et al. (13); reproduced with permission of *Toxicology and Applied Pharmacology*.

REFERENCES

1. Runion HE, Scott LM. Benzene exposure in the United States 1978–1983: an overview. *Am J Ind Med* 7:385–393 (1985).
2. Wallace L. Major sources of exposure to benzene and other volatile organic chemicals. *Risk Anal* 10(1):59–64 (1990).
3. Wallace LA, Pellizzari ED. Personal air exposures and breath concentrations of benzene and other volatile hydrocarbons for smokers and non-smokers. *Toxicol Lett* 35:113–116 (1986).
4. Goldstein BD. Hematotoxicity in humans. *J Toxicol Environ Health Suppl* 2:69–105 (1977).
5. Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and leukemia, and epidemiological risk assessment. *N Engl J Med* 316:1044–1050 (1987).
6. Huff JE, Haseman JK, DeMarini DM, Eustis S, Maronpot RR, Peters AC, Persing RL, Chrisp CE, Jacobs AC. Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F1 mice. *Environ Health Perspect* 82:125–163 (1989).
7. Tice RR, Ivett JL. Cytogenetic analysis of bone marrow damage. In: *Toxicology of the Blood and Bone Marrow* (Irons RD, ed). New York: Raven Press, 1985;119–140.
8. Au WW, Ramanujam VMS, Ward JB Jr, Legator MS. Chromosome aberrations in lymphocytes of mice after subacute low-level inhalation exposure to benzene. *Mutat Res* 260:219–224 (1991).
9. Irons RD. Quinones as toxic metabolites of benzene. *J Toxicol Environ Health* 16:673–678 (1985).
10. Eastmond DA, Smith MT, Irons RD. An interaction of benzene metabolites reproduces the myelotoxicity observed with benzene exposure. *Toxicol Appl Pharmacol* 91:85–95 (1987).
11. Barale R, Marrazzini A, Betti C, Vangelisti V, Loprieno N, Barrai I. Genotoxicity of two metabolites of benzene: phenol and hydroquinone show strong synergistic effects *in vivo*. *Mutat Res* 244:15–20 (1990).
12. Smith MT, Yager JW, Steinmetz KL, Eastmond DA. Peroxidase-dependent metabolism of benzene's phenolic metabolites and its potential role in benzene toxicity and carcinogenicity. *Environ Health Perspect* 82:23–29 (1989).
13. Sabourin J, Bechtold WE, Griffith WC, Birnbaum LS, Lucier G, Henderson RF. Effect of exposure concentration, exposure rate, and route of administration on metabolism of benzene by F344 rats and B6C3F1 mice. *Toxicol Appl Pharmacol* 99:421–444 (1989).
14. Snyder R, Dimitriadis E, Guy R, Hu P, Cooper K, Bauer H, Witz G, Goldstein BD. Studies on the mechanism of benzene toxicity. *Environ Health Perspect* 82:31–35 (1989).
15. Erexson GL, Wilmer JL, Kligerman AD. Sister chromatid exchange induction in human lymphocytes exposed to benzene and its metabolites *in vitro*. *Cancer Res* 45:2471–2477 (1985).
16. Gad-El-Karim MM, Harper BL, Legator MS. Modifications in the myeloclastogenic effect of benzene in mice with toluene, phenobarbital, 3-methylcholanthrene, Aroclor 1254 and SKF-525A. *Mutat Res* 135:225–243 (1984).
17. Andrews LS, Lee EW, Witmer CM, Kocsis JJ, Snyder R. Effects of toluene on the metabolism, disposition and hemopoietic toxicity of [³H]benzene. *Biochem Pharmacol* 26:293–300 (1977).
18. Inoue O, Seiji K, Watanabe T, Kasahara M, Nakatsuka H, Yin S, Li G, Cai S, Jin C, Ikeda M. Mutual metabolic suppression between benzene and toluene in man *Int Arch Occup Environ Health* 60:15–20 (1988).
19. Sato A, Nakajima T. Dose-dependent metabolic interaction between benzene and toluene *in vivo* and *in vitro*. *Toxicol Appl Pharmacol* 48:249–256 (1979).
20. Koop DR, Laethem CL, Schnier GG. Identification of ethanol-inducible P450 isozyme 3a (P450IIE1) as a benzene and phenol hydroxylase. *Toxicol Appl Pharmacol* 98:278–288 (1989).
21. Guengerich FP, Kim D-H, Iwasaki M. Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. *Chem Res Toxicol* 4:168–179 (1991).
22. Nakajima T, Okuyama S, Yonekura I, Sato A. Effects of ethanol and phenobarbital administration on the metabolism and toxicity of benzene. *Chem Biol Interact* 55:23–38 (1985).
23. Baarson KA, Snyder CA, Green JD, Sellakumar A, Goldstein BD, Albert RE. The hematotoxic effects of inhaled benzene on peripheral blood, bone marrow, and spleen cells are increased by ingested ethanol. *Toxicol Appl Pharmacol* 64:393–404 (1982).
24. Rickert DE, Baker TS, Bus JS, Barrow CS, Irons RD. Benzene disposition in the rat after exposure by inhalation. *Toxicol Appl Pharmacol* 49:417–423 (1979).