Investigation of the DNA Adducts Formed in B6C3F1 Mice Treated with Benzene: Implications for Molecular Dosimetry

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We have investigated the formation of DNA adducts in the bone marrow and white blood cells of male B6C3F1 mice treated with benzene using P1-enhanced 32P-postlabeling. No adducts were detected in the bone marrow of controls or mice treated with various doses of benzene once a day. After twice-daily treatment for 1 to 7 days with benzene, 440 mg/kg, one major (no.1) and up to two minor DNA adducts were detected in both the bone marrow and white blood cells. The relative adduct levels in these cells ranged from 0.06 to 1.46 x 10^-7. A significant correlation (r^2 = 0.95) between levels of adducts in bone marrow and white blood cells was observed. After a 7-day treatment with benzene, 440 mg/kg twice a day, the number of cells per femur decreased from 1.6 x 10^7 to 0.85 x 10^7, indicating myelotoxicity. In contrast, administration of benzene once a day produced only a small decrease in bone marrow cellularity. The observed induction of toxicity in bone marrow was paralleled by formation of DNA adducts. In vitro treatment of bone marrow with hydroquinone (HQ) for 24 hr produced the same DNA adducts as found after treatment of mice with benzene, suggesting that HQ is the principal metabolite of benzene leading to DNA adduct formation in vivo. Using 32P-postlabeling the principal DNA adduct formed in vivo was compared with N2-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate. The results of this comparison demonstrates that the DNA adduct formed in vivo co-chromatographs with N2-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate. These studies indicate that metabolic activation of benzene leads to the formation of DNA adducts in bone marrow and white blood cells and suggest that measurement of DNA adducts in white blood cells may be an indicator of biological effect following benzene exposure. — Environ Health Perspect 104(Suppl 6):1189–1193 (1996)

Key words: benzene, hydroquinone, leukemia, myelotoxicity, DNA adducts, exposure, molecular dosimetry, peroxidase activation

Introduction

Benzene is widely used in the chemical industry as an intermediate in the production of other agents and as a fuel additive; it is also found in automobile exhaust and cigarette smoke (1). Thus, human exposure to benzene occurs from a variety of sources (1). Concern regarding this compound arises from evidence that acute exposure to benzene is leukemogenic in humans (2,3).

After absorption, benzene is initially metabolized in the liver by cytochrome 2E1 (4–7). Results from microsomal activation systems and in vitro pharmacokinetic studies have shown that the principal metabolites of benzene are phenol, hydroquinone (HQ), muconaldehyde, and catechol (CAT) (8–10). HQ and CAT accumulate in the bone marrow (11,12), where they are further activated to exert their myelotoxic effects (6). Evidence for further activation of these metabolites by peroxidases (13–15) and prostaglandin H-synthase (16) has been presented.

Our studies of the activation of HQ, CAT, and 1,2,4-benzenetriol (BT) to form DNA adducts in HL-60 cells, mouse bone marrow macrophages, and human bone marrow (17–19) have shown a good correlation between cytotoxicity and the level of DNA adducts formed by the individual metabolites and between cellular peroxidase activity and DNA adduct formation after treatment with HQ (19). In contrast to these in vitro findings, evidence for the formation of DNA adducts in animals treated with benzene has been contradictory. Dose-dependent binding of radiolabeled benzene to DNA, RNA, and protein in various tissues of mice and rats has been reported (20–22). 32P-Postlabeling studies by Bauer et al. (23) have demonstrated DNA adduct formation in the liver of rabbits treated with benzene; however, Reddy et al. (24–26) were unable to detect the formation of DNA adducts in various tissues of either Sprague-Dawley rats or B6C3F1 mice administered benzene or its hydroxylated metabolites.

The purpose of the present study was to investigate the formation of DNA adducts and myelotoxicity in the bone marrow and white blood cells of B6C3F1 mice treated with benzene.

Results

DNA Adduct Formation in Vivo

Male B6C3F1 mice were given injections of benzene (99.9%; Aldrich Chemical Company, Milwaukee, WI) dissolved in corn oil (25–880 mg/kg) either once a day for 1 to 14 days or twice a day by ip injection at 8-hr intervals for 1 to 7 days (27). Controls received an equal volume of corn oil. Following treatment, the animals were anesthetized and blood and bone marrow were collected. The levels of DNA adducts in these tissues were investigated using P1-enhanced 32P-postlabeling (17–19,27). The presence of DNA adducts was very dependent upon the benzene treatment schedule. No DNA adducts were found in the bone marrow of mice treated once a day with benzene (Table 1; Figure 1A) or in controls (Figure 1B). Twice-daily treatment with benzene, 440 mg/kg, for one day produced a single DNA adduct (Figure 1C) with a relative adduct level of 0.06 x 10^-7 (Table 1). When this treatment was extended to 3 days, one major adduct and two minor adducts were detected in the bone marrow of treated mice (Figure 1D). The relative adduct level produced by this treatment procedure was 0.58 x 10^-7 and the distribution of the adducts was 76, 12, and 12% for...
### Table 1. Adduct levels in bone marrow of mice treated with various doses of benzene.

| Benzene dose, mg/kg | Treatment schedule, no. doses/no. days | Adduct level, $\times 10^{-7}$ | Distribution, % |
|---------------------|----------------------------------------|-------------------------------|-----------------|
| 25                  | 1/7                                    | ND                           |                 |
| 25                  | 1/14                                   | ND                           |                 |
| 50                  | 1 for 7 days                           | ND                           |                 |
| 50                  | 1/14                                   | ND                           |                 |
| 440                 | 1/1                                    | 0.13 ± 0.02                  | 100             |
| 440                 | 2/1                                    | 0.22 ± 0.09                  | 75, 8.9, 16.4   |
| 440                 | 2/3                                    | 0.58 ± 0.08                  | 76.5, 11.9, 11.6|
| 440                 | 2/5                                    | 0.89 ± 0.16                  | 74.9, 14.7, 11.1|
| 440                 | 2/7                                    | 1.46 ± 0.26                  | 69.4, 17.2, 13.4|
| 880                 | 1/3                                    | ND                           |                 |
| 100                 | 2/3                                    | 0.13 ± 0.02                  | 100             |
| 250                 | 2/3                                    | 0.22 ± 0.09                  | 75, 8.9, 16.4   |
| 440                 | 2/1                                    | 0.06 ± 0.02                  | 100             |
| 440                 | 2/3                                    | 0.58 ± 0.08                  | 76.5, 11.9, 11.6|
| 440                 | 2/5                                    | 0.89 ± 0.16                  | 74.9, 14.7, 11.1|
| 440                 | 2/7                                    | 1.46 ± 0.26                  | 69.4, 17.2, 13.4|

ND, adducts not detected. *Each value is the mean ± SD of 5 to 11 experiments.

With twice-daily treatment the formation of DNA adducts by benzene was both dose and time dependent (Table 1).

In parallel studies the formation of DNA adducts in white blood cells of B6C3F1 mice after administration of benzene was investigated. Twice-a-day treatment with 440 mg/kg of benzene for 3 days resulted in the formation of the same DNA adduct pattern as observed in bone marrow of the treated animals (Figure 2).

The relative adduct level produced by this treatment was $0.73 \times 10^{-7}$. Similar to the results with bone marrow, the levels of DNA adducts in the white blood cells were dependent on both dose and length of treatment time with benzene and were significantly correlated with the levels of DNA adducts in the bone marrow ($r^2 = 0.97$, $p < 0.001$) (G Lévy, unpublished results).

**Effects on Bone Marrow Cellularity**

Once-daily administration of benzene, 25 or 50 mg/kg, did not affect bone marrow cellularity; administration of benzene at higher concentrations (440 or 880 mg/kg) for up to 3 days produced a small decrease in bone marrow cellularity (Table 2). Twice-daily treatment with benzene, 440 mg/kg, for 1, 3, 5, and 7 days resulted in a statistically significant decrease in bone marrow cellularity for each treatment time. The number of cells per femur decreased from $1.59 \times 10^7$ in controls to $0.84 \times 10^7$ after 7 days of treatment (Table 2).

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**Figure 1.** Detection of benzene–DNA adducts in the bone marrow of B6C3F1 mice treated ip with various doses of benzene. (A) 3 days of treatment with benzene, 440 mg, once a day; (B) vehicle-treated mice (controls); (C) 1 day of treatment with benzene, 440 mg/kg, twice a day; (D) 3 days of treatment with 440 mg/kg of benzene twice a day. The autoradiograms were exposed at $-70^\circ$C for 14 hr.

**Figure 2.** Detection of benzene–DNA adducts formed in white blood cells of B6C3F1 mice following twice-daily ip treatment with 440 mg/kg benzene for 3 days. Films were exposed at $-70^\circ$C for 24 hr.
Table 2. Cellularity of mouse bone marrow treated with benzene.\(^a\)

| Benzene dose, mg/kg | Dose/day | Days of treatment | Bone marrow cells/femur, \(\times 10^7\) |
|---------------------|----------|-------------------|----------------------------------|
| Control             | —        | —                 | 1.59 ± 0.09                       |
| 25                  | 1        | 7                 | 1.5 (1)                           |
| 25                  | 1        | 14                | 1.45 (1)                          |
| 50                  | 1        | 7                 | 1.45 (1)                          |
| 50                  | 1        | 14                | 1.43 (1)                          |
| 440                 | 1        | 1                 | 1.47 ± 0.05 (3)                   |
| 440                 | 1        | 3                 | 1.45 (2)                          |
| 880                 | 1        | 1                 | 1.45 ± 0.04 (3)                   |
| 880                 | 1        | 3                 | 1.45 (2)                          |
| 440                 | 2        | 1                 | 1.48 ± 0.06\(^b\)                 |
| 440                 | 2        | 3                 | 1.13 ± 0.06\(^c\)                 |
| 440                 | 2        | 5                 | 1.05 ± 0.07\(^c\)                 |
| 440                 | 2        | 7                 | 0.84 ± 0.06\(^d\)                 |

\(^a\)Values in parentheses are number of determinations; all other values represent the mean ± SD of six to eight analyses. \(^p<0.05\) versus control. \(^p<0.001\) versus control.

*In Vitro* Studies of Adduct Formation

*In vitro* treatment of mouse bone marrow with 250 \(\mu\)M of HQ for 24 hr produced three DNA adducts (Figure 3A). The average relative adduct level was \(1 \times 10^{-7}\), and the distribution of the adducts was 40, 37, and 22 for adducts 1, 2, and 3, respectively. Co-chromatography experiments showed that these adducts were the same as those formed after *in vivo* exposure to benzene (Figure 3B).

**Structure of DNA Adduct Formed in Vitro**

Previous studies have investigated the DNA adducts formed by the reaction of \(p\)-benzoquinone (BQ) with purified DNA. Three DNA adducts were detected by \(^{32}P\)-postlabeling (17,28,29). Structural analysis and \(^{32}P\)-postlabeling of the isolated products allowed identification of the DNA adducts as \(3'\)-hydroxy)-3,\(N^4\)-benzetheno-2'-deoxyguanosine-3'-phosphate (no. 2), \(3'\)-hydroxy)-1,\(N^6\)-benzetheno-2'-deoxyadenosine-3'-phosphate (no. 3), and \(3'\)-hydroxy)-1,\(N^2\)-benzetheno-2'-deoxyguanosine-3'-phosphate (no. 1) (17,28,29). However, comparison by co-chromatography of these identified DNA adducts with the DNA adduct formed in HL-60 cells treated with either BQ or HQ, demonstrated that the cellular DNA adducts were different from the adducts formed in purified DNA (17). From the reaction of guanosine-3'-phosphate with BQ at pH 1, we have isolated a product corresponding to \(N^2\)-(4-hydroxyphenyl)guanosine-3'-phosphate (17). We have prepared \(N^2\)-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate (30) and analyzed it by \(^{32}P\)-postlabeling (Figure 4A). DNA isolated from the bone marrow of benzene-treated mice was postlabeled and the adducts were resolved on PEI-cellulose sheets (J.T. Baker Inc., Phillipsburg, NJ) and located by autoradiography. DNA adduct 1 was eluted from the PEI-cellulose sheets. Similar procedures were applied to \(^{32}P\)-postlabeled \(N^2\)-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate. Rechromatography experiments to compare the DNA adducts showed that DNA adduct 1 formed in the bone marrow of benzene-treated mice had the same chromatographic mobility as \(N^2\)-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate (Figure 4B).

![Figure 3](image-url)  
Figure 3. (A) Detection of DNA adducts in bone marrow of B6C3F1 mice treated in *in vitro* with 250 \(\mu\)M HQ for 24 hr; (B) co-chromatography of DNA adducts detected in the bone marrow of mice treated in *in vitro* with 250 \(\mu\)M HQ for 24 hr with the DNA adducts detected in the bone marrow of mice treated for 440 mg/kg of benzene twice a day for 3 days.

![Figure 4](image-url)  
Figure 4. (A) Autoradiogram of \(^{32}P\)-postlabeling of \(N^2\)-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate; (B) rechromatography analysis of \(N^2\)-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate with adduct 1 formed in B6C3F1 mice treated twice a day with 440 mg/kg of benzene for 3 days: Lane 1, DNA adduct 1; lane 2, 1:1 mixture of DNA adduct 1 and \(N^2\)-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate; lane 3, \(N^2\)-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate. The exposure times for A and B were 10 min at room temperature and overnight at ~70°C, respectively.
Conclusion
Evidence for the formation of DNA adducts in vivo following benzene administration has been contradictory. In our investigations we have shown that treatment of B6C3F1 mice with benzene results in the formation of DNA adducts in the bone marrow and white blood cells as detected by 32P-postlabeling. Adduct formation was dependent on both the dose and duration of treatment. Linear increases in DNA adduct formation were observed after treatment of B6C3F1 mice with 100 to 440 mg/kg of benzene twice a day. These results are in agreement with the findings of McDonald (31), who also demonstrated linear increases in protein adduct formation in the blood and bone marrow of mice treated with benzene.

The formation of DNA adducts was very schedule dependent. Once-daily administration of benzene did not lead to the formation of DNA adducts; however, adducts were readily detectable after twice-daily administration of benzene. In similar experiments, Reddy et al. (26) did not detect DNA adduct formation in bone marrow of B6C3F1 mice after single-dose administration of benzene. In contrast to our results, the binding of radiolabeled benzene to DNA in various rat tissues after a single treatment has been reported by several laboratories (20–22); however, in these studies the formation of a specific DNA adduct has not been demonstrated. The biological mechanisms responsible for the schedule dependency of DNA adduct formation are unclear. Previous studies have shown that the benzene metabolites HQ, CAT, and 1,2,4-benzenetriol can interact synergistically to produce increased levels of DNA adducts (18). The administration of benzene twice a day may allow this process to occur.

Once-daily treatment with benzene produced only a small decrease in bone marrow cellularity, whereas twice-daily treatment reduced cellularity by 50%. Comparison of the dose-dependent formation of DNA adducts in white blood cells and bone marrow with that of the loss in bone marrow cellularity showed an extremely good correlation ($r^2 = 0.99, p < 0.001$) between these end points. Although these results would indicate that measurement of DNA adducts in white blood cells may be useful as a dosimeter of benzene exposure, they have to be considered together with our observation that no DNA adducts were detected after once-a-day administration of benzene. These data taken together suggest that the formation of DNA adducts in white blood cells may be a better indicator of a biological effect than a molecular dosimeter of benzene exposure.

In addition to DNA adduct formation, the formation of oxidative base damage as measured by 8-hydroxy-2'-deoxyguanosine has been detected in the bone marrow of mice treated in vivo with benzene (32) and following in vitro activation of the hydroxylated benzene metabolites (QP Ye, unpublished results). The contribution of oxidative base damage and DNA adducts to the carcinogenic and leukemogenic effect of benzene remains to be defined. However, it is possible that both of these forms of DNA damage contribute to the induction of mutations and chromosomal breakage and rearrangements observed after benzene administration (33).

In vitro treatment of mouse bone marrow with HQ resulted in a DNA adduct pattern similar to that observed in the bone marrow after in vivo treatment with benzene. Previous studies have shown that adduct 1 was the same in purified mouse bone marrow macrophages and human bone marrow treated with HQ (19). These results suggest that HQ is the principal metabolite of benzene leading to DNA adduct formation in bone marrow. Several lines of evidence suggest that peroxidase enzymes in bone marrow activate HQ to form the DNA adducts detected. In vitro, benzene metabolites can serve as releasing cosubstrates for peroxidase enzymes (13–15), and incubation of HQ with myeloperoxidase, H2O2, and purified DNA results in adduct formation (D Pathak, unpublished result). In addition, the level of DNA adduct formation in cells treated with HQ correlates positively with the levels of cellular peroxidase activity (19). These results support the general model of peroxidase activation of HQ to form DNA adducts (19,34).

The structure of the DNA adduct formed in bone marrow following benzene administration was investigated. Previous studies have compared the DNA adduct formed in HL-60 cells treated with HQ with the DNA adducts formed by reaction of HQ with DNA and found that the DNA adducts formed in HL-60 cells did not correspond to the benzetheno-DNA adducts (17,34). In the present study we have found that the DNA adduct formed in vivo after benzene administration co-chromatographed with $N^2$-(4-hydroxyphenyl)-2'-deoxyguanosine-3'-phosphate. Further studies are required to confirm the structural identification of this DNA adduct.

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