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POINTS OF VIEW

Mechanistic data indicate that 1,3-butadiene is a human carcinogen

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A review of the epidemiological and mechanistic data on 1,3-butadiene indicates that this chemical is a human carcinogen for which the mouse is an appropriate model for assessing human cancer risk. Butadiene is carcinogenic at multiple organ sites in laboratory animals, including the induction of lymphomas in mice, while epidemiological studies have consistently found associations between occupational exposure to butadiene and increased mortality from lymphatic and hematopoietic cancers. Activated oncogenes and inactivated tumor suppressor genes in butadiene-induced tumors in mice are analogous to genetic alterations frequently observed in human cancers. Butadiene is metabolized to mutagenic and carcinogenic epoxides in all mammalian species studied, including humans. These metabolites form N7-alkylguanine adducts which have been detected in liver DNA of mice exposed to butadiene and in urine of exposed workers. Increases in *hprt* mutations were observed in lymphocytes from mice exposed to butadiene and in occupationally exposed humans. The mutational spectra for butadiene and its epoxide metabolites at the *hprt* locus in mouse lymphocytes are similar to the mutational spectrum of ethylene oxide; all of these chemicals exhibit a high percentage of frameshift mutations. Ethylene oxide, an alkylating agent that also forms an N7-alkylguanine adduct, was recently classified by the International Agency for Research on Cancer as a human carcinogen. Based on these data, we suggest that cancer induction by ethylene oxide and butadiene involve similar molecular mechanisms.

Introduction

1,3-Butadiene, a colorless gas (boiling point: −4.4°C), is used largely in the manufacture of synthetic rubber (e.g., styrene-butadiene rubber [SBR] and polybutadiene rubber) and thermoplastic resins (e.g., acrylonitrile-butadiene-styrene). Butadiene, with an annual production volume of approximately 1.5 million tons, ranks twentieth in amount among organic chemicals produced in the United States. Worldwide production of butadiene is approximately 6 million tons per year.

In addition to industrial sources, butadiene has been identified in cigarette smoke, automobile exhaust, and gasoline formulations. Incomplete combustion from mobile sources represents the largest source of butadiene emission. Consequently, low levels of butadiene (0.5–10 p.p.b.) have been detected in ambient air in urban locations.

The finding that inhaled butadiene is carcinogenic at multiple sites in rats (1) and mice (2, 3), even at concentrations as low as 6.25 p.p.m., raises serious public health concerns of human risk associated with exposure to this chemical. Differences in the sites of tumor induction in rats and mice and the magnitude of response between these two species have raised questions over which animal model is more appropriate for assessing human risk. The purpose of this paper is to examine epidemiological data and mechanistic data on butadiene that relate to the metabolism, mutagenicity and potential carcinogenicity of this chemical in humans. Based on this review, we believe there are sufficient data to support the conclusion that 1,3-butadiene is a human carcinogen and that the mouse is an appropriate model for human risk assessment.

Human exposure

Surveys of industries where butadiene is produced and utilized were conducted by NIOSH in the mid 1980s (4). These studies indicated that occupational exposures to butadiene in most process areas were at that time generally < 10 p.p.m. weighted over an eight hour workday; however, excursions in certain job categories were as high as 370 p.p.m. Exposures to butadiene are not homogeneous within specific work areas in the monomer or polymer production industries; thus, it is not unusual to find individual exposures to butadiene varying by several orders of magnitude in certain work areas. The production of butadiene is highly dependent on the demand for synthetic rubber and rubber tires. The synthetic rubber industry in the US developed almost instantaneously during the early 1940s after natural rubber sources in the South Pacific were cut off during World War II. Because there was an immediate demand for large quantities of synthetic rubber and because there were no health concerns for butadiene other than those associated with its flammability, human exposures in this new industry were probably much higher at that time compared to present conditions.

Epidemiological studies

Epidemiological studies have consistently found excess mortality from lymphatic and hematopoietic cancers associated with occupational exposure to butadiene (5–8). In the butadiene production industry, significant increases in lymphosarcomas among production workers (standardized mortality ratio [SMR]: 4.5) were concentrated among men who were first employed before 1946 (5, 6). A nonsignificant increase in mortality from leukemia (SMR: 2.1) was also noted in the 'non-routine' exposure group (6). An elevated standardized mortality ratio from lymphatic and hematopoietic cancers was observed among workers in an SBR plant in Port Neches, Texas, due primarily to excesses for lymphosarcoma and leukemia (7). These increases in mortality were significant for workers employed during World War II (SMRs: 2.2 and 2.8, respectively). A cohort mortality study comprising eight SBR manufacturing plants in North America found a 6.6-fold increase in deaths from leukemia among black production workers (8). Because race was not designated on all records from two of the plants, 15% of the total cohort had unknown race and were considered as whites. However, when informa-

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tion from these plants were omitted from the analysis, the SMR for leukemia among black production workers was 8.3 (9).

The finding of increases in different subtypes of lymphatic and hematopoietic cancers does not detract from the consistency among the different studies because diagnostic criteria for these cancers are imprecise and overlapping and transitions from lymphoma to leukemia are frequently seen in clinical practice (10).

Landrigan has cautioned against using duration of employment as a surrogate of exposure to butadiene because of large variabilities in exposures, especially during the rapid growth phase of the synthetic rubber industry during World War II (10). Dose–response relationships are evident from the findings that excess cancer mortality was greatest among workers exposed during the war years and was greater among workers with highest potential exposure (production and maintenance) compared to office staff. It was anticipated that a nested case-control study would provide a more precise assessment between exposure to butadiene and lymphatic and hematopoietic cancers (11).

To determine whether the occurrence of lymphatic and hematopoietic cancers in the Matanoski *et al.* (8) cohort mortality study was due to differences in exposure among workers, Santos-Burgoa *et al.* (12) conducted a case-control study of lymphatic and hematopoietic cancers at the eight SBR facilities. The advantage of a case-control study is that it avoids dilution of risk that may exist in a cohort study due to the inclusion of unexposed or minimally exposed workers in the 'exposed' group. Controls were selected to be matched individually to the cases (3–4 controls per case) based on the plant at which they worked, subject age, year of hire, and duration of employment. Thus, controls were selected based on characteristics representative of the cases and not of the total cohort. An exposure rank value (0–10) was assigned by a panel of senior plant chemical engineers for each job in these facilities. Cumulative exposure rank scores for each case and control were determined from the sum of the product of exposure rank for each job multiplied by the number of months spent in that job. This analysis identified a strong association between leukemia and exposure to butadiene (odds ratio: 7.6; 95% confidence interval: 1.6–35.6), i.e., workers exposed to butadiene at or above the mean log exposure score had a 7.6-fold greater risk of leukemia than workers below that mean exposure.

Cole *et al.* (13) argued that the case-control study did not show a clear dose-response pattern between butadiene exposure and leukemia and that if the exposure frequency of controls is representative of the total cohort, then the elevated odds ratio was due to a low leukemia rate in the nonexposed group. In response to these claims, Matanoski *et al.* (9) reported that utilizing a new set of controls did not change the findings of the original case-control study and that when exposure to butadiene was included as a continuous variable, a significant dose–response effect was observed between increasing butadiene exposure score and increasing risk for leukemia.

Several important characteristics were identified in the leukemia cases: 96% were hired before 1960, 73% worked in three of the eight plants, and 81% had been employed for at least 10 years in the industry (9). When the original cohort was reanalyzed but limited to these characteristics, significantly elevated rates of mortality were detected from all lymphatic and hematopoietic cancers (SMR: 1.6) and from leukemia (SMR: 1.8). These additional analyses strengthen the conclusion that there is a causal relationship between exposure to butadiene and human cancer.

Metabolism of butadiene

Butadiene metabolism (Figure 1) was first characterized in liver subcellular fractions obtained from Wistar rats and shown to initially involve cytochrome P450 mediated oxidation to 1,2-epoxy-3-butene (14). This monoepoxide may be detoxified by conjugation with glutathione via glutathione-*S*-transferase (GST) or by hydrolysis via epoxide hydrolase. Epoxybutene (BMO) may also be further oxidized to diepoxybutane (BDE) while 1,2-dihydroxy-3-butene formed by hydrolysis of BMO may be oxidized to 3,4-epoxybutane-1,2-diol (15). The latter epoxides are also detoxified by GST or epoxide hydrolase. Thus, three potential alkylating epoxides may be generated during butadiene biotransformation. Metabolism is probably an important factor in the carcinogenicity of butadiene. *In vitro* mutagenicity of butadiene requires metabolic activation (16) whereas the epoxide intermediates are direct acting mutagens in bacteria (17,18), and BMO and BDE induce local neoplasms in mice and rats when administered by skin application or s.c. injection (19).

Csanády *et al.* (20) showed that the same enzymes involved in butadiene transformation in the rat liver are also present in cytoplasm and microsomes from the livers and lungs of rats, mice, and humans; however, quantitative differences exist between species (20–22). Csanády *et al.* (20) measured metabolism of BMO to BDE in mouse liver microsomes but were unable to detect this reaction in rat liver microsomes. The latter finding differs from results of Malvoisin and Roberfroid

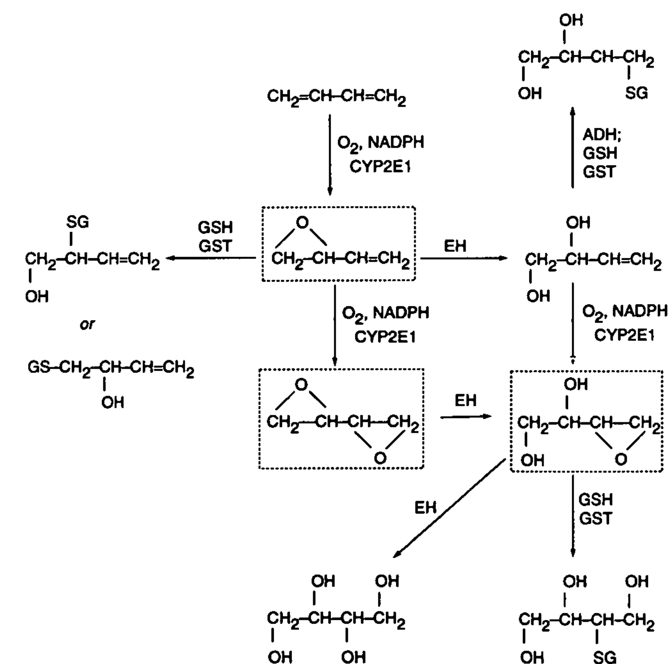

Fig. 1. Metabolism of 1,3-butadiene. The potential reactive epoxide intermediates are 1,2-epoxy-3-butene (BMO), 1,2:3,4-diepoxybutane (BDE), and 1,2-epoxybutane-3,4-diol. Abbreviations: CYP2E1, cytochrome P450 2E1; GST, glutathione-*S*-transferase; EH, epoxide hydrolase; ADH, alcohol dehydrogenase; GSH, glutathione. The three epoxide intermediates and 1,2-dihydroxy-3-butene were first detected *in vitro* (14,15,20); BMO and BDE were subsequently detected *in vivo* (30). Mercapturic acid derivatives formed from the glutathione conjugates of BMO and 1,2-dihydroxy-3-butene have been detected in urine (27,28).

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(15) who measured BDE in incubations containing rat liver microsomes and BMO.

Bond *et al.* (23) reported that the ratio of the apparent pseudo-first-order rate constant (Vmax/Km) for butadiene activation in the liver to the sum of the rate constants for BMO detoxication in the liver were 12 times greater in mice than in rats. However, when biochemical constants reported by Johanson and Filser (24) were used, this ratio is only two times greater for mice than rats. More important, when yields of microsomal and cytosolic protein content and liver size were considered, the activation to detoxication ratio was only 2.8 times greater in mice than in humans and 3.4 times greater in humans than in rats (25,26). These ratios do not take into account interindividual variability in the activities of the enzymes involved.

Metabolites resulting from detoxication of BMO were identified in urine samples from rats, mice, hamsters, monkeys, and humans exposed to butadiene (27, 28), establishing that BMO is an intermediate of butadiene biotransformation in all mammalian species. The reported values of urinary BMO-derived metabolites (28) were calculated to be only 3 times and 5 times greater for rats and mice compared to humans (based on moles of metabolite excreted/kg body weight per p.p.m.-h of exposure to butadiene). Two metabolites derived from BMO account for approximately 80% of the total urinary metabolites resulting from butadiene biotransformation in mice (27). No urinary metabolite derived from BDE has been identified in any species.

We developed a physiologically based pharmacokinetic model, using the biochemical parameter values of Csanády *et al.* (20), to characterize the uptake, metabolism, and clearance of butadiene in rats, mice, and humans (26). This model showed that species differences in response to butadiene are not due solely to biochemical differences in the rates of butadiene activation or in the rates of epoxide detoxication. Blood and lung concentrations of BMO were predicted to be higher in rats exposed to 1 000 or 8 000 p.p.m. butadiene than in mice exposed to 62.5 p.p.m. butadiene, yet blood vessel tumors (hemangiosarcomas of the heart) and lung neoplasms were observed in mice but not in rats at these exposure concentrations. A similar result was obtained by Medinsky *et al.* (29). In a model developed by Johanson and Filser (24), the blood concentration of BMO achieved in mice exposed to butadiene at air concentrations up to 1 000 p.p.m. was less than double that achieved in rats at the same exposures. This species difference in body burden of BMO was not considered to be of sufficient magnitude to explain species differences in cancer response. Thus, factors beyond tissue dosimetry of BMO must be critical in understanding species differences in butadiene-induced carcinogenesis.

Direct measurements of BMO concentrations in blood of rats and mice exposed to butadiene support the above conclusion. The recent finding of BDE in the blood of mice but not rats exposed to butadiene (detection limit: 0.13 μM) (30) emphasizes the need for precise characterization of tissue dosimetry, elimination, DNA adduct formation, and mutagenic behavior of this intermediate across species. Tissue concentrations of BDE may contribute in part to species differences in butadiene carcinogenesis. BDE is much more toxic than BMO (31), and at i.p. doses that killed 30% of the animals BDE was 12 times more mutagenic at the *hprt* locus in mouse splenic T-cells than was BMO (32). The effect of BDE toxicity on its *in vivo* mutagenicity is unclear.

Assessing human risk and susceptibility from physiologically based pharmacokinetic models is complicated by the fact that there are interindividual variations in the expression of enzymes involved in butadiene activation and detoxication and that genetic polymorphisms in these enzymes have been detected (33).

The mouse versus the rat as the appropriate model for assessing human risk

Long-term inhalation studies of butadiene have been conducted in $B6C3F_1$ mice at exposures ranging from 6.25–1250 p.p.m. and in Sprague–Dawley rats at 1 000 and 8 000 p.p.m. Particularly noteworthy in mice, were the induction of early malignant lymphomas and uncommon hemangiosarcomas of the heart (2,3). Further, malignant lung neoplasms were induced at all exposure concentrations. Other sites of tumor induction in mice included the liver, forestomach, Harderian gland, ovary, mammary gland, and preputial gland. In rats, butadiene was carcinogenic to the mammary gland, brain, Zymbal gland, uterus, pancreas, testis, and thyroid gland (1). The only common site of tumor induction in these species was the mammary gland. At issue is whether the differences in carcinogenic target sites between rats and mice are peculiar for butadiene and which species is most appropriate for assessing human cancer risk.

A comparison of sites of neoplasia induced by butadiene to those resulting from exposure to selected epoxide or epoxide-forming chemicals that are classified by the International Agency for Research on Cancer (IARC) as Group 1 (carcinogenic to humans) or Group 2A (probably carcinogenic to humans) agents, namely benzene, ethylene oxide, vinyl chloride, and acrylonitrile, can shed some light on this question (34). For this group of epoxide or epoxide-forming genotoxic carcinogens, it is not unusual to observe differences in sites of neoplasia between these two species. Lymphatic/hematopoietic cancers and neoplasms of the lung, liver, Harderian gland, and mammary gland were more typically induced in mice than in rats; whereas neoplasms of the brain and Zymbal gland were more commonly induced in rats than in mice exposed to these chemicals. Similar to butadiene, inhalation exposure of rats or mice to ethylene oxide or vinyl chloride produced lung tumors in mice only. Furthermore, a good correspondence has been noted between sites of carcinogenesis in humans associated with exposure to these chemicals and sites of tumor induction in animal models, particularly with the mouse (Table I).

Butadiene is genotoxic in the bone marrow of mice, but not in rats, producing six- to eight-fold increases in sister chromatid exchanges (SCEs), micronuclei, and chromosomal aberrations (35,36). Single i.p. injections of mice with BMO induced 10-fold increases in the frequencies of SCEs and chromosomal aberrations in mouse bone marrow cells (37). Several other monofunctional epoxides, including ethylene oxide, propylene oxide, epoxybutane, and styrene oxide, have also been shown to induce SCEs, micronuclei, or chromosomal aberrations (38,39). Butadiene, BMO, and BDE induced increases in sister chromatid exchanges in cultured human lymphocytes (40). Preliminary studies of workers employed in butadiene production did not show increases in SCEs or chromosomal aberrations in peripheral lymphocytes(41). These results were attributed to low ambient levels of butadiene.

The correspondence between lymphomas induced in mice exposed to butadiene and lymphatic and hematopoietic cancers

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Table I. Sites of carcinogenesis in humans associated with exposure to 1,3-butadiene, benzene, ethylene oxide, vinyl chloride, or acrylonitrile: correspondence with results from animal studies[a]

Chemical	Cancer sites in humans	Animal model with corresponding cancer
1,3-Butadiene	Lymphatic/hematopoietic	Mouse
Benzene	Lymphatic/hematopoietic	Mouse
	Lung	Mouse
Ethylene oxide	Lymphatic/hematopoietic	Mouse, rat
	Stomach	None established
Vinyl chloride	Liver	Mouse, rat
	Brain	Rat
	Lymphatic/hematopoietic	None established
	Lung	Mouse
Acrylonitrile	Lung	None established[b]
	Prostate	None established

[a]Taken from reference 27.
[b]Acrylonitrile has been studied in rats, but not in mice.

associated with occupational exposure to butadiene is especially noteworthy with respect to assessment of human risk. Neither lymphomas nor leukemias were induced in rats exposed to butadiene. Relevant to the selection of the appropriate model for human risk assessment are the observations of radiation-induced leukemia/lymphoma in humans and animals. Causal associations between exposure to ionizing radiation and leukemia in humans have been extensively documented (42). Furthermore, ionizing radiation induced leukemia and lymphomas in several strains of mice (43), whereas a similar irradiation protocol (five total-body irradiations of 150 rads each at weekly intervals) did not increase the incidence of leukemias or lymphomas in rats (44). The human leukemogen benzene also produces lymphomas in mice but not in rats (45). Because the rat appears to be exceptionally insensitive to leukemia/lymphoma induction, the mouse must be considered as the more appropriate model for assessing human risk for lymphatic and hematopoietic cancers.

DNA adducts

The epoxide metabolites of butadiene are DNA alkylating agents. N^7-(2-hydroxy-3-buten-1-yl)guanine and its regioisomer N^7-(1-hydroxy-3-buten-2-yl)guanine are formed by reacting BMO with guanosine, deoxyguanosine, or double stranded DNA (46). These adducts are congeners of the major adduct formed by the reaction of ethylene oxide with calf thymus DNA, i.e., N^7-(2-hydroxyethyl) guanine (47). N6-alkyladenine adducts have been detected by a HPLC/^{32}P-postlabeling procedure after incubating calf thymus DNA with BMO (48) or BDE (49). The same N7-guanine alkylation products identified by Citti et al. (46) were detected in liver DNA of mice but not of rats exposed to 500 ppm butadiene (50). In addition, N^7-(2,3,4-trihydroxybutyl) guanine, an expected reaction product between guanine and BDE or 3,4-epoxybutane-1,2-diol, was detected in mouse liver DNA. Peltonen et al. (51) recently used HPLC/^{32}P-postlabeling to identify N^7-(2-hydroxy-3-buten-1-yl)guanine and N^7-(1-hydroxy-3-buten-2-yl)guanine in the urine of a worker exposed to butadiene. Thus, the same N^7-alkylguanine adduct found in liver DNA of mice exposed to butadiene is excreted by humans exposed this chemical.

In vivo mutagenicity

Goodrow *et al.* (52) examined tumor tissues from B6C3F$_1$ mice exposed to butadiene for the presence of activated proto-oncogenes. Activated K-*ras* genes with codon 13 mutations (mostly G → C transversions) were found in several lung and liver neoplasms and in lymphomas that were induced by exposure to butadiene. These findings support mechanistic-based relationships between animal and human neoplasia, because activated K-*ras* proto-oncogenes are frequently detected in human cancers. Inhalation exposure of transgenic mice to butadiene for 1 or 4 weeks produced increases in point mutations in the lung and bone marrow (53,54). Genetic changes in cancer genes in these tissues are likely precursor events in the development of lung and lymphatic neoplasms. No increases in deletion mutations were observed in bone marrow cells of mice exposed to 625 p.p.m. butadiene (54). Mutagenicity studies of BD in rats are not available.

Allelic losses on chromosome 11 at several loci surrounding the *p53* tumor suppressor gene and on chromosome 14 at the retinoblastoma tumor suppressor gene were detected at a high frequency in mammary gland carcinomas induced by butadiene in mice (55). In lung carcinomas induced by butadiene, losses of heterozygosity (LOH) were most frequent on chromosome 4 in the region of *MTS1*, the gene which encodes for an inhibitor of the cyclin D/CDK4 kinase complex. These patterns of allelic losses likely reflect inactivation of tumor suppressor genes in the carcinogenic process and are analogous to genetic alterations that are frequently observed in a wide variety of human cancers. LOH in butadiene-induced tumors cannot be attributed solely to direct effects of BDE. Similar allelic losses have been observed in carcinomas, but not in benign tumors, obtained from untreated mice or from mice in which carcinomas were induced by single or multiple exposures to chemicals lacking bifunctional reactive groups (56, 57). LOH is a late event in multistep carcinogenesis and can occur long after exposure to carcinogens has ceased (58). Tumors induced by BD in rats have not been analyzed for oncogene activation or tumor suppressor gene inactivation.

Exposure of B6C3F$_1$ mice to BMO, BDE, or ethylene oxide produced dose-related increases in the frequencies of hypoxanthine-guanine phosphoribosyltransferase (*hprt*) mutations in splenic T-cells (32, 59). Exposure to butadiene or *N*-ethyl-*N*-nitrosourea (ENU) also increased the mutational frequency at the *hprt* locus (32, 60). Analyses of the mutant sequences in exon 3 of the *hprt* gene indicated that all of the compounds produced transition and transversion mutations at AT and GC base pairs in mouse splenic T-cells (32,59,60). Of these chemicals, the fraction of *hprt* mutants that had base substitution or frameshift mutations in exon 3 was lowest for BDE. In addition to forming monoadducts, this bifunctional agent can form DNA crosslinks, which may result in large deletion mutations. Large deletions involving loss of exon 3 in the *hprt* gene of mouse lymphocytes are not detected by denaturing-gradient gel electrophoresis, the analytical method used to characterize these mutations. The ability of BDE, but not BMO, to induce a high frequency (~50%) of large deletion mutations was demonstrated by Southern blot analyses of treated TK6 cells (31). Thus, although BDE exhibits a higher mutational frequency at the *hprt* locus than does BMO, the lower fraction of exon 3 mutants found for BDE is probably due to the nature of the mutations and the analytical method used. There was no evidence of large deletions induced by

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BMO or ENU, a potent carcinogen and well characterized point mutagen (61), probably because these monofunctional alkylating agents cannot form DNA crosslinks. Since the fraction of exon 3 mutants at the *hprt* locus was similar for butadiene, BMO, and ENU, it is likely that large deletions, similar to those caused by BDE, were not produced to any great extent in mice exposed to 625 p.p.m. butadiene for two weeks. Further, the activating point mutations found in K-*ras* genes in butadiene-induced tumors (52) are consistent with the base substitution mutations observed at the *hprt* locus in splenic T-cells of mice exposed to butadiene, BMO, or BDE (32). Thus, there is no reason to assume that cancer-causing mutations in mice exposed to butadiene are a consequence of large deletion mutations.

In addition to base substitution mutations, 40–50% of the exon 3 mutants induced by butadiene, BMO, BDE, or ethylene oxide contained single base frameshift mutations. A high percentage of the frameshift mutations induced by these chemicals involved a single guanine insertion in a run of six guanines at bases 207–212; this may represent a mutagenic 'hot spot' that is targeted by these chemicals. No frameshift mutations were observed in ENU-treated mice, consistent with a mechanism of alkylation different from that exhibited by epoxides. Because the epoxide intermediates of butadiene biotransformation form DNA adducts similar to those of ethylene oxide, i.e., N7-alkyl guanine, it is not surprising that the mutational spectra for butadiene, its epoxide metabolites, and ethylene oxide are similar.

N7-alkylguanine adducts are not expected to cause mispairing mutations. Skopek and coworkers suggest that N-alkylation of guanine and subsequent glycosylase mediated depurination of this product yields an apurinic site which may lead to miscoding during replication (causing point mutations) and/or may promote polymerase slippage (causing frameshift mutations) (32,59). Adducts formed from exposure to ENU (e.g., O^6-ethylguanine and O^4-ethylthymine) do interfere with base pairing and lead to transition and transversion mutations, but no frameshift mutations (60). These findings suggest that mutations induced by ethylene oxide and butadiene may be originating by similar mechanisms, which are different from that of ENU. It is noteworthy that ethylene oxide was recently updated by IARC from a Group 2A carcinogen (probably carcinogenic to humans) to a Group 1 carcinogen (carcinogenic to humans) based on its carcinogenicity in experimental animals, associations between exposure to ethylene oxide and mortality from lymphatic and hematopoietic cancers in workers, and mechanistic considerations (38).

In a pilot study of nonsmoking workers exposed to butadiene (1–3 p.p.m.) compared to low exposed subjects (0.03 p.p.m.) and nonexposed subjects, there was a correlation (r = 0.85) between the *hprt* mutant frequency in peripheral lymphocytes and urinary concentrations of a butadiene metabolite (1,2-dihydroxy-4-[*N*-acetylcysteinyl]butane) (62). These findings indicate that humans can metabolize butadiene to a mutagenic intermediate even at low butadiene exposures.

Summary

The major findings from the epidemiological and mechanistic data reviewed here include: (i.) 1,3-Butadiene is a trans-species carcinogen, producing multiple organ neoplasia in rats and mice. Particularly noteworthy is the induction of lymphomas in mice. (ii.) Epidemiological studies have consistently found associations between occupational exposure to butadiene and increased risk of lymphatic and hematopoietic cancers. (iii.) Butadiene is metabolized to mutagenic and carcinogenic epoxide intermediates in all mammalian species examined, including humans. (iv.) For epoxides and epoxide-forming chemicals, a good correspondence has been observed between findings from epidemiological studies and animal studies. Human and animal studies on the carcinogenic effects of ionizing radiation and of benzene indicate that the mouse rather than the rat is the more appropriate model for assessing human risk for lymphatic and hematopoietic cancers. (v.) The same N7-alkylguanine adduct detected in liver DNA of mice exposed to butadiene was identified in the urine of workers exposed to butadiene. (vi.) Activated K-*ras* genes and inactivated tumor suppressor genes were observed in butadiene-induced tumors in mice. These changes are analogous to the genetic alterations frequently observed in a wide variety of human cancers. (vii.) Dose-related increases in *hprt* mutations have been observed in lymphocytes isolated from mice exposed to butadiene or its epoxide metabolites and in occupationally exposed humans. (viii.) The mutational spectra for butadiene and its epoxide intermediates are similar to that of the human carcinogen ethylene oxide, suggestive of a common mechanism of action for these chemicals.

Based on animal and human data available in 1991, an IARC expert panel concluded that 1,3-butadiene is probably carcinogenic to humans (19). The present cumulative weight of evidence leads to the conclusion that butadiene is a human carcinogen and that the mouse is an appropriate model for assessing human cancer risk for this chemical.

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