PART TWO: HAZARD ASSESSMENT

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2-1 TOXICOLOGICAL EFFECTS OF BENZENE

2-1.1 Introduction

Several excellent reviews of the toxicological properties of benzene have been published recently: Fishbein (Ref. 2-1.9 [14]), Synder (Ref. 2-1.9 [32]), Aksoy (Ref. 2-1.9 [1]) and Mehlman (Ref. 2-1.9 [22]). This section will therefore address only selected aspects of the extremely large toxicological data base available for this compound in order to provide a perspective from which to evaluate other parts of this document.

2-1.2 Major Sources of Human Benzene Exposure

It must be appreciated that benzene is ubiquitous. According to estimates from the National Research Council (Ref. 2-1.9 [24]), the dietary intake of benzene may be as high as 250 μg daily, perhaps explaining benzene concentrations of 8-20 ppb in the breath of individuals with no known exposure to this compound. The benzene content of specific foods is reported to range from 2 ppb for canned beef to 2100 ppb for a boiled egg (Ref. 2-1.9 [23]). Recent results from the National Toxicology Program (Ref. 2-1.9 [25]) indicate that virtually 100% of benzene administered orally is absorbed into the body.

Benzene concentrations in ambient air (urban and rural) have been estimated to range from 1-100 ppb (Ref. 2-1.9 [17]). Urban air is reported to contain higher levels than rural air, presumably due to the contribution of automotive emissions of benzene (Ref. 2-1.9 [5]). After reviewing these data, the National Research Council (1980) calculated that an individual living in an urban environment containing a mean atmospheric benzene concentration of 16 ppb (50 $\mu g/m^3$) who breathes an average of 24 m^3 of air per day and absorbs approximately 50% of the dose (i.e., equilibrium state) will absorb approximately 600 μg of benzene daily.

[16 ppb = 50 $\mu g/m^3$ x 24 m^3/day x 50% absorption = 600 μg/day]

Benzene is present in cigarette smoke at levels of 47-64 ppm, leading to estimates of the amount of benzene inhaled from a single cigarettes ranging from 10-31 μg. Using the upper estimate, a person smoking two packs (i.e., 40 cigarettes) per day will absorb up to 992 μg of benzene (assumes 80% of dose is absorbed; non-equilibrium state). [Note: This discussion will not consider the contribution of secondary inhalation of cigarette smoke to the overall benzene exposure of a non-smoker.]

[40 cigarettes/day x 31 μg benzene/cigarette x 80% absorption = 992 μg/day]

The solubility of benzene in water is reported to be 1780 mg/l at 25 C (Ref. 2-1.9 [2]). In a report issued by the EPA Office of Drinking Water (Ref. 2-1.9 [11]), it was estimated that 97.7% of the population served by public water systems is receiving water either free of benzene contamination or having levels less than 0.5 μg/l. Estimates of daily human water consumption range from 0.8 to 2 l/day. Assuming that the average adult consumes 2 liters of water daily, it can be calculated that drinking water with a benzene content of 0.5 μg/l would contribute 1 μg of benzene to the average daily dose (100% absorption assumed).

[0.5 μg/l x 2 l/day = 1.0 μg/day]

Summarizing the above calculations for what are considered major sources of human benzene exposure:

	Non-Smoker	Smoker
Food	250 μg/day	250 μg/day
Air	600 μg/day	600 μg/day
Cigarettes	—	992 μg/day
Water	1 μg/day	1 μg/day
TOTAL	851 μg/day	1843 μg/day

2-1.3 The Pharmacokinetics of Benzene

The primary routes of benzene exposure are considered to be oral and inhalation. While there are data that benzene applied as a liquid or in solution to human skin can be absorbed fairly rapidly (Ref. 2-1.9 [4]), this route is generally discounted as being significant because of the rapid evaporation of benzene which effectively reduces the time of skin contact.

Recent data from the National Toxicology Program (Ref. 2-1.9 [26]) indicates that virtually all of an oral dose of benzene dissolved in vegetable oil is absorbed in rats and mice. It is reasonable to assume that dietary fiber content may reduce both the rate and efficiency of benzene absorption somewhat by complexing the hydrocarbon, but experimental evidence for this is unavailable. To be conservative, 100% absorption of benzene from food and water was assumed in the above calculations.

The respiratory absorption of a hydrocarbon vapor such as benzene is a complex process which has only partially been characterized. Initially, when an animal (or man) is placed into an atmosphere containing benzene vapor, virtually all of the hydrocarbon is absorbed into the blood stream and then distributed to the various tissues of the body. Each tissue will absorb some of the benzene from the blood with some tissues (e.g., those having a high

content of fat) absorbing relatively greater proportions of benzene compared to other tissues. The benzene absorbed by each tissue may be sequestered, released back to the blood unchanged, or processed by the specific metabolic enzymes which characterize the cells of that tissue. In time, a state of dynamic equilibrium (often called "steady state") is established between the air, blood, and other body compartments. As more benzene is absorbed from the air, some of the previously absorbed benzene is exhaled unchanged from the body, some is metabolized to specific derivatives which may be further metabolized even in other distant tissues, and some is removed by the kidneys and excreted in the urine. As the animal approaches steady state, the apparent (i.e., net) absorption of the compound into the body can be seen to decrease substantially. As noted in Section 2-1.2 above, conservative estimates of 50-80% absorption have been assumed in calculating the contribution of ambient air and cigarette smoking to the total burden of benzene. Recent data from the NTP (1986) indicate that from a 6 hour exposure to 11 ppm of benzene vapor, the apparent absorption of benzene in mice is 50%, whereas at 1000 ppm, the apparent absorption is 9.7%. Values for similarly exposed rats are 33% absorption at 13 ppm and 15% absorption at 870 ppm.

Significant differences in the respiratory characteristics of commonly used laboratory animals exist and greatly influence the amount and rate at which a hydrocarbon vapor is absorbed into the body. Small animals, with their high metabolic rate, must have a relatively large supply of oxygen to the body (Ref. 2-1.9 [34]). While this could have been accomplished evolutionarily by development of larger lungs relative to their body size, small animals such as mice and rats instead breathe more rapidly. It might be expected therefore that rodents should reach steady state more quickly than a man exposed to the same vapor concentration, but definitive experimental data in this regard have not been identified.

The Lovelace Inhalation Toxicology Research Institute (ITRI), under contract with NTP, have characterized the respiratory parameters of the B6C3F1 mouse and the F344 rat, (unpublished information from the butadiene research program). According to ITRI data, the average B6C3F1 mouse weighed 27.5 g and breathed 35 ml of air per minute (i.e., minute volume); the average F344 rat weighed 392 g and had a minute volume of 289.7 ml. Expressed on a kilogram body weight basis, the minute volume of the mouse is 1274 ml/kg and of the rat is 737 ml/kg. From this perspective, it is understandable why Sabourin *et al.* (1986) concluded that at similar exposure levels of benzene vapor, mice received 150-200% of the dose received by rats per kilogram body weight. Such differences in respiratory characteristics between species are especially important to exposures where the steady state condition has either not been reached or has been perturbed. Consideration of species differences must be incorporated in the quantitative modeling of animal inhalation data for estimation of human health risks. In particular, if one assumes a 70-kg man who breathes 7500 ml of air per minute, it can be calculated that the human minute volume/kg body weight is about one-seventh that of the rat and about one-twelfth that of the mouse.

A similar picture of steady-state equilibrium can be developed for benzene absorbed from the gastrointestinal tract. As noted above, recent data from NTP (Sabourin *et al.*, 1986) suggest that essentially all of a dose of benzene (dissolved in corn oil) administered by gavage is absorbed by rats and mice. Two points should be emphasized with regard to oral exposures. First, the concentration of benzene in the blood as a result of the administration of an oral bolus is seen to be a transient peak or spike. Dissolving benzene in a vehicle such as corn oil essentially results in a retardation in the absorption of benzene into the blood stream, such that all of the benzene is eventually absorbed, but it requires a longer period of time.

Benzene is metabolized via a number of possible pathways, summarized in Figure 2-1.8 [1]. Available information indicates that benzene must be metabolized in order to exert its toxic effects. However, it is not clear at the present time which of the various metabolic pathways activates benzene to more toxic derivatives and which pathways result in detoxification. Various investigators have suggested that toxicity may be the result of covalent binding of benzene metabolites to cellular macromolecules such as *DNA* and protein, and a reactive benzene epoxide was postulated to be formed during the metabolism of benzene by the cytochrome P-450 enzyme system (Ref. 2-1.9 [19]). Recent data, however, call into question whether benzene oxide is in fact formed to a significant degree during the metabolism of benzene (Ref. 2-1.9 [20]). Investigators at the Chemical Industry Institute of Toxicology (Ref. 2-1.9 [16], [18]) suggest that polyphenol derivatives (e.g., hydroquinone and 1,2,4 -benzenetriol) may be responsible for the toxic effects of benzene, perhaps via the autooxidative formation of highly reactive radicals which could bind to macromolecular targets. Goldstein *et al.* (Ref. 2-1.9 [15]) suggest that the benzene ring is cleaved metabolically forming muconaldehyde which is also capable of reacting with essential macromolecules. The role of various isomers of diphenol formed by cellular peroxidases, such as myeloperoxidase in the bone marrow in benzene toxicity remains to be evaluated (Ref. 2-1.9 [28]). See Figure 2-1.8 [1].

While it is not yet possible to identify which metabolite(s) of benzene is responsible for the profound cellular toxicity associated with this compound, quantitative risk modeling must recognize that significant qualitative and quantitative differences in the specific metabolic pathways for benzene are seen between species. The phenolic metabolites in the urine of benzene-treated mice, for example, have been found to comprise 50-65% *glucuronide* conjugates, 26-38% sulfate conjugates, and approximately 5% unconjugated phenol (Ref. 2-1.9 [33]). In contrast, Cornish and Ryan (Ref. 2-1.9 [6]) observed that approximately 70% of the phenolic metabolites found in the urine of benzene-treated rats were *sulfate* conjugates. In man, virtually all of the phenolic compounds in the urine following benzene exposure exist as *sulfate* conjugates until the concentration of phenol in the urine reaches approximately 400 mg/l when the sulfate pathway has apparently been saturated and products of glucuronide conjugation begin to appear (Ref. 2-1.9 [30]). Such data

emphasize that although all three species possess similar metabolic pathways, glucuronidation predominates in the mouse, whereas sulfation predominates in the rat and man. It should also be noted from these data that the specific metabolites which are formed at high doses may be substantially different from those formed at lower (environmentally relevant?) doses, and as a result, it would not be surprising to find entirely different toxic profiles under the two conditions.

Similar arguments can be made even between tissues with the same animal. The liver, for example, is known to be capable of metabolizing benzene to a wide variety of reactive derivatives, but it is not considered to be a target organ for benzene toxicity. The reasons for this insensitivity are undoubtedly complex, but could be due to the effective shunting of potentially toxic benzene metabolites into various conjugation pathways which effectively detoxify such metabolites. In contrast, the cells of the bone marrow appear to be exceptionally sensitive to the toxic effects of benzene, reflecting perhaps a greater emphasis on certain activation pathways in marrow cells or less effective detoxification by enzymatic conjugation, or less effective repair of cellular damage. Future research may provide a clearer understanding of the biological basis of such differences.

2-1.4 Toxicity to Blood Formation

Toxic effects have long been recognized in the bone marrow of animals and man exposed repeatedly to high levels of benzene vapor (Ref. 2-1.9 [27]). This organ is located in the hollow spaces of various bones and is the primary site of blood formation. In simple terms, the bone marrow can be viewed as a tissue filling a container of fixed volume, comprising a dynamic mixture of cells which are in various stages of becoming mature red blood cells (RBCs) and white blood cells (WBCs). See Figure 2-1.8 [2].

Most commonly, benzene toxicity is expressed as a decreased formation of various types of blood cells; and therefore, decreased concentrations of these cells are found in the circulating blood (i.e., anemia, pancytopenia, etc.) Severe cases of benzene intoxification may progress to a fatal condition where all blood formation essentially ceases (i.e., aplastic anemia).

The mechanism(s) by which benzene affects bone marrow suppression is incompletely understood, but is known to be complex. Much of this uncertainty is perhaps due to the biological complexity of the bone marrow itself. In the clinical and toxicological literature, for example, one of the common early manifestations of benzene toxicity is a decrease in the number of circulating lymphocytes (i.e., lymphocytopenia), suggesting that the lymphocytic stem cell line may be particularly sensitive to the cytotoxic/cytostatic effects of benzene. Of interest, increased circulating levels of other cell types may also be seen at the same time as lymphocytopenia (e.g., an increase in the number of eosinophilic granulocytes in the blood). It is not clear whether this increase in circulating eosinophils should most appropriately be considered a direct manifestation of benzene toxicity or simply the compensatory proliferation of eosinophilic WBC precursors into the bone marrow space made vacant by the killing of lymphocyte precursors by benzene. A similar phenomenon is seen in the anemia of leukemic crisis, which develops when the bone marrow becomes filled with malignant leukemia cells leaving no room for the proliferation of other types of blood cells. It should be noted that in many cases of severe bone marrow suppression, other tissues (e.g., liver and spleen) may be observed to reassume their embryonic functions of blood formation (i.e., extramedullary hemopoiesis.)

2-1.5 Benzene and Leukemia

A relationship between repeated high-level benzene exposure and the occurrence of leukemia in man was recognized as early as 1928 (Ref. 2-1.9 [9]). Acute myelogenous leukemia (AML), and to a lesser extent its variants (e.g., acute erythroleukemia, acute myelomonocytic leukemia), are the types of leukemia most commonly associated with occupational exposures to high levels of benzene vapor, suggesting that the myeloid/erythroid stem cell line may be particularly sensitive to the leukemogenic effect of benzene. (See Figure 2-1.8 [2]). Other types of leukemia (e.g., acute lymphocytic leukemia and chronic leukemias of various cell types) are less clearly linked to benzene.

Leukemia is characterized by the uncontrolled proliferation of a specific type of blood cell, and the term was originally derived from the increased number of circulating WBCs or leukocytes (i.e., leuk -) in the blood (i.e., -emia). Nonetheless, leukemias are considered by most scientists to be neoplastic diseases of the bone marrow and other blood-forming organs. Leukemias which manifest themselves predominantly in tissues other than the bone marrow are commonly referred to as lymphomas. It should be appreciated that the diagnostic distinction between leukemia and lymphoma is an artifact of medical history. The two terms, however, persist in the clinical/epidemiological literature to reflect whether the disease was first diagnosed in the bone marrow or in extramedullary sites. Of significance to epidemiological evaluations, the true incidences of specific leukemias are often clouded since the transformation of leukemia into lymphoma, and vice versa, is commonly encountered in the clinic.

The distinction between the leukemias and nonleukemic malignant neoplasms has been the subject of long standing debate among scientists, although the most popular paradigm would classify leukemias as cancers. The debate, however, is not complete, and there is considerable evidence to suggest that leukemogenesis and carcinogenesis represent two highly distinct biological processes. Dameshek (Ref. 2-1.9 [7]) and Wasserman (Ref. 2-1.9 [36]), for example, suggested that myelogenous leukemias are specific manifestations of a more general condition which was termed the "myeloproliferative syndrome." According to these authors, this syndrome is manifested not only as leukemia, but also as such neoplastic conditions as polycythemia vera, aplastic anemia, or agnogenic myeloid metaplasia. Walsh (Ref. 2-1.9 [35]) provides an excellent discussion of myeloproliferative syndrome and notes that leukemia is the terminal complication in 10% to 15% of patients with polycythemia vera,

and that an association of acute leukemia with agnogenic myeloid metaplasia has also been reported. As an alternative mechanism, Dameshek (Ref. 2-1.9[8]) and Sinkovics *et al.* (Ref. 2-1.9 [31]) have suggested that certain leukemias may be a particular clinical manifestation of autoimmune disease. Also of interest is the report of Battifora *et al.* (Ref. 2-1.9[3]) that myelogenous leukemia is "induced" in rats by a dietary mineral deficiency (magnesium). Such observations tend to emphasize leukemogenesis as a biological process which may be distinct from our current models of carcinogenesis. If that be the case, then the mathematical models commonly assumed to estimate human cancer risk may be highly inappropriate for use with leukemia.

Until recently, attempts to induce leukemia/lymphoma in experimental animals with benzene had been unsuccessful. However, several investigators have now reported the induction of a lymphoma in the thymus of C57BL mice and derivatives of that strain by a number of chemicals including benzene. This lymphoma is characterized by the proliferation of T-lymphocytes, and is *not* believed to be the result of a direct "carcinogenic" effect of benzene on T-cell precursors. Rather this tumor may be the secondary result of benzene associated activation of a latent endogenous virus (MuLV) which is known to be carried by this strain of mouse. While similar viruses are known to occur in man, available evidence links these human viruses also with leukemias involving the T-lymphocyte. It is significant that it is myeloid, not lymphocytic leukemias, which have been associated with high level benzene exposures in man. Therefore, the significance, if any, of murine leukemia and of benzene associated viral activation to human health is unclear.

No evidence of viral involvement in human AML has been identified to my knowledge. In this regard, Cronkite and his colleagues at the Brookhaven National Laboratory (unpublished data) have recently identified AML in CBA/Ca mice treated with benzene. This strain is being characterized in a number of laboratories and may eventually prove to be a suitable animal model for benzene leukemogenesis.

2-1.6 Benzene and Solid Tumors

Maltoni and his colleagues at the Institute of Oncology in Bologna have conducted a number of studies on benzene which they summarized in 1985 (Ref. 2-1.9 [21]). Beginning in 1977, they reported that a wide variety of solid tumors had been observed (Experiment BT901) in Sprague-Dawley rats (13 weeks old at the start of the study) receiving *50 or 250 mg/kg* of benzene dissolved in olive oil by gavage daily, 4-5 days/week for *52* weeks, then held until spontaneous death. These tumors included carcinomas of the Zymbal gland (females only at both doses) and oral cavity (females at high dose only), as well as increases in the incidence of mammary tumors (type unspecified; suggestive increase in females at high dose only) and non-thymic hemolymphoreticular neoplasms (type unspecified; males only at high dose). It should be noted that Maltoni *et al.* report only crude tumor incidences from their studies and do not provide results of statistical evaluations of their data.

In a separate experiment (BT902/906), Maltoni *et al.* administered benzene in olive oil by gavage at a daily dose of *500 mg/kg* to 7-week-old Sprague Dawley rats, 4-5 days/week, for *104* weeks, which were then held until spontaneous death. According to the authors, under the conditions of this bioassay, benzene caused an increased incidence of a number of tumors:

- Zymbal gland carcinomas (equally distributed among males and females)
- Carcinomas of the oral cavity (equally distributed among males and females)
- Carcinomas of the nasal cavities (suggestive increase in males only)
- Skin carcinomas (males only)
- Forestomach dysplasias (males and females) and forestomach tumors (females only)
- Hepatocarcinomas (reported by authors but do not appear to be increased to this reviewer)
- Liver angiosarcomas (males and females)
- Increase in the number of other malignant tumors, some of which are extremely rare in the Sprague-Dawley rat, such as lung adenocarcinomas (tumor observed in one male) and soft tissue liposarcomas (tumor observed in two males).

In addition, benzene caused a decrease in circulating WBCs, due primarily to a decrease in circulating lymphocytes (males and females) when determined during the 84th week of the experiment. Increases in the incidence of mammary tumors and non-thymic hemolymphoreticular neoplasms (seen at the lower doses given in BT 901) were not seen in this study. Maltoni *et al.* suggest that the differences between the results of experiments BT 901 and BT 902/906 must be correlated to the different doses (daily dose and length of treatment) of administered benzene, rather than to differences in the age of the animals at the start of each experiment. The technical basis for this statement, however, is not clear. Once again it should be noted that the conclusions from this study are subject to technical debate because of the lack of statistical evaluation.

Maltoni *et al.* began in 1983 a study using 6-week-old Wistar rats (BT907) and Swiss mice (BT908) exposed by gavage to benzene in olive oil at a daily dose of 500 mg/kg, 4-5 days/week for 104 weeks (rat) and 78 weeks (mouse). Preliminary information from these studies was included in Maltoni *et al.*, 1985. In the Wistar rat, Zymbal gland carcinomas (male and female), non-thymic hemolymphoreticular neoplasias (suggestive increase in females), and an increase in total malignant tumors (males and females) were observed. In the Swiss mouse, Zymbal gland dysplasias (males and females) and carcinomas (males only), mammary carcinomas (females only), pulmonary ademonas (males and females), and an increase in total malignant tumors (suggestive increase in females) are reported. Results of statistical evaluations are not reported.

The National Toxicology Program has conducted two-year toxicology and carcinogenesis studies of benzene in F344 rats and B6C3F1 mice. Male F344 rats were administered benzene in corn oil by gavage at daily doses of 0, 50, 100, or 200 mg/kg, 5 days/week, 103 weeks. Female F344 rats and male and female B6C3F1 mice were administered benzene in corn oil by gavage at daily doses of 0, 25, 50, or 100 mg/kg, 5 days/week, 103 weeks. In rats, increased tumor incidences were seen for the Zymbal gland (males and females), oral cavity (males and females), and skin (males only). In the benzene treated mice, increased tumor incidences were reported for Zymbal gland (males and females), lymphoma, (males and females), lung (males and females), Harderian gland (males, marginal in females), ovary (females), and liver (males, marginal in females) (NTP, 1986).

Maltoni and his colleagues have also evaluated the carcinogenic potential of benzene vapor via inhalation. In experiments BT4004/4006, 13-week-old pregnant female Sprague-Dawley rats (gestation day 12 at start of study) were exposed to benzene vapor at the following concentrations: 200 ppm/4 hours day, 5 days/week, 7 weeks; then exposed at 200 ppm, 7 hours/day, 5 days/week, 12 weeks; then at 300 ppm, 7 hours/day, 5 days/week, 85 weeks, giving a total of 104 weeks of benzene exposure (Group I). These animals were then observed until spontaneous death. The offspring from the above rats were exposed to benzene vapor as follows: transplacentally during the prenatal period (Note: gestation in the rat is approximately 21 days); by inhalation and probably by ingestion (via milk) during weaning; and afterward by inhalation as for the parental animals (Group II). One group of offspring was removed from further exposure after the 15th week of the above treatment schedule (Group III). The offspring in Groups II and III were also held for observation until spontaneous death. The results in these three treatment groups will be discussed separately.

Among the benzene treated pregnant rats (Group I), suggestive increases in Zymbal gland carcinoma (3/53 = 5.7% in treated rats vs. 1/60 = 1.7%) and malignant mammary tumors (6/54 = 11.1% vs. 2/60 = 3.3%) were seen. Increases in other types of tumors were seen near the end of the study but are of unclear significance due to the low number of surviving animals.

Among the offspring exposed to benzene vapor for 15 weeks (Group III), an increased incidence of Zymbal gland carcinomas (male and female), oral cavity carcinomas (female, suggestive in males), carcinomas of the nasal cavity (female), malignant mammary tumors (suggestive in female), and hematomas (female) were observed. In the offspring exposed to benzene vapor for 104 weeks (Group II), an increased incidence of Zymbal gland carcinoma (males and females), carcinomas of the oral cavity (female, suggestive in male), nasal cavity carcinomas (reported by the authors, but considered only suggestive by this reviewer), and malignant mammary tumors (suggestive in females) were reported. Increased incidences of other tumors were seen near the end of the study, but again the low number of surviving animals makes difficult the interpretation of the biological significance of such observations.

The studies of Maltoni *et al.* (1985) and the National Toxicology Program (1986) have demonstrated without question that high level benzene exposures can produce an increased incidence of a wide variety of tumors in rats and mice. It is somewhat more complicated, however, to conclude that these effects are due to a direct carcinogenic effect of benzene on these highly diverse tissues, and that these animal data are appropriate for quantitative risk modeling for extrapolation to environmentally relevant levels of benzene exposure in man.

Before current models can be applied, three confounding factors must be considered further:

- As discussed above, recent data from the National Toxicology Program (1986) indicated that all of the dosages of benzene utilized in the above cancer bioassays have been at levels where the usual metabolic pathways may have been "wholly or partially saturated." Therefore, it is possible that benzene in these animals was forced into metabolic pathways which would not normally be significant in defining the toxic profile of this compound.
- The role of murine leukemia virus in the development of thymic lymphoma in the B6C3F1 mouse was discussed above. It is not clear whether or not current risk modeling techniques are appropriate for virally mediated neoplasia.
- Benzene is well known to be immunosuppressive, such that it is possible that all of the tumors reported by Maltoni *et al.* (1985) and by NTP (1986) are the secondary result of benzene-induced inability of the animal to monitor and destroy spontaneously occurring transformed cells. Certainly, this type of mechanism would explain the occurrence of tumors of the oral cavity in the NTP benzene inhalation study, as well as the development of carcinomas of the skin in the benzene gavage studies.

2-1.7 Conclusions

As discussed above, the biology of leukemia, bone marrow function, and carcinogenesis as relates to benzene exposure is extremely complex. The methods of quantitative risk modeling have only recently been applied to biological phenomena such as carcinogenesis, and because it is such a young science, it is not surprising that current models of quantitative risk extrapolation depend on assumptions which are well recognized as being simplistic in the extreme. Nonetheless, such methods are now, and will continue to be, used to assist in the formulation of human health policy and regulation, since a more definitive understanding of the mechanisms of benzene associated toxicity and the relevance of such mechanisms to human health may not be sufficiently developed in the near future to offer an acceptable alternative to the risk manager.

It is imperative that those who perform risk modeling recognize the limitations of our biological understanding and document fully the various simplifying assumptions made and resulting uncertainties when estimating by extrapolation the risks to human health due to environmental benzene exposures. It is also important that as new biological understanding becomes avail-

able the risk models be improved and previous decisions be reevaluated.

In 1980, the EPA Office of Water Regulations and Standards (Ref. 2-1.9 [13]) issued an ambient water quality criterion for benzene of 0.66 μg/l which, at their calculations, corresponded to a risk of one additional cancer for every million people exposed for their lifetime to this concentration of benzene in their drinking water. This value was in fact based on a quantitative risk assessment performed in 1978 by the EPA Carcinogen Assessment Group (CAG) (Ref. 2-1.9 [12]) using occupational leukemia data from three epidemiological studies of workers exposed to high levels of benzene vapor. The 1980 water criterion assumes several simplifications which would be questioned on the basis of our present knowledge of benzene:

- The CAG risk calculation assumed that the relative risk of leukemia is "independent of the duration" of exposure, but is simply dependent on the total exposure. That is, CAG assumed that exposure to 1 ppm of benzene vapor for 10 years (equivalent to 10 ppm-years) would have the same toxicity as would exposure to 3650 ppm for 1 day (also equivalent to 10 ppm-years). This does not agree with the available clinical experience with benzene.
- During the past few months, better estimates of the actual benzene exposures seen by the cohort used in one of the critical epidemiological studies modeled by CAG have become available. These suggest that the levels of benzene exposure assumed by CAG were substantially lower than those actually experienced by the worker, and that as a result, the calculated risk is overestimated by the CAG calculations.
- The authors of the water quality criteria document assumed that benzene is as equally toxic by the oral route as by the inhalation route. This simplification fails to recognize that blood drains from the gastrointestinal tract to the liver which is the primary site of benzene metabolism. In contrast, inhaled benzene is distributed throughout the body prior to metabolism by liver enzymes.
- The authors of the water quality criteria document did not consider fully the relative contribution of the multi-media sources of normal benzene exposure. Using the formulas in the criteria document, it is interesting to note that while the leukemia risk associated with the daily ingestion of water containing 0.66 μg/l of benzene (1.32 μg/day) is 1 per million, the risk associated with eating a boiled egg every day is 79.5 per million.

FIGURE 2-1.8 [1] MAMMALIAN METABOLISM OF BENZENE

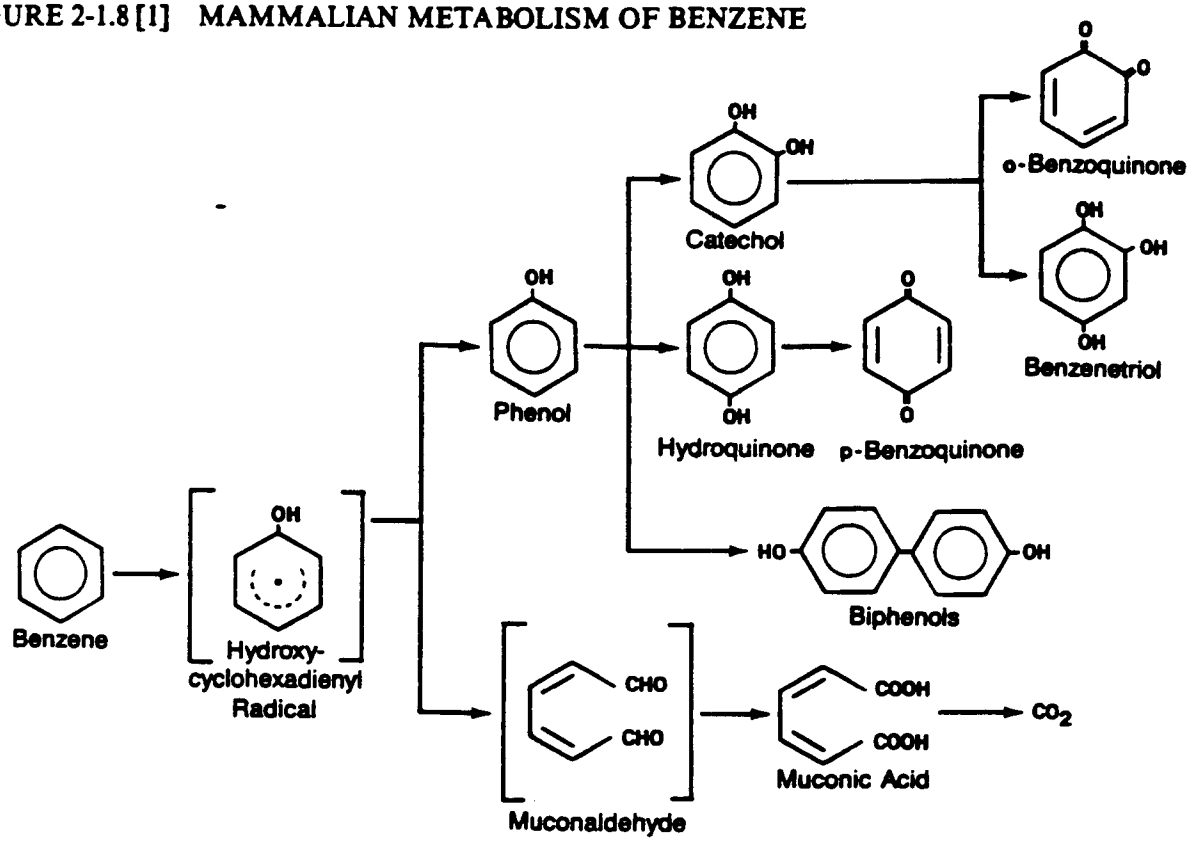
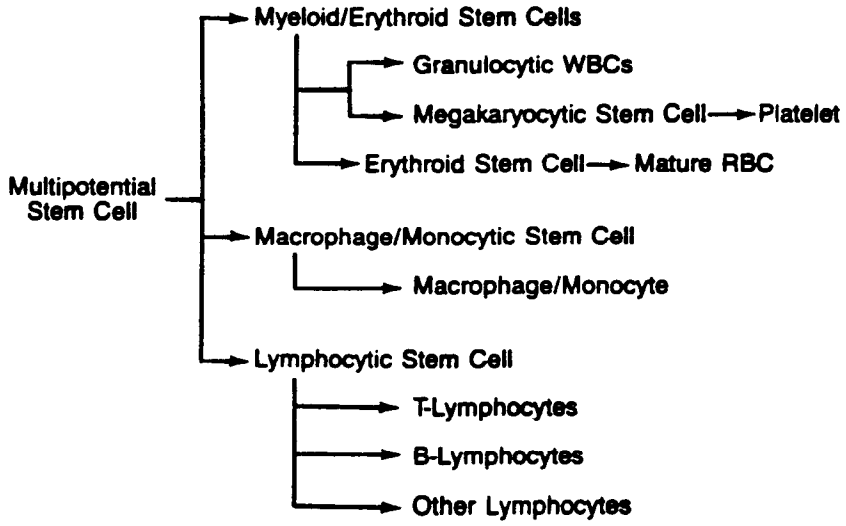


FIGURE 2-1.8 [2] SCHEMATIC OF BLOOD CELL DIFFERENTIATION AND MATURATION



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2-4 NONDRINKING-WATER EXPOSURE

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2-4.1 Occurrence

2-4.1(1) Food

Data on the occurrence of benzene in food are limited. Mara and Lee (Ref. 2-4.4 [11]) reported that benzene occurs naturally in fruits, fish, vegetables, nuts, dairy products, beverages, and eggs. These authors report concentrations ranging from 2 micrograms per kilogram (μg/kg) for canned beef to 2,100 μg/kg for eggs. Cooked meats are reported to have higher benzene levels than raw meats, and it is postulated that the increased benzene levels observed after cooking meats is due to the breakdown of aromatic amino acids such and tyrosine (Ref. 2-4.4 [5]).

Low levels (<10 μg/kg) of benzene in food could be due to a partitioning from the ambient levels of atmospheric benzene. The high levels observed in eggs indicate an intrinsic mechanism for the biochemical formation of benzene. Table 2-4.3 [1] summarizes the reported occurrence of benzene in foods.

2-4.1(2) Air

The materials balance for benzene indicates that 95 percent of environmental releases of benzene are to the atmosphere, and three-quarters of this release is associated with fuel combustion (Ref. 2-4.4 [5]). As a result of these emissions, it is not surprising that ambient air levels of benzene have been correlated with traffic volumes (Ref. 2-4.4 [2]).

Atmospheric benzene is ubiquitous; remote regions have measured concentrations usually ranging from 1 to 3.5 micrograms per cubic meter (μg/m^3). Higher levels are observed in urban and industrial environments. Table 2-4.3 [2] summarizes benzene concentration ranges and averages for various atmospheric environments.

Indoor benzene levels have been studied in industrial settings. Inside chemical plants, reported concentrations range from 2,000 to 10,000 μg/m^3. The current Occupational Safety and Health Administration (OSHA) regulation on workplace exposure is 32,000 μg/m^3 (10 parts per million, ppm) for the time-weighted average (TWA) concentration for an 8 hour exposure with a peak maximum concentration of 160,000 μg/m^3 (50 ppm) for any 15 minute period during an 8 hour day (Ref.2-4.4 [1]).

Indoor benzene levels in residences have been reported by Sample and Gilbert (Ref. 2-4.4 [14]) to have a median value of 15.0 μg/m^3 and an arithmetic mean of 25.8 μg/m^3 for 353 nighttime observations of benzene. There is a minimal correlation between indoor concentrations and outside ambient levels. The impact of smoking on indoor benzene concentrations appears to be important in households containing one or more smokers. These households exhibit at least 50 percent greater concentrations than households of nonsmokers. One cigarette can generate approximately 90 micrograms (μg) of benzene (Ref. 2-4.4 [5]). The portion of the benzene in the mainstream smoke is predominantly absorbed by the smoker and not exhaled. Mainstream smoke is that which the smoker inhales; however, the sidestream smoke which is released to the room often contains twice the quantity of some chemicals as the mainstream smoke (Ref.2-4.4 [6]). Therefore, of the 90 μg of benzene released from each cigarette, possibly 60 μg is released to the smoker's environment through the sidestream smoke.

2-4.2 Exposure

Reported benzene concentrations in foods do not involve all food groups. It is not known how representative these concentrations are of the concentrations in foods in general. Dietary intake of benzene has been estimated to be as high as 250 micrograms per day (μg/day) from beef, eggs, and rum alone (Ref. 2-4.4 [13]). Assuming that the average adult male weighs 70 kg, an intake of 250 μg/day would be equivalent to 3.6 micrograms per kilogram per day (μg/kg/day). In the absence of further data, Letkiewicz *et al.* (Ref. 2-4.4 [8]) assumed the dietary intake of benzene was at that level. Gilbert *et al.* (Ref. 2-4.4 [5]) estimated the ingestion due to only those foods with reported benzene concentrations (i.e., butter, cooked beef, eggs, and haddock), resulting in a daily ingestion intake of 31 to 108 μg/day.

Exposure to benzene in the atmosphere is highly variable; reported levels range between low parts-per-billion values in outside air to low parts-per-million in certain industrial settings. Median air concentrations of benzene have been calculated by Brodzinsky and Singh (Ref. 2-4.4 [3]) for rural/remote areas (4.5 μg/m^3), urban/suburban areas (8.9 μg/m^3), and source-dominated areas (9.6 μg/m^3). Thus, in urban/ suburban areas, people inhale approximately 180 μg of benzene each day (at 20 cubic meters, m^3, of air inhaled each day). As a comparison, a one-pack-per-day smoker inhales approximately 600 μg/day of benzene from mainstream smoke. Exposure by these routes is substantial, but highly variable in the general population.

Average annual atmospheric benzene concentrations and the size of exposed populations have been calculated by Mara and Lee (Ref. 2-2.4 [11]) based on air dispersion models. Approximately half of the population of the United States was estimated to be exposed to average atmospheric benzene concentrations between 3.5 and 13 μg/m^3.

A newborn, formula-fed infant's respiratory intake of benzene can be expected to range from 1.0 to 2.2 μg/kg/day, whereas the intake of a nonsmoking, 70-kilogram (kg) adult male may vary between 1.5 to 360 μg/kg/day, depending on ambient benzene concentrations (Ref. 2-4.4 [8]).

TABLE 2-4.3 [1] Foods Reported to Contain Benzene

Fruits[a]	Vegetables[a]	Meat, Fish, and Poultry
Apple	Bean	Cooked beef (2 to 19 μg/kg)[c]
Citrus Fruit	Leek	Chicken (<10 μg/kg)[d]
Cranberry and Bilberry	Mushroom	Egg, hard boiled (500 to 1,900 μg/kg)[e]
Currants	Onion, *roasted*	Egg, uncooked (2100 μg/kg)[b]
Guava	Parsley	Haddock (100 to 200 μg/kg)[f]
Pineapple	Potato	Lamb, heated (<10 μg/kg)[d]
Strawberry	Soya Bean	Mutton, heated (<10 μg/kg)[d]
Tomato	Trassi, *cooked*	Veal, heated (<10 μg/kg)[d]
Nuts[a]	**Dairy Products**	**Beverages**
Filbert, *roasted*	Butter (0.5 μg/kg)[b]	Cocoa[a]
Peanut, *roasted*	Blue Cheese[a]	Coffee[a]
Macademia Nut	Cheddar Cheese[a]	Jamaican Rum (120 μg/kg)[g]
	Other Cheese[a]	Tea[a]
		Whiskey[a]

[a] Ref. 2-4.4 [16]
[b] Ref. 2-4.4 [15]
[c] Ref. 2-4.4 [13]
[d] Ref. 2-4.4 [12]
[e] Refs. 2-4.4 [9], [10]
[f] Irradiated and non-irradiated haddock, respectively.
[g] Ref. 2-4.4 [7]
[h] Ref. 2-4.4 [11]

Source: Ref. 2-4.4 [5]

TABLE 2-4.3 [2] Summary of Benzene Occurrence in Air

Environment	Benzene Concentration (μg/m³)
Remote (Range)	1 to 3.5
Urban (Range)	4 to 160
Residential — Remote from Traffic (Average)	4.5
Near Chemical Plant (Average)	14
Near Refineries (Average)	9
Gas Stations (Range)	<1 to 32

Sources: Refs. 2-4.4 [5], [8]

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DPL1T - PHENOL (9CI) 12/01/80

Accidental spillage of phenol caused contamination of wells in a rural area. Human illness characterized by diarrhea, mouth sores, dark urine and burning of the mouth was reported. Estimated phenol intake was 10 to 240 mg/day. Physical and laboratory examinations 6 months after the exposure revealed no residual abnormality in exposed persons (75).

HSDB - PHENOL 04/16/87
ENVIRONMENTAL FATE/EXPOSURE SUMMARY - ENVS

(1) NOTE: This is a summary of environmental fate data included in this HSDB record. Phenol is a common and important industrial chemical and enters the environment in wastewater and spills connected with its use in resins, plastics, adhesives, or other uses. It is frequently found in wastewater from other commercial processes. Once in the environment, its primary removal mechanism is biodegradation which is generally rapid (days). Since phenol is a benchmark chemical for biodegradability studies, there is a large body of information on its degradation which concludes that phenol rapidly degrades in sewage, soil, freshwater and seawater. Acclimation of resident populations of microorganisms is rapid. Under anaerobic conditions degradation is slower and microbial adaptation periods longer. Biodegradation is rapid enough that phenol may degrade in soil and subsoil before reaching groundwater. Monitoring studies support these conclusions: phenol is rarely found in drinking water, and the levels found in rivers and lakes tend to be quite low. Exceptions are spills in which high phenol concentrations are toxic to microorganisms or when soil residence time is very short; then phenol will collect in groundwater and may remain for some time. Phenol is very soluble in water and poorly adsorbed on soil, clay, or aquifer material. Phenol's evaporation rate from water is low although it has an intermediate vapor pressure. This latter fact allows evaporation from spills on soil to occur. Phenol will not bioconcentrate in the food chain. However, there is experimental evidence that phenol metabolites may bioconcentrate in fish. In air, phenol would be expected to photolyze and react with hydroxyl radicals. It should also photodegrade in water, especially humic waters, and is catalytically degraded on sand. Inhalation exposure to phenol is largely restricted to occupational environments. General exposure will occur through the use of disinfectants and cleaners containing phenol. (SRC)

HSDB - PHENOL 04/16/87

(1) Phenol is degraded by bacteria, fungi, yeast and algae commonly found in the environment(1-17). Degradation is to carbon dioxide or methane and carbon dioxide in aerobic and anaerobic systems, repectively(1-17). Phenol is a benchmark chemical for biodegradability studies and therefore there are a large number of studies done in a variety of systems(SRC). Degradation is generally rapid and acclimation is rarely required(1-17). Removal in activated sludge reactors is frequently better than 90% with retention of 8 hours(4). Partial inhibition has been noted at concentrations as low as 50 ppm(5). Utilization is also very high in anaerobic reactors although acclimation periods are longer and degradation slower - about 2 weeks(6,7). The results of die-away tests in rivers and lakes or in water in contact with soil report complete degradation in 1-2 days(8,9,10,11,12,14). Degradation is somewhat slower in salt water and a half-life of 9 days has been reported in an estuarine river(13,17). Degradation in soil is completed in 2-5 days even in subsurface soils(15).

detected in finished drinking water in US(4). (GROUNDWATER) Maximum of 1130 ppm in 9 wells in Wisconsin after a spill(5). 6.5-10,000 ppb in 2 aquifers 15 months after completion of coal gasification project(6).

HSDB - PHENOL 04/16/87
[PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82]
(1) ...CONCN OF ABOUT 4 PPM WILL IMPART A DECIDED PHENOL TASTE TO VEGETABLES & FRUIT GROWN WITHIN RADIUS OF MORE THAN A MILE FROM A PLANT WHERE SUCH VAPORS ESCAPE.

HSDB - PHENOL 04/16/87
(1) Calculated acceptable daily intake = 0.1 mg/kg.

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