NEEDS FOR RESEARCH ON BENZENE METABOLISM AND DOSIMETRY

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In the past, benzene was used extensively in the production of paints, resins, rubber, inks, and dyes. Evidence that persons exposed to high levels of benzene for extended periods of time suffer an increased risk of aplastic anemia and acute myelogenous leukemia (AML) (Ayres & Taylor, 1989), prompted the adoption of regulations by the U.S. government that limited occupational exposures to benzene (Wallace et al., 1990). Recent reports of increased hematotoxicity and leukemia among benzene-exposed workers in China corroborate the existing evidence that benzene causes both aplastic anemia and AML (Travis et al., 1994; Xia et al., 1995). As in previous studies, AML in the Chinese cohort was associated with constant, high-level exposures or high cumulative exposures.

Benzene is found in gasoline at a relative abundance of 1% by volume and is used in the chemical industry as a feedstock for the synthesis of many organic chemicals (Infante et al., 1977). Common sources of environmental exposure include gasoline fumes, automobile exhaust, and both mainstream and sidestream tobacco smoke (Runion & Scott, 1985). A clear concern is whether or not these ubiquitous, low-level exposure present a significant health risk to humans for AML, and what level of exposure can be considered to be of negligible risk. From a risk-management viewpoint, the purpose in understanding and quantifying the dosimetry and metabolism of benzene and its metabolites would be to use this information in characterizing the exposure-dose relationship for benzene. In particular, one would like to know how the concentration of key metabolites in bone marrow, including phenol, hydroquinone, muconaldehyde, and possibly benzene oxide, relates to the level of benzene to which an individual is exposed. These metabolites (with the possible exception of benzene oxide, the effects of which have not been investigated) appear to play an important role in benzene-induced myelotoxicity (Smith, 1996; Barale et al., 1990) and likely are significant in the induction of AML. Therefore, any nonlinearity in the exposure-dose relationship for these metabolites would be expected, in turn, to lead to nonlinearity in the exposure-response relationship for benzene-induced AML. Hence, determining or quantifying the shape of these exposure-dose relationships should

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improve estimates of the exposure-response relationship, particularly in extrapolating from high-level exposures at which benzene-induced AML is observed to low-level exposures of current concern.

There has been considerable effort to characterize the metabolism and disposition of benzene and its metabolites in rodents (e.g., Rickert et al., 1979; Gilmour et al., 1986; Sabourin et al., 1989; Schlosser et al., 1993; Mathews et al., 1998), as well as some work in nonhuman primates (Sabourin et al., 1992). These laboratory animal data are useful currently in that they can allow one to develop and validate physiologically based pharmacokinetic (PBPK) models in animals before attempting to extrapolate such models to humans. Further, one could potentially use rodent PBPK models to examine the relationship between benzene dosimetry and benzene-induced effects in rodents that might be considered precursor events and/or representative of human risks for AML. However, since there is not currently a confirmed animal model for AML induced by inhalation exposure to benzene, such modeling efforts are of limited utility beyond validating the PBPK model-development process.

There are two notable exceptions to the completeness of the data set for rodents. The first is the dosimetry of trans,trans-muconaldehyde (MUC). While it has been shown that exposure to MUC reproduces many of the myelotoxic effects of benzene exposure in rodents (Smith, 1996), blood levels of MUC from benzene exposure have not been reported. Thus, while MUC has been show to have the potential to play a key role in benzene-induced toxicity, its actual role, which depends on how much reaches the bone marrow during benzene exposures, is uncertain.

The second metabolite that has the potential to play a key role, and for which there are only very limited dosimetry data to date, is benzene oxide (Lindstrom et al., 1997). In fact, not only is the dosimetry largely unknown, but the effects of benzene oxide on bone marrow have not been evaluated. Since benzene oxide is an epoxide, and is known to form hemoglobin adducts, now that it is known to achieve measurable blood levels one would suspect that it plays some role in benzene-induced toxicity. Thus, both the pharmacokinetics and the pharmacodynamics of benzene oxide should be examined.

There have also been some studies of benzene dosimetry in humans (e.g., Inoue et al., 1986, 1998a, 1998b), but these have been restricted to analyses of changes in (expired) air concentration, blood levels of benzene itself, and urinary levels of metabolites, with the later being confounded by dietary levels of phenolics (Boogard & van Sittert, 1997). So one of the largest unknowns is the blood levels of benzene metabolites in humans resulting from benzene exposure. It is theoretically possible to estimate these levels using physiologically based pharmacokinetic (PBPK) modeling, given data now available on metabolism of benzene by human liver in vitro. But the existence of data that would allow such predictions to be checked would add considerable certainty to the process.
Another unknown is the potential presence of cytochrome P-450 2E1 (CYP2E1) in human bone marrow. CYP2E1 is found in rabbit bone marrow (Schnier et al., 1989), but not that of the mouse (Genter & Recio, 1994). While the level of CYP2E1 is likely to be low in bone marrow compared to liver, the production of small amounts of reactive metabolites by CYP2E1 oxidation in the target tissue might have as much impact as the production of larger quantities of such metabolites in the liver, since in the later case much of the metabolites produced may not reach the bone marrow.

The final area where experimental confirmation is with regard to the theory of Medinsky and coworkers (Medinsky et al., 1996) that aspects of benzene and phenol metabolism can be explained by zonation of metabolic enzymes in the liver. Hedli et al. (1997) reported the results of comparing benzene metabolism in the isolated, perfused mouse liver, specifically comparing the results of normal (orthgrade) versus reversed (retrograde) perfusion. The results of Hedli et al. (1997) are compatible with and support the zonation hypothesis, but this hypothesis predicts the primary effect to be on the metabolism of phenol, not benzene. In particular, phenol is a substrate for sulfotransferases, which are concentrated in periportal regions of the liver, while CYPE1, which would oxidize phenol to hydroquinone, is concentrated more highly in centrilobular regions. Thus with normal perfusion of phenol one would expect the primary metabolite observed to phenol sulfate as compared to hydroquinone, while with reverse perfusion a much higher proportion of hydroquinone (and its conjugates) experiments to test this aspect of the hypothesis have not been performed, and would be a valuable contribution in supporting or refuting it.

REFERENCES


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