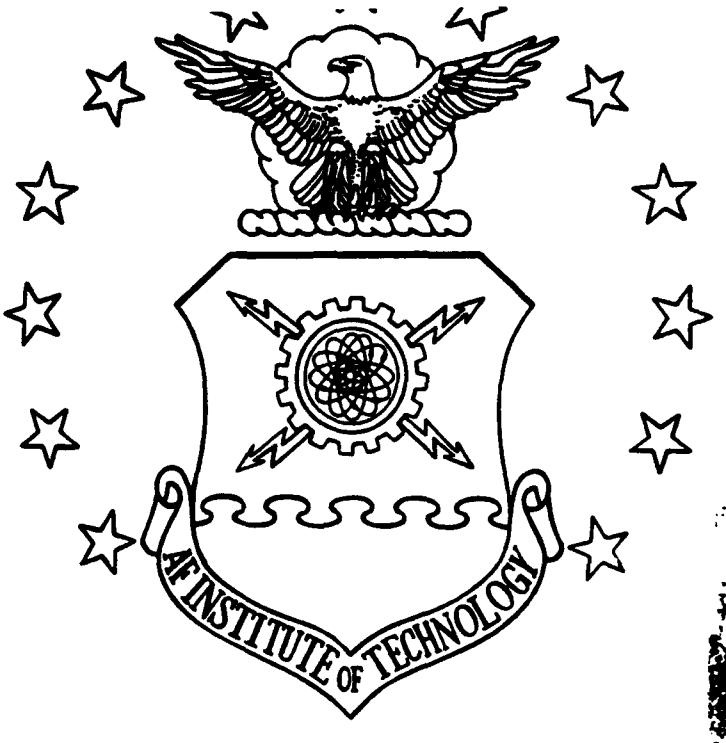

A COMPARATIVE PHARMACOKINETIC STUDY OF THE ROLE OF GENDER AND DEVELOPMENTAL DIFFERENCES IN OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO BENZENE

DEPARTMENT OF THE AIR FORCE
AIR UNIVERSITY
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Wright-Patterson Air Force Base, Ohio

AFIT/GEE/ENV/94S-12

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THESIS

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THESIS

Presented to the Falculty of the School of Engineering
of the Air Force Institute of Technology
In Partial Fulfillment of the
Requirements for the Degree of
Masters of Science in Engineering and Environmental Management

Elizabeth A. Brown, B.S.
Captain, USAF

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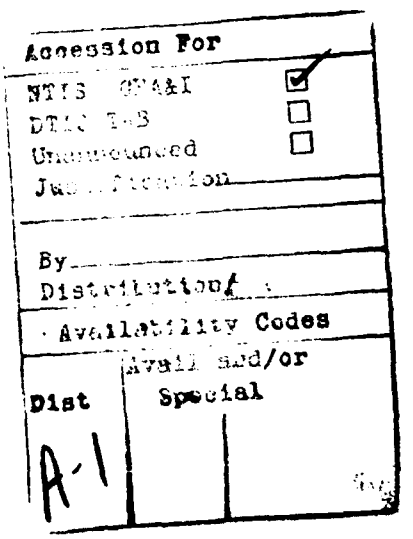

The views expressed in this thesis are those of the author and do not reflect the official policy or position of the Department of Defense or the U.S. Government.

Preface

The purpose of this study was to investigate the difference between men and women in their exposure to benzene, and to predict the potential and significance of an infant's exposure to benzene due to its mother's occupational and personal activities. The comparison was accomplished by conducting a sensitivity analysis of the benzene-specific physiologically based pharmacokinetic (PBPK) model to determine which human physical characteristics had the greatest influence on selected dose-metrics. The results of the sensitivity analysis assisted in the interpretation of the male and female results associated with exposure. The infant exposure prediction was accomplished by simulating a nursing mother's exposure through four scenarios which included occupational and environmental exposures. The dose-metrics were recorded for both the mother and infant, allowing for prediction of trends in exposure for both subjects.

Throughout this research effort, I have received exceptional instruction, advice, and guidance from others. I would like to thank my faculty advisor, Lieutenant Colonel Michael Shelley, for his constant support and patience. His interest in and understanding of the subject was a great inspiration for the accomplishment of this work. I would also like to thank Dr. Jeffrey Fisher at the Armstrong Laboratory Toxicology Division for the many hours he spent explaining the "art" of PBPK modeling and simulation, and for the volumes of literature he provided. His willingness to assist me while burdened by an extremely busy schedule of his own was greatly appreciated.

Elizabeth A. Brown

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Abstract

The purpose of this study is two-fold. First, it attempts to determine whether or not physiological differences between men and women result in gender-specific exposures with respect to benzene. Second, the potential for a lactating woman's occupational and personal benzene exposure to impact a nursing infant's exposure is assessed. This assessment highlights the possibility of subjecting an infant to the detrimental effects of industrial chemicals through breast feeding.

This study involves the use of physiologically based pharmacokinetic (PBPK) modeling to investigate the influence of physiological parameters on benzene exposure and to evaluate the ability of inhaled benzene to transfer from a mother to a nursing infant by way of breast milk. Two PBPK models were developed. The first model describes a 4-compartment adult human. The second model is a 5-compartment lactating woman with a 4-compartment nursing infant "attached". The fifth compartment represents mammary tissue and connects the infant compartments by way of breast milk flow. Both models are run through four scenarios that involve various combinations of occupational, smoking, and background benzene concentrations. Two measures of internal benzene exposure were used; the area under the venous blood concentration curve and the amount metabolized.

The gender comparison is facilitated by a sensitivity analysis which identifies the physiological parameters that impact the simulation output in this research. The most sensitive parameters were found to be the chemical-specific blood/air partition coefficient and maximum velocity of metabolism.

These values were both determined to be higher in women and caused an increase in the percentage of benzene metabolized during the different exposure scenarios. Because benzene metabolites are suspected of being the cause of adverse health effects, women appear to be more susceptible.

The study of lactating women and infants is essentially theoretical, since no empirical data exists to validate the chemical-specific infant parameters. By comparing the intake and amount metabolized across the various scenarios, there is evidence that at least 65% of an infant's benzene exposure can be attributed to contaminated breast milk. It is also likely that a large portion of the ingested exposure can be eliminated by developing a working or nursing schedule for the mother which provides at least two hours between cessation of high exposure events and feeding the infant.

A COMPARATIVE PHARMACOKINETIC STUDY OF THE ROLE OF GENDER AND DEVELOPMENTAL DIFFERENCES IN OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO BENZENE

I. Introduction

Objectives

The primary objective of this research is to determine whether or not physiological and biochemical differences between men and women result in gender-specific internal exposures for benzene. Secondly, this study will examine the potential for lactating women to expose their infants to benzene through nursing, and then determine if the infant's exposure can be reduced by modification of the mother's behavior.

Specific Problem

Benzene has been determined to cause cancer and other adverse health effects in humans. The precise mechanism for benzene toxicity is unknown, and individual susceptibility may be a factor for the development of chronic benzene toxicity (ATSDR, 1993:83). There are physical gender and developmental differences that may have an impact on the response to

benzene exposure in men, women and infants. With more women entering the workplace and potentially exposing their infants to occupational chemicals, there is a need for a comparative study to determine if there is a significant impact due to sex or developmental stage.

This thesis will use physiologically based pharmacokinetic (PBPK) modeling to develop and compare occupational, personal, and environmental benzene exposure scenarios for adult men, adult women, lactating women, and nursing infants. The research will attempt to determine if there is a difference in exposure due to sex and developmental stage, and it will quantify potential infant exposures to benzene as a result of the mother's exposure.

General Background

Assessing human health risks associated with exposure to volatile organic chemicals (VOCs) is a difficult task. Exposure assessments are used to develop guidelines and standards for exposure to VOCs, and accuracy in these assessments can affect how well a population is protected from health risks. Until recently, guidelines and standards were thought to adequately safeguard the average human population. However, as gender and developmental differences are more precisely defined, questions arise as to whether or not generic exposure assessments accurately quantify health risks for various sectors of the general population (ATSDR, 1993:94).

To date, most exposure standards are based on and supported by experimental research and epidemiological studies involving the human male population, since it has historically made up the majority of the workforce and has had the most exposure to chemicals. The basic assumption for

guidelines and standards has been that all human bodies respond similarly to chemical exposure; weight variations may be taken into account, but gender and development stages are rarely considered in exposure studies.

Gender and development are worthy of consideration because the physiological characteristics of women and infants vary from those of men not only in size and weight, but also in percentage of body fat, internal organ dimensions, breathing rates, and total body blood volume. These factors can have a significant impact on exposure and health risks associated with VOCs (Nomiyama and Nomiyama, 1974; Sato et al., 1975). Additionally, more women are entering the workplace and performing jobs for which the Occupational Safety and Health Administration (OSHA) has established exposure standards based on studies conducted only with men (ATSDR, 1993). These women may not be adequately protected by the existing standards due to physiological differences.

The increasing presence of women in the workplace requires exposure assessment to be taken one step further. Because benzene readily partitions to the fat in breast milk, women who return to work after having a baby can indirectly expose their nursing infants to benzene through occupational exposure. An infant exposure assessment is needed to predict the extent to which infants are exposed in this manner and the significance of that exposure with regard to the development of their organs and metabolic systems.

As stated earlier, the occupational population is changing and more research is needed to ensure VOC exposure guidelines adequately protect that changing population and its children. Although benzene and its adverse effects have been studied extensively, more work must be done regarding

variations in metabolic activity associated with sex and age and the connection to health effects (ATSDR, 1993:94). The need for more information provides the basis for this thesis.

Possible Benefits

A comparison of benzene exposure assessments for men and women will help determine if there is a need for considering gender-specific differences in the assessment of VOC exposure. Consideration of occupational and environmental benzene exposure will support or promote further study into the need for personal protection in the workplace and exposure guidelines for non-occupational activities. At this time, very little information is available concerning chemical exposure incurred by infants. The results of this research may help initiate further study and provide behavior modification suggestions to reduce the potential for infant exposure to benzene.

Overview

This thesis consists of four more chapters. The following chapter is a review of the literature concerning benzene, PBPK modeling, recent studies focusing on sources and health effects of benzene and its metabolites, and gender and developmental differences which may influence human exposure. Chapter three will describe the methodology used to obtain and compare data for this research effort, and the analytical results will be presented and discussed in chapter four. Finally, chapter five will draw conclusions, discuss uncertainties, and provide recommendations for refinement and further study.

II. Literature Review

The purpose of the literature review is to emphasize the need for this comparative research by describing the characteristics and hazards of benzene. Furthermore, it is intended to familiarize the reader with the concept and capabilities of physiologically based pharmacokinetic (PBPK) modeling. This section will conclude with a discussion and listing of physiological gender and developmental differences obtained from various sources which are critical for this study.

Benzene Related Research

Benzene is a ubiquitous VOC which has been studied extensively; however, comparative research based on gender or physiological development is seriously lacking. Studies of the adverse health effects associated with long-term exposure, the routes by which benzene enters the body, and the toxicity resulting from metabolism are plentiful and well documented in a generic sense, but they have left the differentiation of health effects between men and women unfinished. Additionally, very little information is available concerning infant exposure to and the transfer of benzene to infants via breast feeding. This section provides the justification for this research project.

Background. Benzene is a colorless, sweet-smelling, highly flammable VOC found in the environment and is produced by both natural sources and human activities. More than 98% of the benzene produced in the United States is derived from petrochemical and petroleum refining industries. A

small portion is also generated during the manufacture of coke from coal. Over the past 13 years, the average annual U. S. benzene production was between 11 and 12 billion pounds (ATSDR, 1993:103).

In industry, benzene has been widely used as a solvent and as a component of pesticides and adhesives, but because it has been classified as a suspected human carcinogen, its use is steadily declining. Today, benzene is most commonly used as an intermediate for the manufacture of other chemicals and end products such as styrene and plastics. It is also a component of gasoline since it naturally occurs in crude oil and has anti-knocking characteristics that are particularly beneficial when using unleaded fuel. The percentage by volume of benzene in unleaded fuel is 1-2% (ATSDR, 1993:105).

Environmental Sources. Environmental sources can be divided into three categories based on media (i.e., air, water and soil). Since benzene is a volatile compound, the primary medium addressed in this thesis is air.

Although there are minor contributions from natural sources, the greatest quantity of benzene is released into the atmosphere by "major point sources" such as automobile traffic, refueling operations, and industrial emissions (ATSDR, 1993:107-109). While these sources may account for the majority of environmental benzene, they are not necessarily the main sources of human exposure.

In 1979, the EPA initiated a Total Exposure Assessment Methodology (TEAM) study to assess human exposure to VOCs, including benzene. The study found that the main sources of human benzene exposure were associated with personal activities such as smoking, inhaling second-hand smoke, and pumping gasoline (Wallace, 1987, 1989a:167). These personal

activities are more efficient at delivering the substance to the receptor than major point sources such as industrial emissions or automobile exhaust (Wallace, 1989b:297).

In fact, smoking accounts for approximately 50% of the total population exposure to benzene. Major point sources were found to be of less concern, accounting for only 20% of the total population exposure (Wallace, 1989a:168; ATSDR, 1993:118). The TEAM study found the mean urban outdoor benzene concentration to be 1.9 parts per billion (ppb). In comparison, the mean indoor concentration in homes without smokers was 7 micrograms per cubic meter (2.2 ppb) and in homes with one or more smokers was 10.5 micrograms per cubic meter (3.4 ppb) (ATSDR, 1993:115; Wallace, 1989a:166).

Occupational Sources. People working in jobs that use or produce benzene are exposed to the highest concentrations of the substance. Workers may be exposed to potentially high benzene levels in seven major industry sectors: petrochemical plants, petroleum refineries, coke and coal-chemical plants, tire manufacturers, bulk fuel terminals, bulk fuel plants, and tank truck transport routes (ATSDR, 1993:118). In such occupational areas, OSHA set the 8-hour time weighted average (TWA) permissible exposure level for benzene at 10 ppm and requires engineering controls and breathing protection when this limit can not be feasibly met (ACGIH, 1991:116; OSHA, 1987).

Health Concerns. OSHA set the benzene exposure limit very low because the substance has been labeled a suspected human carcinogen (ACGIH, 1991:115), although the mechanism for toxicity is not well defined (Travis, 1989:400). Benzene is a lipophilic compound meaning it is attracted to fats, waxes and other similar substances; therefore, benzene has a high

affinity for body fat. This property might suggest that women absorb a larger amount of benzene because their body fat level is typically greater than that of men. However, the literature indicates that the human male population is more susceptible to developing leukemia and other illnesses which are linked to extended benzene exposure (HSDB, 1993).

In the United States, for example, women average 8 cases of leukemia per 100,000 while men average 11 cases per 100,000 each year. Additionally, animal studies have found evidence that indicates male mice are more sensitive than female mice to chromosomal damage in bone marrow due to benzene exposure. Because bone marrow is the site of blood cell production, chromosomal aberrations in these cells may influence the occurrence of leukemia (ATSDR, 1993:69).

Long-term (chronic) benzene exposure is of greatest concern to humans. The primary target for adverse effects from chronic exposure is the hematological (blood and blood-forming organs) system (ATSDR 1993:88). Chronic exposure to benzene vapors causes pancytopenia and can eventually result in aplastic anemia or leukemia (ATSDR, 1993:20).

Pancytopenia is characterized by a reduction in red and white blood cells and a reduction of platelets. It is caused by a decrease in the ability of red bone marrow to produce a sufficient quantity of blood cells. Aplastic anemia is a more severe condition. It occurs when the bone marrow stops functioning and blood cells fail to reach maturity. Aplastic anemia is thought to be a precursor to leukemia (ATSDR 1993:20).

Leukemia is a form of bone marrow cancer characterized by an increase in white blood cells and impaired blood clotting. The most common form of the disease in humans is acute myelogenous leukemia, which can lead to death

(ATSDR, 1993:34-39, 88-89). The leukemia-causing potential of benzene has been estimated by the Environmental Protection Agency (EPA) based on three separate epidemiological studies (Ott et al., 1978:3-10; Rinsky et al., 1987:1044-1050; Wong et al., 1983:365-395). All three of these research efforts were exclusively conducted with white males (ATSDR, 1993:35-37). Therefore, the influence of gender-specific differences on the adverse effects of exposure can not be determined from these studies.

Other epidemiological studies have strengthened the link between benzene and leukemia but have not provided a gender comparison (Aksoy, 1984:347-350; Infante, 1977:76-78; Yin et al., 1987:113-130). The Infante report was based on a study of white males, while the Aksoy study involved "Turkish workers" with no differentiation being made between the effects on male and female employees. The research conducted by Yin et al. focused on 300 Chinese solvent workers who were exposed to benzene, toluene (another VOC) or a mixture of the two. The workers were divided into three groups based on the type of chemical solvent they were exposed to. The three groups were additionally divided by sex, and each worker was examined for hematotoxic effects. Although the potential for a gender comparison existed, the study only compared the groups on the basis of the type of solvent exposure.

Exposure Routes. Exposure pathways for benzene to enter the human body include inhalation, ingestion and dermal contact. The primary route of exposure is inhalation, and a nursing infant may be additionally exposed through ingestion of contaminated milk. The dermal pathway is insignificant when compared to inhalation and ingestion and will not be considered in this study.

Inhalation. When benzene is released into the environment, 99.9% of the substance is emitted into the air. Because of benzene's volatility, inhalation is the primary exposure pathway for absorption into the human body. As a result, more than 99% of the adult total personal daily intake of the chemical is through inhalation (ATSDR 1993:107).

Once inhaled, benzene is distributed throughout the body by absorption, or assimilation, into the blood. As exposure continues, absorption declines because the blood concentration becomes equilibrated with the air concentration of the substance. A study of 23 people allowed to inhale 47-110 ppm benzene for 2-3 hours showed absorption to be highest in the first few minutes of exposure and then to rapidly decrease. Absorption was 70-80% in the first 5 minutes but was reduced to 50% after 1 hour (Srbova et al., 1950; ATSDR, 1993:48).

Because this compound is lipophilic, it is disproportionately distributed to fatty tissue groups. For example, benzene concentrations in various tissues of an 18-year-old white male who died from a combination of benzene poisoning and asphyxiation (he was found with a plastic bag over his head in which was a folded handkerchief) were as follows: 2.0 mg% in blood (mg% = mg per 100 ml of blood or mg per 100g of tissue), 3.9% in brain, 1.6 mg% in liver, 1.9 mg% in kidney, 1 mg% in stomach, 1.1 mg% in bile, 2.23 mg% in abdominal fat, and 0.06 mg% in urine (Winek and Collom, 1971:260; ATSDR 1993:51). As expected, a high concentration of benzene was found in the fat tissue. The high concentration in the brain was likely a result of the circumstances surrounding the youth's death and sampling procedures.

The majority of inhaled benzene is removed unchanged from the body by exhalation (ATSDR, 1993). The elimination rate and percentage excreted by

the lungs is dependent on the dose and route of exposure. In a study of six male and six female human volunteers exposed to 52-62 ppm benzene for 4 hours, respiratory retention was approximately 30%. Respiratory retention is measured as the amount of substance not exhaled. The percentage retained (R) is calculated as follows:

$$R = (C_i - C_e)/C_i \times 100$$

where C_i = benzene concentration in inhaled air;
C_e = benzene concentration in exhaled breath.

Retention was measured by collecting exhaled breath for 3 minutes at hourly intervals during exposure. There was no significant gender difference in respiratory excretion of the compound (Nomiyama and Nomiyama, 1974:80; ATSDR, 1993:48).

Another study, however, exposed male and female workers to 25 ppm benzene for 2 hours and showed that benzene was retained longer in the female subjects (Sato et al., 1975:327; ATSDR, 1993:51). This study measured both blood and exhaled breath concentrations during exposure and for 5 hours following exposure. During exposure, the blood concentration levels were higher in men while the exhaled breath concentrations of both men and women were essentially equivalent. However, 4 hours after exposure had stopped, the female blood and exhaled breath levels were higher than those of the male workers. These findings were concluded to be a result of the higher fat content of females.

Ingestion. There is little definitive information available concerning human oral exposure to benzene with the exception of individual case studies of accidental or intentional poisoning. These case studies do indicate that benzene can be absorbed into the body by the ingestion pathway.

The potential for infants to ingest occupational chemicals through nursing has been the focus of several studies in recent years (Byczkowski and Fisher, 1992; Fisher et al., 1993; Schreiber, 1993). These studies have predicted the concentration of various VOCs in breast milk following occupational exposures and modeled the potential infant exposure. Benzene has not been the focus of these studies.

Metabolism. Once benzene is taken into the body through an exposure route, it is metabolized by the liver. The liver is believed to play a critical role in the activation of toxicity in the human body (ATSDR, 1993:53). There is a general consensus in the field that benzene metabolites (products of metabolism) are the primary agents for toxicity (Medinsky, 1989:194). This theory is supported by animal studies. One such study, which involved the partial removal of liver tissue from rats, produced a reduction in both the metabolism and toxicity of benzene. These findings indicate metabolites formed in the liver influence the chemical's toxic effects (Sammett et al., 1979; ATSDR, 1993:53).

The major metabolites produced through the metabolism of benzene are phenol, hydroquinone and muconic dialdehyde, all of which can produce hemotoxic effects (ATSDR 1993:57). Benzene can also stimulate its own metabolism by increasing the activity of the P-450 enzyme system. This, in turn, increases the rate at which toxic metabolites are formed (ATSDR, 1993:55).

Because metabolism is a key component for benzene toxicity, PBPK modeling is an ideal tool for conducting exposure assessments for this compound. Unlike other modeling techniques, PBPK can account for the route and duration of chemical exposure, the rate of metabolism and

chemical distribution to specific organs and tissue groups. These capabilities provide more physiological realism for exposure assessments than other methods.

Modeling

Accurate and timely estimates of health hazards are essential to protect the human population. When epidemiological data is unavailable, mathematical modeling may be the only way to assess health risks associated with a chemical. Pharmacokinetic modeling has improved with technology and continues to be the most accurate analytical assessment tool available for volatile organic chemicals. The following section contains descriptions of modeling techniques and pertinent PBPK research.

Pharmacokinetic Modeling. Pharmacokinetic modeling is an assessment tool designed to describe the dynamic activity of chemicals in biological systems. The models are validated with data from experimental animal research or epidemiological studies. Pharmacokinetic modeling began with the classical method and has evolved into a physiologically based technique.

Classical pharmacokinetic modeling. Until ten years ago, this type of modeling was the primary tool for assessing human chemical exposure. The classical technique attempts to predict the dose-response relationship between a chemical and an effect in a body. This is accomplished by describing the body as a system of interconnected compartments with each compartment representing tissues or fluids which are kinetically similar. The parameters used in such models are considered to be representative of

functionally homogeneous tissues with common chemical disposition characteristics.

The composition of a compartment depends on the chemical being studied and how well the entire body can be monitored (Tuey, 1980:44-45). Because the compartments do not correspond directly to real anatomical tissue, the predicted response can not be correlated to a specific target tissue. A target tissue is defined as one for which a chemical exerts an adverse effect -- the site of response. For example, the lungs are a target tissue for tobacco smoke. When a person smokes, the lung tissue is exposed to chemicals such as benzene and nicotine; extended exposure can result in lung cancer and emphysema.

Classical modeling provides useful characterizations of the overall time course of chemical disposition, but it can be limited when trying to correlate model results with empirical data (Tuey, 1980:54). Restricting the model size to one or two compartments is sometimes done to improve the fit of the model with empirical data. However, this approach may oversimplify biological systems. A newer modeling technique which uses physical and biochemical parameters such as blood flow and metabolic rates can bypass some of the limitations of the classical method.

Physiologically Based Pharmacokinetic (PBPK) Modeling. PBPK modeling is a newer modeling technique that has been refined over the past ten years. Unlike classical, PBPK modeling can predict chemical doses received by a target tissue of an experimental subject. It is a more accurate tool for complex exposure assessments since it employs a physiologically realistic model to predict parts of the human body that are most susceptible to adverse effects from chemical exposure.

PBPK modeling attempts to provide more accurate predictions by incorporating the time-dependent uptake, distribution, metabolism and elimination of a chemical in a body (Clewell, 1988:A125). The models describe a biological system as a number of physiologically realistic compartments and mathematically represent the behavior of a substance within that system. Various tissue groups and organs are organized into compartments on the basis of similar blood flows, chemical solubility characteristics, and metabolic activity. Each compartment is connected to other appropriate compartments through arterial and venous blood flow routes, thereby creating a physically realistic model.

Figure 2-1 is a graphic representation of a generic PBPK model. The alveolar space and lung blood boxes represent the breathing function and are not considered tissue compartments. This portion of the model is required to initiate chemical distribution following inhalation exposure. Because chemicals are often attracted to or accumulated in fat tissue, it is of particular interest in PBPK modeling and, therefore, has its own compartment. Blood flows rapidly through internal organs such as the heart, kidney and brain so these tissues are grouped together into the richly perfused compartment. The slowly perfused compartment commonly consists of skin and muscle tissue, and the liver compartment accounts for metabolism and initiates chemical distribution after an oral exposure.

In a PBPK model, systems of linear ordinary differential equations describe the mass-balance relationships in a body. They represent the rate of change of each well-defined compartment's input, output, and metabolic activity. Once parameter values are integrated into the equations, they can then be solved simultaneously with computer assistance.

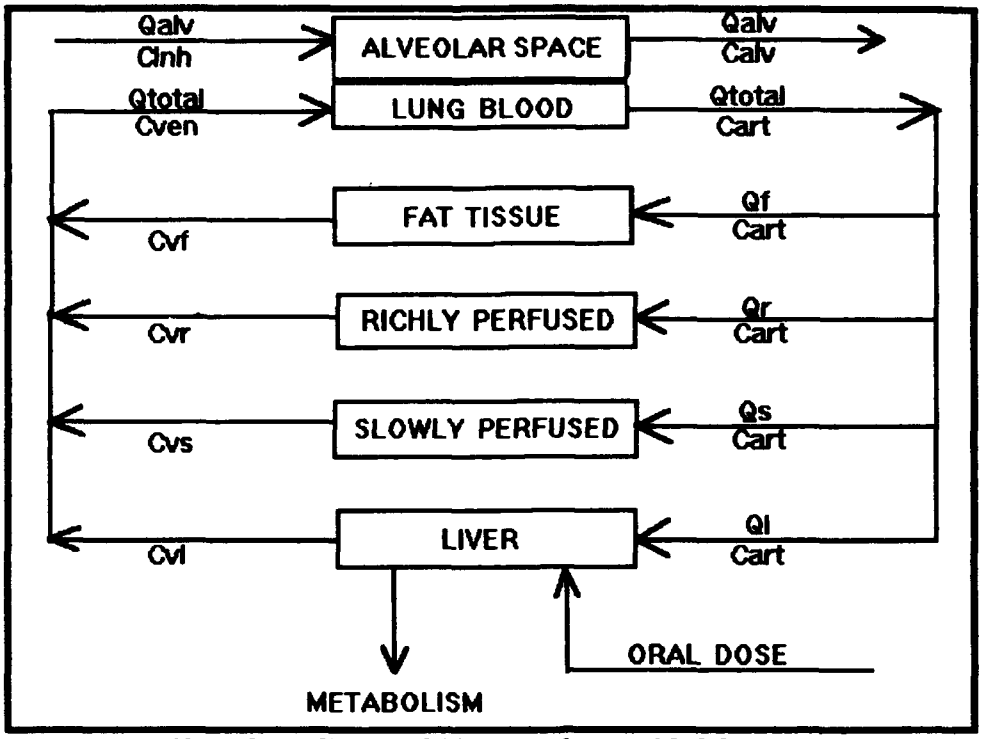

Figure 2-1. Physiologically Based Pharmacokinetic Model

Q variables represent blood flow rates.

Cart variables are arterial chemical concentrations.

Cv variables are venous chemical concentrations.

Model parameters have actual values that define a specific tissue group. For example, the experimentally determined blood flow rate to the liver is necessary to define the liver compartment in a model. This input provides physiological realism and can be changed to study its influence on the model.

The equations and parameters of a model can be arranged to describe a variety of experimental subjects and can also predict responses to various chemical exposure scenarios. Additionally, differences within a species can be incorporated into a PBPK model to provide a more accurate picture of chemical responses across that species.

An advantage of this technique is that exposure responses can be more realistically estimated with fewer animal studies and without endangering human life. Also, target tissue effects for a multitude of scenarios can be assessed in a short period of time once the basic model has been developed and parameters have been defined.

PBPK Research

The first widely recognized PBPK toxicology model was achieved in 1984 by Ramsey and Andersen (1984:159) with their simulation of the behavior of styrene (another VOC) in rats and humans. Their model described the body with four tissue groups: highly perfused, moderately perfused, slowly perfused, and metabolizing tissue, each of which was defined by parameters that could be changed to describe either a human or a rat. The model was run with rat parameters and then verified by comparing simulated styrene concentrations in blood with actual data from rat experiments. The rat simulation was found to be accurate, thereby providing a rational basis for using PBPK modeling to simulate chemical exposure in humans (Ramsey and Andersen, 1984:172). Because of its success and improved accuracy, this model has been used as the foundation for PBPK research worldwide.

Benzene-Specific Modeling Efforts. Although PBPK modeling is a rather new technique, a number of research efforts have employed the tool to assess the risks of benzene exposure. Travis et al. (1990) examined the pharmacokinetics of benzene for mice, rats and humans with PBPK modeling. Their research involved simulating benzene exposure by inhalation, ingestion and injection. By comparing the analytical results with empirical data, they demonstrated the capability of PBPK modeling to

describe the behavior of benzene in three different species across various routes of exposure. Some of the physical parameters used to define the human male model have been incorporated into this thesis (Travis et al., 1990:404). These parameters include the slowly and richly perfused tissue volume fractions and the Michaelis-Menten constant.

Bois et al. (1990) developed a PBPK model to examine the relationship between benzene and cancer. This model was unique because it used a range of viable values for physical parameters instead of single empirical values. It also investigated the role of benzene metabolites as opposed to benzene in the formation of carcinogenesis. The results indicated that the carcinogenic effects of benzene are not caused by a single metabolic transformation pathway but more likely by the involvement of several metabolites. The Bois work highlighted the importance of benzene metabolites and provided justification for emphasis of metabolism in this work.

Nursing Infant Exposure Modeling. The study of infant physiology and the effects of occupational chemicals on infants is attracting greater interest in the research community. While it has been used to examine various chemicals, a PBPK model of an infant has not yet been used to assess nursing infant exposure to benzene. Predicted infant exposure to other VOCs has been modeled and is of value for this thesis.

One of the first studies to use PBPK modeling to predict infant exposure to VOCs through breast feeding was conducted by Schreiber (1993). She developed a model to determine the concentration of perchloroethylene (PCE -- a dry-cleaning solvent and VOC) in human breast milk as a function of occupational and residential exposure scenarios. The results of the modeling effort indicated that a nursing infant may receive high levels of the chemical

as a result of its mother's occupational exposure. This work employs a 4-compartment PBPK model for a lactating woman and a milk fat percentage of 4% as used in this thesis.

To further refine Schreiber's work, Byczkowski and Fisher (1992) expanded the PBPK model for PCE (Figure 2-2). Building on Schreiber's 4-compartment model, they added a milk compartment and integrated a nursing infant model. This research provides the basis for the nursing infant exposure model for benzene.

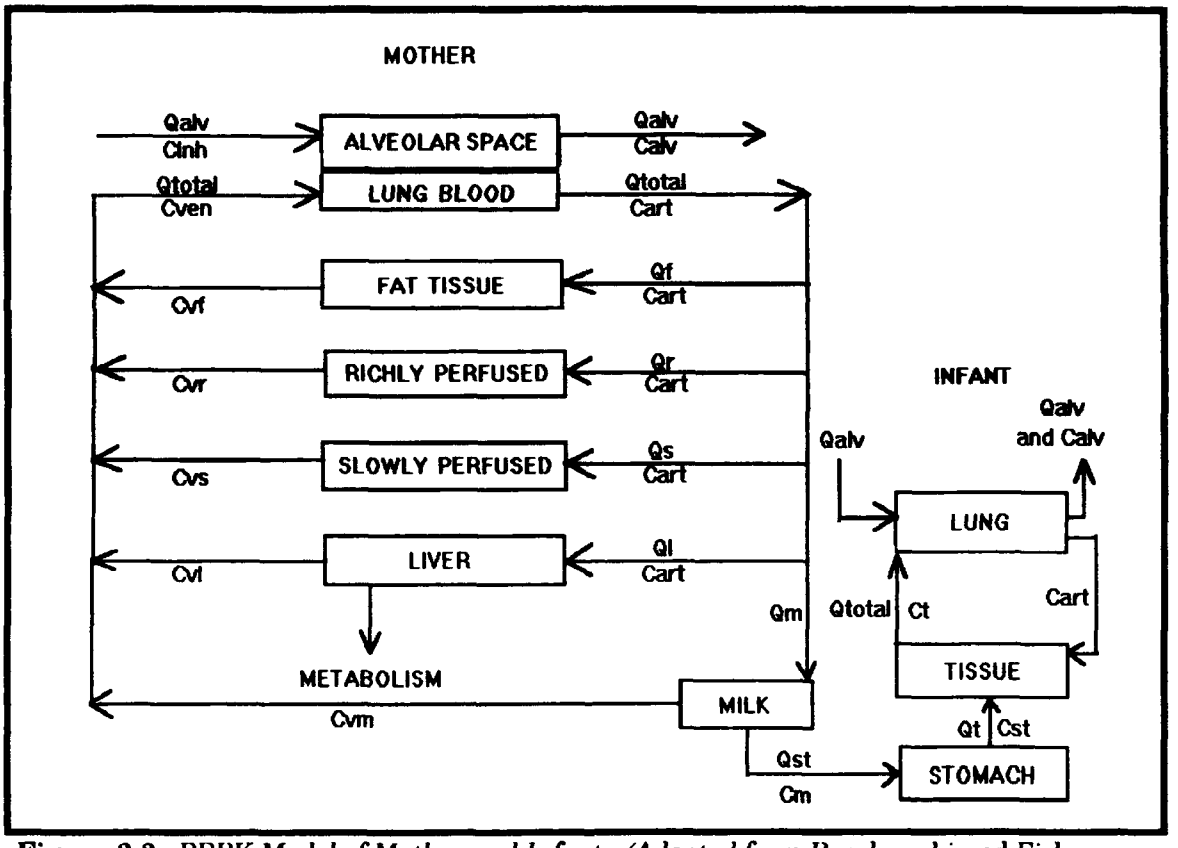

Figure 2-2. PBPK Model of Mother and Infant. (Adapted from Byczkowski and Fisher, 1992:11).

The final study in this area used PBPK modeling to evaluate the ability of inhaled organic chemicals to transfer to human breast milk by way of the

circulatory system (Fisher et al., 1993). Blood and milk samples were taken from nine women to determine blood/air and milk/air partition coefficients for nineteen chemicals, one of which was benzene. This is the only literature published which provides empirical data on lactating women and uses a PBPK model of a nursing mother to predict nursing infant exposure to benzene, but it does not include an infant model. It is, however, a source of chemical-specific parameters for women.

As the referenced literature demonstrates, PBPK modeling can predict variations in chemical response related to intraspecies differences. This makes it the appropriate tool for comparing the effects of benzene on men and women and predicting infant exposure through breast feeding. The next step in this research is to determine the distinguishing factors between subjects which impact exposure.

Gender-Specific and Developmental Variations

While the physical and biochemical variations between men and women are abundant, only a select set of differences is considered in this study. Furthermore, there is little empirical data for human infants on which to base model parameters; therefore, the infant model is more theoretical than the adult models. The human values and chemical-specific parameters used in this research are listed in Table 2-1. Detailed references and derivations for the values are provided in Appendix B.

Men. Sources of male physiological data were easily found. Alveolar ventilation, blood flow fractions to various tissues, and the volume of some tissue groups were compiled from two medical reference manuals (Snyder et al., 1975; Smith and Kampline, 1990). Human partition coefficients for the

tissue groups were obtained from work conducted by Paterson and Mackay (1989:324).

Partition coefficients are functions of unique chemical properties and are unitless concentration ratios of that chemical in two different phases. For example, benzene's blood/air partition coefficient for a man was defined by Paterson and other sources as 7.8 (Paterson and Mackay, 1989:324; HSDB, 1993; Fiserova-Bergerova, 1983:16). This means that at equilibrium, the ratio of the benzene concentration in the blood to the concentration in air is 7.8. Partition coefficients are needed for the various tissue compartments in order to accurately predict the behavior of particular substances.

Other tissue volume fractions and the Michaelis-Menten constant were obtained from human benzene research conducted by Travis et al. (1990:404). Since no allometric equation was available for the Michaelis-Menten constant, the Travis value is used for all of the subjects. The maximum rate of metabolism was obtained from empirical male data collected by Sato et al. (1975:325). Further explanation of the derivation of this value is provided in the methodology section.

Women. Unlike the male model, the parameters for the female model were not as readily available. Alveolar ventilation, cardiac output and some tissue group volumes were provided in medical texts (Snyder et al., 1975; Smith and Kampline, 1990), and the blood flow values were calculated as a percentage of the total cardiac output. While the Michaelis-Menten constant was provided by Travis et al. and the maximum rate of metabolism was obtained from empirical female data collected by Sato et al. (1975:325), other chemical-specific parameters were not defined for women.

	PARAMETER	MAN	WOMAN	LAC. WOMAN	INFANT
Body Weight (kg)	**BW**	**70.0** [a]	**60.0** [a]	**60.0** [a]	**7.0** [c]
Alveolar Ventilation (l/hr) [a]	**QP**	**450.0**	**363.0**	**363.0**	**93.0**
Cardiac Output (l/hr) [b]	**QC**	**336.0**	**288.0**	**288.0**	**33.6**
Blood Flow (l/hr)					
Liver [b]	**QL**	**84.0**	**72.0**	**64.8**	**8.4**
Fat [b]	**QF**	**26.9**	**23.0**	**20.7**	**2.7**
Slowly Perfused [b]	**QS**	**95.8**	**82.1**	**73.9**	**9.6**
Richly Perfused	**QR**	**129.3** [b]	**110.9** [b]	**99.8** [g]	**12.9** [b]
Mammary [i]	**QMT**	–	–	**28.8**	–
Tissue Volume Fractions (%)					
Liver [a]	**VLC**	**2.6**	**2.3**	**2.3**	**3.4**
Fat [a]	**VFC**	**20.0**	**30.0**	**30.0**	**30.0**
Slowly Perfused [d]	**VSC**	**64.0**	**55.0**	**50.0**	**55.0**
Richly Perfused [d]	**VRC**	**6.0**	**5.0**	**5.0**	**4.0**
Mammary [i]	**VMC**	–	–	**5.0**	–
Partition Coefficients					
Blood/Air	**PB**	**7.8** [e]	**8.2** [f]	**8.2** [f]	**8.2** [f]
Liver/Blood [e]	**PL**	**2.95**	**2.80**	**2.80**	**2.80**
Fat/Blood [e]	**PF**	**54.5**	**51.8**	**51.8**	**51.8**
Slowly Perfused/Blood [e]	**PS**	**2.05**	**2.00**	**2.00**	**2.00**
Richly Perfused/Blood [e]	**PR**	**1.92**	**1.80**	**1.80**	**1.80**
Breast milk [f]	**PM**	–	–	**4.0**	–
Metabolic Parameters					
Michaelis-Menten Constant (mg/l) [d]	**KM**	**.35**	**.35**	**.35**	**.35**
Max. Velocity of Metabolism (mg/hr-kg)	**VMAX**	**13.89h**	**19.47h**	**19.47h**	**3.25d**

Table 2-1. Gender and Development Values.

a. Snyder et al. (1975).
b. Smith and Kampline (1990).
c. Polin and Fox (1992).
d. Travis et al. (1990).
e. Paterson and Mackay (1989).
f. Fisher et al. (1993).
g. Mepham (1983).
h. Sato et al. (1975).
i. Byczkowski and Fisher (1993).

Fortunately, the researchers at the Armstrong Laboratory have been able to obtain benzene partition coefficient values for lactating women with the help of nine volunteers (Fisher et al., 1993:12). These chemical-specific parameters were assumed the same for adult women as the values determined experimentally for lactating women. The tissue/blood partition coefficients were calculated for women by dividing the Paterson et al. (1989:324) tissue/air values by the empirical blood/air partition coefficient determined by Fisher et al. (1993:12) for lactating women.

Lactating Women. As mentioned in the previous section, the partition coefficients for lactating women were calculated on the basis of empirical data. For consistency, the majority of physical values and metabolism parameters were assumed the same as those of adult women. However, the blood flow values for the tissue groups are different. Because fat tissue is mobilized from the mammary tissue to other parts of the body during lactation, mammary tissue consists primarily of skin structures (Mepham, 1983:5; 1987:28) which are highly productive and require increased blood flow. During lactation, blood flow to the mammary tissue (QMT) is considered to be 10% of the total cardiac output (Byczkowski and Fisher, 1993). Therefore, all other blood flows are adjusted proportionally to account for the increased blood flow to this tissue group.

The slowly perfused tissue volume fraction (VSC) is reduced slightly to reflect the creation of a separate compartment representing mammary tissue in the model. The total volume of mammary tissue and the milk/blood partition coefficient were extracted from the research conducted by Byczkowski and Fisher (1993) and Fisher et al. (1993:12), respectively.

Infants. While the tissue volume fractions could be defined (Snyder, 1975; Polin and Fox, 1992), blood flow rates and maximum metabolism velocity values had to be scaled to an average nursing infant's weight. The gender of the infant was not a factor in this study, so the male and female values for maximum velocity of metabolism were averaged and then scaled to an infant's body weight of 7.0 kilograms. Furthermore, benzene-specific values for nursing infants were non-existent. As a result, the infant partition coefficients were assumed the same as those for the adult woman and lactating woman. The rationale behind this assumption was that an infant's body chemistry more closely resembles that of the mother's during early development.

Summary

The review of literature suggests there are exposure variations between men, women and infants with respect to benzene. Furthermore, personal activities such as smoking are also thought to be substantial sources of exposure. These impacts can be assessed with the use of PBPK modeling and illustrative exposure scenarios. To assess the influence of various physiological factors on benzene exposure, a sensitivity analysis will be conducted which will allow for a comparison to be made between men and women. To assess the impact of a mother's occupational and personal activities on her infant's exposure to benzene, venous blood concentrations of benzene and the amount metabolized will be recorded for each scenario. A detailed methodology is provided in the following chapter.

III. METHODOLOGY

This section defines the concepts and elements involved in model development and verification and goes on to describe the process by which this research was conducted. Exposure assessment is explained followed by a description of the four exposure scenarios developed for this study. These sections are followed by a discussion on model verification and the dose-metrics (measures of interest in exposure scenarios) selected for gender comparison. Sensitivity analysis will then be covered, followed by a description of the study of lactating women and infants. It concludes with a summary of the chapter.

Exposure Assessment

The physiological values for men, women, and infants are important elements for conducting an exposure assessment. However, these values alone are of little significance. They must be matched with situations which the population is likely to experience in order to provide a meaningful exposure assessment.

Exposure assessment is the key component of risk assessment. It is the process of measuring or estimating the intensity, frequency and duration of exposure to a substance (Shelley, 1993). The process consists of two steps -- evaluation of the transport pathways from a source to the point of human contact and estimation of the amount of contact between humans and the substance of interest (Masters, 1991:210).

As an example, let us consider benzene which is a constituent of unleaded gasoline that volatilizes when it hits the air. In the first step of the exposure assessment process, we might evaluate whether or not benzene fumes are transported from the fuel nozzle through the air and into a person's lungs. If we determine benzene does not reach the lungs, then the person is not exposed by this transport pathway and the process stops. If the lungs are exposed, we proceed to step two and attempt to estimate the amount of benzene contact a person has through the pre-established transport pathway. This estimate involves measurements of both chemical concentration and duration of exposure -- the two elements essential for the development of exposure scenarios.

Exposure Scenarios

The exposure scenarios developed for this research involve specified benzene amounts or concentrations and various exposure durations. Inhalation scenarios were developed using ACGIH and OSHA's maximum 8-hour time weighted average (TWA) exposure for benzene of 10 ppm, and Wallace's values for background and smoking concentrations (Wallace, 1989b). The background level in a non-smoking household is 2.2 ppb, while the level is 3.4 in a household with at least one smoker.

The scenarios are used to directly compare benzene exposure between men and women and to demonstrate the potential intensity of infant exposure to benzene as a result of the activities of its mother. The mother is exposed to four different scenarios. The infant inhales background levels of benzene and ingests varying amounts of the compound through breast feeding as a function of the mother's exposure. The infant ingestion

exposures were adapted from other studies (Schreiber, 1993; Byczkowski and Fisher, 1992). All of the simulations were conducted for a period of 28 days to ensure steady state conditions were achieved.

Inhalation Exposures.

a. Background Only: Non-smoking, non-occupationally exposed men, women, and lactating women receiving a residential background concentration of 2.2 ppb benzene 24 hours per day, for 28 days.

b. Smoking: Men, women, and lactating women smoking 32 cigarettes over a 14 hour period resulting in a daily inhalation of 1.8 mg (0.129 mg/hr) of benzene and receiving a residential background concentration exposure of 3.4 ppb benzene, 24 hours per day, for 28 days.

c. Working: Occupationally exposed non-smoking men, women, and lactating women inhaling air containing benzene at OSHA's TWA of 10 ppm for 8 hours a day, 5 days a week for 4 weeks. Subjects additionally receive a residential background concentration exposure of 2.2 ppb benzene for 16 hours, 5 days a week for 4 weeks. Two weekend days are simulated every 5 days with a 48 hour exposure at the background level of 2.2 ppb benzene.

d. Working and Smoking: Occupationally exposed men, women, and lactating women smoking 32 cigarettes over a 14 hour period resulting in a daily inhalation of 1.8 mg (0.129 mg/hr) of benzene 7 days per week for 4 weeks. Subjects also inhale air at OSHA's TWA of 10 ppm for 8 hours per day, 5 days a week for 4 weeks. Additionally, they receive a residential background concentration exposure of 3.4 ppb benzene for 16 hours, 5 days a week for 4 weeks. Two weekend days are simulated every 5 days with a 48 hour exposure at the background level of 3.4 ppb benzene and 14 hours per weekend day smoking exposure.

At this point, it is necessary to describe an anomaly in the modeling of the smoking exposure. From Wallace (1989a), the average smoker smokes 32 cigarettes per day and takes in 1.8 mg of benzene over that period and no distinguishing difference is made between the sexes as to the amount of benzene taken in. The model used in this research averages the 1.8 mg over a 14 hour period which is assumed to be the waking hours in which a person smokes. Furthermore, the resulting dose is divided by the alveolar ventilation of men and women to obtain a concentration for exposure. Since women have a smaller lung capacity, they must take in a higher concentration of benzene over the 14 hour period to inhale the same quantity of benzene as men.

In actuality, this model may underestimate the true benzene exposure resulting from smoking. This is because higher levels of benzene would be inhaled over the short periods when each cigarette is smoked. Averaging the amount of benzene taken in over a 14 hour period simplifies the modeling effort but increases uncertainty with the accuracy of results and reduces the realism of the modeling effort.

Ingestion Exposures. The inhalation scenarios defined for the lactating woman's benzene exposure are simulated with an infant model "attached" in the computer program, and the infant model incorporates a breastmilk consumption rate. From Schreiber (1993:519), it is assumed a 7.0 kg infant ingests 0.7 liters of breast milk per day. This amount averages to 0.033 liters per hour. However, when the mother works, the author assumes the infant is fed a milk formula that is not contaminated with benzene during the first eight hours of the day. Therefore, the infant will ingest 0.436 liters of

contaminated breastmilk when the mother works as opposed to 0.7 liters when she does not work.

The infant model structure is based on the work of Byczkowski and Fisher (1993) which used a model composed of three compartments representing the lungs, gastrointestinal tract and body tissue. The model in this research is similar, but the tissue compartment has been divided into fat, liver, slowly perfused and richly perfused compartments (Fig. 3-1). Additionally, the milk compartment has been divided into mammary tissue and milk to more closely simulate reality.

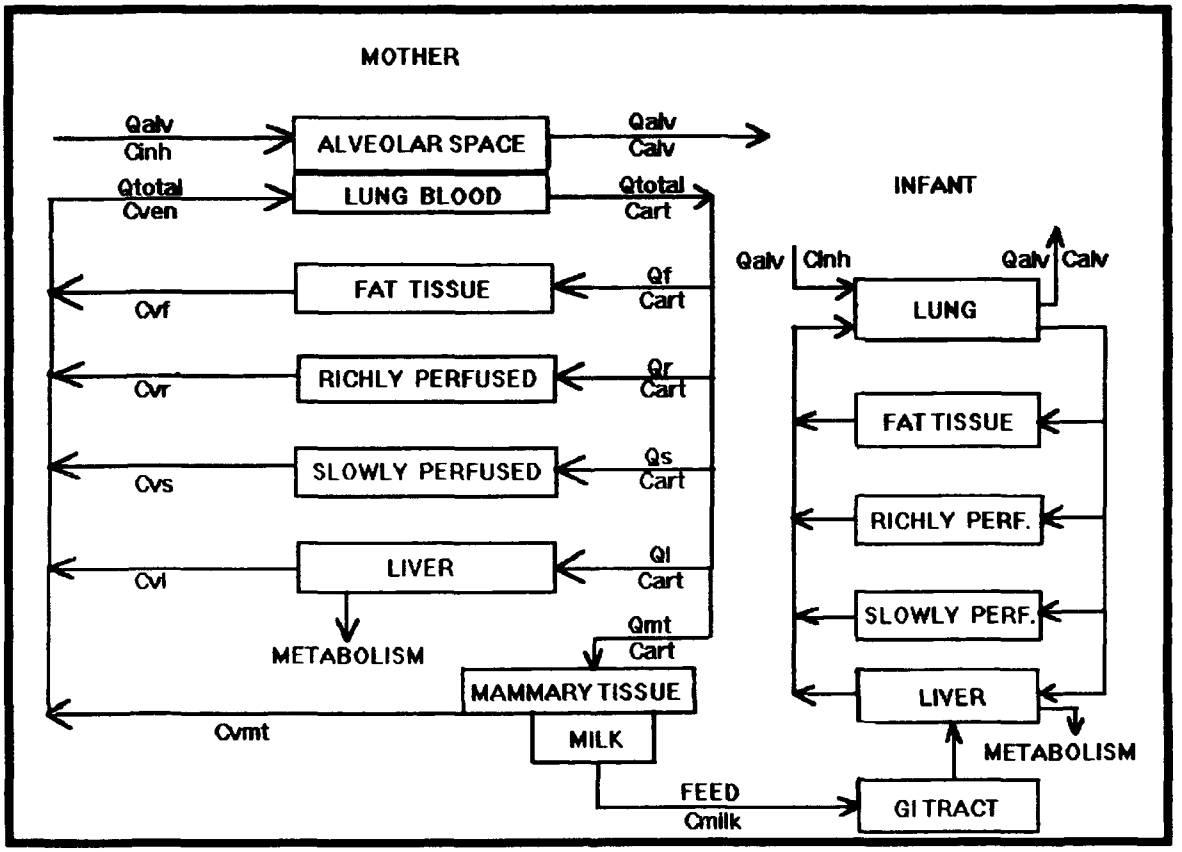

Figure 3-1. Modified PBPK Model of Mother and Infant. (Model used for this study.)

Computer Simulation

The SimuSolv (Mitchell and Gauthier Associates, Inc., 1986) software package is the computer programming tool used to design the PBPK models and simulate the exposure scenarios. The package employs the Advanced Continuous Simulation Language (ACSL) (Mitchell and Gauthier Associates, Inc., 1993), and contains the basic model structure complete with the differential equations needed for simulation. Once the physiological parameters and benzene-specific values were defined for each subject, they were input into SimuSolv as datafiles. A model was developed for each of the four inhalation scenarios for adult men and women, and four more models of the same scenarios were developed for the lactating woman and infant. By calling up various datafiles, the models could simulate exposure received by any of the subjects. The model code for each scenario is provided in Appendices C-J. The datafiles are listed in Appendix K.

Model Validation

Very little empirical human data was available for model validation of male and female subjects. However, the Sato et al. study (1975:325) provided saturation and desaturation curves of benzene in blood and exhaled breath for both men and women (Figure 3-2). The research involved five male and five female Japanese medical students with average body weights of 60.4 and 55.4 kg, respectively. Besides the fact that all of the volunteers aged between 21 and 24 years old, no other physical data was provided. Data points were extracted from the curves in the literature and the PBPK model predictions were overlaid on the data to validate the adult man and woman models for

this research (Figure 3-3 and 3-4). The physical parameters used to simulate the students and data points extracted are provided in Appendix L.

Definitive metabolic parameter values for VMAX were not available in literature for men or women; therefore, this value was determined by fitting the male and female model output to the empirical data from the Sato et al. study. The male model fits the data points quite well, but the female model does not provide the same quality of fit. It predicts a higher peak and more rapid decline in the venous blood concentration than is illustrated by the data points. A possible explanation for this occurrence is that the body fat levels or fat/blood partition coefficient of the female students was higher than estimated by the author. Therefore, the selected parameter values allowed

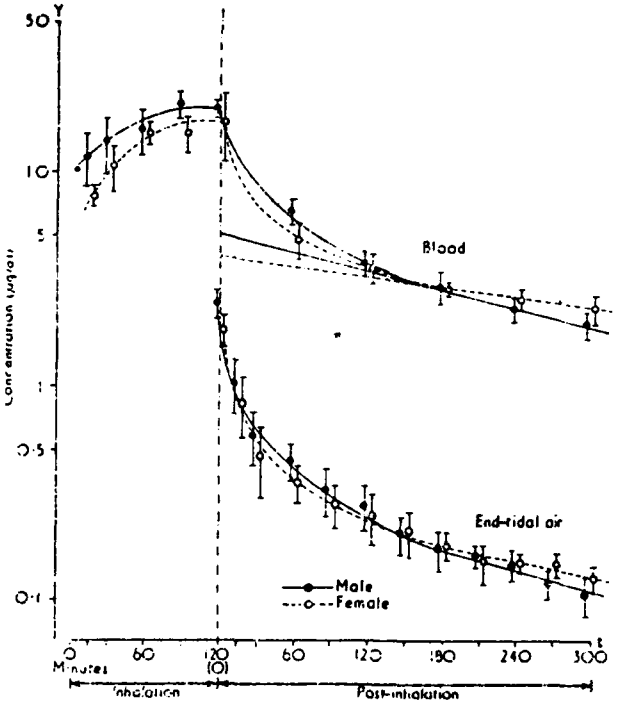

Figure 3-2. Human Saturation and Desaturation Curves Adapted from Sato et al. (1975).

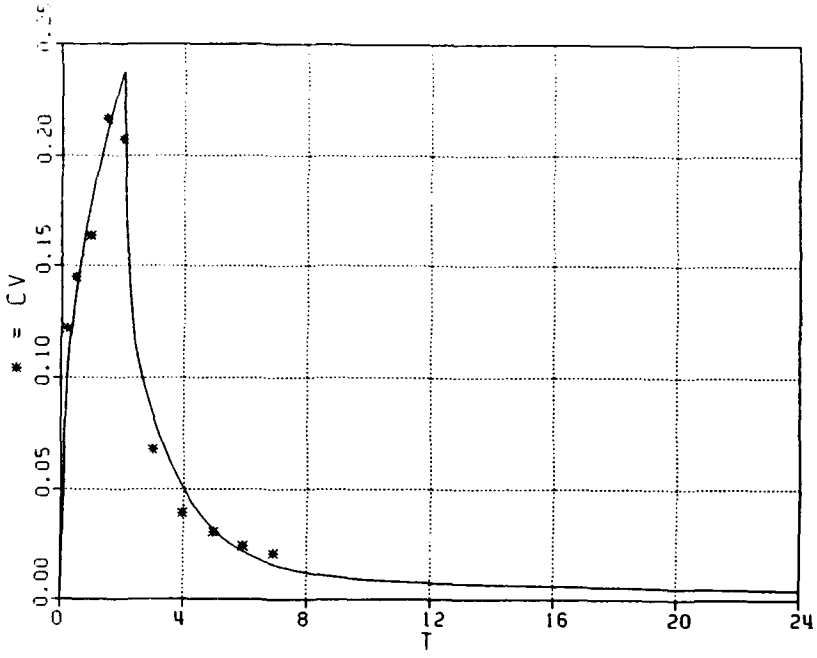

Figure 3-3. Model Validation (Man). CV is in mg/l and T is in hours.

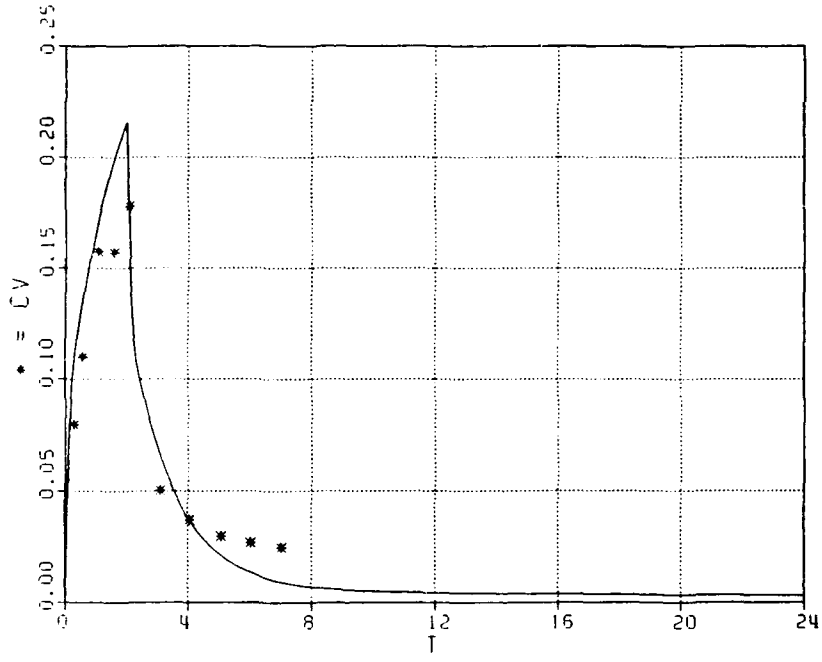

Figure 3-4. Model Validation (Woman).

for more benzene to remain in the blood and not partition to the fat where it would be released more slowly into the blood once exposure ceased.

The VMAX value for an infant was determined by using the allometric equation provided by Fisher et al. (1993:13) which scales an empirical VMAXC value to a specified body weight.

$$V_{MAX} = V_{MAXC} \times (\text{Body Weight})^{\exp .74}$$

The value for KM was assumed the same for infants and adults since the value did not change when optimized against the empirical data, and a scaling equation could not be found. The other chemical and physiological parameters used in the infant model were obtained from literature. Since no empirical data was available to validate the infant model, the results are theoretical.

Dose-Metric Selection

Dose-metrics are chemical amounts or concentrations in specific tissues which are reflective of the effective dose of a chemical of concern. In other words, they are measures that are thought to be related to the effects of a chemical. One of the metrics selected for study was the area under the venous blood concentration curve (AUCV). This metric was evaluated to obtain a concentration-time product. It represents the opportunity for benzene to act in a body by way of the blood and can be specified for specific tissue groups. The venous blood concentration was used for evaluation because empirical data was available for model validation using this measurement (Sato et al., 1975).

Additionally, the amount of benzene metabolized (AM) was evaluated. This value is of interest because the adverse effects of benzene are thought to

be caused by metabolites of the substance (Medinsky et al., 1989). A comparison of this metric across the subjects provides an indication of which subject is more susceptible to adverse effects from benzene exposure as a result of metabolites.

Sensitivity Analysis

Sensitivity analysis was conducted to identify the physical parameters that significantly effect the model output. The analysis addressed all of the parameters listed in Table 2-1 (with the exception of the Michaelis-Menten constant which is the same for all subjects) to determine which factors impacted benzene exposure. This was accomplished by increasing the parameters by 1% and measuring the AUCV and AM for the 28-day experimental period.

The analysis involved running the male model through the occupational scenario with the parameter values provided in Table 2-1 to establish baseline outputs for the AUCV and AM. These parameter values were obtained from various sources and are considered mean values. Next, the parameters were individually increased from the mean value by 1% and a new simulation was run for each parameter change. The dose-metric values resulting from the changes in each parameter were then compared to the baseline values to determine the impact on model output.

When increasing the parameters by 1%, adjustments had to be made in related parameters. For example, when the percent volume of liver tissue was increased, the percent volume of richly perfused tissue was reduced accordingly since the liver is a richly perfused tissue group. Likewise, because blood flows must add up to the total cardiac output, when blood flow

to the liver was increased, the blood flow to the richly perfused tissue was reduced to compensate for the change. The relationship between fat and the slowly perfused tissue was treated similarly.

Once the sensitive parameters were identified, the output produced for men and women could be interpreted when compared. This analysis provides insight as to the likelihood of and reason for differences in benzene concentrations in venous blood and the amount of benzene metabolized between men and women.

For direct comparison between the sexes, the amount of benzene inhaled and the amount metabolized were measured for each scenario using both the adult man and adult woman parameters. The amount metabolized was divided by the amount inhaled to obtain the percent metabolized. Since benzene metabolites are thought to impact toxicity, this comparison provides justification for stricter or gender-specific exposure guidelines and standards.

Benzene Exposure of Lactating Mothers and Infants

The amount of benzene taken in by the infant due to the mother's exposure is a point of interest which can be investigated by this modeling effort. The first step is to alter the datafile used for an adult woman to one representing a lactating woman. Then an infant model is integrated with the model that simulates the mother. Finally, the composite is exposed to benzene through the same scenarios as the adult man and woman. The infant receives an exposure through inhalation of background concentrations and ingestion of contaminated breast milk (see Figure 3-1).

The amount of benzene inhaled by and transferred from the mother and the total amount taken in by the infant through inhalation and ingestion can

be predicted for each of the four exposure scenarios. This exercise provides insight into the potential for nursing mothers to expose their infants to occupational VOCs and the impact of the mother's personal activities on her infant. In addition to the amounts taken in, the amount metabolized by both the mother and infant was recorded to assess the exposure of the two subjects.

Summary

To assess the impact of gender differences on benzene exposure, it is necessary to conduct a sensitivity analysis to determine which physical parameters have the greatest influence on the dose-metrics selected for study. Once the sensitive parameters are identified, a comparison between men and women with regard to those parameters can be conducted and interpreted. The magnitude of an infant's exposure to benzene may be influenced by the occupational and personal activities of its mother if she is breast feeding. By simulating inhalation and ingestion exposures through four potential scenarios, it is possible to predict an infant's exposure to benzene. The following chapter provides data and discussion of these two issues.

IV. Data Description and Analysis

Introduction

This chapter presents the raw data obtained by conducting simulations using PBPK modeling. A sensitivity analysis was conducted to identify influential parameters with which to compare men and women. Additionally, simulations were run using a model of a lactating woman and infant to predict the total exposure received by an infant due to its mother's activities. The information used for the comparison of adult men and women will be presented and discussed first followed by the lactating mother and infant data. A brief summary will be provided at the end of the section.

Sensitivity Analysis Results

The results of the sensitivity analysis are presented in Table 4-1. The analysis was conducted using the occupational scenario described in chapter three. For the purpose of this study, sensitivity greater than 0.05% is considered significant to allow the impact of body fat to be addressed. As can be seen from the results, several parameters exhibit significant results. The sensitive parameters and the extent to which dose-metrics are affected are listed in Table 4-2. A positive sensitivity indicates that as a parameter value is increased, the dose-metric value increases, while a negative sensitivity indicates that the dose-metric value decreases as the parameter value is increased. The relevant portions of Table 2-1 have been reproduced in Table 4-3 to facilitate data analysis and discussion.

	Model Output			Sensitivity (%)	
Parameter	1% CHANGE	AUCV	AM (mg)	AUCV	AM (mg)
MEAN		26.17	665.43		
BW	70.7	26.17	665.47	–	.01
QP	454.5	26.26	667.04	.34	.24
QC	339.36	26.17	666.79	–	.20
QL	84.84	26.15	666.62	-.08	.18
QF	27.17	26.17	665.62	–	.03
QS	96.76	26.18	664.79	.02	-.10
QR	130.59	26.21	663.57	.15	-.28
VLC	3.6%	26.17	665.45	–	–
VFC	21.0%	26.16	665.01	-.05	-.06
VSC	65.0%	26.19	665.85	.08	.06
VRC	7.0%	26.17	665.42	–	–
PB	7.88	26.36	669.84	.73	.66
PL	2.98	26.17	665.43	–	–
PF	55.05	26.17	665.38	–	-.01
PS	2.07	26.17	665.53	–	.02
PR	1.94	26.17	665.45	–	–
VMAX	14.03	26.10	669.07	-.27	.55

Table 4-1. Sensitivity analysis results. AUCV is in mg-hr/l and AM is in mg.

The most significant sensitivity corresponds to the blood/air partition coefficient (PB), followed by the maximum velocity of metabolism (VMAX). These results are expected since the ability of benzene to partition from the

PARAMETER	AUCV	AM
QP	XXX	XX
QC		XX
QL	-X	XX
QS		-X
QR	XX	-XXX
VFC	-X	-X
VSC	X	X
PB	XXXX	XXXX
VMAX	-XXX	XXXX

Table 4-2. Effect of Sensitive Parameters on Dose-Metrics.

X=0.05<Sensitivity≤ 0.1% XXX=0.5%>Sensitivity>0.25%

XX=0.25%>Sensitivity> 0.1% XXXX=Sensitivity>0.5%

air to blood determines the concentration in the blood and the concentration made available to other tissue groups. The increase in PB naturally increases the venous blood concentration and increases the concentration delivered to the liver for metabolism. An increase in VMAX causes a significant decrease in AUCV and an even more significant increase in AM. This is because as the rate of metabolism is increased, more benzene is metabolized as the blood travels through the body, leaving less of a concentration in the venous blood.

Alveolar ventilation (QP) and blood flow to richly perfused tissue (QR) are the next most sensitive parameters followed by the blood flow to the liver (QL). As the amount of benzene taken into the lungs increases, the amount of benzene distributed throughout the body also increases. Therefore, more of the chemical is processed by the liver and a larger concentration is found

	PARAMETER	MAN	WOMAN
Body Weight (kg)	**BW**	**70.0**	**60.0**
Alveolar Ventilation (l/hr)	**QP**	**450.0**	**363.0**
Cardiac Output (l/hr)	**QC**	**336.0**	**288.0**
Blood Flow (l/hr)			
Liver	**QL**	**84.0**	**72.0**
Fat	**QF**	**26.9**	**23.0**
Slowly Perfused	**QS**	**95.8**	**82.1**
Richly Perfused	**QR**	**129.3**	**110.9**
Tissue Volume Fractions (%)			
Liver	**VLC**	**2.6**	**2.3**
Fat	**VFC**	**20.0**	**30.0**
Slowly Perfused	**VSC**	**64.0**	**55.0**
Richly Perfused	**VRC**	**6.0**	**5.0**
Partition Coefficients			
Blood/Air	**PB**	**7.8**	**8.2**
Liver/Blood	**PL**	**2.95**	**2.80**
Fat/Blood	**PF**	**54.5**	**51.8**
Slowly Perfused/Blood	**PS**	**2.05**	**2.00**
Richly Perfused/Blood	**PR**	**1.92**	**1.80**
Max. Velocity of Metabolism (mg/hr-kg)	**VMAX**	**13.89**	**19.47**

Table 4-3. Parameter Values Based on Gender.

in the venous blood. When QR is increased, QL must be correspondingly decreased which allows for a higher concentration of benzene in the venous blood since less flow is going to the liver for processing. The result is a significant decrease in the AM. The opposite effect is apparent when QL is increased, although the effect is less significant because the proportional increase of blood flowing to the liver is not of the same magnitude as the increase in QR. When the implications of these results are considered

together, it can be concluded that the blood flow to the liver is the truly sensitive parameter affecting the dose metrics.

An increase in cardiac output (QC) has little effect on the concentration of benzene in the venous blood over time, but does cause an increase in the amount of benzene metabolized. This result is expected because the same amount of the substance is taken into the body regardless of cardiac output, thereby explaining the minimal change in venous concentration. In other words, the breathing rate has not changed so the same amount of benzene is available to be taken up by the blood, regardless of how fast the blood is being pumped through the body. The increase in AM is caused by the increased cardiac output sending more contaminated blood through the liver to be metabolized.

Although the sensitivity to changes in the volumes of fat and slowly perfused tissues is low, the results are worthy of discussion. As can be seen from Table 4-2, as the fat volume (VFC) is increased, the venous blood concentration and amount metabolized are decreased. Alternatively, the AUCV and AM increase with an increase in the volume of slowly perfused tissue (VSC). These results seem contradictory at first glance considering the fact that fat tissue is actually a slowly perfused tissue group.

The reason for the opposing results lies in the partition coefficients for fat (PF) and slowly perfused tissue (PS). Because PF is much higher than PS or any other partition coefficient, when VFC is increased, more benzene can be partitioned to the fat thereby removing it from the blood and making it unavailable for metabolism. This explains the decrease in AUCV and AM when the VFC is increased. The partition coefficients are also a factor in the

sensitivity detected for increases in VSC, however, this is primarily a result of the differing proportions of the two tissue groups.

Because fat is a component of the slowly perfused tissue group, when one volume is increased the other is decreased accordingly to keep the total tissue volume constant. The VSC is a higher fraction of the total body tissue with a low partition coefficient, and increases or decreases in this proportion have less of an impact than changes in the VFC fraction which has a very high partition coefficient. Therefore, when the VSC is increased and the VFC is decreased, the effect of less fat for benzene to partition to increases the venous blood concentration and leaves more benzene in the blood for the liver to metabolize. This provides explanation for the increases in AUCV and AM when the VSC is increased. Taking the implications of these results together, it is apparent that the truly sensitive parameter is VFC.

The last parameter to display slightly significant sensitivity is QS. The decrease in AM as QS is increased is again a result of correspondingly reducing QF and the difference in magnitude between the two parameters. The author theorizes that when less fat tissue is available for the benzene to partition to, more chemical is excreted from the body by way of the lungs and less is available for metabolism over the experimental period of 28 days. Because QF is decreased when QS is increased, less benzene reaches the liver which results in a decrease in AM. Although QF does not appear to be a sensitive parameter in the analysis, it is the driving factor behind the results for QS.

All of the parameters discussed above have been determined to be different in men and women through the literature review. With this

sensitivity data, a comparison between the sexes can be made. The following section discusses the implications of these findings.

Adult Man and Adult Woman Comparison

All of the physical and chemical parameter values obtained from the literature and listed in Table 4-3 differ between men and women. Each of the parameters determined to be sensitive are discussed in the following section.

Table 4-4 provides the effects on the dose-metrics when the female parameter value is substituted for the male value. For example, when the model is run with the male values obtained from the literature, the AUCV output is 26.17 mg days per liter. When it is run with the QP value changed to that of a woman, the AUCV value is 24.29 mg days per liter -- a decrease of 7.2%. Table 4-4 is an expansion of Table 4-2 which lists the parameters that were found to be sensitive when the male parameters were increased by 1% and the model was run through the "work" scenario.

Both the AUCV and AM increased by more than 0.5% when the PB is increased by 1%. As noted in Table 4-4, a woman's PB is 5.1% higher than a man's and results in a relatively large increase in both AUCV and AM. The magnitude of the differences in dose-metrics is only exceeded by those caused by the woman's higher VMAX and lower QP.

The VMAX for benzene in an adult woman was found to be much higher than that of a man -- approximately 40.2% higher. This factor negates the increased AUCV caused by a higher PB. However, it greatly increases the amount of benzene metabolized. Because metabolites are thought to play a

PARAMETER	FEMALE VS. MALE VALUE	AUCV (M)	AUCV (W)	% Difference	AM (M)	AM (W)	% Difference
QP	19.3% LOWER	26.17	24.28	- 7.2%	665.43	627.97	- 5.6%
QC	14.3% LOWER	26.17	26.25	0.3%	665.43	643.75	- 3.3%
QL	14.3% LOWER	26.17	26.56	1.5%	665.43	646.04	- 2.9%
QS	14.3% LOWER	26.17	26.10	- 0.3%	665.43	672.68	1.1%
QR	14.3% LOWER	26.17	25.73	- 1.7%	665.43	687.52	3.3%
VFC	50.0% HIGHER	26.17	25.99	- 0.7%	665.43	660.64	-0 .7%
VSC	14.1% LOWER	26.17	25.99	- 0.7%	665.43	660.64	- 0.7%
PB	5.1% HIGHER	26.17	27.13	3.7%	665.43	687.75	3.4%
VMAX	40.2% HIGHER	26.17	23.70	- 9.4%	665.43	788.08	18.4%

Table 4-4. Comparison of Effects of Female Values for Sensitive Parameters on Dose-Metrics. M represents values for the man model and W represents values for the woman model. AUCV is in mg-hr/l and AM is in mg.

major role in benzene toxicity, these two parameters may highly influence the probability of women suffering health effects from chronic exposure.

As QP is increased, both dose-metric values increase. Since women have a QP almost 20% lower than that of men, this factor reduces the benzene exposure women receive. A lower QP assists in counteracting the influences of a higher PB and VMAX by reducing the amount of chemical taken into the body. This, in turn, reduces the concentration of benzene in the venous blood and the amount metabolized over the 28-day research period.

The remaining sensitive parameters have additional effects on the dose-metrics but to a lesser degree. A woman's lower QR will reduce the concentration in the venous blood while increasing the amount metabolized as compared to a man's QR. This result is more a function of substituting the female QR value for the male value and correspondingly increasing the QL

value to ensure the blood flows total up to equal QC in order for the model to run. As Table 4-4 shows, the magnitude of the results is virtually the same when the female value for QL is examined, but the dose-metrics are affected in the opposite direction.

When investigating the effect of different blood flows on the AUCV and AM, the lower QC in women may be the most informative parameter. The male value for QC and all of the other blood flow parameters were reduced by 14.3% to study the impact of a woman's lower total cardiac output on the dose-metrics. The combined effect of changing all of these parameters was only a 0.3% increase in AUCV and 3.3% decrease in amount metabolized -- relatively small values when compared to the effects of a higher PB and VMAX and lower QP.

As with the PB and VMAX, women have a higher VFC than men. This difference has been theorized by Sato et al. (1975) to be the reason for higher benzene retention in women than men. The higher fraction in women does appear to cause a decrease in the AUCV and AM indicating more benzene is being retained in body tissue. However, even when a woman's value is 50% larger than a man's, the effect of more body fat has a low impact on dose-metrics.

Table 4-4 emphasizes the point that the chemical-specific parameters have a substantial impact on the dose-metrics. To determine the extent of the impact of the physiological and chemical-specific parameters, the model was run with the entire male datafile, and then the female datafile. The output provides a basis for direct comparison of benzene exposure incurred by men and women.

Direct Comparison of Male and Female Models

The results in Table 4-4 indicate that the differences in dose-metrics between men and women are primarily caused by the variation in the chemical specific parameters. To evaluate the significance of these parameters, the partition coefficients in the WOMAN datafile were set equal to the male values, and the "work" scenario was simulated for a woman. Table 4-5 compares the values for AUCV and AM when the male and female mean parameter values for PB, PL, PF, PS, PR and VMAX are used (MAN and WOMAN) and when these chemical-specific parameters are set equal ('WOMAN').

Datafile	AUCV (mg-hr/l)	AM (mg)	% Difference from Male AUCV	% Difference from Male AM
MAN	26.17	665.43		
WOMAN	22.64	723.99	-13.5	8.8
'WOMAN'	24.34	603.76	-7.0	-9.3

Table 4-5. Gender Comparison when Chemical-Specific Parameters are Equal.

The table demonstrates that when the mean parameter values are used, the female output for AUCV is 13.5% less than that of a man, and the woman's AM is 8.8% greater than the male AM. When the chemical-specific parameters are set equal and no longer influence the output, the woman's AUCV is only 7.0% less than a man's while her AM becomes 9.3% less than the man's value. These results indicate that the physical parameters such as QP and QR influence almost 50% of a human's venous benzene concentration and the amount metabolized in this study.

To further investigate the difference between men and women, the two subjects are exposed through the four scenarios described in the methodology to display the effects of the differing parameters on the dose-metrics. The results are provided in Table 4-6. The amount of benzene inhaled (AI),

MAN

	Background	Smoke	Work	Work/Smoke
AI (mg)	2.13	51.52	2301.74	2352.77
AUCV (mg-hr/l)	.02	.55	26.17	26.75
AM (mg)	.67	16.18	665.43	679.97
% Metabolized	**31.5**	**31.4**	**28.9**	**28.9**

WOMAN

	Background	Smoke	Work	Work/Smoke
AI (mg)	1.71	51.56	1866.71	1907.88
AUCV (mg-hr/l)	.02	.59	22.64	23.26
AM (mg)	.70	21.01	723.99	743.69
% Metabolized	**40.9**	**40.7**	**38.8**	**39.0**

Table 4-6. Direct Gender Comparison of AUCV and AM.

AUCV, and the AM were measured for men and women under the conditions of the scenarios. The amount metabolized was divided by the amount inhaled to obtain the percentage of benzene metabolized.

By comparing the data collected over the 28 day experimental period, it is apparent that men inhale more and have a higher blood concentration than women in the scenarios with the exception of the smoking exposure. It is

because of the anomaly discussed in the methodology that women have higher AI and AUCV values than men in this scenario. The metabolism data, however, provides results that may be unexpected.

Women consistently metabolize 23 - 26% more of the benzene inhaled than men. The explanation for this occurrence can be found in Table 4-4. The higher VMAX and lower QP decrease the AUCV for women while the higher PB and VMAX of women substantially increase the AM. The other less sensitive parameters also affect the amount metabolized, emphasizing the fact that all the parameters must be considered when evaluating the results.

Exposure Incurred by Lactating Women and Infants

To determine the contribution of a mother's benzene exposure to an infant's total exposure, the amount inhaled by the mother during the four scenarios was measured as was the infant's ingestion and inhalation amounts. The concentration in the blood over time and the amount metabolized were computed to help make comparisons between the subjects and various scenarios. The results are provided in Table 4-7.

As the mother's exposure to benzene increases, the ingestion exposure for the infant becomes more substantial. For example, when the mother and infant are only exposed to a background concentration, the oral intake makes up less than 1.0% of the infant's total intake of benzene. In the scenario where the mother works, the infant receives over 65.0% of its total exposure through the ingestion pathway. The percentage decreases slightly when the mother works and smokes because the infant is exposed to a higher background level at home, thereby increasing the infant's total exposure by

way of inhalation. Furthermore, the infant's blood concentration and amount metabolized doubles when its mother smokes as compared to the background scenario.

	Background	Smoke	Work	Work/Smoke
Amount Inhaled (mg) (MOTHER)	1.71	51.56	1856.67	1907.86
Oral Intake (mg) (INFANT)	Less than .01	.09	.86	.93
Total Intake (mg) (INFANT)	.44	.77	1.30	1.60
OI/TI x 100 = % Ingested	.7	11.7	66.3	57.7
AUCV (MOTHER)	.02	.61	23.09	23.72
AUCV (INFANT)	.02	.04	.06	.07
AM (MOTHER)	.68	20.38	704.24	723.41
AM (INFANT)	.12	.25	.69	.79

Table 4-7. Intake, AUCV (mg-hr/l), and AM (mg) for Lactating Women and Infants.

To compare the exposure of infants to their mothers, the AM is divided by the body weight (BW) of the subject. The results are provided in Table 4-8. As can be seen in this table, infants have a higher AM/BW ratio than their mothers in the background scenario. This is primarily because the infant's

	Background	Smoke	Work	Work/Smoke
AM/BW (mg/kg) (MOTHER)	.01	.34	11.74	12.06
AM/BW (mg/kg) (INFANT)	.02	.04	.10	.11

Table 4-8. AM/BW Ratios for Lactating Women and Infants.

body weight is much less than the mother's and because the infant is receiving an ingestion exposure in addition to the background exposure both subjects receive. However, the ingestion exposure is quite small and does not substantially affect the amount metabolized.

These results allow for an interesting comparison regarding the occupational and smoking scenarios. The mother, who is exposed to the maximum allowable concentration of benzene, metabolizes about 12.0 mg of benzene per kg of body weight. The infant metabolizes an amount that is less than 1.0% of the mother's amount. In the smoking scenario, the infant metabolizes more than 10% of the amount metabolized by the mother -- 10 times more than in the occupational exposures. While the actual quantity metabolized is less, these results indicate that an infant is receiving an exposure more closely related to that of the mother when she smokes.

To further compare the exposure of mothers and infants, the AM is divided by AI for the mother and the total intake for the infant and then multiplied by 100 to obtain a percentage. The results are listed in Table 4-9.

	Background	Smoke	Work	Work/Smoke
% Metabolized (MOTHER)	39.5	39.5	37.9	37.9
% Metabolized (INFANT)	27.9	32.1	52.8	49.5

Table 4-9. Percent Metabolized by Lactating Women and Infants.

As can be seen in this table, infants of working mothers metabolize a larger percentage of their total benzene intake. The author theorizes that because the oral intake received by the infants of working mothers is an order of magnitude larger than that of the other infants, more benzene is

distributed directly to the liver for processing, thereby increasing the percent metabolized. Because these results indicate that infants of working mothers metabolize 17 - 25% more benzene, they support modifications to the breast feeding schedules of working mothers.

Figure 4-1 graphically describes the behavior of benzene in the lactating woman's breast milk over the course of a workday. The graph indicates that the benzene concentration is highest at the end of the 8 hour workday and declines rapidly for the next 2 hours. As a result, the infant will receive its greatest ingestion exposure when fed during the two hours after occupational exposure has ceased.

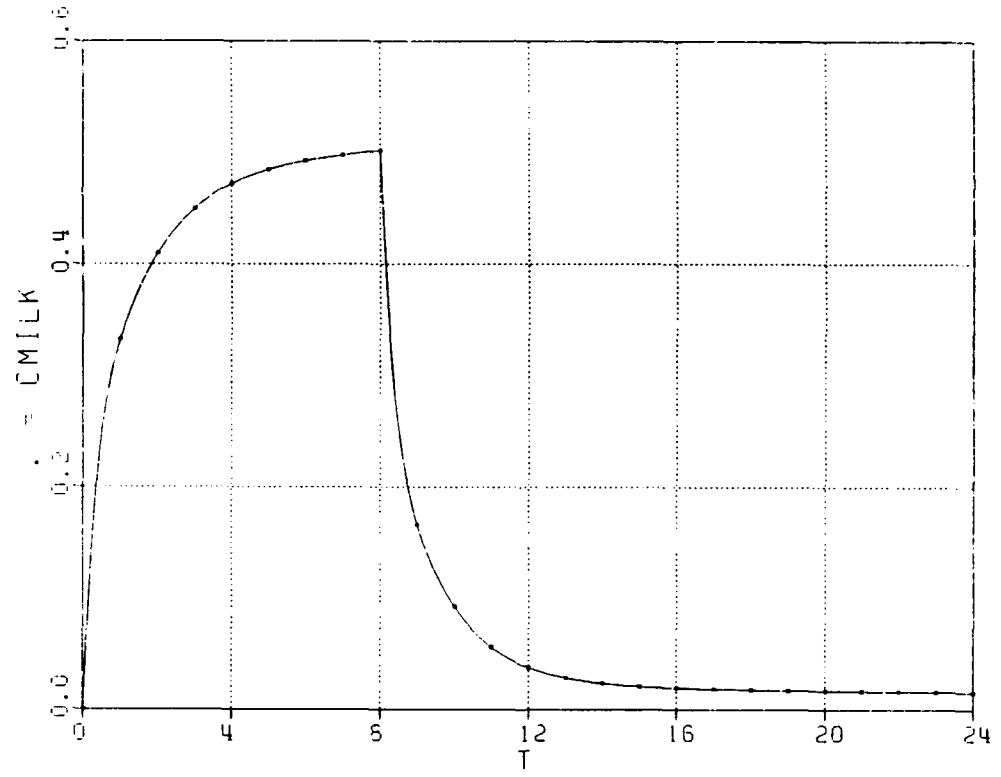

Figure 4-1. Benzene Concentration in Breastmilk. CMILK is in mg/l and T is in hours.

Figure 4-2 shows the concentration of benzene in the milk and the corresponding dose taken in by the infant over the course of one workday. Since the infant is not fed breastmilk during the first 8 hours of the day, it receives no oral dose until the mother returns from work.

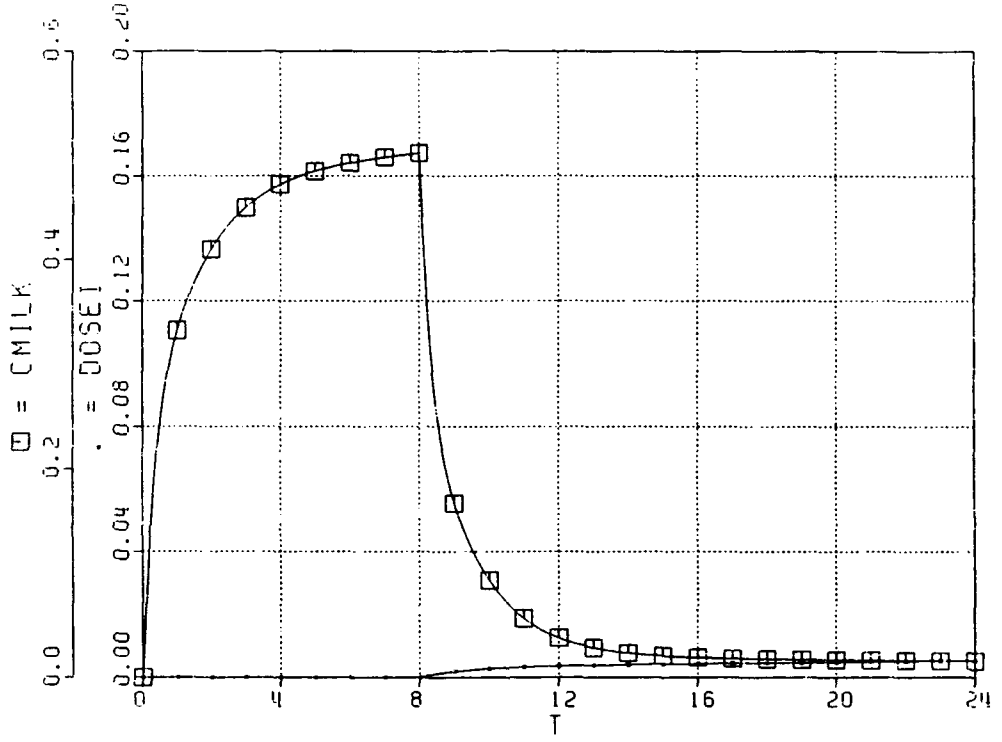

Figure 4-2. Breastmilk Concentration and Ingested Dose. CMILK is in mg/l and DOSE1 is in mg.

By combining the information presented in Figure 4-1 and 4-2, it can be predicted that a significant percentage of the oral intake will be eliminated by delaying the time between the end of the mother's occupational exposure and the first feeding. Figure 4-3 shows the decrease in the infant's dose when the first feeding is delayed by two hours.

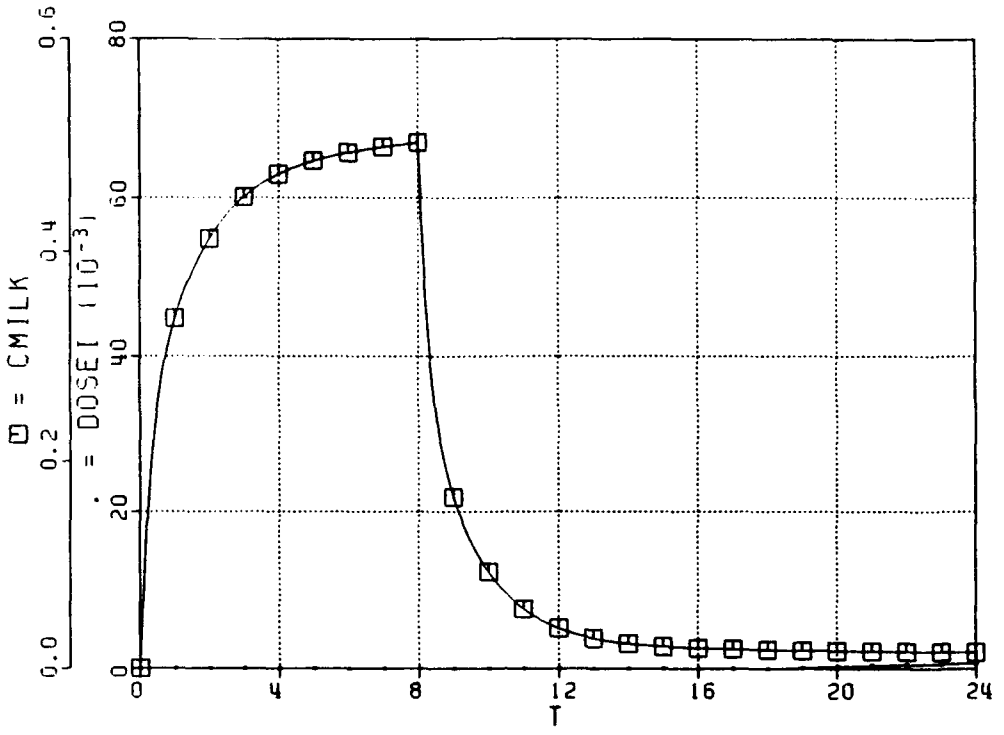

Figure 4-3. Breastmilk Concentration and Ingested Dose when First Feeding is Delayed. CMILK is in mg/l and DOSEI is in mg.

When the mother works, but delays breast feeding her infant until two hours after her occupational exposure has ceased, the oral intake is reduced from .86 mg to .45 mg -- a drop of 47.7% (see Table 4-10). Additionally, the amount of benzene metabolized by the infant is reduced by more than 39%. The percent metabolized, however, only decreases to 47.2%. This is because the infant still receives an oral exposure, which goes directly to the liver, ten times as great as the infants in the non-work scenarios (refer to Table 4-7).

When the mother waits four hours before feeding, the oral intake is reduced even further, but the total intake is only reduced by about 8.0% and there is little change in the percent metabolized. Therefore, delaying feeding

	Work	Work (Delay Feeding 2 Hours)	Work (Delay Feeding 4 Hours)
Oral Intake (mg) (INFANT)	.86	.45	.38
% Reduction		**47.7**	**55.8**
Total Intake (mg) (INFANT)	1.30	.89	.82
OI/TI x 100 = % Ingested	66.2	50.6	46.3
% Reduction		**23.6**	**30.1**
AM (INFANT)	.69	.42	.37
% Reduction		**39.1**	**46.4**
AM/TI x 100=% Metabolized	53.1	47.2	45.1

Table 4-10. Comparison of infant results when feeding is delayed two and four hours following occupational exposure in the work scenario.

more than two hours after occupational exposure has stopped will provide only minimal reductions in an infant's exposure.

Summary

The data description and analysis provided in this section presents the results of the sensitivity analysis conducted to determine the parameters which significantly affect the model output generated through simulation. Nine parameters were found to significantly effect the selected dose-metrics, with the most significant being the blood/air partition coefficient and maximum rate of metabolism. These two chemical-specific parameters were followed in sensitivity by the physical parameters of alveolar ventilation and blood flow to the richly perfused tissue. By using the sensitive parameters, a

comparison of men and women with regard to benzene exposure was accomplished.

The impact of a mother's benzene exposure on her nursing infant was found to be more significant when the mother incurred an occupational exposure. The ingested amount can make up over 65% of the infant's total intake if the mother feeds her infant immediately after exposure to high concentrations of benzene. This percentage can be decreased to 50% by waiting for a period of two hours after work to begin breast feeding. When the amount metabolized was divided by body weight to obtain a comparable ratio, the infant metabolized 1/100 of the amount metabolized by the mother, indicating the infants total exposure is relatively small.

V. Conclusions and Recommendations

Conclusions

PBPK modeling is an extremely useful tool for predicting human exposure to VOCs since it provides physiological realism which may not be considered in more traditional modeling techniques. PBPK modeling can provide results with minimal animal testing and epidemiological data. However, these results are only accurate if the physical and chemical parameters are correct.

Man vs. Woman Comparison. PBPK modeling effectively determined that gender-specific differences play a key role in the benzene exposure a man or woman receives in a given scenario. With this tool, a sensitivity analysis was conducted to determine the parameters that had the greatest effect on model output. Once these parameters were identified, a gender comparison for benzene exposure was accomplished.

The chemical-specific physiological parameters were found to be the most sensitive in this study, and because those parameters were higher in the female model, it is concluded that women incur a more significant exposure with regard to benzene. The combined effect of all of the differing parameters was that women metabolized 23 - 26% more benzene than men in the exposure scenarios, with the occupational scenarios being the highest.

These results raise questions as to w[illegible]he literature suggests that men are more susceptible than women to adve[illegible]e health effects as a result of chronic benzene exposure (HSDB, 1993). It is possible that so little research has been done with regard to both men and women that the research is biased and the effects on women are relatively unknown or underestimated.

On the other hand, if men are more likely to develop leukemia as opposed to women, the concentration of benzene in the blood may be a contributing factor to the development of the disease, since men's blood concentration levels were consistently higher both in this and the Sato (1975) study. Another possible explanation is that men and women produce different proportions of benzene metabolites -- some of which influence the incidence of leukemia more than others. Unfortunately, investigation of such explanations was beyond the scope of this work.

Because metabolites are believed to play a major role in the development of adverse health effects, the results of this research indicate that the TWA level should be reduced to adequately protect the increasing female working population. If this can not be done, then women should be provided more protective standards and guidelines than those established on the basis of studies conducted exclusively with men.

Many of the existing exposure guidelines incorporate factors of safety to account for uncertainty and individual differences such as age and weight to protect workers. However, as science closes the gap on uncertainty and these safety factors are correspondingly reduced, women may not be sufficiently protected if gender differences are not considered. The results of this study support the position that women incur a higher internal benzene exposure than men. Therefore, more stringent exposure standards and guidelines are required to safeguard all workers in the occupational setting.

In the case of benzene, the TWA is currently under consideration for reduction to 0.1 ppm. Based on work done by Rinsky et al. (1987) with 1,165 white males, a worker exposed to 10 ppm for 40 years has a 155 times greater potential to develop leukemia than an unexposed worker. Those exposed to

1.0 ppm for 40 years has a 1.7 times greater chance, while a worker exposed to 0.1 ppm has nearly the same odds of developing leukemia as an unexposed worker (ACGIH, 1991:116; ATSDR, 1993:36). If this reduction is adopted, all workers will benefit.

A final conclusion that can be drawn from the comparison of men and women concerns the issue of smoking. This research provides further incentive to refrain from or to stop smoking. The two non-occupational scenarios illustrate that men and women can reduce the amount of benzene in their blood and the amount metabolized (men's AUCV and AM levels are reduced by 24% while women's are reduced by 30%). The occupational scenarios do not provide such reductions due to the overwhelming effect of the high occupational exposure concentration.

Lactating Women and Infants. As with the gender comparison, PBPK modeling proved a useful method for assessing the benzene exposure incurred by lactating women and their infants. By simulating various exposure scenarios which mothers may experience, the results of this study indicate that nursing infants may intake at least 65% of their total benzene exposure through ingestion of contaminated breastmilk. While this is a large percentage, it can be reduced by 47.7%, thereby reducing the total intake, by delaying nursing sessions following high benzene exposure.

In addition to adjusted nursing schedules, these findings support the development of exposure schedules for nursing mothers in the workplace. For example, lactating women might engage in occupational activities involving TWA levels of benzene for the first six hours of the workday and then spend the last two hours in uncontaminated areas accomplishing other tasks. This would allow the women to continue working in their field of

expertise while simultaneously limiting the amount of benzene they pass on to their infants. As a result, both the business and the mother benefit since she can continue working, and the infant benefits from a reduced exposure. The ability to adjust the exposure would, however, depend on the capabilities and needs of the business.

The AM/BW ratios [illegible]ating woman and infant provide support for an adjustment to a working mother's occupational exposure or nursing schedule. When the mother is exposed to benzene levels that have been deemed acceptable by OSHA, she metabolizes about 12 milligrams for every kilogram of body weight. A working mother's infant, on the other hand, metabolizes up to 0.11 mg/kg -- 1/100 of the amount metabolized by the mother. This may appear acceptable, but the infant is actually metabolizing five times more benzene than when it is only exposed to background concentrations. Reducing the TWA to 0.1 ppm would greatly decrease these percentages.

While smoking was simulated in the scenarios, and the results provided insight into the impact of smoking on a mother's and infant's exposure to benzene, the effects were less dramatic than those produced in the occupational situations. Nevertheless, it is obvious from the results that eliminating smoking would significantly reduce the concentration of benzene in the blood and the amount of benzene metabolized by both subjects. The mother's AUCV and AM would be reduced by a factor of 30 (in the non-occupational scenarios) while the infant's levels would be cut in half.

Using the model output to characterize the behavior of benzene in a lactating woman, it is probable that a mother can reduce the amount of benzene she passes on to her infant by waiting to nurse for a short period of

time after smoking a cigarette. However, the benefits would appear to be minimal, and modeling a precise nursing schedule as a function of a mother's benzene exposure in order to reduce the infant's total exposure was beyond the scope of this research.

Study Uncertainties

As with most any research effort, the results are conditional upon assumptions made and methodology used for accomplishment of this study. The following topics highlight the uncertainties which may effect the outcome of this work and should provide the reader with an idea of the study's limitations. The precise quantification of uncertainty was beyond scope of this effort, and while the list of uncertainies is not exhaustive, it includes the factors of primary significance.

Accuracy and Availability of Data. Human empirical data is often extremely limited when studying the adverse health effects of known or probable carcinogenic chemicals. While volumes of animal data are available, extrapolation of that data to humans creates additional uncertainty. The male and female PBPK models in this study were developed and validated by extracting data points from a graph provided in one paper published by Sato et al. (1975), and very little physical information was known about the volunteers in that particular study. However, the limited information provided by the Sato et al. research provided the empirical data with which the model was validated and was, therefore, the backbone of this study.

Additionally, even less information exists concerning benzene exposure with regard to infants. The average body weight and tissue volume fractions

of a nursing infant can be found in literature, but the chemical-specific parameters are non-existent. Therefore, these parameters are scaled from adult parameters which contributes to the uncertainty of the infant results.

Performance of Sensitivity Analysis. The sensitivity analysis addressed all of the parameters used to represent a human being (with the exception of the Michaelis-Menten constant which was assumed the same for all subjects). While the results may seem comprehensive, they may not be complete. The sensitive parameters were identified on an individual basis, but in reality, two or more parameters may interact and increase or decrease the impact on model output. In other words, the parameters that individually displayed low sensitivity may significantly influence the results when combined with other parameters. To reduce uncertainty associated with parameter sensitivity, a thorough investigation of combined sensitivity should be conducted.

Generalization of Scenarios. The exposure scenarios developed for this research effort attempt to simulate actual situations that human beings may experience with regard to benzene. However, the scenarios are somewhat generalized in order to keep complexity manageable. In addition, it was the behavior of the chemical in different subjects that was the point of interest in this study as opposed to precise quantification of benzene exposure in various situations. Imposing too many specific timing requirements on the model limits application to other similar situations.

As mentioned in the methodology, the smoking exposure concentration averaged the amount of benzene a person takes in across the number of cigarettes smoked over 14 hours per day. While this simplifies the scenario, it neglects the effects of the short bursts of benzene exposure received when

each cigarette is smoked. This generalization may substantially increase the venous blood concentrations and amount of benzene metabolized in smokers.

The shorter, more intense benzene exposures associated with cigarette smoking may also influence the transfer of the chemical to an infant through breast feeding. That is, the infant may incur short bursts of higher exposure as a result of its mother's smoking habits. This factor has the potential to increase the infant's true exposure, but may be difficult to model as smoking patterns are probably not uniform.

Finally, the nursing schedule has been generalized for modeling purposes and is not likely to occur in reality. The PBPK model simulates a mother feeding her infant a designated quantity of milk each hour. As with the smoking exposure, this neglects the effects of short, intense benzene exposures on the infant and the ability of the mother to accommodate such a schedule. A more realistic nursing schedule would decrease the frequency of nursing and may increase or decrease the oral dose to the infant depending on the timing of the mother's benzene exposure.

Dose-metric Selection. The area under the curve for venous blood concentration and the amount of benzene metabolized were chosen for evaluation for different reasons. The AUCV was chosen because the empirical data provided venous blood values for validation and because it was a measure that could be examined easily across all of the simulations.

The AM, on the other hand, was selected for investigation based on the literature review and the assumption that metabolites are responsible for adverse health effects. While the results indicate that women metabolize more benzene than men, this study does not determine the type or quantity

of metabolites produced. This factor may be crucial in the development of toxic effects such as aplastic anemia and leukemia.

Recommendations

Data collection. The key issue in this study is that the accuracy of the results depends on the accuracy of the input parameter values. While it is unethical to expose human beings to known or probable carcinogens, many people are still exposed to such chemicals in the workplace and in other countries where regulations are less stringent. Further study of the chemical-specific parameters would improve the ability to estimate the actual exposure received by men and women, and identification of specific metabolites that produce toxic effects may help predict the occurrence of health hazards. While infant data will most likely remain unavailable, the development of scaling factors based on body weight and tissue group fraction would improve the evaluation of infant exposure.

Scenario and Model Development. As mentioned earlier, several aspects of the models and scenarios lead to uncertainty in the results. More precise modeling of the smoking scenarios would be quite beneficial for the adult models since smoking exposes the body to short, concentrated bursts of benzene which may substantially influence the results. Additionally, the nursing schedules could be made more realistic by decreasing the frequency and duration of feeding while ensuring the infant still takes in the same amount of milk. Refinement of the situations to more closely simulate reality may be an improvement, but may also limit the ability to apply results to other similar scenarios.

Summary

From the results obtained during data collection it is determined that benzene exposure is a function of gender differences -- primarily the differences in the chemical-specific parameters. Additionally, lactating women have the potential to increase their infant's exposure to benzene through breast feeding. The magnitude of that increase is a function of the intensity and timing of the mother's exposure. Both of these factors support a decrease in the current TWA level established by OSHA.

Although uncertainties exist and further research is needed to confirm the findings of this study, PBPK modeling has proven a useful approach to reaching these conclusions. The employment of a sensitivity analysis and exposure scenarios allows for realistic comparison between different subjects without extensive animal testing or excessive quantities of human data. Furthermore, once the model is developed and parameters verified, it can be used to predict exposures on various sectors of the population.

Appendix A. Abbreviations and Acronyms

AI:	Amount Inhaled
AM:	Amount Metabolized
AUCV:	Area Under the Venous Blood Concentration Curve
BW:	Body Weight
CMILK:	Breastmilk Concentration
CV:	Venous Blood Concentration
DOSEI:	Ingested Dose
EPA:	Environmental Protection Agency
KM:	Michaelis-Menten Constant
OD:	Oral Dose
OSHA:	Occupational Safety and Health Administration
PB:	Blood/Air Partition Coefficient
PBPK:	Physiologically Based Pharmacokinetics
PCE:	Perchloroethylene
PF:	Fat/Blood Partition Coefficient
PL:	Liver/Blood Partition Coefficient
PM:	Milk/Blood Partition Coefficient
ppb:	Parts Per Billion
ppm:	Parts Per Million
PR:	Richly Perfused/Blood Partition Coefficient
PS:	Slowly Perfused/Blood Partition Coefficient
QC:	Cardiac Output
QF:	Blood Flow to Fat
QL:	Blood Flow to Liver

QMT:	Blood Flow to Mammary Tissue
QP:	Alveolar Ventilation
QR:	Blood Flow to Richly Perfused Tissue
QS:	Blood Flow to Slowly Perfused Tissue
R:	Respiratory Retention Percentage
T:	Time
TEAM:	Total Exposure Assessment Methodology
TI:	Total Intake
TWA:	Time Weighted Average
VFC:	Fraction of Fat Tissue
VLC:	Fraction of Liver Tissue
VMC:	Fraction of Mammary Tissue
VMAX:	Maximum Velocity of Metabolism
VOC:	Volatile Organic Compound
VRC:	Fraction of Richly Perfused Tissue
VSC:	Fraction of Slowly Perfused Tissue

Appendix B. Parameter References and Derivations

BW	Adult body weights were obtained from Snyder et al. (1975:13), and the infant body weight was taken from Polin et al. (1992:1690).
QP	Snyder et al. (1975:346).
QC	Derived from Smith et al. (1990:111) as 80 ml/kg/min.
QL	Smith et al. (1990:141) defines QL as 25% of QC.
QF	Smith et al. (1990:141) defines QF as 8% of QC.
QS	QS is the sum of the blood flow to muscle (21%) and skin (7.5%) times the total QC. The percentages were specified by Smith et al. (1990:141).
QR	QR is the sum of the blood flow to the brain (14%), heart (4.5%), and kidney (20%) times the total QC. The percentages were specified by Smith et al. (1990:141). The lactating woman's QR value is reduced by QMT because mammary tissue is considered richly perfused tissue (Mepham, 1987:28).
QMT	Obtained from model code (Byczkowski and Fisher, 1993).
VLC	Snyder (1975:145-146).
VFC	Snyder (1975:41-42).
VSC	VSC is a lumped compartment composed primarily of muscle and skin. Travis et al. (1990:404) defined muscle as 58% of a man's body weight, so the male VSC value was increased to 64% to account for skin. Because women have more body fat and less muscle, their VSC is estimated to be 55%. The value for lactating women is reduced from that of an adult woman's to account for the mobilization and potential conversion of slowly perfused tissue to richly perfused tissue during lactation. The infant value for VSC is the same as an adult woman's since their body fat percentages are the same.

VRC	VRC is also a lumped compartment consisting of vessel rich organs. Travis et al.(1990:404) estimated this volume as 5% of total body weight while Schreiber (1993:523) considered the kidney alone to account for 5% of total body tissue. The values for VRC ranged from 3% (Smith and Kampline, 1990:141) to 10% (Fisher et al. 1993:10), therefore, the author selected midrange values for this study.
VMC	Obtained from model code (Byczkowski and Fisher, 1993).
PB	The man's value was provided by Paterson et al. (1989:324) and the value for the other subjects was adapted from Fisher et al. (1993:12).
PL, PF, PS, PR	The tissue to blood partition coefficients were derived by dividing the tissue to air coefficients provided by Paterson et al. (1989:324) by the PB defined for each subject.
PM	Fisher et al. (1993:12).
KM	Travis et al. (1990:404).
VMAX	The values for man and woman were obtained by optimizing the fit of the model to the data obtained from Sato et al. (1975:325). The value obtained for the woman was used for the lactating woman, also. The infant value was calculated with the allometric equation provided by Fisher et al. (1993:13).

Appendix C. Model Code "BCKONLY"

```
PROGRAM ADULT.CSL                    $'BCKONLY MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=450.                    $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QC=336.                    $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QL=84.                     $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QF=26.9                    $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QS=95.8                    $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QR=129.3                   $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  BW=70.                     $'BODY WEIGHT (KG)'
CONSTANT  VLC=2.6                    $'% LIVER TISSUE'
CONSTANT  VFC=20.                    $'% FAT TISSUE'
CONSTANT  VSC=64.                    $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VRC=6.                     $'% RICHLY PERFUSED TISSUE'
CONSTANT  PB=7.8                     $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.95                    $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=54.5                    $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.05                    $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.92                    $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                   $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=13.89                 $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  KM=.35                     $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  BCK=.0022                  $'BACKGROUND BENZENE CONC. (PPM)'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.               $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  DAYS=28.                   $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.

CONSTANT  CINT=.1                    $'COMMUNICATION INTERVAL'
INTEGER   DAY
          DAY=-1                     $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                  $'END OF INITIALIZATION'

DYNAMIC

ALGORITHM  IALOG=2                   $'GEAR METHOD FOR EQUATIONS'

'CI=CONC IN INHALED AIR (MG/L)'

DISCRETE CAT1
          INTERVAL CAT=24.           $'EXECUTE CAT1 EVERY 24 HOURS'
          DAY=DAY+1

          CI=BCK*MW/24450            $'CONVERT BCK FROM PPM TO MG/L IN AIR'
END                                  $'END OF CAT1'
```

```
DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                                   $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                                   $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                                   $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                                   $'VOLUME OF RICHLY PERF. TISSUE (KG)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CI)/(QC+(QP/PB))               $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                           $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                                    $'CONC. EXHALED (MG/L)'
CXPPM=(0.7*CX+0.3*CI)*24450./MW             $'CONC. EXHALED (PPM)'
RAX=QP*CX                                   $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                            $'AMOUNT EXHALED (MG)'

'AI=AMOUNT INHALED'
RAI=QP*CI                                   $'RATE INHALED (MG/HR)'
AI=INTEG(RAI,0.)                            $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                             $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                            $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                              $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                                    $'CONC. IN SLOWLY PERF. (MG/KG)'

'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                             $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                            $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                              $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                                    $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                             $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                            $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                              $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                                    $'CONC. IN FAT (MG/KG)'

'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                             $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                            $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                              $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                                    $'CONC. IN LIVER (MG/KG)'

'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)                     $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                            $'AMOUNT METABOLIZED (MG)'
```

```
'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC      $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                        $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX                  $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                          $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                       $'TERMINATE SIMULATION'

END                                      $'END OF DERIVATIVE'
END                                      $'END OF DYNAMIC'
END                                      $'END OF PROGRAM'
```

Appendix D. Model Code "SMOKE"

```
PROGRAM ADULT.CSL                    $'SMOKE MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=450.                    $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QC=336.                    $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QL=84.                     $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QF=26.9                    $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QS=95.8                    $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QR=129.3                   $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  BW=70.                     $'BODY WEIGHT (KG)'
CONSTANT  VLC=2.6                    $'% LIVER TISSUE'
CONSTANT  VFC=20.                    $'% FAT TISSUE'
CONSTANT  VSC=64.                    $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VRC=6.                     $'% RICHLY PERFUSED TISSUE'
CONSTANT  PB=7.8                     $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.95                    $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=54.5                    $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.05                    $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.92                    $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                   $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=13.89                 $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  KM=.35                     $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  CONCS=.089                 $'SMOKING INHALED CONCENTRATION (PPM)'
CONSTANT  BCK=.0034                  $'SMOKER BACKGROUND CONC. (PPM)'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.               $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  DAYS=28.                   $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.

CONSTANT  TSMK=14.                   $'LENGTH OF SMOKING EXPOSURE (HRS)'
CONSTANT  CINT=.1                    $'COMMUNICATION INTERVAL'
INTEGER   DAY
          DAY=-1                     $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                  $'END OF INITIALIZATION'

DYNAMIC

ALGORITHM IALOG=2                    $'GEAR METHOD FOR EQUATIONS'

'CIS=CONCS. IN INHALED AIR (MG/L)'

DISCRETE CAT1
          INTERVAL CAT=24.           $'EXECUTE CAT1 EVERY 24 HOURS'
          DAY=DAY+1

          CIS=CONCS*MW/24450         $'CONVERT SMOKE FROM PPM TO MG/L IN AIR'
        SCHEDULE CAT2 .AT. T+TSMK      $'END OF SMOKING EXPOSURE'
END                                  $'END OF CAT1'
```

```
DISCRETE CAT2

        CIS = BCKS*MW/24450.        $'CONVERT BCKS. FROM PPM TO MG/L IN AIR'
END                                 $'END OF CAT2'

DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                           $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                           $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                           $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                           $'VOLUME OF RICHLY PERF. TISSUE (KG)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CIS)/(QC+(QP/PB))      $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                   $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                            $'CONC. EXHALED (MG/L)'
CXPPM=(0.7*CX+0.3*CIS)*24450./MW    $'CONC. EXHALED (PPM)'
RAX=QP*CX                           $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                    $'AMOUNT EXHALED (MG)'

'AI=AMOUNT INHALED'
RAI=QP*CIS                          $'RATE INHALED (MG/HR)'
AI=INTEG(RAI,0.)                    $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                     $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                    $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                      $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                            $'CONC. IN SLOWLY PERF. (MG/KG)'

'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                     $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                    $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                      $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                            $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                     $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                    $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                      $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                            $'CONC. IN FAT (MG/KG)'

'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                     $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                    $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                      $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                            $'CONC. IN LIVER (MG/KG)'
```

```
'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)                    $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                           $'AMOUNT METABOLIZED (MG)'
'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC        $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                          $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX                    $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                            $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                         $'TERMINATE SIMULATION'

END                                        $'END OF DERIVATIVE'
END                                        $'END OF DYNAMIC'
END                                        $'END OF PROGRAM'
```

Appendix E. Model Code "WORK"

```
PROGRAM ADULT.CSL                    $'WORK MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=450.                    $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QC=336.                    $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QL=84.                     $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QF=26.9                    $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QS=95.8                    $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QR=129.3                   $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  BW=70.                     $'BODY WEIGHT (KG)'
CONSTANT  VLC=2.6                    $'% LIVER TISSUE'
CONSTANT  VFC=20.                    $'% FAT TISSUE'
CONSTANT  VSC=64.                    $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VRC=6.                     $'% RICHLY PERFUSED TISSUE'
CONSTANT  PB=7.8                     $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.95                    $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=54.5                    $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.05                    $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.92                    $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                   $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=13.89                 $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  KM=.35                     $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  CONC=10.                   $'OCCUP. INHALED CONCENTRATION (PPM)'
CONSTANT  BCK=.0022                  $'BACKGROUND BENZENE CONC. (PPM)'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.               $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  WDAYS=5.                   $'NUMBER OF WEEKDAYS'
CONSTANT  WEDAYS=2.                  $'NUMBER OF WEEKEND DAYS'
CONSTANT  DAYS=28.                   $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.

CONSTANT  TCHNG=8.                   $'LENGTH OF OCCUP. EXPOSURE (HRS)'
CONSTANT  CINT=.1                    $'COMMUNICATION INTERVAL'
INTEGER   DAY
          DAY=-1                     $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                  $'END OF INITIALIZATION'

DYNAMIC

ALGORITHM IALOG=2                    $'GEAR METHOD FOR EQUATIONS'

'CI=CONC IN INHALED AIR (MG/L)'

DISCRETE CAT1
          INTERVAL CAT=24.           $'EXECUTE CAT1 EVERY 24 HOURS'
          DAY=DAY+1
          IF(MOD(DAY,7).GE.5) GOTO OUT
```

```
            CI=CONC*MW/24450              $'CONVERT OCC. FROM PPM TO MG/L IN AIR'
          SCHEDULE CAT2 .AT. T+TCHNG        $'END OF OCCUP. EXPOSURE'
            OUT. . CONTINUE               $'SKIP TO CAT2'
END                                       $'END OF CAT1'
DISCRETE CAT2

            CI = BCK*MW/24450.            $'CONVERT BCK. FROM PPM TO MG/L IN AIR'
END                                       $'END OF CAT2'

DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                                 $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                                 $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                                 $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                                 $'VOLUME OF RICHLY PERF. TISSUE (KG)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CI)/(QC+(QP/PB))             $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                         $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                                  $'CONC. EXHALED (MG/L)'
CXPPM=(0.7*CX+0.3*CI)*24450./MW           $'CONC. EXHALED (PPM)'
RAX=QP*CX                                 $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                          $'AMOUNT EXHALED (MG)'

'AI=AMOUNT INHALED'
RAI=QP*CI                                 $'RATE INHALED (MG/HR)'
AI=INTEG(RAI,0.)                          $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                           $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                          $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                            $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                                  $'CONC. IN SLOWLY PERF. (MG/KG)'

'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                           $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                          $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                            $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                                  $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                           $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                          $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                            $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                                  $'CONC. IN FAT (MG/KG)'
```

```
'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                          $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                         $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                           $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                                 $'CONC. IN LIVER (MG/KG)'
'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)                  $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                         $'AMOUNT METABOLIZED (MG)'

'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC      $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                        $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX                  $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                          $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                       $'TERMINATE SIMULATION'

END                                      $'END OF DERIVATIVE'
END                                      $'END OF DYNAMIC'
END                                      $'END OF PROGRAM'
```

Appendix F. Model Code "WORKSMOKE"

```
PROGRAM ADULT.CSL                    $'WORKSMOKE MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=450.                    $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QC=336.                    $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QL=84.                     $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QF=26.9                    $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QS=95.8                    $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QR=129.3                   $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  BW=70.                     $'BODY WEIGHT (KG)'
CONSTANT  VLC=2.6                    $'% LIVER TISSUE'
CONSTANT  VFC=20.                    $'% FAT TISSUE'
CONSTANT  VSC=64.                    $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VRC=6.                     $'% RICHLY PERFUSED TISSUE'
CONSTANT  PB=7.8                     $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.95                    $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=54.5                    $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.05                    $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.92                    $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                   $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=13.89                 $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  KM=.35                     $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  CONC=10.                   $'OCCUP. INHALED CONCENTRATION (PPM)'
CONSTANT  CONCS=.089                 $'SMOKING INHALED CONCENTRATION (PPM)'
CONSTANT  BCKS=.0034                 $'BACKGROUND BENZENE CONC. (PPM)'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.               $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  WDAYS=5.                   $'NUMBER OF WEEKDAYS'
CONSTANT  WEDAYS=2.                  $'NUMBER OF WEEKEND DAYS'
CONSTANT  DAYS=28.                   $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.

CONSTANT  TCHNG=8.                   $'LENGTH OF OCCUP. EXPOSURE (HRS)'
CONSTANT  TSMK=14.                   $'LENGTH OF SMOKING EXP (HRS)'
CONSTANT  CINT=.1                    $'COMMUNICATION INTERVAL'
INTEGER   DAY
          DAY=-1                     $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                  $'END OF INITIALIZATION'

DYNAMIC

ALGORITHM IALOG=2                    $'GEAR METHOD FOR EQUATIONS'

'CI=CONC IN INHALED AIR (MG/L)'
'CIS=CONCS IN INHALED SMOKING AIR (MG/L)'
```

```
DISCRETE CAT1
        INTERVAL CAT=24.          $'EXECUTE CAT1 EVERY 24 HOURS'
        DAY=DAY+1
        CIS=CONCS*MW/24450        $'SMOKING EXPOSURE (MG/L)'
        SCHEDULE CAT3 .AT. T+TSMK$'STOP SMOKING'

        IF(MOD(DAY,7).GE.5) GOTO NEXT

        CI=CONC*MW/24450          $'CONVERT OCC. FROM PPM TO MG/L IN AIR'
      SCHEDULE CAT2 .AT. T+TCHNG    $'END OF OCCUP. EXPOSURE'
        NEXT. . CONTINUE          $'SKIP TO CAT2'
END                               $'END OF CAT1'

DISCRETE CAT2

        CI = BCKS*MW/24450.       $'CONVERT BCKS. FROM PPM TO MG/L IN AIR'
END                               $'END OF CAT2'

DISCRETE CAT3

        CIS=0.                    $'NO SMOKING EXPOSURE'
END                               $'END OF CAT3'

DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                         $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                         $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                         $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                         $'VOLUME OF RICHLY PERF. TISSUE (KG)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CI+QP*CIS)/(QC+(QP/PB)) $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                 $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                          $'CONC. EXHALED (MG/L)'
CXPPM=(0.7*CX+0.3*(CI+CIS))*24450./MW $'CONC. EXHALED (PPM)'
RAX=QP*CX                         $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                  $'AMOUNT EXHALED (MG)'

'AI=AMOUNT INHALED'
RAI=QP*(CI+CIS)                   $'RATE INHALED (MG/HR)'
AI=INTEG(RAI,0.)                  $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                   $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                  $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                    $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                          $'CONC. IN SLOWLY PERF. (MG/KG)'
```

```
'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                          $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                         $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                           $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                                 $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                          $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                         $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                           $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                                 $'CONC. IN FAT (MG/KG)'

'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                          $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                         $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                           $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                                 $'CONC. IN LIVER (MG/KG)'


'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)                  $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                         $'AMOUNT METABOLIZED (MG)'

'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC      $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                        $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX                  $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                          $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                       $'TERMINATE SIMULATION'

END                                      $'END OF DERIVATIVE'
END                                      $'END OF DYNAMIC'
END                                      $'END OF PROGRAM'
```

Appendix G. Model Code "MOMBCKONLY"

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PROGRAM MOM.CSL                    $'MOMBCKONLY MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=363.                  $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QPI=93.                  $'ALVEOLAR VENTILATION INFANT (L/HR)'
CONSTANT  QC=288.                  $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QCI=33.6                 $'CARDIAC OUTPUT INFANT (L/HR)'
CONSTANT  QL=72.                   $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QLI=8.4                  $'BLOOD FLOW TO LIVER INFANT (L/HR)'
CONSTANT  QF=23.                   $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QFI=2.7                  $'BLOOD FLOW TO FAT INFANT (L/HR)'
CONSTANT  QS=82.1                  $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QSI=9.6                  $'BLOOD FLOW TO SLOW. PERF. INFANT (L/HR)'
CONSTANT  QR=82.1                  $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  QRI=12.9                 $'BLOOD FLOW TO RICH. PERF. INFANT (L/HR)'
CONSTANT  BW=60.                   $'BODY WEIGHT (KG)'
CONSTANT  BW=7.                    $'BODY WEIGHT INFANT (KG)'
CONSTANT  VLC=2.3                  $'% LIVER TISSUE'
CONSTANT  VLCI=3.4                 $'% LIVER TISSUE INFANT'
CONSTANT  VFC=30.                  $'% FAT TISSUE'
CONSTANT  VFCI=30.                 $'% FAT TISSUE INFANT'
CONSTANT  VSC=53.                  $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VSCI=54.                 $'% SLOWLY PERFUSED TISSUE INFANT'
CONSTANT  VRC=5.                   $'% RICHLY PERFUSED TISSUE'
CONSTANT  VRCI=5.                  $'% RICHLY PERFUSED TISSUE INFANT'
CONSTANT  VMC=5.                   $'% MAMMARY TISSUE'
CONSTANT  PB=8.2                   $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.8                   $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=51.8                  $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.                    $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.8                   $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                 $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=19.47               $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  VMAXI=3.25               $'MAX. VEL. OF METAB. INFANT (MG/HR-1KG)'
CONSTANT  KM=.35                   $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  VMILK=.05                $'VOLUME OF MILK (L)'
CONSTANT  FEEDI=.033               $'MILK YIELD (L/HR)'
CONSTANT  IOU                      $'INFANT ORAL UPTAKE (/HR)'
CONSTANT  BCK=.0022                $'BACKGROUND BENZENE CONC. (PPM)'
CONSTANT  BCKIN=1.                 $'INFANT EXPOSED TO BACKGROUND'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.             $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  DAYS=28.                 $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.
CONSTANT  CINT=.1                  $'COMMUNICATION INTERVAL'
INTEGER   DAY
          DAY=-1                   $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                $'END OF INITIALIZATION'
```

```
DYNAMIC

ALGORITHM IALOG=2                    $'GEAR METHOD FOR EQUATIONS'

'CI=CONC IN INHALED AIR (MG/L)'
'FEED=FEED INFANT'

DISCRETE CAT1
        INTERVAL CAT=24.             $'EXECUTE CAT1 EVERY 24 HOURS'
        DAY=DAY+1

        CI=BCK*MW/24450              $'CONVERT BCK FROM PPM TO MG/L IN AIR'
        FEED=FEEDI.                  $'FEED INFANT'
END                                  $'END OF CAT1'

DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                            $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                            $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                            $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                            $'VOLUME OF RICHLY PERF. TISSUE (KG)'
VM=VMC*BW                            $'VOLUME OF MAMMARY TISSUE (KG)'
VLI=VLC*BW                           $'VOLUME OF LIVER TISSUE INFANT (KG)'
VFI=VFC*BW                           $'VOLUME OF FAT TISSUE INFANT (KG)'
VSI=VSC*BW                           $'VOLUME OF SLOW.PERF. INFANT (KG)'
VRI=VRC*BW                           $'VOLUME OF RICH. PERF. INFANT (KG)'

GIW=VGIC*BWI                         $'WEIGHT OF INFANT GI TRACT (KG)'
BCKI=BCK*MW/24450.                   $'INFANT BREATHING ZONE CONC. (MG/L)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CI)/(QC+(QP/PB))        $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                    $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                             $'CONC. EXHALED (MG/L)'
CXPPM=(0.7*CX+0.3*CI)*24450./MW      $'CONC. EXHALED (PPM)'
RAX=QP*CX                            $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                     $'AMOUNT EXHALED (MG)'

'AI=AMOUNT INHALED'
RAI=QP*CI                            $'RATE INHALED (MG/HR)'
AI=INTEG(RAI,0.)                     $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                      $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                     $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                       $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                             $'CONC. IN SLOWLY PERF. (MG/KG)'
```

```
'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                          $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                         $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                           $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                                 $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                          $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                         $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                           $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                                 $'CONC. IN FAT (MG/KG)'

'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                          $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                         $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                           $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                                 $'CONC. IN LIVER (MG/KG)'
'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)                  $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                         $'AMOUNT METABOLIZED (MG)'

'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC      $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                        $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX                  $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                          $'BALANCE (MG)'

'AMAT=AMOUNT IN MAMMARY TISSUE'
RMAT=QMT*(CA-CVMT)-RINF                  $'RATE ENTERS MAMMARY (MG/HR)'
AMAT=INTEG(RMAT,0.)                      $'AMOUNT IN MAMMARY TISSUE (MG)'
CVMT=AMAT/(M*PR)                         $'VENOUS CONC. LEAVING (MG/L)'

'CMILK=CONCENTRATION IN MILK'
CMILK=CVMT*PM                            $'CONCENTRATION IN MILK (MG/L)'

'ELIMINATION RATE FROM MILK TO INFANT (MG/HR)'
RINF=FEED*CMILK                          $'RATE ENTERS INFANT (MG/HR)'
AINF=INTEG(RINF,0.)                      $'AMOUNT IN INFANT (MG)'
DOSEI=AINF/BWI                           $'DOSE RECEIVED BY INFANT (MG/KG)'

PROCEDURAL
        IF (T.GE.24) IDM=(DOSE*24)/T
        IF (T.GE.24) IDI=(AINI*24)/(BWI*T)
END                                      $'END OF PROCEDURAL. IDM,IDI (MG/KG/DAY)'
```

```
'AMOUNT REMAINING IN INFANT GI TRACT (MG)'
MR=INTEG(RMR,0.)                          $'AMOUNT IN GI TRACT (MG)'
RMR=RINF-RAIN                             $'RATE OF INFANT GI LOADING (MG/HR)'
RAIN=MR*IOU                               $'RATE OF INFANT GI ABSORPTION (MG/HR)'
AAI=INTEG(RAIN,0.)                        $'AMOUNT ABSORBED BY INFANT (MG)'
CGI=MR/GIW                                $'CONC. IN INFANT GI TRACT (MG/KG)'

'CAI=INFANT ARTERIAL CONCENTRATION (MG/L)'
CAI=(QCI*CV+QPI*BCKI*BCKIN)/(QCI+(QPI/PB))  $CONC. IN BLOOD (MG/L)'
AUCBI=INTEG(CAI,0.)                       $'AUC ARTERIAL BLOOD (MG*HR/L)'
AINI=INTEG(BCKI*BCKIN*QPI,0.)             $'AMOUNT INHALED FROM BCK. INF (MG)'

'AINHI=AMOUNT INHALED BY INFANT'
RINHI=QPI*BCKI                            $'RATE INHALED (MG/HR)'
AINHI=INTEG(RINHI,0.)                     $'AMOUNT INHALED (MG)'
TINT=AINF+AINHI                           $'TOTAL INFANT INTAKE (MG)'

'AXI=AMOUNT EXHALED BY INFANT'
CXI=CAI/PB                                $'CONC. EXHALED (MG/L)'
CXPPMI=(0.7*CXI)*24450./MW                $'CONC. EXHALED (PPM)'
RAXI=QPI*CXI                              $'RATE EXHALED (MG/HR)'
AXI=INTEG(RAXI,0.)                        $'AMOUNT EXHALED (MG)'

'ASI=AMOUNT IN INFANT SLOWLY PERFUSED TISSUE'
RASI=QSI*(CAI-CVSI)                       $'RATE ENTERS SLOW. PERF. (MG/HR)'
ASI=INTEG(RASI,0.)                        $'AMOUNT IN SLOW. PERF. (MG)'
CVSI=ASI/(VSI*PSI)                        $'VENOUS CONC. LEAVING (MG/L)'
CSI=ASI/VSI                               $'CONC. IN SLOWLY PERF. (MG/KG)'

'ARI=AMOUNT IN INFANT RICHLY PERFUSED TISSUE'
RARI=QIR*(CAI-CVRI)                       $'RATE ENTERS RICH. PERF. (MG/HR)'
ARI=INTEG(RARI,0.)                        $'AMOUNT IN RICH. PERF. (MG)'
CVRI=ARI/(VRI*PRI)                        $'VENOUS CONC. LEAVING (MG/L)'
CRI=ARI/VRI                               $'CONC. IN SLOWLY PERF. (MG/KG)'

'AFI=AMOUNT IN INFANT FAT TISSUE'
RAFI=QFI*(CAI-CVFI)                       $'RATE ENTERS FAT (MG/HR)'
AFI=INTEG(RAFI,0.)                        $'AMOUNT IN FAT (MG)'
CVFI=AFI/(VFI*PFI)                        $'VENOUS CONC. LEAVING (MG/L)'
CFI=AFI/VFI                               $'CONC. IN FAT (MG/KG)'

'ALI=AMOUNT IN INFANT LIVER TISSUE'
RALI=QLI*(CAI-CVLI)                       $'RATE ENTERS LIVER (MG/HR)'
ALI=INTEG(RALI,0.)                        $'AMOUNT IN LIVER (MG)'
CVLI=ALI/(VLI*PLI)                        $'VENOUS CONC. LEAVING (MG/L)'
CLI=ALI/VLI                               $'CONC. IN LIVER (MG/KG)'

'AMI=AMOUNT METABOLIZED BY INFANT'
RAMI=(VMAXI*CVLI)/(KM+CVLI)               $'RATE OF METABOLISM (MG/HR)'
AMI=INTEG(RAMI,0.)                        $'AMOUNT METABOLIZED (MG)'
```

```
'CVI=MIXED INFANT VENOUS BLOOD CONCENTRATION'
CVI=(QFI*CVFI+QLI*CVLI+QSI*CVSI+QRI*CVRI)/QCI      $'CONC. IN VENOUS BLOOD (MG/L)'
AUCVI=INTEG(CVI,0.)                                $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION FOR INFANT'
TMASSI=AFI+ALI+ASI+ARI+AMI+AXI                     $'TOTAL MASS (MG)'
MASBAI=TMASSI-TINT                                 $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                                 $'TERMINATE SIMULATION'

END                                                $'END OF DERIVATIVE'
END                                                $'END OF DYNAMIC'
END                                                $'END OF PROGRAM'
```

Appendix H. Model Code "MOMSMOKE"

```
PROGRAM MOM.CSL                          $'MOMSMOKE MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=363.                        $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QPI=93.                        $'ALVEOLAR VENTILATION INFANT (L/HR)'
CONSTANT  QC=288.                        $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QCI=33.6                       $'CARDIAC OUTPUT INFANT (L/HR)'
CONSTANT  QL=72.                         $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QLI=8.4                        $'BLOOD FLOW TO LIVER INFANT (L/HR)'
CONSTANT  QF=23.                         $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QFI=2.7                        $'BLOOD FLOW TO FAT INFANT (L/HR)'
CONSTANT  QS=82.1                        $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QSI=9.6                        $'BLOOD FLOW TO SLOW. PERF. INFANT (L/HR)'
CONSTANT  QR=82.1                        $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  QRI=12.9                       $'BLOOD FLOW TO RICH. PERF. INFANT (L/HR)'
CONSTANT  BW=60.                         $'BODY WEIGHT (KG)'
CONSTANT  BW=7.                          $'BODY WEIGHT INFANT (KG)'
CONSTANT  VLC=2.3                        $'% LIVER TISSUE'
CONSTANT  VLCI=3.4                       $'% LIVER TISSUE INFANT'
CONSTANT  VFC=30.                        $'% FAT TISSUE'
CONSTANT  VFCI=30.                       $'% FAT TISSUE INFANT'
CONSTANT  VSC=53.                        $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VSCI=54.                       $'% SLOWLY PERFUSED TISSUE INFANT'
CONSTANT  VRC=5.                         $'% RICHLY PERFUSED TISSUE'
CONSTANT  VRCI=5.                        $'% RICHLY PERFUSED TISSUE INFANT'
CONSTANT  VMC=5.                         $'% MAMMARY TISSUE'
CONSTANT  PB=8.2                         $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.8                         $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=51.8                        $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.                          $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.8                         $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                       $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=19.47                     $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  VMAXI=3.25                     $'MAX. VEL. OF METAB. INFANT (MG/HR-1KG)'
CONSTANT  KM=.35                         $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  VMILK=.05                      $'VOLUME OF MILK (L)'
CONSTANT  FEEDI=.033                     $'MILK YIELD WEEKDAY (L/HR)'
CONSTANT  IOU                            $'INFANT ORAL UPTAKE (/HR)'
CONSTANT  CONCS=.111                     $'SMOKING INHALED CONCENTRATION (PPM)'
CONSTANT  BCKS=.0034                     $'BACKGROUND BENZENE CONC. (PPM)'
CONSTANT  BCKIN=1.                       $'INFANT EXPOSED TO BACKGROUND'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.                   $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  WDAYS=5.                       $'NUMBER OF WEEKDAYS'
CONSTANT  WEDAYS=2.                      $'NUMBER OF WEEKEND DAYS'
CONSTANT  DAYS=28.                       $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.
CONSTANT  TSMK=14.                       $'LENGTH OF SMOKING EXPOSURE (HRS)'
```

```
CONSTANT   CINT=.1                    $'COMMUNICATION INTERVAL'
INTEGER    DAY
           DAY=-1                     $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                   $'END OF INITIALIZATION'

DYNAMIC

ALGORITHM  IALOG=2                    $'GEAR METHOD FOR EQUATIONS'

'CIS=CONC IN INHALED AIR (MG/L)'
'FEED=FEED INFANT'

DISCRETE CAT1

           INTERVAL CAT=24.           $'EXECUTE CAT1 EVERY 24 HOURS'
           DAY=DAY+1

           CIS=CONCS*MW/24450         $'CONVERT SMOKE FROM PPM TO MG/L IN AIR'
           FEED=FEEDI                 $'FEED INFANT '
         SCHEDULE CAT2 .AT. T+TSMK    $'END OF SMOKING EXPOSURE'
END                                   $'END OF CAT1'

DISCRETE CAT2

           CIS = BCKS*MW/24450.       $'CONVERT BCKS. FROM PPM TO MG/L IN AIR'
END                                   $'END OF CAT2'

DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                             $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                             $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                             $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                             $'VOLUME OF RICHLY PERF. TISSUE (KG)'
VM=VMC*BW                             $'VOLUME OF MAMMARY TISSUE (KG)'
VLI=VLC*BW                            $'VOLUME OF LIVER TISSUE INFANT (KG)'
VFI=VFC*BW                            $'VOLUME OF FAT TISSUE INFANT (KG)'
VSI=VSC*BW                            $'VOLUME OF SLOW.PERF. INFANT (KG)'
VRI=VRC*BW                            $'VOLUME OF RICH. PERF. INFANT (KG)'

GIW=VGIC*BWI                          $'WEIGHT OF INFANT GI TRACT (KG)'
BCKI=BCKS*MW/24450.                   $'INFANT BREATHING ZONE CONC. (MG/L)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CIS)/(QC+(QP/PB))        $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                     $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                              $'CONC. EXHALED (MG/L)'
CXPPM=(0.7*CX+0.3*CIS)*24450./MW      $'CONC. EXHALED (PPM)'
RAX=QP*CX                             $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                      $'AMOUNT EXHALED (MG)'
```

```
'AI=AMOUNT INHALED'
RAI=QP*CIS                          $'RATE INHALED (MG/HR)'
AI=INTEG(R                          $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                     $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                    $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                      $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                            $'CONC. IN SLOWLY PERF. (MG/KG)'

'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                     $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                    $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                      $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                            $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                     $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                    $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                      $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                            $'CONC. IN FAT (MG/KG)'

'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                     $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                    $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                      $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                            $'CONC. IN LIVER (MG/KG)'
'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)             $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                    $'AMOUNT METABOLIZED (MG)'

'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC     $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                   $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX             $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                     $'BALANCE (MG)'

'AMAT=AMOUNT IN MAMMARY TISSUE'
RMAT=QMT*(CA-CVMT)-RINF             $'RATE ENTERS MAMMARY (MG/HR)'
AMAT=INTEG(RMAT,0.)                 $'AMOUNT IN MAMMARY TISSUE (MG)'
CVMT=AMAT/(M*PR)                    $'VENOUS CONC. LEAVING (MG/L)'

'CMILK=CONCENTRATION IN MILK'
CMILK=CVMT*PM                       $'CONCENTRATION IN MILK (MG/L)'

'ELIMINATION RATE FROM MILK TO INFANT (MG/HR)'
RINF=FEED*CMILK                     $'RATE ENTERS INFANT (MG/HR)'
AINF=INTEG(RINF,0.)                 $'AMOUNT IN INFANT (MG)'
DOSEI=AINF/BWI                      $'DOSE RECEIVED BY INFANT (MG/KG)'
```

```
PROCEDURAL
          IF (T.GE.24)  IDM=(DOSE*24)/T
          IF (T.GE.24)  IDI=(AINI*24)/(BWI*T)
END                                        $'END OF PROCEDURAL, IDM,IDI (MG/KG/DAY)'

'AMOUNT REMAINING IN INFANT GI TRACT (MG)'
MR=INTEG(RMR,0.)                           $'AMOUNT IN GI TRACT (MG)'
RMR=RINF-RAIN                              $'RATE OF INFANT GI LOADING (MG/HR)'
RAIN=MR*IOU                                $'RATE OF INFANT GI ABSORPTION (MG/HR)'
AAI=INTEG(RAIN,0.)                         $'AMOUNT ABSORBED BY INFANT (MG)'
CGI=MR/GIW                                 $'CONC. IN INFANT GI TRACT (MG/KG)'

'CAI=INFANT ARTERIAL CONCENTRATION (MG/L)'
CAI=(QCI*CV+QPI*BCKI*BCKIN)/(QCI+(QPI/PB))  $CONC. IN BLOOD (MG/L)'
AUCBI=INTEG(CAI,0.)                        $'AUC ARTERIAL BLOOD (MG*HR/L)'
AINI=INTEG(BCKI*BCKIN*QPI,0.)              $'AMOUNT INHALED FROM BCK, INF (MG)'

'AINHI=AMOUNT INHALED BY INFANT'
RINHI=QPI*BCKI                             $'RATE INHALED (MG/HR)'
AINHI=INTEG(RINHI,0.)                      $'AMOUNT INHALED (MG)'
TINT=AINF+AINHI                            $'TOTAL INFANT INTAKE (MG)'

'AXI=AMOUNT EXHALED BY INFANT'
CXI=CAI/PB                                 $'CONC. EXHALED (MG/L)'
CXPPMI=(0.7*CXI)*24450./MW                 $'CONC. EXHALED (PPM)'
RAXI=QPI*CXI                               $'RATE EXHALED (MG/HR)'
AXI=INTEG(RAXI,0.)                         $'AMOUNT EXHALED (MG)'

'ASI=AMOUNT IN INFANT SLOWLY PERFUSED TISSUE'
RASI=QSI*(CAI-CVSI)                        $'RATE ENTERS SLOW. PERF. (MG/HR)'
ASI=INTEG(RASI,0.)                         $'AMOUNT IN SLOW. PERF. (MG)'
CVSI=ASI/(VSI*PSI)                         $'VENOUS CONC. LEAVING (MG/L)'
CSI=ASI/VSI                                $'CONC. IN SLOWLY PERF. (MG/KG)'

'ARI=AMOUNT IN INFANT RICHLY PERFUSED TISSUE'
RARI=QIR*(CAI-CVRI)                        $'RATE ENTERS RICH. PERF. (MG/HR)'
ARI=INTEG(RARI,0.)                         $'AMOUNT IN RICH. PERF. (MG)'
CVRI=ARI/(VRI*PRI)                         $'VENOUS CONC. LEAVING (MG/L)'
CRI=ARI/VRI                                $'CONC. IN SLOWLY PERF. (MG/KG)'

'AFI=AMOUNT IN INFANT FAT TISSUE'
RAFI=QFI*(CAI-CVFI)                        $'RATE ENTERS FAT (MG/HR)'
AFI=INTEG(RAFI,0.)                         $'AMOUNT IN FAT (MG)'
CVFI=AFI/(VFI*PFI)                         $'VENOUS CONC. LEAVING (MG/L)'
CFI=AFI/VFI                                $'CONC. IN FAT (MG/KG)'

'ALI=AMOUNT IN INFANT LIVER TISSUE'
RALI=QLI*(CAI-CVLI)                        $'RATE ENTERS LIVER (MG/HR)'
ALI=INTEG(RALI,0.)                         $'AMOUNT IN LIVER (MG)'
CVLI=ALI/(VLI*PLI)                         $'VENOUS CONC. LEAVING (MG/L)'
CLI=ALI/VLI                                $'CONC. IN LIVER (MG/KG)'
```

```
'AMI=AMOUNT METABOLIZED BY INFANT'
RAMI=(VMAXI*CVLI)/(KM+CVLI)          $'RATE OF METABOLISM (MG/HR)'
AMI=INTEG(RAMI,0.)                   $'AMOUNT METABOLIZED (MG)'

'CVI=MIXED INFANT VENOUS BLOOD CONCENTRATION'
CVI=(QFI*CVFI+QLI*CVLI+QSI*CVSI+QRI*CVRI)/QCI     $'CONC. IN VENOUS BLOOD (MG/L)'
AUCVI=INTEG(CVI,0.)                  $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION FOR INFANT'
TMASSI=AFI+ALI+ASI+ARI+AMI+AXI       $'TOTAL MASS (MG)'
MASBAI=TMASSI-TINT                   $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                   $'TERMINATE SIMULATION'

END                                  $'END OF DERIVATIVE'
END                                  $'END OF DYNAMIC'
END                                  $'END OF PROGRAM'
```

Appendix I. Model Code "MOMWORK"

```
PROGRAM MOM.CSL                    $'MOMWORK MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=363.                  $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QPI=93.                  $'ALVEOLAR VENTILATION INFANT (L/HR)'
CONSTANT  QC=288.                  $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QCI=33.6                 $'CARDIAC OUTPUT INFANT (L/HR)'
CONSTANT  QL=72.                   $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QLI=8.4                  $'BLOOD FLOW TO LIVER INFANT (L/HR)'
CONSTANT  QF=23.                   $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QFI=2.7                  $'BLOOD FLOW TO FAT INFANT (L/HR)'
CONSTANT  QS=82.1                  $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QSI=9.6                  $'BLOOD FLOW TO SLOW. PERF. INFANT (L/HR)'
CONSTANT  QR=82.1                  $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  QRI=12.9                 $'BLOOD FLOW TO RICH. PERF. INFANT (L/HR)'
CONSTANT  BW=60.                   $'BODY WEIGHT (KG)'
CONSTANT  BW=7.                    $'BODY WEIGHT INFANT (KG)'
CONSTANT  VLC=2.3                  $'% LIVER TISSUE'
CONSTANT  VLCI=3.4                 $'% LIVER TISSUE INFANT'
CONSTANT  VFC=30.                  $'% FAT TISSUE'
CONSTANT  VFCI=30.                 $'% FAT TISSUE INFANT'
CONSTANT  VSC=53.                  $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VSCI=54.                 $'% SLOWLY PERFUSED TISSUE INFANT'
CONSTANT  VRC=5.                   $'% RICHLY PERFUSED TISSUE'
CONSTANT  VRCI=5.                  $'% RICHLY PERFUSED TISSUE INFANT'
CONSTANT  VMC=5.                   $'% MAMMARY TISSUE'
CONSTANT  PB=8.2                   $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.8                   $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=51.8                  $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.                    $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.8                   $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                 $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=19.47               $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  VMAXI=3.25               $'MAX. VEL. OF METAB. INFANT (MG/HR-1KG)'
CONSTANT  KM=.35                   $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  VMILK=.05                $'VOLUME OF MILK (L)'
CONSTANT  FEEDI=.033               $'MILK YIELD WEEKDAY (L/HR)'
CONSTANT  IOU                      $'INFANT ORAL UPTAKE (/HR)'
CONSTANT  CONC=10.                 $'OCCUP. INHALED CONCENTRATION (PPM)'
CONSTANT  BCK=.0022                $'BACKGROUND BENZENE CONC. (PPM)'
CONSTANT  BCKIN=1.                 $'INFANT EXPOSED TO BACKGROUND'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.             $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  WDAYS=5.                 $'NUMBER OF WEEKDAYS'
CONSTANT  WEDAYS=2.                $'NUMBER OF WEEKEND DAYS'
CONSTANT  DAYS=28.                 $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.
CONSTANT  TCHNG=8.                 $'LENGTH OF OCCUP. EXPOSURE (HRS)'
```

```
CONSTANT  CINT=.1                    $'COMMUNICATION INTERVAL'
INTEGER   DAY
          DAY=-1                     $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                  $'END OF INITIALIZATION'

DYNAMIC

ALGORITHM IALOG=2                    $'GEAR METHOD FOR EQUATIONS'

'CI=CONC IN INHALED AIR (MG/L)'
'FEED=FEED INFANT'

DISCRETE CAT1
          INTERVAL CAT=24.           $'EXECUTE CAT1 EVERY 24 HOURS'
          DAY=DAY+1
          IF(MOD(DAY,7).GE.5) GOTO NEXT


          CI=CONC*MW/24450           $'CONVERT OCC. FROM PPM TO MG/L IN AIR'
          FEED=0.                    $'NO FEEDING INFANT DURING WORK'
        SCHEDULE CAT2 .AT. T+TCHNG     $'END OF OCCUP. EXPOSURE'
          NEXT. . CONTINUE           $'SKIP TO CAT2'
END                                  $'END OF CAT1'


DISCRETE CAT2

          CI = BCK*MW/24450.         $'CONVERT BCK. FROM PPM TO MG/L IN AIR'
          FEED=FEEDI                 $'FEED INFANT'
END                                  $'END OF CAT2'
DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                            $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                            $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                            $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                            $'VOLUME OF RICHLY PERF. TISSUE (KG)'
VM=VMC*BW                            $'VOLUME OF MAMMARY TISSUE (KG)'
VLI=VLC*BW                           $'VOLUME OF LIVER TISSUE INFANT (KG)'
VFI=VFC*BW                           $'VOLUME OF FAT TISSUE INFANT (KG)'
VSI=VSC*BW                           $'VOLUME OF SLOW.PERF. INFANT (KG)'
VRI=VRC*BW                           $'VOLUME OF RICH. PERF. INFANT (KG)'

GIW=VGIC*BWI                         $'WEIGHT OF INFANT GI TRACT (KG)'
BCKI=BCK*MW/24450.                   $'INFANT BREATHING ZONE CONC. (MG/L)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CI)/(QC+(QP/PB))        $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                    $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                             $'CONC. EXHALED (MG/L)'
```

```
CXPPM=(0.7*CX+0.3*CI)*24450./MW          $'CONC. EXHALED (PPM)'
RAX=QP*CX                                $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                         $'AMOUNT EXHALED (MG)'

'AI=AMOUNT INHALED'
RAI=QP*CI                                $'RATE INHALED (MG/HR)'
AI=INTEG(RAI,0.)                         $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                          $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                         $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                           $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                                 $'CONC. IN SLOWLY PERF. (MG/KG)'

'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                          $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                         $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                           $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                                 $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                          $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                         $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                           $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                                 $'CONC. IN FAT (MG/KG)'

'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                          $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                         $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                           $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                                 $'CONC. IN LIVER (MG/KG)'
'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)                  $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                         $'AMOUNT METABOLIZED (MG)'

'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC      $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                        $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX                  $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                          $'BALANCE (MG)'



'AMAT=AMOUNT IN MAMMARY TISSUE'
RMAT=QMT*(CA-CVMT)-RINF                  $'RATE ENTERS MAMMARY (MG/HR)'
AMAT=INTEG(RMAT,0.)                      $'AMOUNT IN MAMMARY TISSUE (MG)'
CVMT=AMAT/(M*PR)                         $'VENOUS CONC. LEAVING (MG/L)'
```

```
'CMILK=CONCENTRATION IN MILK'
CMILK=CVMT*PM                          $'CONCENTRATION IN MILK (MG/L)'

'ELIMINATION RATE FROM MILK TO INFANT (MG/HR)'
RINF=FEED*CMILK                        $'RATE ENTERS INFANT (MG/HR)'
AINF=INTEG(RINF,0.)                    $'AMOUNT IN INFANT (MG)'
DOSEI=AINF/BWI                         $'DOSE RECEIVED BY INFANT (MG/KG)'

PROCEDURAL
        IF (T.GE.24)  IDM=(DOSE*24)/T
        IF (T.GE.24)  IDI=(AINI*24)/(BWI*T)
END                                    $'END OF PROCEDURAL, IDM,IDI (MG/KG/DAY)'

'AMOUNT REMAINING IN INFANT GI TRACT (MG)'
MR=INTEG(RMR,0.)                       $'AMOUNT IN GI TRACT (MG)'
RMR=RINF-RAIN                          $'RATE OF INFANT GI LOADING (MG/HR)'
RAIN=MR*IOU                            $'RATE OF INFANT GI ABSORPTION (MG/HR)'
AAI=INTEG(RAIN,0.)                     $'AMOUNT ABSORBED BY INFANT (MG)'
CGI=MR/GIW                             $'CONC. IN INFANT GI TRACT (MG/KG)'

'CAI=INFANT ARTERIAL CONCENTRATION (MG/L)'
CAI=(QCI*CV+QPI*BCKI*BCKIN)/(QCI+(QPI/PB))  $CONC. IN BLOOD (MG/L)'
AUCBI=INTEG(CAI,0.)                    $'AUC ARTERIAL BLOOD (MG*HR/L)'
AINI=INTEG(BCKI*BCKIN*QPI,0.)          $'AMOUNT INHALED FROM BCK, INF (MG)'

'AINHI=AMOUNT INHALED BY INFANT'
RINHI=QPI*BCKI                         $'RATE INHALED (MG/HR)'
AINHI=INTEG(RINHI,0.)                  $'AMOUNT INHALED (MG)'
TINT=AINF+AINHI                        $'TOTAL INFANT INTAKE (MG)'

'AXI=AMOUNT EXHALED BY INFANT'
CXI=CAI/PB                             $'CONC. EXHALED (MG/L)'
CXPPMI=(0.7*CXI)*24450./MW             $'CONC. EXHALED (PPM)'
RAXI=QPI*CXI                           $'RATE EXHALED (MG/HR)'
AXI=INTEG(RAXI,0.)                     $'AMOUNT EXHALED (MG)'

'ASI=AMOUNT IN INFANT SLOWLY PERFUSED TISSUE'
RASI=QSI*(CAI-CVSI)                    $'RATE ENTERS SLOW. PERF. (MG/HR)'
ASI=INTEG(RASI,0.)                     $'AMOUNT IN SLOW. PERF. (MG)'
CVSI=ASI/(VSI*PSI)                     $'VENOUS CONC. LEAVING (MG/L)'
CSI=ASI/VSI                            $'CONC. IN SLOWLY PERF. (MG/KG)'

'ARI=AMOUNT IN INFANT RICHLY PERFUSED TISSUE'
RARI=QIR*(CAI-CVRI)                    $'RATE ENTERS RICH. PERF. (MG/HR)'
ARI=INTEG(RARI,0.)                     $'AMOUNT IN RICH. PERF. (MG)'
CVRI=ARI/(VRI*PRI)                     $'VENOUS CONC. LEAVING (MG/L)'
CRI=ARI/VRI                            $'CONC. IN SLOWLY PERF. (MG/KG)'
'AFI=AMOUNT IN INFANT FAT TISSUE'
RAFI=QFI*(CAI-CVFI)                    $'RATE ENTERS FAT (MG/HR)'
AFI=INTEG(RAFI,0.)                     $'AMOUNT IN FAT (MG)'
CVFI=AFI/(VFI*PFI)                     $'VENOUS CONC. LEAVING (MG/L)'
CFI=AFI/VFI                            $'CONC. IN FAT (MG/KG)'
```

```
'ALI=AMOUNT IN INFANT LIVER TISSUE'
RALI=QLI*(CAI-CVLI)                    $'RATE ENTERS LIVER (MG/HR)'
ALI=INTEG(RALI,0.)                     $'AMOUNT IN LIVER (MG)'
CVLI=ALI/(VLI*PLI)                     $'VENOUS CONC. LEAVING (MG/L)'
CLI=ALI/VLI                            $'CONC. IN LIVER (MG/KG)'

'AMI=AMOUNT METABOLIZED BY INFANT'
RAMI=(VMAXI*CVLI)/(KM+CVLI)            $'RATE OF METABOLISM (MG/HR)'
AMI=INTEG(RAMI,0.)                     $'AMOUNT METABOLIZED (MG)'

'CVI=MIXED INFANT VENOUS BLOOD CONCENTRATION'
CVI=(QFI*CVFI+QLI*CVLI+QSI*CVSI+QRI*CVRI)/QCI    $'CONC. IN VENOUS BLOOD (MG/L)'
AUCVI=INTEG(CVI,0.)                    $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION FOR INFANT'
TMASSI=AFI+ALI+ASI+ARI+AMI+AXI         $'TOTAL MASS (MG)'
MASBAI=TMASSI-TINT                     $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                     $'TERMINATE SIMULATION'

END                                    $'END OF DERIVATIVE'
END                                    $'END OF DYNAMIC'
END                                    $'END OF PROGRAM'
```

Appendix J. Model Code "MOMWORKSMOKE"

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PROGRAM MOM.CSL                    $'MOMWORKSMOKE MODEL FOR BENZENE'

INITIAL

CONSTANT  QP=363.                  $'ALVEOLAR VENTILATION (L/HR)'
CONSTANT  QPI=93.                  $'ALVEOLAR VENTILATION INFANT (L/HR)'
CONSTANT  QC=288.                  $'CARDIAC OUTPUT (L/HR)'
CONSTANT  QCI=33.6                 $'CARDIAC OUTPUT INFANT (L/HR)'
CONSTANT  QL=72.                   $'BLOOD FLOW TO LIVER (L/HR)'
CONSTANT  QLI=8.4                  $'BLOOD FLOW TO LIVER INFANT (L/HR)'
CONSTANT  QF=23.                   $'BLOOD FLOW TO FAT (L/HR)'
CONSTANT  QFI=2.7                  $'BLOOD FLOW TO FAT INFANT (L/HR)'
CONSTANT  QS=82.1                  $'BLOOD FLOW TO SLOWLY PERFUSED (L/HR)'
CONSTANT  QSI=9.6                  $'BLOOD FLOW TO SLOW. PERF. INFANT (L/HR)'
CONSTANT  QR=82.1                  $'BLOOD FLOW TO RICHLY PERFUSED (L/HR)'
CONSTANT  QRI=12.9                 $'BLOOD FLOW TO RICH. PERF. INFANT (L/HR)'
CONSTANT  BW=60.                   $'BODY WEIGHT (KG)'
CONSTANT  BW=7.                    $'BODY WEIGHT INFANT (KG)'
CONSTANT  VLC=2.3                  $'% LIVER TISSUE'
CONSTANT  VLCI=3.4                 $'% LIVER TISSUE INFANT'
CONSTANT  VFC=30.                  $'% FAT TISSUE'
CONSTANT  VFCI=30.                 $'% FAT TISSUE INFANT'
CONSTANT  VSC=53.                  $'% SLOWLY PERFUSED TISSUE'
CONSTANT  VSCI=54.                 $'% SLOWLY PERFUSED TISSUE INFANT'
CONSTANT  VRC=5.                   $'% RICHLY PERFUSED TISSUE'
CONSTANT  VRCI=5.                  $'% RICHLY PERFUSED TISSUE INFANT'
CONSTANT  VMC=5.                   $'% MAMMARY TISSUE'
CONSTANT  PB=8.2                   $'BLOOD/AIR PARTITION COEFFICIENT'
CONSTANT  PL=2.8                   $'LIVER/BLOOD PARTITION COEFFICIENT'
CONSTANT  PF=51.8                  $'FAT/BLOOD PARTITION COEFFICIENT'
CONSTANT  PS=2.                    $'SLOWLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  PR=1.8                   $'RICHLY PERFUSED PARTITION COEFFICIENT'
CONSTANT  MW=78.11                 $'MOLECULAR WEIGHT (G/MOL)'
CONSTANT  VMAX=19.47               $'MAX. VEL. OF METABOLISM (MG/HR-1KG)'
CONSTANT  VMAXI=3.25               $'MAX. VEL. OF METAB. INFANT (MG/HR-1KG)'
CONSTANT  KM=.35                   $'MICHAELIS-MENTEN CONSTANT (MG/L)'
CONSTANT  VMILK=.05                $'VOLUME OF MILK (L)'
CONSTANT  FEEDI=.033               $'MILK YIELD WEEKDAY (L/HR)'
CONSTANT  IOU                      $'INFANT ORAL UPTAKE (/HR)'
CONSTANT  CONC=10.                 $'OCCUP. INHALED CONCENTRATION (PPM)'
CONSTANT  CONCS=.111               $'SMOKING INHALED CONCENTRATION (PPM)'
CONSTANT  BCKS=.0034               $'BACKGROUND SMOKING CONC. (PPM)'
CONSTANT  BCKIN=1.                 $'INFANT EXPOSED TO BACKGROUND'

'TIMING COMMANDS'
TSTOP=(DAYS+PDAYS)*24.             $'LENGTH OF EXPERIMENT (DAYS)'
CONSTANT  WDAYS=5.                 $'NUMBER OF WEEKDAYS'
CONSTANT  WEDAYS=2.                $'NUMBER OF WEEKEND DAYS'
CONSTANT  DAYS=28.                 $'NUMBER OF EXPERIMENT DAYS'
CONSTANT  PDAYS=0.
```

```
CONSTANT  TCHNG=8.                    $'LENGTH OF OCCUP. EXPOSURE (HRS)'
CONSTANT  TSMK=14.                    $'LENGTH OF SMOKING EXPOSURE (HRS)'
CONSTANT  CINT=.1                     $'COMMUNICATION INTERVAL'
INTEGER   DAY
          DAY=-1                      $'START ON MON.,-1, TUES.,0, WED.,1, ETC'
END                                   $'END OF INITIALIZATION'

DYNAMIC

ALGORITHM IALOG=2                     $'GEAR METHOD FOR EQUATIONS'

'CI=CONC IN INHALED AIR (MG/L)'
'CIS=CONCS IN INHALED SMOKE (MG/L)'
'FEED=FEED INFANT'

DISCRETE CAT1
          INTERVAL CAT=24.            $'EXECUTE CAT1 EVERY 24 HOURS'
          DAY=DAY+1
          CIS=CONCS*MW/24450.         $'CONVERT SMOKE FROM PPM TO MG/L'
          SCHEDULE CAT3 .AT. T+TSMK   $'STOP SMOKING EXPOSURE'

          IF(MOD(DAY,7).GE.5) GOTO NEXT

          CI=CONC*MW/24450            $'CONVERT OCCUP. FROM PPM TO MG/L'
          FEED=0.                     $'NO FEEDING INFANT DURING WORK'
        SCHEDULE CAT2 .AT. T+TCHNG      $'END OF OCCUP. EXPOSURE'
          NEXT. . CONTINUE            $'SKIP TO CAT2'
END                                   $'END OF CAT1'

DISCRETE CAT2

          CI = BCKS*MW/24450.         $'CONVERT BCKS. FROM PPM TO MG/L IN AIR'
          FEED=FEEDI                  $'FEED INFANT'
END                                   $'END OF CAT2'

DISCRETE CAT3

          CIS=0.
END                                   $'END OF CAT3'

DERIVATIVE

'SCALED PARAMETERS'
VL=VLC*BW                             $'VOLUME OF LIVER TISSUE (KG)'
VF=VFC*BW                             $'VOLUME OF FAT TISSUE (KG)'
VS=VSC*BW                             $'VOLUME OF SLOWLY PERF. TISSUE (KG)'
VR=VRC*BW                             $'VOLUME OF RICHLY PERF. TISSUE (KG)'
VM=VMC*BW                             $'VOLUME OF MAMMARY TISSUE (KG)'
VLI=VLC*BW                            $'VOLUME OF LIVER TISSUE INFANT (KG)'
VFI=VFC*BW                            $'VOLUME OF FAT TISSUE INFANT (KG)'
VSI=VSC*BW                            $'VOLUME OF SLOW.PERF. INFANT (KG)'
VRI=VRC*BW                            $'VOLUME OF RICH. PERF. INFANT (KG)'
```

```
GIW=VGIC*BWI                                  $'WEIGHT OF INFANT GI TRACT (KG)'
BCKI=BCKS*MW/24450.                           $'INFANT BREATHING ZONE CONC. (MG/L)'

'CA=ARTERIAL CONCENTRATION (MG/L)'
CA=(QC*CV+QP*CI+QP*CIS)/(QC+(QP/PB))          $'CONC. IN BLOOD (MG/L)'
AUCB=INTEG(CA,0.)                             $'AUC ARTERIAL BLOOD (MG*HR/L)'

'AX=AMOUNT EXHALED'
CX=CA/PB                                      $'CONC. EXHALED (MG/L)'
CXPPM=(0.7*CX+0.3*(CI+CIS))*24450./MW         $'CONC. EXHALED (PPM)'
RAX=QP*CX                                     $'RATE EXHALED (MG/HR)'
AX=INTEG(RAX,0.)                              $'AMOUNT EXHALED (MG)'

'AI=AMOUNT INHALED'
RAI=QP*(CI+CIS)                               $'RATE INHALED (MG/HR)'
AI=INTEG(RAI,0.)                              $'AMOUNT INHALED (MG)'

'AS=AMOUNT IN SLOWLY PERFUSED TISSUE'
RAS=QS*(CA-CVS)                               $'RATE ENTERS SLOW. PERF. (MG/HR)'
AS=INTEG(RAS,0.)                              $'AMOUNT IN SLOW. PERF. (MG)'
CVS=AS/(VS*PS)                                $'VENOUS CONC. LEAVING (MG/L)'
CS=AS/VS                                      $'CONC. IN SLOWLY PERF. (MG/KG)'

'AR=AMOUNT IN RICHLY PERFUSED TISSUE'
RAR=QR*(CA-CVR)                               $'RATE ENTERS RICH. PERF. (MG/HR)'
AR=INTEG(RAR,0.)                              $'AMOUNT IN RICH. PERF. (MG)'
CVR=AR/(VR*PR)                                $'VENOUS CONC. LEAVING (MG/L)'
CR=AR/VR                                      $'CONC. IN SLOWLY PERF. (MG/KG)'

'AF=AMOUNT IN FAT TISSUE'
RAF=QF*(CA-CVF)                               $'RATE ENTERS FAT (MG/HR)'
AF=INTEG(RAF,0.)                              $'AMOUNT IN FAT (MG)'
CVF=AF/(VF*PF)                                $'VENOUS CONC. LEAVING (MG/L)'
CF=AF/VF                                      $'CONC. IN FAT (MG/KG)'

'AL=AMOUNT IN LIVER TISSUE'
RAL=QL*(CA-CVL)                               $'RATE ENTERS LIVER (MG/HR)'
AL=INTEG(RAL,0.)                              $'AMOUNT IN LIVER (MG)'
CVL=AL/(VL*PL)                                $'VENOUS CONC. LEAVING (MG/L)'
CL=AL/VL                                      $'CONC. IN LIVER (MG/KG)'
'AM=AMOUNT METABOLIZED'
RAM=(VMAX*CVL)/(KM+CVL)                       $'RATE OF METABOLISM (MG/HR)'
AM=INTEG(RAM,0.)                              $'AMOUNT METABOLIZED (MG)'


'CV=MIXED VENOUS BLOOD CONCENTRATION'
CV=(QF*CVF+QL*CVL+QS*CVS+QR*CVR)/QC      $'CONC. IN VENOUS BLOOD (MG/L)'
AUCV=INTEG(CV,0.)                             $'AUC VENOUS BLOOD (MG*HR/L)'
```

```
'MASS BALANCE EQUATION'
TMASS=AF+AL+AS+AR+AM+AX                    $'TOTAL MASS (MG)'
MASBAL=TMASS-AI                            $'BALANCE (MG)'

'AMAT=AMOUNT IN MAMMARY TISSUE'
RMAT=QMT*(CA-CVMT)-RINF                    $'RATE ENTERS MAMMARY (MG/HR)'
AMAT=INTEG(RMAT,0.)                        $'AMOUNT IN MAMMARY TISSUE (MG)'
CVMT=AMAT/(M*PR)                           $'VENOUS CONC. LEAVING (MG/L)'

'CMILK=CONCENTRATION IN MILK'
CMILK=CVMT*PM                              $'CONCENTRATION IN MILK (MG/L)'

'ELIMINATION RATE FROM MILK TO INFANT (MG/HR)'
RINF=FEED*CMILK                            $'RATE ENTERS INFANT (MG/HR)'
AINF=INTEG(RINF,0.)                        $'AMOUNT IN INFANT (MG)'
DOSEI=AINF/BWI                             $'DOSE RECEIVED BY INFANT (MG/KG)'

PROCEDURAL
        IF (T.GE.24)  IDM=(DOSE*24)/T
        IF (T.GE.24)  IDI=(AINI*24)/(BWI*T)
END                                        $'END OF PROCEDURAL, IDM,IDI (MG/KG/DAY)'

'AMOUNT REMAINING IN INFANT GI TRACT (MG)'
MR=INTEG(RMR,0.)                           $'AMOUNT IN GI TRACT (MG)'
RMR=RINF-RAIN                              $'RATE OF INFANT GI LOADING (MG/HR)'
RAIN=MR*IOU                                $'RATE OF INFANT GI ABSORPTION (MG/HR)'
AAI=INTEG(RAIN,0.)                         $'AMOUNT ABSORBED BY INFANT (MG)'
CGI=MR/GIW                                 $'CONC. IN INFANT GI TRACT (MG/KG)'

'CAI=INFANT ARTERIAL CONCENTRATION (MG/L)'
CAI=(QCI*CV+QPI*BCKI*BCKIN)/(QCI+(QPI/PB))  $CONC. IN BLOOD (MG/L)'
AUCBI=INTEG(CAI,0.)                        $'AUC ARTERIAL BLOOD (MG*HR/L)'
AINI=INTEG(BCKI*BCKIN*QPI,0.)              $'AMOUNT INHALED FROM BCK, INF (MG)'

'AINHI=AMOUNT INHALED BY INFANT'
RINHI=QPI*BCKI                             $'RATE INHALED (MG/HR)'
AINHI=INTEG(RINHI,0.)                      $'AMOUNT INHALED (MG)'
TINT=AINF+AINHI                            $'TOTAL INFANT INTAKE (MG)'

'AXI=AMOUNT EXHALED BY INFANT'
CXI=CAI/PB                                 $'CONC. EXHALED (MG/L)'
CXPPMI=(0.7*CXI)*24450./MW                 $'CONC. EXHALED (PPM)'
RAXI=QPI*CXI                               $'RATE EXHALED (MG/HR)'
AXI=INTEG(RAXI,0.)                         $'AMOUNT EXHALED (MG)'

'ASI=AMOUNT IN INFANT SLOWLY PERFUSED TISSUE'
RASI=QSI*(CAI-CVSI)                        $'RATE ENTERS SLOW. PERF. (MG/HR)'
ASI=INTEG(RASI,0.)                         $'AMOUNT IN SLOW. PERF. (MG)'
CVSI=ASI/(VSI*PSI)                         $'VENOUS CONC. LEAVING (MG/L)'
CSI=ASI/VSI                                $'CONC. IN SLOWLY PERF. (MG/KG)'
```

```
'ARI=AMOUNT IN INFANT RICHLY PERFUSED TISSUE'
RARI=QIR*(CAI-CVRI)                    $'RATE ENTERS RICH. PERF. (MG/HR)'
ARI=INTEG(RARI,0.)                     $'AMOUNT IN RICH. PERF. (MG)'
CVRI=ARI/(VRI*PRI)                     $'VENOUS CONC. LEAVING (MG/L)'
CRI=ARI/VRI                            $'CONC. IN SLOWLY PERF. (MG/KG)'

'AFI=AMOUNT IN INFANT FAT TISSUE'
RAFI=QFI*(CAI-CVFI)                    $'RATE ENTERS FAT (MG/HR)'
AFI=INTEG(RAFI,0.)                     $'AMOUNT IN FAT (MG)'
CVFI=AFI/(VFI*PFI)                     $'VENOUS CONC. LEAVING (MG/L)'
CFI=AFI/VFI                            $'CONC. IN FAT (MG/KG)'

'ALI=AMOUNT IN INFANT LIVER TISSUE'
RALI=QLI*(CAI-CVLI)                    $'RATE ENTERS LIVER (MG/HR)'
ALI=INTEG(RALI,0.)                     $'AMOUNT IN LIVER (MG)'
CVLI=ALI/(VLI*PLI)                     $'VENOUS CONC. LEAVING (MG/L)'
CLI=ALI/VLI                            $'CONC. IN LIVER (MG/KG)'

'AMI=AMOUNT METABOLIZED BY INFANT'
RAMI=(VMAXI*CVLI)/(KM+CVLI)            $'RATE OF METABOLISM (MG/HR)'
AMI=INTEG(RAMI,0.)                     $'AMOUNT METABOLIZED (MG)'

'CVI=MIXED INFANT VENOUS BLOOD CONCENTRATION'
CVI=(QFI*CVFI+QLI*CVLI+QSI*CVSI+QRI*CVRI)/QCI    $'CONC. IN VENOUS BLOOD (MG/L)'
AUCVI=INTEG(CVI,0.)                    $'AUC VENOUS BLOOD (MG*HR/L)'

'MASS BALANCE EQUATION FOR INFANT'
TMASSI=AFI+ALI+ASI+ARI+AMI+AXI         $'TOTAL MASS (MG)'
MASBAI=TMASSI-TINT                     $'BALANCE (MG)'

TERMT (T.GE.TSTOP)                     $'TERMINATE SIMULATION'

END                                    $'END OF DERIVATIVE'
END                                    $'END OF DYNAMIC'
END                                    $'END OF PROGRAM'
```

Appendix K. Data Files for Models

MAN
SET QP=450., QC=336., QF=26.9, QL=84., QS=95.8, QR=129.3
SET VMAX=13,89, KM=.35, BW=70.
SET VFC=.20, VLC=.026, VSC=.64, VRC=.06
SET PB=7.8, PL=2.95, PF=54.5, PS=2.05, PR=1.92
SET CONCS=.089
END

WOMAN
SET QP=363., QC=288., QF=23., QL=72., QS=82.1, QR=110.9
SET VMAX=19.47, KM=.35, BW=60.
SET VFC=.30, VLC=.023, VSC=.55, VRC=.05
SET PB=8.2, PL=2.8, PF=51.8, PS=2., PR=1.8
SET CONCS=.111
END

LWOMAN
SET QP=363., QC=288., QF=20.7, QL=64.8, QS=73.9, QR=99.8, QMT=28.8
SET VMAX=19.47, KM=.35, BW=60.
SET VFC=.30, VLC=.023, VSC=.50, VRC=.05, VMC=.05
SET PB=8.2, PL=2.8, PF=51.8, PS=2., PR=1.8, PM=4.
SET CONCS=.111
END

INFANT
SET QP=93., QC=33.6, QF=2.7, QL=8.4, QS=9.6, QR=12.9
SET VMAX=3.25 KM=.35, BW=7.
SET VFC=.30, VLC=.034, VSC=.55, VRC=.04
SET PB=8.2, PL=2.8, PF=51.8, PS=2., PR=1.8
END

Appendix L. Validation Data

MAND
SET BW=60.4, VFC=.15, VSC=.69
SET CONC=25., BCK=0.
SET DAYS=1., TCHNG=2.

EXTRACTED DATA POINTS FROM FIGURE 3-2 FOR MAN.

TIME (HRS)	CV (MG/L)
.183	.12196
.45	.14509
.933	.16364
1.45	.21667
1.967	.2073
2.967	.06781
3.95	.03927
4.967	.03061
5.933	.02428
6.917	.02090

WOMAND
SET BW=55.4, VFC=.25, VSC=.60
SET CONC=25., BCK=0.
SET DAYS=1., TCHNG=2.

EXTRACTED DATA POINTS FROM FIGURE 3-2 FOR WOMAN.

TIME (HRS)	CV (MG/L)
.283	.07960
.567	.11005
1.05	.15742
1.567	.15693
2.083	.17799
3.083	.05018
4.050	.03704
5.083	.02973
6.033	.02681
7.033	.02479

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Vita

Captain Elizabeth A. Brown was born on 8 February 1965, in Sacramento, California. She graduated from Vandalia-Butler High School in Vandalia, Ohio in 1983 and attended Ohio University, graduating with a Bachelor of Science in Civil Engineering in June 1987. Upon graduation, she received a commission in the USAF and served her first tour of duty at Cannon AFB, New Mexico. She began work in the environmental section, conducting inspections on base wide hazardous waste management programs and instructing the hazardous waste management course. From there, she became the chief of project programming and justified work for that base's multi-million dollar expansion during the realignment of installations. She was then assigned as chief of the heavy repair section in March 1990 and remained in that position when her squadron was deployed to Saudi Arabia for Operation Desert Shield and Desert Storm in August 1990. Upon return in April 1991 she received an assignment to RAF Bentwaters, England. There she was chosen to develop and manage the facility closure program and organize the return of the base to the British government. She was further assigned as the chief of the engineering branch in November 1992 until entering the School of Engineering, Air Force Institute of Technology, in May 1993.

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September 1994 Master's Thesis

A COMPARATIVE PHARMACOKINETIC STUDY OF THE ROLE OF GENDER AND DEVELOPMENTAL DIFFERENCES IN OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO BENZENE

Elizabeth A. Brown, Captain, USAF

Air Force Institute of Technology, WPAFB OH 45433-6583

AFIT/GEE/ENV/94S-12

The purpose of this study is two-fold. First, it shows that physiological differences between men and women result in gender-specific exposures with respect to benzene. Second, it assesses the potential for a lactating woman's occupational and personal benzene exposure to impact a nursing infant's exposure, highlighting the possibility of subjecting an infant to the effects of industrial chemicals via breast feeding.

This study employs physiologically based pharmacokinetic (PBPK) modeling to investigate the influence of physiological parameters and to evaluate the ability of inhaled benzene to transfer from mother to infant through breastmilk. The models are run through scenarios that simulate occupational, smoking, and background exposures.

The gender comparison is facilitated by a sensitivity analysis. The blood/air partition coefficient and maximum velocity of metabolism were found to substantially impact model output. These values were both higher in women and caused an increase in the percentage of benzene metabolized in all of the exposure scenarios.

The study of lactating women and infants is essentially theoretical. There is evidence that over 65% of an infant's benzene exposure can be attributed to contaminated breastmilk. A large portion of the ingested exposure can be eliminated by adjusting the mother's working or nursing schedule.

Benzene, physiologically based pharmacokinetics, pbpk, exposure, smoking, gender, infant, human, breast feeding. 119

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