## 5.0 BENZENE

### 5.1 Chemical and Physical Properties (EPA, 1988)

Benzene is a clear, colorless, aromatic hydrocarbon which has a characteristic sickly, sweet odor.  It is both volatile and flammable.  Selected chemical and physical properties of benzene are presented in Table 5-1.

Benzene contains 92.3 percent carbon and 7.7 percent hydrogen with the chemical formula $C_6H_6$.  The benzene molecule is represented by a hexagon formed by the six sets of carbon and hydrogen atoms bonded together with alternating single and double bonds.  The benzene molecule is the cornerstone for aromatic compounds, most of which contain one or more benzene rings.

Benzene is nonpolar, meaning it carries no major area of charge in any portion of the molecule and no net electrical charge considering the molecule as a whole.  It is relatively soluble in water and is capable of mixing with polar solvents (solvents which carry major portions of opposing charges within the molecule) such as chloroform, acetone, alcohol, and carbon tetrachloride without separating into two phases.

Benzene is a highly stable aromatic hydrocarbon, but it does react with other compounds primarily by substitution of a hydrogen atom.  Some reactions occur which can rupture or cleave the molecule.

Table 5-1.  Chemical and Physical Properties of Benzene.

| Property | Value |
|---|---|
| Molecular weight | 78.11 g/mole |
| Melting point | 5.5°C (41.9°F) |
| Boiling point | 80.1°C (176.2°F) |
| Density at 20°C (68°F) | 0.879 g/ml |
| Vapor Pressure at 25°C (77°F) | 0.13 atm. |
| Flash point (closed cup) | -11.1°C (12.02°F) |
| Solubility in water at 25°C | 1.8 g/L |
| Conversions at 25°C | 1 ppm = 3.25 mg/m$^3$<br>1 mg/liter = 313 ppm |

## 5.2 Formation and Control Technology

Benzene is present in both exhaust and evaporative emissions. Data show the benzene level of gasoline to be about 1.5%, with diesel fuel containing relatively insignificant levels of benzene. Some exhaust benzene is unburned fuel benzene. Some work indicates that non-benzene aromatics in the fuels can cause about 70 to 80% of the exhaust benzene formed. Some benzene also forms from engine combustion of non-aromatic fuel hydrocarbons. The fraction of benzene in the exhaust varies depending on control technology and fuel composition but is generally about 3 to 5%. The fraction of benzene in the evaporative emissions also depends on control technology (e.g., whether the vehicle has fuel injection or a carburetor) and fuel composition (e.g., benzene level and RVP) and is generally about 1%. These data also show that diesel vehicles account for only about 3% of the total mobile source benzene emitted (Carey, 1987).

Control techniques are available and in use for both evaporative and exhaust emissions of benzene. For example, positive crankcase ventilation (PCV) and evaporative controls reduce evaporative emissions of benzene. Fuel evaporative controls were installed on all 1971 light-duty gasoline vehicles. An absorption/regeneration system, one of the most common evaporative control techniques, is a canister of activated carbon that traps vapors such as benzene. The vapors are ultimately fed back to the combustion chamber. Catalysts on automobiles have been effective in reducing benzene exhaust emissions. The amount of reduction achieved is dependent on the type of catalyst technology used and the drive cycle of the vehicle (EPA, 1988). It is also dependent on the exhaust hydrocarbon standard to which the vehicle has been certified.

Section 202(a)(6) of the Act states that the EPA shall promulgate standards for control of refueling emissions, after consultation with the Department of Transportation. EPA decided not to promulgate such standards in March of 1992 after questions were raised by the National Highway Traffic Safety Administration on the safety of the onboard carbon canisters. This decision was also based on information concerning the effectiveness of this technology to combat ozone. The EPA then issued guidance for vapor recovery technology, known as Stage 2, to be installed on gasoline pumps (EPA, 1992a). On January 22, 1993 a Federal appellate court directed EPA to promulgate standards requiring automakers to control refueling emissions for new cars and light-duty trucks.

## 5.3  Emissions

### 5.3.1  Emission Fractions Used in the MOBTOX Emissions Model

Benzene fractions were determined using a series of equations relating fuel properties to THC percent benzene in exhaust and evaporative emissions rather than the actual vehicle data in Appendix B2. However, actual vehicle data were used to

corroborate the accuracy of these equations.  Please refer to
Appendix B2 for the emission fractions used in this section.

5.3.1.1  Benzene Exhaust Emission Fractions

For benzene exhaust from gasoline vehicles, separate
equations were used for three-way catalysts, three-way plus
oxidation catalysts, and other catalyst types.  For vehicles with
a three-way catalyst, running on baseline gasoline, the following
equation was used:

3-way Bz%THC = 1.077 + 0.7732*(volume % benzene)
              + 0.0987*(volume % aromatics - volume % benzene).

This equation was obtained by the EPA Regulatory Development and
Support Division (RDSD) from work done by Chevron Oil Company
(Chevron 1991).  An analogous equation for NMHC is being used by
RDSD in the Supplemental NPRM, on regulation of fuels and fuel
additives in reformulated and conventional gasoline (EPA, 1991a).
For vehicles with a three-way plus oxidation catalyst, running on
baseline gasoline, the equation used was:

3-way + ox Bz%THC = 0.6796*(volume % benzene)
                   + 0.0681*(volume % aromatics) - 0.3468.

This equation was obtained from the draft Regulatory Impact
Analysis for RVP regulations (EPA, 1987a).  For vehicles with no
catalyst or an oxidation catalyst, the equation used was:

other Bz%THC = 0.8551*(volume % benzene)
              + 0.12198*(volume % aromatics) - 1.1626.

This equation was also given in the draft Regulatory Impact
Analysis for RVP regulations.  The same benzene fractions were
used for HDGVs.  Benzene fractions for LDDVs, LDDTs, and HDDVs
were based on the benzene fractions of THC used in the 1987 EPA
motor vehicle air toxics report (0.0240 for LDDVs and LDDTs;
0.0110 for HDDVs) (Carey, 1987).  These were then adjusted to
give benzene fractions of TOG using the TOG/THC ratios given in
Table 3-7.

Next, it was necessary to determine whether an adjustment
factor should be applied to the gasoline vehicle equations for
MTBE and ethanol blends.  To calculate an appropriate adjustment
factor, percent exhaust benzene for individual vehicles in
various studies was compared for baseline and oxygenated blends
(Appendix B4).  The comparison between fuels was done on a
vehicle by vehicle basis because of the large amount of
individual variation in emissions among vehicles.  If data for
different vehicles running on a fuel type are pooled and then
compared, it is difficult to isolate trends probably due to car
to car variations.  Also, if data for different MTBE or ethanol
blends (with the different aromatic, olefin content, etc.) are
pooled, fuel effects may also make comparison difficult.  This
comparison was performed for 15% MTBE and 10% ethanol.  Then, an

average percent change (expressed as a fraction) was calculated for each catalyst type.  This average percent change was added to 1, representing the baseline emissions with gasoline, and the equations were then multiplied by the resultant factor.  Since the average percent change was calculated for 15% MTBE, for blends with other MTBE levels the average percent change was multiplied by a ratio of percent MTBE to 15.  Actual benzene TOG fractions (from Appendix B2) were compared to predicted benzene THC, with and without the adjustment factor (Appendix B5).  No significant difference was observed in the accuracy of the equations, with and without the adjustment factor, with both typically predicting TOG benzene levels within +/- 20%.  Based on these comparisons, the THC equations without adjustment factors were used to determine benzene percent TOG fractions for MTBE and ethanol blends, since these seemed to be just as accurate.

Once the appropriate equations for benzene were chosen, the fuel properties (% aromatics, benzene, and oxygen) to use with the equations were then determined.  The resultant emission fractions are contained in Appendix B6.

For reformulated gasoline in CY 2000+, the fraction of exhaust benzene (and the other toxics mentioned in CAAA Section 219) is assumed to remain the same relative to CY 1995-1999. However, the mass of TOG will be reduced as required by the CAAA. As a result, the mass of benzene is assumed to be reduced proportionately to TOG for exhaust.

As mentioned earlier, under the California standards, fuel characteristics for oxygenates are similar to those under the reformulated gasoline regulations.  However, under Phase 2 of CARB's reformulated fuel regulations, which go into effect in 1996, RVP will be limited to 7.0 psi.  Since RVP has little effect on benzene exhaust fractions, it was assumed that benzene exhaust fractions under the California standards are the same as under reformulated gasoline regulations.

5.3.1.2  Benzene Diurnal and Hot Soak Evaporative Emission Fractions

For benzene evaporative emissions from gasoline vehicles, two equations were used to determine fractions -- one for diurnal emissions, and one for hot soak emissions.  The equation used for diurnal emissions from vehicles running on gasoline MTBE blends was:

Diurnal Benzene = [(1.3758 - (0.0579*(weight % oxygen/2.0)
                  - 0.080274*RVP)]*(volume % benzene).

The equation used for hot soak emissions from vehicles running on MTBE fuel was:

Hot Soak Benzene = [(1.4448 - (0.0684*(weight % oxygen/2.0)
                   - 0.080274*RVP)]*(volume % benzene).

To calculate diurnal and hot soak emissions from vehicles running
on gasohol, the oxygen term (which was developed specifically for
MTBE) was eliminated.  The oxygen term used for MTBE fuel
accounts for test data which have shown that the presence of MTBE
tends to reduce benzene's evaporative and running loss benzene
emissions.  However, test data with ethanol have not shown such
an effect on benzene emissions separate from its effect on
overall evaporative VOC emissions.  Thus, the diurnal and hot
soak equations for gasohol (and gasoline) are:

Diurnal Benzene = [1.3758 - (0.080274*RVP)]*(volume % benzene)

Hot Soak Benzene = [1.4448 - (0.080274*RVP)]*(volume % benzene).

For both MTBE and gasohol, these equations were derived from GM's
tank vapor emissions model (1991) for representative tank
temperatures, and were used in RDSD's reformulated gasoline NPRM,
(EPA, 1991a), and in the supplemental NPRM (EPA, 1992b).  The
supplemental NPRM states that this model was derived for vehicles
typical of in-use emissions rather than vehicles meeting the
emission standards.  Once again, the same emission fractions were
used for HDGVs, LDGVs, and LDGTs.  Evaporative emissions from
LDDVs, LDDTs, and HDDVs were assumed to be negligible.

     The accuracy of these equations was tested in predicting
evaporative benzene levels from fuel properties in baseline
gasoline, MTBE blends, and gasohol by comparing predicted benzene
levels to benzene levels from actual vehicle data (Appendix B5).
The equations underpredicted evaporative benzene emissions
significantly (e.g., % predicted versus % observed) for vehicles
with carburetors, and even more significantly for fuel injected
vehicles.  This may be because the model that the equations were
based on was derived for "typical in-use" vehicles, and almost
all the vehicles in the database were vehicles with lower
evaporative emissions.  The equations were used in these
analyses, in order to be consistent with the reformulated fuels
NPRM.  In any case, evaporative benzene emissions are less than
20% of total vehicle benzene emissions so this underprediction is
not serious.

     Diurnal and hot soak benzene emission fractions for various
programs included in modeling components are included in Appendix
B6.  It was also assumed that the fraction of benzene in overall
evaporative emissions remains the same, regardless of
temperature, since all MOBTOX runs were done at a single
temperature range (68°-84°).  Benzene evaporative emissions are
small compared to exhaust benzene so using a single temperature
range versus explicitly setting evaporative emissions of benzene
equal to zero in winter months is probably justified.  Higher
benzene exhaust emissions in winter months are not being
considered, so these approximations may cancel one another.

     For exhaust benzene emissions, RVP was not part of the
equations used to predict emission fractions.  RVP does affect
evaporative emission fractions, however.  For example, an RVP of

8.1 was assumed for federal reformulated fuels in CY 1995-1999 for Class C areas, but an RVP of 7.8 in CY 2000+.  This results in slightly higher diurnal and hot soak benzene fractions for CY 2000+ compared to 1995-1999.  The overall mass of evaporative benzene decreases, however, because the reduction in overall evaporative THC is greater at lower RVPs.  Also, for California standards, the benzene exhaust fractions are assumed to be the same as those for EPA 1995-1999 reformulated gasoline standards. For the 1995 scenarios, the diurnal and hot soak benzene fractions came from EPA's reformulated gasoline regulations. However, since CARB's Phase II reformulated fuel regulations, taking effect in 1996, specify an RVP of 7.0, scenarios for 2000 and 2010 used different benzene diurnal and hot soak emission fractions, calculated using the different RVP value.

5.3.1.3  Benzene Running, Resting, and Refueling Loss Evaporative Emission Fractions

Running loss evaporative emission fractions for benzene were assumed to be the same as for hot soak.  Resting loss emission fractions were assumed to be the same as for diurnal.  Refueling loss benzene fractions were set at 0.01, following the VOC/PM Speciation Data System (EPA, 1990a).

## 5.3.2  Emission Factors for Baseline and Control Scenarios

The fleet average benzene emission factors as determined by the MOBTOX emissions model are presented in Table 5-2.  When comparing the base control scenarios relative to 1990, the emission factor is reduced by 46% in 1995, by 60% in 2000, and by 68% in 2010.  The expansion of reformulated fuel use in 1995 reduces the emission factor by another 7% relative to 1990.  In 2000, the expanded control scenarios reduce the emission factor by another 6 to 9%, and in 2010, by another 4 to 6%, relative to 1990.

**Table 5-2.  Annual Emission Factor Projections for Benzene.**

| Year-Scenario | Emission Factor g/mile | Percent Reduction from 1990 |
|---|---|---|
| 1990 Base Control | 0.0882 | – |
| 1995 Base Control | 0.0472 | 46 |
| 1995 Expanded Reformulated Fuel Use | 0.0413 | 53 |
| 2000 Base Control | 0.0351 | 60 |
| 2000 Expanded Reformulated Fuel Use | 0.0301 | 66 |
| 2000 Expanded Adoption of California Standards | 0.0305 | 65 |
| 2010 Base Control | 0.0285 | 68 |
| 2010 Expanded Reformulated Fuel Use | 0.0248 | 72 |
| 2010 Expanded Adoption of California Standards | 0.0228 | 74 |

### 5.3.3  Nationwide Motor Vehicle Benzene Emissions

The nationwide benzene metric tons are presented in Table 5-3.  Total metric tons are determined by multiplying the emission factor from Table 5-2 (g/mile) by the VMT determined for the particular year.  The VMT, in billion miles, was determined to be 1793.07 for 1990, 2029.74 for 1995, 2269.25 for 2000, and 2771.30 for 2010.  When comparing the base control scenarios relative to 1990, the metric tons are reduced by 39% in 1995, by 50% in 2000, and remains constant at 50% in 2010.

### 5.3.4 Other Sources of Benzene

Mobile sources account for approximately 85% of the total benzene emissions.  Of the mobile source contribution, the majority comes from the exhaust.  The remaining benzene emissions (15%) come from stationary sources.  Many of these are related to industries producing benzene, sometimes as a side product, and those industries that use benzene to produce other chemicals.  Coke ovens are responsible for 10% of the 15% with the other 5% attributable to all other stationary sources (Carey, 1987).

Approximately 70% of mobile source benzene emissions (60% of total benzene emissions) can be attributed to onroad motor vehicles, with the remainder attributed to nonroad mobile sources.  This figure is based on a number of crude estimates and assumptions.  First, it was estimated that 25% of total VOC emissions are from onroad vehicles, and 10% are from nonroad sources (based on a range of 7-13%).  These estimates were obtained from EPA's Nonroad Engine and Vehicle Emissions Study (NEVES) (EPA, 1991b).  Thus, about 70% of mobile source VOC is attributable to onroad vehicles.  This VOC split was adjusted by onroad and nonroad benzene fractions (described below) to come up with the estimate of 70% of mobile source benzene from on-road vehicles.

For nonroad vehicles, benzene was estimated to be about 3.0% of exhaust hydrocarbon emissions and 1.7% of evaporative hydrocarbon emissions, based on the NEVES report (EPA, 1991b).  The 1.7% evaporative emissions estimate is actually an estimate for refueling emissions of nonroad gasoline engines.  Since no estimate existed for benzene evaporative emissions, it was assumed that percent benzene evaporative emissions was the same as refueling.  The split between exhaust and evaporative benzene emissions was assumed to be 80% exhaust to 20% evaporative.  Thus, the overall benzene fraction of nonroad hydrocarbon emissions was estimated to be 2.74%.

For onroad vehicles, benzene was estimated to be 3.89% of exhaust hydrocarbon and 1.04% of evaporative hydrocarbon emissions.  The exhaust fraction is a 1990 fleet average toxic fraction, with fractions in Appendix B2 weighted using 1990 VMT fractions.  The evaporative fraction is the benzene fraction given in Appendix B6

**Table 5-3.  Nationwide Metric Tons Projection for Benzene.**

| Year-Scenario | Emission Factor g/mile | Metric Tons |
|---|---|---|
| 1990 Base Control | 0.0882 | 158,149 |
| 1995 Base Control | 0.0472 | 95,804 |
| 1995 Expanded Reformulated Fuel Use | 0.0413 | 83,828 |
| 2000 Base Control | 0.0351 | 79,651 |
| 2000 Expanded Reformulated Fuel Use | 0.0301 | 68,304 |
| 2000 Expanded Adoption of California Standards | 0.0305 | 69,212 |
| 2010 Base Control | 0.0285 | 78,982 |
| 2010 Expanded Reformulated Fuel Use | 0.0248 | 68,728 |
| 2010 Expanded Adoption of California Standards | 0.0228 | 63,186 |

for gasoline-fueled vehicles.  The split between exhaust and
evaporative hydrocarbon emissions was estimated to be 60% exhaust
to 40% evaporative.  Thus, the overall benzene fraction for
onroad hydrocarbon emissions was 2.74%.  If the VOC split is
adjusted by these benzene fractions for onroad and nonroad
emissions, 70% of benzene from mobile sources is estimated to
come from on road vehicles.

Data from EPA's Total Exposure Assessment Methodology (TEAM)
Study identified the major sources of exposure to benzene for
much of the U.S. population.  The TEAM study is described in
detail in a four-volume EPA publication (EPA, 1987b).  The study
measured 24-hour personal exposures in air and drinking water for
20 to 25 target volatile compounds for a selected group of
subjects from six cities.  Subjects were selected according to
census information, socioeconomic factors, and their proximity to
potential industrial and mobile sources.  Large numbers of homes
were visited by trained interviewers to collect information on
age, sex, occupation, smoking status, and other factors for each
person in the household.  A total of 700 subjects representing
more than 800,000 residents of the various cities were sampled.

The final results of TEAM total benzene exposure (Wallace,
1989), show the most important source of benzene exposure is
active smoking of tobacco.  Smoking accounts for about half of
the total population exposure to benzene.  Personal exposures due
to riding in automobiles, passive smoking, and exposure to
consumer products account for roughly one-quarter of the total
exposure, with outdoor concentrations of benzene, due mainly to
vehicle exhaust, accounting for the remaining portion.
Occupational exposures, pumping gasoline, living near chemical
plants or petroleum refining operations, food, water, and
beverages appear to account for no more than a few percent of
total nationwide exposure to benzene.

## 5.4  Atmospheric Reactivity and Residence Times

Laboratory evaluations indicate that benzene is minimally
reactive in the atmosphere, compared to the reactivity of other
hydrocarbons.  This then gives benzene long-term stability in the
atmosphere.  Oxidation of benzene will occur only under extreme
conditions, involving a catalyst or elevated temperature or
pressure.  Photolysis is possible only in the presence of
sensitizers and is dependent on wavelength absorption.

The information that follows on transformation and residence
times has been largely excerpted from a report produced by
Systems Applications International for the EPA (Ligocki et al.,
1991).

## 5.4.1 Atmospheric Transformation Processes

A variety of atmospheric transformation processes of importance to air toxics can occur in urban atmospheres. Species can be destroyed by reaction with atmospheric oxidants, or by photolysis. The oxidant of most importance on a global scale is the hydroxyl radical (OH), which is produced photolytically everywhere in the atmosphere and reacts with nearly every organic substance. In urban atmospheres, ozone ($O_3$) can also be an important oxidant. At night, OH concentrations drop off significantly because little OH is produced in the absence of sunlight, but concentrations of the nitrate radical ($NO_3$) can increase to fairly high levels when high concentrations of nitrogen oxides ($NO_x$) are present. Other atmospheric oxidants are the hydroperoxyl radical ($HO_2$), the oxygen atom, and the chlorine atom (Cl), which may be important under some circumstances. A few atmospheric species react directly with nitrogen dioxide ($NO_2$).

Photolysis refers to decomposition following absorption of ultraviolet radiation. While reaction with oxidants is common to virtually all organic molecules, photolysis usually involves oxygenated intermediates containing the carbonyl (C=O) bond, such as formaldehyde and acetaldehyde. (Whitten, 1983).

Many atmospheric species react rapidly in the aqueous phase of clouds, fogs, and aqueous aerosols. For highly soluble and highly reactive species, this can be a major atmospheric transformation pathway.

Atmospheric transformation can also include the condensation of gaseous species onto atmospheric aerosols. This process is a function of the vapor pressure of the species, the amount of aerosol present in the atmosphere, and the temperature. Although benzene, 1,3-butadiene, formaldehyde, and acetaldehyde exhibit sufficiently high vapor pressures that they will not condense onto aerosols to any significant degree, this process can be of major importance for other types of air toxics such as polycyclic organic matter associated with diesel and gasoline particulate.

## 5.4.2 Gas Phase Chemistry of Benzene

The aromatic ring structure of benzene is extremely stable and resistant to chemical attack. Therefore, of all the toxic species to be addressed in this report, benzene is the least reactive in the atmosphere. Not only does benzene oxidize slowly, but one of its key oxidation products, phenol, suppresses ozone formation under $NO_x$-limited conditions because it acts as a free radical scavenger.

## 5.4.2.1 Gas Phase Reactions

The only benzene reaction which is important in the lower atmosphere is reaction with the OH radical. Yet even this reaction is relatively slow. The reaction proceeds by OH addition, forming a complex which can decay back to the original reactants. At relevant tropospheric temperatures, this decay rate is negligible. The temperature dependence of this reaction is not well known. Benzene reacts more slowly with OH radicals than do most other aromatic species. Toluene and m-xylene react five times and 19 times as fast as benzene, respectively (Atkinson, 1990).

The reactions of benzene with oxygen atoms, ozone ($O_3$), and nitrate ($NO_3$) have been measured. Since the rate of these reactions are slower than rate of reaction of benzene with OH, and/or their concentrations in the atmosphere are generally much lower than OH concentrations, these reactions are not important in the atmospheric transformation of benzene.

Reactions with Cl atoms are known to be important in the stratosphere, where they are associated with the ozone depletion cycle. However, Cl concentrations in the troposphere are low, roughly three orders of magnitude smaller than OH concentrations (Singh and Kasting, 1988). Since the reaction rate is only a factor of ten larger than the OH rate, this reaction is not important in the lower atmosphere.

## 5.4.2.2 Reaction Products

The observed stable products from the atmospheric oxidation of benzene are phenols (phenol and nitrophenol), and aldehydes (mainly glyoxal [CHO]$_2$) with reported yields of 24 percent for phenol (Atkinson et al., 1989) and 21 percent for glyoxal (Tuazon et al., 1986). Nitrophenol yields of 3 percent at low $NO_x$ concentrations have been reported (Atkinson, 1990). Thus, the known products do not completely account for all the mass reacted. Phenol is highly reactive under smog conditions and will react rapidly with OH radicals during the daytime and with $NO_3$ radicals at nighttime. Glyoxal is also highly reactive, with a chemistry similar to that of formaldehyde. Both phenol and glyoxal, besides being highly reactive, are also highly water-soluble, and will be removed rapidly by incorporation into clouds or rain.

## 5.4.3 Aqueous Phase Chemistry of Benzene

Benzene reacts rapidly in aqueous solution with the OH radical and the sulfate radical ($SO_4^-$), forming products that are removed by their incorporation into rain. Despite the rapid reaction of benzene in aqueous solution, its low solubility limits the importance of aqueous-phase processes for this compound and it will not be incorporated into clouds or rain to any large degree.

## 5.4.4 Atmospheric Residence Times

### 5.4.4.1 Definition and Limitations

In assessing the potential impact of emissions of toxic species into the atmosphere, it is important to have some measure of their atmospheric persistence.  Species which persist for long periods of time can accumulate to high concentrations during stagnation periods and can be transported further from their sources than species which are destroyed rapidly.  Common measures of atmospheric persistence are the residence time, or lifetime ($\tau$), and the half-life, both of which are measures of the time required for a fixed concentration of a species to decay to a certain percentage of its initial concentration.  The residence time and the half-life are times at which the concentration has been reduced to 37% and 50% of its original value, respectively.  The atmospheric residence time is thus a mathematical formulation which provides a common ground for comparison of the persistence of different chemical species.

One limitation of residence time calculations is that they cannot be used to predict ambient concentrations of toxic species.  Concentrations are determined by atmospheric dispersion characteristics combined with emissions patterns, formation, and removal rates.  In urban areas, the effective residence time of toxic species in the atmosphere may be determined by the time required to transport emissions out of the air basin, rather than the time required for their chemical or physical removal within the air basin.  Also, residence time calculations do not incorporate chemical production rates for secondary species.  Thus, residence time calculations may indicate that a species such as formaldehyde is removed rapidly during the daytime, when actually formaldehyde is being produced more rapidly than it is being removed.  Finally, residence time calculations consider atmospheric reactions as destruction processes and do not consider the possible transformation of toxic species into equally toxic products.

Despite these limitations, atmospheric residence time calculations can be valuable when viewed in context with these other issues.

### 5.4.4.2 Chemical and Physical Processes

A variety of chemical and physical processes must be taken into consideration when determining the residence time of a compound.  Chemical processes include gas-phase chemical reactions, photolysis, and in-cloud chemical destruction.  Physical processes include wet and dry deposition.  With regard to gas-phase chemical reactions, typical atmospheric oxidant concentrations are required for residence time calculations.  Concentrations of OH radicals are of particular importance, since chemical residence times for many atmospheric species are determined by their rate of reaction with the OH radical.  At night, photolysis is absent and OH radical concentrations are

very low.  Other chemical reactions, such as reaction with $NO_3$ radical or $O_3$, may be important at night.

For species which photolyze, photolysis can compete with the OH reaction as the dominant daytime removal mechanism. Photolysis rates depend only upon the amount of ultraviolet (UV) radiation reaching the lower troposphere, and thus can be determined on the basis of latitude, altitude, and time of year.

Cloud cover is often neglected in atmospheric residence time calculations.  Yet, many areas of the United States experience a significant degree of cloud cover throughout much of the year. Cloud cover affects the residence time of atmospheric pollutants in two major ways.  First, clouds attenuate the solar UV radiation at ground level, slowing photolysis rates and decreasing radical concentrations.  Second, clouds are themselves a reactive medium in which chemical transformation will take place.  Therefore, the presence of clouds may increase or decrease the atmospheric residence time of specific pollutants.

The physical processes of wet and dry deposition can also be significant removal routes for some atmospheric pollutants.  Wet deposition refers to the capture and removal of species by hydrometers including rain, snow, hail, etc.  Dry deposition refers to the loss of atmospheric species to surfaces by diffusion, sedimentation, impaction, etc.  The atmospheric residence time due to physical processes depends upon whether the species is present in the atmosphere only as a vapor, or partially adsorbed to particles.  This partitioning is determined by the vapor pressure of the species.  For calculation purposes, all precipitation was assumed to be in the form of rain, since partitioning of organic compounds from the atmosphere to snow or other forms of frozen precipitation is less well understood.

The rate of dry deposition of volatile organic compounds is highly uncertain.  A method proposed for incorporation into regional air quality models was used to calculate dry deposition rates, although its validity has not been demonstrated for organic species.

For species which are present in the atmosphere as gases or vapors, deposition processes may be reversible.  For instance, volatile compounds present in rain which falls on a surface such as a street or sidewalk and subsequently evaporates will return to the atmosphere.  It has been proposed that formaldehyde rapidly deposits to dew-covered surfaces overnight and in the early morning, and then is released when the dew evaporates at mid-morning (Ireson et al., 1990).  To the extent possible, these types of reversible processes should not be considered in atmospheric residence time calculations.

5.4.4.3 Generation of Input Values

The oxidant concentrations required for the residence time calculations were obtained from trajectory model simulations for the four cities, Los Angeles, St. Louis, New York, and Atlanta.

These locations were chosen to represent a variety of regions within the United States, and were also chosen because summer model input data were available for these cities. The simulations were conducted using the Ozone Isopleth Plotting Model, Version 4 with Carbon Bond Mechanism IV (OZIPM-4) (Hogo and Gery, 1988). This is a model which is used routinely to predict ozone formation as a function of VOC and $NO_x$ emissions; however, as an intermediate step, it calculates radical concentration such as OH.

Simulations began at 9 a.m. and continued through 4 a.m. the following day. The calculations were conducted for daytime and nighttime, and then weighted by the length of the day and night to obtain 24-hour averages. Because these simulations were for severe ozone episodes, the oxidant concentrations generated may be somewhat larger than seasonal average values.

For each city, calculations were conducted for both the summer (July) and winter (January) seasons. For each season, residence time calculations were also conducted for clear-sky and cloudy conditions.

The winter simulations used the same summer input files except for the following: (1) the time zone was increased 1 hour to convert to standard time, (2) the temperatures were changed to start at the average winter low and smoothly reach the average winter high at about 1400 hours, (3) the date was set to 15 January, and (4) the mixing height maximum was adjusted downward. Each of the residence time calculations was conducted for clear-sky conditions and cloudy conditions. Cloudy conditions take into account the UV transmission factor, the in-cloud OH concentration, the gas-phase oxidant concentrations, and the cloud liquid water content.

The residence times are most useful for comparison purposes rather than as absolute numbers, because of the necessary assumptions and simplifications which went into the calculations. More details regarding the model input files and parameters used in calculating residence times, such as oxidant concentrations and rates of reaction, are given in Ligocki et al., 1991.

5.4.4.4 Benzene Residence Times

Residence times for benzene were calculated by considering gas phase chemical reactions with OH and $NO_3$, in-cloud chemical reaction with OH, and wet and dry deposition. The results of the residence time calculation for benzene are presented in Table 5-4.

**TABLE 5-4.** Atmospheric residence time calculation for benzene. All times are in hours unless otherwise noted.

| | Los Angeles | | St. Louis | | Atlanta | | New York | |
|---|---|---|---|---|---|---|---|---|
| | July | Jan | July | Jan | July | Jan | July | Jan |
| Clear sky – day | 40 | 300 | 30 | 500 | 30 | 500 | 50 | 900 |
| Clear sky – night | 3000 | 14000 | 4000 | 18000 | 3000 | 14000 | 4000 | 18000 |
| Clear sky – avg | 70 | 700 (30 d) | 50 | 1100 (46 d) | 50 | 1100 (45 d) | 90 | 2200 (92 d) |
| Cloudy – day | 80 | 600 | 60 | 800 | 50 | 800 | 100 | 1600 |
| Cloudy – night | 800 | 7000 | 900 | 8000 | 300 | 7000 | 1500 | 12000 |
| Cloudy – avg | 120 | 1300 (56 d) | 90 | 1800 (75 d) | 80 | 1700 (71 d) | 150 (6 d) | 3600 (150 d) |
| Monthly Climatological Average | 80 | 900 (37 d) | 70 | 1500 (62 d) | 60 | 1400 (58 d) | 110 | 2900 (120 d) |

Calculated residence times ranged from 2 days under summer, clear-sky conditions, to several months under winter, cloudy-sky conditions.  These values can be compared to estimated benzene half-lives of 4 days under summer, urban conditions (CARB, 1984) and 6 days under summer conditions at 60°N latitude (Nielsen et al., 1983).

The main atmospheric destruction pathway for benzene is the reaction with OH radical.  Even at night, the residence time of benzene was found to be determined primarily by the reaction with OH, with a slight contribution from in-cloud destruction.  The reaction with $NO_3$ was found to be unimportant for benzene.

As discussed above, estimates of residence times due to dry deposition should be regarded as highly uncertain.  The residence times of benzene due to dry deposition are estimated to be on the order of 20 days for summer, daytime conditions and one year or more for all other conditions.

In-cloud chemical destruction and wet deposition will not be rapid removal processes for benzene.  The residence times due to in-cloud chemistry ranged from 11 days in the summer to over 2 years in the winter.  The calculated residence times due to wet removal ranged from 3 years in the winter to 10 years in the summer.

Residence times for different cities within a given season varied by factors of 2-3.  A much larger effect was predicted for the difference between summer and winter conditions at all sites, with winter residence times 10-30 times greater than summer residence times.

The major uncertainties in these calculations for benzene are the OH radical concentrations, which vary from day to day by roughly a factor of two.  The uncertainty in the OH rate constant is much smaller than this (about 20 percent).  Although the uncertainty in the deposition velocity is much larger than a factor
of two, it does not have a large effect on the overall uncertainty because dry deposition is only of minor importance as a removal mechanism.

These results suggest that, on an urban scale, atmospheric transformation of benzene would not be expected to be a significant determinant of ambient benzene concentrations.  Under all conditions examined, the calculated residence time of benzene was greater than one day.  Therefore, significant day-to-day carryover of benzene concentrations would be expected.

## 5.4.5 Limited Urban Airshed Modeling of Air Toxics

Much of the information below on the Urban Airshed Model and the benzene results are excerpted from reports conducted for two EPA offices (Office of Mobile Sources and Office of Policy, Planning, and Evaluation) by Systems Applications International

(SAI) (Ligocki et al., 1991, Ligocki and Whitten, 1991, Ligocki et al., 1992).  The modified version of the UAM used in these reports, with explicit treatment of several toxics, will be referred to as UAM-Tox.  UAM-Tox in Ligocki et al. (1991) and Ligocki and Whitten (1991) which was used to model St. Louis, did not include explicit chemistry for acetaldehyde and POM.  UAM-Tox in Ligocki et al. (1992) which was used to model the Baltimore-Washington area and Houston, does treat these toxics explicitly, however.  Details of inputs and modifications for the UAM are presented in the above references.  The treatment of each toxic in UAM-Tox is discussed in the results section for each toxic.

The Urban Airshed Model (UAM) is a three-dimensional grid model designed to simulate all important physical and chemical processes which occur in the atmosphere.  In a grid model, the region of interest (domain) is divided into grid cells which are equally spaced in the horizontal directions, and may have varying heights depending upon the atmospheric mixed-layer height. Within each grid cell, concentrations are assumed to be uniform, and any emissions which are injected into that cell will instantaneously spread throughout the cell.  The model incorporates mathematical representations of the processes of transport, diffusion, chemical reaction, and deposition.  Based upon inputs such as emissions, winds, mixing heights, initial concentrations of each species, and concentrations of each species on the boundaries of the domain, the model computes concentrations for each species for each grid cell for each hour of the simulation.

The UAM has been used primarily for the simulation of ozone and the development of control strategies for ozone precursors. It has been evaluated in terms of its ability to predict concentrations of ozone and a few other species such as $NO_x$ and peroxyacetyl nitrate (PAN).  The UAM has not been evaluated for the prediction of concentrations of air toxics, and such an evaluation was beyond the scope of the study summarized here. Until such an evaluation is conducted, the model results are most useful for the comparisons they provide of the importance of atmospheric transformation.

To illustrate the effects of atmospheric persistence and transformation on ambient concentrations in an urban area, an initial urban airshed modeling study of benzene, 1,3-butadiene, formaldehyde, and acetaldehyde was conducted for a hypothetical day in the summer of 1990 in the St. Louis area (Ligocki et al., 1991; Ligocki and Whitten, 1991).  A summer day was selected in order to maximize the potential effects of atmospheric transformation.  The St. Louis urban area was selected primarily because the necessary model inputs were readily available; however, St. Louis is also of interest because relatively high benzene concentrations have been measured there (McAllister et al., 1990).  Only one city was modeled due to resource constraints.  Understanding how the calculated results may vary in different cities with different emissions and air quality patterns would help address some of the uncertainty in the

results.  Subsequently, additional urban airshed modeling was done for multi-day episodes in the Baltimore-Washington area and Houston, as part of another study (Ligocki et al., 1992).  Both of these areas are severe ozone nonattainment areas, and will participate in the federal reformulated gasoline program. Modeling was conducted for hypothetical episodes in 1995 and 1999, and took into account provisions of the CAA.  Since toxics provisions of the reformulated gasoline program are year round, a winter episode was simulated for Baltimore.  The Baltimore and Houston areas represent opposite ends of the spectrum in terms of expected air quality benefits of reformulated gasoline.

The St. Louis episode selected for the initial study was an historical episode from July 13, 1976.  The meteorological and air quality inputs for that episode were originally developed for the EPA as part of the St. Louis Ozone Modeling Project (Schere and Sheffler, 1982;  Cole et al., 1983).  This episode also was modeled by SAI as part of the EPA Five Cities Study (Morris et al., 1989).  Levels of air pollutants have declined significantly in most cities over the past 15 years.  Although the available inputs for this simulation were for a 1976 episode, it was judged to be more useful to conduct the simulation for current conditions.  Therefore, the emission inventory was updated to a summer weekday in 1990.  The episode represents a hypothetical day in 1990 in which the dispersion characteristics correspond to an actual day in 1976.  Details of other inputs and modifications for the UAM are presented in detail in Ligocki et al. (1991) and Ligocki and Whitten (1991).  The treatment of each toxic in the UAM is discussed in the results sections for each toxic.

For modeling in the Baltimore-Washington area, the episode selected was an historical episode from July 5-7, 1988.  The July 5-7 episode is part of a larger, regional-scale ozone episode that has been modeled with the Regional Oxidant Model (Possiel et al., 1990).  A number of simulations were conducted for this episode in the base year of 1988, 1995, and 1999.  Base, federal reformulated gasoline, California phase 2 reformulated gasoline and reduced motor vehicle $NO_x$ simulations were conducted. Simulations were also done for both summer and winter, and with motor vehicles removed.  For modeling in the Houston area, the episode selected was an historical episode from September 3-5, 1987.  Simulations for summer were conducted for this episode in the base year of 1987, and for base case, reformulated gasoline, and no motor vehicle scenarios in 1995.

5.4.5.1 General Results From the UAM Simulations

Two base-case UAM simulations were conducted for the St. Louis study.  The simulations used identical input parameters, but in one of them all chemistry was "turned off" assuming the toxic species of concern to be inert.  The second simulation assumes all "chemistry on", referred to as the reactive simulation.  The UAM simulations began at 1 a.m. local daylight time and ran through 11 p.m.

Results are presented as time-series plots of concentration at a specific grid cell. The time-series plots are presented in Appendix D and include predicted total concentrations of each toxic from both the reactive and inert simulations, and also include concentrations of the mobile- and stationary-source components from the reactive simulation. All values presented in the time series plots are hourly averages.

The simulations indicated that summertime concentrations of primary toxic species derived from mobile sources will be greatest during morning commute hours, when emissions are maximized, atmospheric dispersion is poor, and photochemistry is slow. The afternoon commute hours are less likely to produce peaks in mobile-source toxics in the summertime because they occur while mixing heights are higher and photochemistry is at its peak.

The Baltimore-Washington area and Houston simulations also indicated that concentrations of primary toxics species will be greatest during morning commute hours.

Federal reformulated gasoline simulations for 1995 and 1999 in the Baltimore-Washington area indicated a decrease in peak ozone of 0.2 pphm in 1995 (1.1% of total) and 0.15 pphm in 1999 (0.85% of total). This decrease corresponded to 20% of the peak ozone attributed to motor vehicles. For Houston, federal reformulated gasoline usage produced smaller ozone benefits, with a decrease in peak ozone of 0.013 pphm in 1995 (0.04% of total). This decrease corresponds to only 2% of the peak ozone attributable to motor vehicles. In both the Baltimore-Washington area and Houston, use of federal reformulated gasoline resulted in reductions of ambient benzene, acetaldehyde, and POM concentrations. For butadiene, there was virtually no effect on ambient concentrations. For formaldehyde, there were both decreases and increases, depending on the simulation.

The combination of the UAM results with results from the residence time calculations provides an estimate of the differences in concentrations which might be expected under wintertime conditions. Differences in emission rates and atmospheric dispersion parameters will also be important factors in determining wintertime concentrations. A comparison of summer and winter simulations in Baltimore indicated that, although benzene emissions from motor vehicles were lower in winter than in summer, motor vehicle-related concentrations of benzene were higher. Even so, the motor vehicle fraction of the simulated concentrations was

similar in winter, due to an increase in stationary source
concentrations.

## 5.4.5.2 UAM Results for Benzene

Benzene was treated explicitly in the UAM-Tox.  Mobile and
stationary emissions of benzene were tagged separately and
carried through simulations separately in the model.  The gas
phase reactions discussed previously were added to the chemistry
subroutines.  Because the focus of the study was on destruction
of the toxic species rather than on the subsequent chemistry of
their reaction products, no products were included in the UAM
modifications for benzene.

### St. Louis Simulation

A time-series plot of predicted benzene concentrations in
St. Louis at the grid cell with the largest mobile-source benzene
concentration is presented in Figure D-1 of Appendix D.  At the
time of the mobile-source benzene concentration peak, mobile-
source benzene contributed roughly half of the total benzene
concentration of 0.54 ppb.  As the day progressed, the mobile-
source benzene concentration decreased, while the total benzene
increased to a peak of 0.7 ppb at 11 a.m.  There was no evidence
of a peak in the mobile-source concentration during the afternoon
commute, probably due to the fact that the mixing height during
the afternoon commute was still roughly 1500 m, compared to 400 m
in the morning.  Thus all emissions would be diluted into a much
larger air volume in the afternoon.

The low reactivity of benzene is apparent from the
comparison of the "inert" benzene and total benzene curves in
Figure D-1.  There is no difference between the two curves until
mid-morning, and even in the mid-afternoon the difference between
the two curves is less than 0.1 ppb.  Thus, atmospheric
transformation was shown to have only a minor effect on ambient
concentrations during afternoon hours, and virtually no effect
during other times of day.  This illustrates the conclusion drawn
from the residence time calculations, that atmospheric chemical
transformation of benzene in a urban environment is less
important than location of sources and atmospheric dispersion
characteristics in the assessment of benzene concentrations.
Little seasonal effect would be expected for benzene.

The benzene concentration at the end of the simulation was
0.7 ppb (Figure D-1).  Because benzene is not destroyed
chemically at night (Table 5-2), in the absence of strong winds
this concentration would be expected to persist into the
following day.  Therefore, the initial concentration of benzene
of 0.1 ppb used for this simulation is likely to be too low.
Future benzene simulations should be conducted for multiple days
in order to

quantify the importance of day-to-day carryover of benzene concentrations.

The effect of initial concentration assumptions for benzene was examined in a sensitivity study in which the concentration fields from the end of the base-case simulation were used as the initial concentrations.  This has the effect of increasing the initial concentrations of benzene.  The peak concentrations within the city do not increase substantially from their base-case values.  The afternoon maximum concentration only increases by 0.1 ppb.  This result indicates that the meteorology of the simulated episode was such that concentrations were dominated by local emissions.  For other episodes and other locations, more stagnant conditions might exist, and the importance of the initial concentrations might be greater.

When a comparison of simulated concentrations of benzene is made with ambient measured concentrations, the simulated concentrations were much lower than typical measured concentrations.  This discrepancy may be due to uncertainties in the emission inventory for benzene.  Another possibility is that the ambient monitors were located in areas not represented well in the UAM.  The American Petroleum Institute (API) has stated that these differences may also be due to the fact that the UAM is not able to predict the concentrations and residence times of reactive air toxics well, and concentrations of the more reactive compounds show better agreement due to compensating errors in the model (API, 1991).  For a full accounting of API's analysis please consult API, 1991.

Houston and Baltimore-Washington Area Simulations

Simulations for the summer Baltimore-Washington area episode resulted in significant decreases in ambient levels of benzene with use of federal reformulated gasoline, amounting to as much as 12 percent of ambient benzene concentrations.  Use of California reformulated gasoline resulted in slightly larger decreases in ambient benzene.  Maximum daily average benzene concentration for the 1988 base scenario was 2.2 ppb.  Motor-vehicle related benzene accounted for about 58% of total benzene emissions.  This agrees with the 60% estimate obtained in Section 5.3.4 for motor vehicles.
The summer Baltimore-Washington area simulations do not significantly underpredict benzene like the St. Louis simulation. In fact, simulated benzene concentrations were in good agreement with the average measured values from the UATMP data base. Ligocki et al. attribute this to an effort made to improve the emission mass fractions in the motor vehicle, area, and point source speciation profiles.

In the winter 1988 base scenario, the maximum daily average benzene concentration was 3.6 ppb, about 40 percent higher than in summer.  Motor-vehicle related benzene accounted for about 37% of total benzene emissions.  Simulations for the winter Baltimore-Washington area episode resulted in significant

decreases in ambient levels of benzene with use of reformulated gasoline, on the order of 7 percent. Motor vehicle benzene emissions were about 30 percent lower with reformulated gasoline use, and comprised a smaller fraction of total benzene emissions. However, the motor vehicle-related concentration of ambient benzene would be higher in winter, due to less atmospheric transformation. Comparison of simulated concentrations with measured concentrations indicate that the model may underpredict winter benzene concentrations.

For the summer 1987 base scenario in Houston, the maximum daily average benzene concentration was 41.4 ppb. Motor-vehicle related benzene accounted for about 21% of total benzene emissions. The maximum motor vehicle contribution to ambient benzene was 25%, based on the 1995 no motor vehicle scenario. Thus, motor vehicle-related benzene contributed less to overall ambient benzene in Houston than in Baltimore. Simulations for the summer Houston episode predicted little effect on maximum daily average concentration of benzene with use of reformulated gasoline at the site of maximum concentration, since in Houston maximum daily average concentrations are primarily influenced by point sources due to many large industrial facilities. However, for the entire Houston modeling domain, the maximum decrease in daily average concentration was about 8 percent. Comparison of simulated concentrations with measured concentrations suggest the model accurately predicts benzene concentrations.

## 5.5 Exposure Estimation

### 5.5.1 Annual Average Exposure Using HAPEM-MS

The data presented in Table 5-5 represent the results determined by the HAPEM-MS modeling that was described previously in Section 4.1.1. These numbers have been adjusted to represent the increase in VMT expected in future years.

The HAPEM-MS exposure estimates in Table 5-5 represent the 50th percentiles of the population distributions of exposure, i.e., half the population will be above and half below these values. High end exposures can also be estimated by using the 95th percentile of the distributions. According to the HAPEM-MS sample output for benzene, the 95th percentile is 1.8 times higher than the 50th percentile for urban areas, and 1.2 times high for rural areas. Applying these factors to the exposure estimates in Table 5.5, the 95th percentiles for urban areas range from 1.69 $\mu g/m^3$ for the 2010 expanded adoption of the California standards scenario to 4.81 $\mu g/m^3$ for the 1990 base control scenario. The 95th percentiles for rural areas range from 0.61 to 1.74 $\mu g/m^3$, respectively.

**Table 5-5. Annual Average HAPEM-MS Exposure Projections for Benzene.**

| Year-Scenario | Exposure ($\mu g/m^3$) | | |
|---|---|---|---|
| | Urban | Rural | Nationwide |
| 1990 Base Control | 2.67 | 1.45 | 2.36 |
| 1995 Base Control | 1.56 | 0.84 | 1.40 |
| 1995 Expanded Reformulated Fuel Use | 1.37 | 0.74 | 1.20 |
| 2000 Base Control | 1.25 | 0.68 | 1.10 |
| 2000 Expanded Reformulated Fuel Use | 1.08 | 0.58 | 0.98 |
| 2000 Expanded Adoption of California Standards | 1.10 | 0.59 | 0.98 |
| 2010 Base Control | 1.18 | 0.64 | 1.05 |
| 2010 Expanded Reformulated Fuel Use | 1.04 | 0.56 | 0.93 |
| 2010 Expanded Adoption of California Standards | 0.94 | 0.51 | 0.84 |

## 5.5.2  Comparison of HAPEM-MS Exposures to Ambient Monitoring Data

As stated in section 4.1.2, four national air monitoring programs/databases contain data on benzene.  The Aerometric Information Retrieval System (AIRS), the Toxic Air Monitoring System (TAMS), the Urban Air Toxic Monitoring Program (UATMP), and
the National Ambient Volatile Organic Compounds Data Base (NAVOC) all have a significant amount of data for benzene.  The urban exposure data for benzene from all four databases is summarized in Table 5-6.  The AIRS data base contains data on benzene from 1987 to 1989  (EPA, 1989).  The location and number of the sites varies between years.  Referring back to Table 4-2 in Section 4.1.2 and to Table C-1 in Appendix C, 23 sites monitored benzene in 1987, 36 in 1988, and 13 in 1989.  The cities where monitoring sites are located are listed below.

| | |
|---|---|
| Birmingham, AL | St. Louis, MO |
| Oakland, CA | Louisville, KY |
| Fresno, CA | Atlanta, GA |
| Bakersfield, CA | Chicago, IL |
| Los Angeles, CA | Baton Rouge, LA |
| Merced, CA | Lowell, MA |
| Riverside, CA | Boston, MA |
| Sacramento, CA | Detroit, MI |
| San Bernadino, CA | Port Huron, MI |
| San Diego, CA | Dearborn, MI |
| San Francisco, CA | Lansing/E. Lansing, MI |
| Stockton, CA | New York, NY |
| Santa Barbara, CA | Cleveland, OH |
| San Jose, CA | Dallas, TX |
| Modesto, CA | Houston, TX |
| Oxnard, CA | Deer Park, TX |
| Miami, FL | Burlington, VT |
| Jacksonville, FL | Tacoma, WA |

The average level of benzene (averaged equally by the number of sites) was 6.92 µg/m$^3$ (2.13 ppb) in 1987, 4.13 µg/m$^3$ (1.27 ppb) in 1988, and 4.16 µg/m$^3$ (1.28 ppb) in 1989.  Because the number of sites differs from year to year and the number of samples taken at the various sites varies greatly, it is misleading to directly compare these numbers.  However, these numbers do provide a general idea of the amount of benzene being emitted.

Looking at the data on an individual site basis, St. Louis had the highest level of benzene, 31.0 µg/m$^3$ (9.54 ppb) in 1987 at an industrial suburban site.  However, only 5 samples were collected at that site in 1987.  The lowest level of benzene was found in Boston, 2.50 µg/m$^3$ (0.77 ppb) in 1987 at an industrial urban site in the downtown area; however, only 4 samples were collected.  In 1988, a commercial urban downtown site in Cleveland had the highest local average of all the sites monitoring benzene, 11.25 µg/m$^3$ (3.46 ppb) with 4 samples collected.  Two commercial suburban sites

**Table 5-6.  Air Monitoring Results for Benzene.**

| Program | Years | Ambient Data[a] μg/m³ | Estimated Motor Vehicle Contribution[b] μg/m³ |
|---------|-------|------------------------|------------------------------------------------|
| AIRS | 1989 | 4.16 | 2.50 |
| | 1988 | 4.13 | 2.48 |
| | 1987 | 6.92 | 4.15 |
| UATMP | 1989 | 6.37 | 3.82 |
| | 1990 | 4.78 | 2.87 |
| TAMS | 1987–89 | 4.26 | 2.55 |
| NAVOC | 1987 | 7.18 | 4.31 |

[a]Caution should be taken in comparing these numbers.  The methods of averaging the data are not consistent between air monitoring databases and the sampling methodology is also inconsistent.

[b]The ambient data are adjusted to represent the motor vehicle contribution to the ambient concentration, which for benzene is estimated to be 60%, based on emissions inventory apportionment.

in Jacksonville, Florida had the lowest sample levels of benzene, both 1.82 µg/m$^3$ (0.56 ppb) with 17 and 5 samples collected.  A residential suburban site in Houston had the highest average levels of benzene, 6.34 µg/m$^3$ (1.95 ppb) in 1989 with 20 samples collected.  Also in 1989, Lowell, Massachusetts had the lowest average benzene level at a residential suburban site, 2.28 µg/m$^3$ (0.70 ppb), with 17 samples collected.

Referring to Table 4.2 and Table C-2, ten sites in the Toxic Air Monitoring System (TAMS) collected samples of benzene between 1987 and 1989.  Boston, Chicago, and Houston each had three sites and Seattle/Tacoma had one.  Averaged together, these sites had a benzene level of 4.26 µg/m$^3$ (1.31 ppb).  The highest local average  level of benzene was at an urban industrial area in Houston, 6.66 µg/m$^3$ (2.05 ppb).  The lowest average local level of benzene was found at an industrial area in Tacoma, 2.02 µg/m$^3$ (0.62 ppb).  It should be noted that Tacoma was added as a site in TAMS later than the other sites.  Therefore, data were collected for benzene starting in 1988 instead of 1987.  As stated in Section 4.1.2, TAMS is a subset of AIRS and so it has a limited number of sites.

In the 1989 Urban Air Toxics Monitoring Program (UATMP), 397 measurements of benzene were taken at 14 sites.  These sites were in the cities listed below.

| | |
|---|---|
| Baton Rouge, LA | Chicago, IL |
| Camden, NJ | Dallas, TX |
| Fort Lauderdale, FL | Houston, TX |
| Miami, FL | Pensacola, FL |
| St. Louis, MO | New Sauget, IL |
| Washington, D.C. | Wichita, KS |

The highest average was 12.9 µg/m$^3$ (3.97 ppb) at an urban commercial site in downtown St. Louis, Missouri.  Thirty samples were collected at this site.  The lowest average was 1.95 µg/m$^3$ (0.60 ppb) at a suburban industrial site in Pensacola, Florida. Only seven samples were collected at this site.  The next lowest average was 2.99 µg/m$^3$ (0.92 ppb) at a urban commercial site in Dallas, Texas.  Twenty-five samples were collected at this site, providing a statistically more valid average.  The overall average of the averages for each site was 6.37 µg/m$^3$ (1.96 ppb). For more detailed information on UATMP, please refer to Table C-3.

In the 1990 Urban Air Toxics Monitoring Program (UATMP), 349 measurements of benzene were taken at 12 sites.  These sites were in the cities listed below.

<pre>
        Baton Rouge, LA                Chicago, IL
        Camden, NJ                     Houston, TX
        Orlando, FL                    Pensacola, FL
        Port Neches, TX                Sauget, IL
        Toledo, OH                     Washington, D.C.
        Wichita, KS
</pre>

The highest average was 8.74 µg/m$^3$ (2.69 ppb) at an suburban
residential site in Houston, Texas.  Twenty-eight samples were
collected at this site.  The lowest average was 2.73 µg/m$^3$ (0.84
ppb) at a suburban residential site in Toledo, Ohio.  Twenty-one
samples were collected at this site.  The overall average of the
averages for each site was 4.78 µg/m$^3$ (1.47 ppb).

In the National Ambient Volatile Organic Compounds (NAVOC)
program, 564 measurements of benzene were taken in 31 cities.
These cities are listed below.

<pre>
        Bakersfield, CA                Chula Vista, CA
        Citrus Heights, CA             Concord, CA
        El Cajon, CA                   El Monte, CA
        Fremont, CA                    Fresno, CA
        Long Beach, CA                 Los Angeles, CA
        Merced, CA                     Modesto, CA
        Richmond, CA                   Rubidoux, CA
        San Francisco, CA              San Jose, CA
        Santa Barbara, CA              Simi Valley, CA
        Stockton, CA                   Upland, CA
        Philadelphia, PA               San Leandro, CA
        Livermore, CA                  San Rafael, CA
        Napa, CA                       Vallejo, CA
        Santa Rosa, CA                 Redwood City, CA
        Mountain View, CA              Oakland, CA
        Baton Rouge, LA
</pre>

The highest measurement was 11.7 µg/m$^3$ (3.60 ppb), which was
found at an urban site in San Francisco.  However, this was only
one sample instead of an average.  The highest average was 11.47
µg/m$^3$ (3.53 ppb), which was found at an urban site in Fresno and
consisted of 11 samples.  The lowest measurement of benzene was
2.60 µg/m$^3$ (0.80 ppb), which was found at an urban site in
Oakland.  Once again, this was only one measurement instead of an
average of multiple measurements.  The lowest average was 3.51
µg/m$^3$ (1.08 ppb), which was found at an urban site in Livermore,
California, and consisted of 8 samples.  The overall average of
the averages from the 31 cities was 7.18 µg/m$^3$ (2.21 ppb).  For
more detailed data, please refer to Table C-4.

The premise of the HAPEM-MS model is that the dispersion and
atmospheric chemistry of benzene is similar to CO.  The average
atmospheric lifetime of CO ranges from one to four months (EPA,
1990b).  Since both benzene and CO have long atmospheric
lifetimes, the HAPEM-MS model should be a reliable indicator of
benzene exposure from motor vehicles.  To test the reasonableness
of the HAPEM-MS modeling results, the HAPEM-MS results for 1990

are compared to ambient monitoring results for recent years. Before comparing the HAPEM-MS results to the ambient data, the ambient monitoring data should be adjusted in two ways. First, the ambient monitoring data should be adjusted to represent the amount that is attributed to motor vehicles. The data derived from emission inventories estimate that 60% of the ambient benzene can be apportioned to motor vehicles. The numbers in the second column of Table 5.6 are 60% of the ambient levels and thus represent estimated ambient motor vehicle levels.

Second, the estimated ambient motor vehicle level should be adjusted to account for integrated exposure, i.e., time spent indoors and in various microenvironments. Pezda et al. (1991) refer to data collected in California (Robinson et al., 1989), which indicate that people spend 5.9% of their time outdoors, 61.9% indoors at home, 24.6% at work, and 7.6% during some form of transportation (car, bus, train, etc.). Using these activity patterns, it is next necessary to estimate how much of the ambient mobile source level people in these microenvironments are exposed to. HAPEM-MS provides the following microenvironment factors: indoors residence - 0.495; indoors other - 0.619; outdoors - 0.758; and inside motor vehicle - 1.554. These microenvironment factors are based on correlations between CO measured by personal exposure monitors and CO measured by fixed site monitors located within 10 km.

Combining the activity patterns and microenvironment factors, an adjustment factor to the ambient motor vehicle level to account for integrated motor vehicle exposure is calculated as shown below:

$$[(0.059)(0.758)+(0.619)(0.495)+(0.246)(0.619)+(0.076)(1.554)] = 0.622$$

The ambient motor vehicle level ranges from 2.48 to 4.31 µg/m$^3$. Applying the factor of 0.622 to this range, the integrated motor vehicle exposure is estimated to range from 1.54 to 2.68 µg/m$^3$. Since the unit risk estimate for benzene is an upper bound estimate, and the HAPEM-MS 1990 base control number matches the upper end of the range, the HAPEM-MS 1990 base control level of 2.67 µg/m$^3$ will be used to estimate cancer deaths. See Section 5.3.3 for the discussion of total integrated benzene exposure in the TEAM study (EPA, 1987; Wallace, 1989).

## 5.5.3  Short-Term Microenvironment Exposures

The primary emphasis for benzene and other exposures in microenvironments are relatively localized scenarios which are highly impacted by motor vehicle emissions. These microenvironments include in-vehicle exposure, parking garage exposure, and exposure to vehicle refueling emissions. The information contained in Table 5-7 is excerpted from four studies that have measured microenvironment exposures to benzene. These four studies are the EPA's Total Exposure Assessment Methodology

(TEAM) Study (EPA, 1987b), Commuter's Exposure to Volatile
Organic Compounds, Ozone, Carbon Monoxide, and Nitrogen Dioxide
(Chan et al., 1989), In-Vehicle Air Toxics Characterization Study
in the South Coast Air Basin (Shikiya et al., 1989), and Air
Toxics Microenvironment Exposure and Monitoring Study (Wilson et
al., 1991).  See the information in Section 4.2 for more details
about the methodology.

The TEAM Study (EPA, 1987b; Wallace, 1989) was planned in
1979 and completed in 1985.  The goals of this study were:  1) to
develop methods to measure individual total exposure (exposure
through air, food and water) and resulting body burden to toxic
and carcinogenic chemicals, and 2) to apply these methods with a
probability-based sampling framework to estimate the exposures
and body burdens of urban populations in several U.S. cities.
This was achieved through the use of small personal samplers, a
specially designed spirometer (used to measure the chemicals in
exhaled breath), and a survey designed to insure the inclusion of
potentially highly exposed groups.

The study, Commuter's Exposure to Volatile Organic
Compounds, Ozone, Carbon Monoxide, and Nitrogen Dioxide (Chan et
al., 1989), focused on the driver's exposure to VOC's in the
Raleigh, NC area.  The primary objective of this study was to
measure driver's exposure to all possible VOC and some combustion
gases during one rush-hour driving period (18 sampling days, two
trips per day).  Factors that could influence driver's exposure,
such as different roadways, car models, vehicle ventilation modes
and times of driving were also tested.  Car exterior samples were
also collected from the exterior of the moving vehicles by
setting sampling probes on the middle of the car roof.  Another
objective was to find the relationships between fixed-site
measurements and drivers' exposure (one fixed-site monitor
matched per trip).  Lastly, the pedestrian's exposure to VOC in
urban walking was evaluated with six walking samples.

The study by the South Coast Air Quality Management District
(SCAQMD), In-Vehicle Air Toxics Characterization Study in the
South Coast Air Basin (Shikiya et al., 1989), was conducted to
refine the assessment of health risk due to exposure to toxic air
pollutants.  This study examines the relative contribution of in-
vehicle exposure to airborne toxics to an individual's total
exposure by measuring concentrations within vehicle interiors
during home-to-work commutes.  Other objectives of this study
were to develop statistical and concentration measurement methods
for a vehicular survey and to identify measures which might
reduce commuters' exposure to toxic air pollutants.  Vehicles of
home-to-work

**Table 5-7. Microenvironment Exposure to Benzene (µg/m$^3$).**

| Scenarios | In-Vehicle | | Service Station | | Parking Garage | | Office Building | |
|---|---|---|---|---|---|---|---|---|
| | Mean | Max. | Mean | Max. | Mean | Max. | Mean | Max. |
| TEAM Study (EPA, 1987b) | -- | 40-60[a] | -- | 3000[b] | -- | -- | -- | -- |
| Raleigh, NC Study[c] (Chan et al., 1989) | 10.9 | 42.8 | -- | -- | -- | -- | -- | -- |
| SCAQMD Study[d] (Shikiya et al., 1989) | 42.5 | 267.1 | -- | -- | -- | -- | -- | -- |
| SCAQMD Study[e] (Wilson et al., 1991) | -- | -- | -- | 288 | -- | 67.1 | -- | 16.0 |

[a]Maximum benzene concentrations could not be reliably determined because exposures were averaged over a 12 hour period; however, maximum concentrations of 3 to 4 times normal exposures were calculated.
[b]This concentration was estimated, rather than measured directly.
[c]A one-hour measurement was taken for each experimental trip.
[d]The estimated sampling time period was 1.5 hours/round-trip.
[e]The measurements from this study are five minutes levels.

commuters from a non-industrial park were sampled for in-vehicle
concentrations of 14 toxic air pollutants, carbon monoxide, and
lead.

The second study by SCAQMD, Air Toxics Microenvironment
Exposure and Monitoring Study (Wilson et al., 1991), attempted to
monitor exposures to motor vehicle emissions in microenvironments
other than in-vehicle.  The study randomly sampled 100 self-
service filling stations and took samples at 10 parking garages
and 10 offices nears the garages in Los Angeles, Orange,
Riverside, and San Bernadino Counties of Southern California.
The study took five-minute samples of 13 motor vehicle air
pollutants in each microenvironment and in the ambient
environment.

Maximum microenvironment exposure levels of benzene related
to motor vehicles were determined in these studies to range from
40 $\mu g/m^3$ from in-vehicle exposure to 288 $\mu g/m^3$ from exposure
during refueling.  This compares to ambient levels of 4.13 to
7.18 $\mu g/m^3$ determined through air monitoring studies and
presented in Table 5-6.  Since for the majority of the population
these are short-term acute exposures to benzene, the concern
would be with non-cancer effects.  Health information for
non-cancer effects is limited and no RfC has been developed by
EPA.  Several studies recently conducted in rats and mice have
observed depressed cell proliferation in specific bone marrow
cells at short-term exposures of $3.2\times10^4$ $\mu g/m^3$ benzene.  Please
see Section 5.8 for more information on non-cancer effects.

Due to more stringent fuel and vehicle regulations, short-
term exposure to benzene in these microenvironments is expected
to decrease in future years.

## 5.6  Carcinogenicity of Benzene and Unit Risk Estimates

### 5.6.1  Most Recent EPA Assessment

The information presented in Section 5.6.1 has been
abstracted from EPA's Interim Quantitative Cancer Unit Risk
Estimates Due to Inhalation of Benzene (EPA, 1985), EPA's
Integrated Risk Information System (EPA, 1992c), and the Motor
Vehicle Air Toxics Health Information (Clement, 1991).  The
carcinogenicity risk assessment for benzene was last updated on
IRIS in January 1992, and contains data published through 1987.
However, it is essentially unchanged from the risk assessment
published in 1985.  EPA's Office of Research and Development has
just recently started the process to review the benzene risk
assessment.  Data published since the 1985 risk assessment for
benzene is summarized in Section 5.6.3.

## 5.6.1.1   Description of Available Carcinogenicity Data

Genotoxicity

Benzene has been found to induce chromosomal aberrations (i.e., abnormalities in the chromosomes) in bone marrow cells from rabbits (Kissling and Speck 1973), mice (Meyne and Legator 1980), and rats (Anderson and Richardson 1979).  Several investigators have reported positive results for benzene in mouse micronucleus assays (Meyne and Legator 1980).  The micronucleus assay is a laboratory method in which blood cells are examined to determine if broken chromosomes have formed small extra nuclei in the cytoplasm of the cell.  Benzene was not mutagenic (i.e., did not cause changes in the genetic material) in several bacterial and yeast systems (e.g., Crebelli et al. 1986; De Flora et al. 1984; Glatt et al. 1989; Lee et al. 1988; Tanooka 1977), in the sex-linked recessive lethal mutation assay with *Drosophila melanogaster* (fruit fly) (Kale and Baum 1983) or in the mouse lymphoma cell forward mutation assay (Oberly et al. 1984).

Animal Studies

Exposure of rodents to benzene either by gavage (compound is administered directly into the stomach by means of a stomach tube inserted down the throat) or inhalation has resulted in tumor formation.  Maltoni and Scarnato (1979) and Maltoni et al. (1983) administered 0, 50, 250, and 500 mg/kg benzene by gavage to Sprague-Dawley[1] rats (30-40/sex/dose) for life.  Rats demonstrated dose-related increases in the incidence of mammary tumors (females), Zymbal gland carcinomas (a malignant tumor of a gland that surrounds the ear canal in rats that secretes an oily substance), oral cavity carcinomas, and leukemias/lymphomas in both sexes.  Leukemia is an acute or chronic disease that is characterized by unrestrained growth of leukocytes (white blood cells) and their precursors in the tissues[2].  Lymphoma is a general

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[1] The names and/or numbers preceding rats or mice throughout this document denote specific laboratory strains.

[2] Leukemia may be divided into granulocytic leukemias (which include myelocytic, monocytic, and erythroblastic cell types) and lymphocytic leukemias. Both granulocytic and lymphocytic leukemia may, in turn, be separated into acute and chronic forms.  In acute myeloid leukemia (AML) there is diminished production of normal erythrocytes, granulocytes, and platelets which leads to death by anemia, infection, or hemorrhage.  These events can be rapid.  In chronic myeloid leukemia (CML) the leukemic cells retain the ability to differentiate (i.e., be responsive to stimulatory factors) and perform function; later there is a loss of the ability to respond.

term for inappropriate growth of new tissue or neoplastic[3] growth in the lymphatic system.

In a National Toxicology Program (NTP 1986) study, benzene was administered by gavage to Fischer-344/N rats (50/sex/dose) at doses of 0, 50, 100, or 200 mg/kg and to B6C3F$_1$ mice (50/sex/dose) at doses of 0, 25, 50, or 100 mg/kg .  The animals were treated 5 times/week for 103 weeks.  There were significant increases in the incidence of various neoplastic growths in both sexes of both rats and mice.  Both species had an increased incidence of carcinomas of the Zymbal gland.  Male and female rats had oral cavity tumors, and males showed an increased incidence of skin tumors.  Males were observed to have tumors of the Harderian (a gland located within the eye of the rat) and preputial gland (a small gland located near the head of the penis that secretes an odiferous discharge important to mating), and females had tumors of the mammary gland and ovaries.  In general, the increased incidence was dose-related.

Inhalation exposure of male C57B1 mice to 300 ppm benzene on a workday schedule (6 hours/day, 5 days/week) for 488 days resulted in slight increases in the incidence of hematopoietic neoplasms (Snyder et al. 1989).  However, there was no increase in tumor incidence in male AKR mice exposed to 100 ppm or male CD-1 mice exposed to 100 or 300 ppm benzene.  Likewise, male Sprague-Dawley rats exposed by inhalation to 300 ppm benzene were not observed to have an increased incidence of neoplasia.

Maltoni et al. (1983) treated male and female Sprague-Dawley rats in the following manner.  Starting at 13 weeks of age, rats were exposed to 200 ppm benzene by inhalation 4 hours/day, 5 days/week for 7 weeks.  Animals were then exposed to the same concentration for 7 hours/day, 5 days/week for 12 weeks, and finally 300 ppm 7 hours/day, 5 days/week for 85 weeks.  A time-weighted average (TWA) of 241 ppm for an 8 hours/day, 5 days/week exposure was calculated.  In this study, a statistically significant increase in the incidence of liver tumors (hepatomas) and carcinomas of the Zymbal gland was found.

Goldstein et al. (1980) conducted studies in male Sprague-Dawley rats exposed to 0 ppm (67/group), 75 ppm (40/group), or 225 ppm (45/group) benzene by inhalation for an unreported period of time.  In this study, one animal contracted leukemia in the 75 ppm concentration group.  In addition, AKR, C57BL, and CD-1 mice were exposed to 0 ppm (210/group), 75 ppm (50/group), or 225 ppm (160/group) benzene again for an unreported period of time. After this treatment, two animals in the high-concentration exposure group developed leukemia.

Human data

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[3]Neoplastic growth is characterized by new and abnormal formation of tissue, usually as a tumor.  By custom, this refers to the pathological process in tumor formation, i.e., cancer.

Rinsky et al. (1981) followed 748 Pliofilm® (a film made of rubber hydrochloride) workers (all white males) exposed to benzene at levels that averaged from 10-100 ppm over an 8-hour workday (8-hour time-weighted average, TWA) for at least 24 years (17,020 person-years, an expression of cumulative dose).  Seven deaths resulted from leukemia in this group.  This increased incidence was statistically significant with a standard mortality ratio (SMR) of 560.  The standard mortality ratio is the number of deaths, either total or cause-specific, in a given group expressed as a percentage of the number of deaths that would have been expected in that group if they were the same as the age-and-sex-specific rates in the general population.  For the 5 leukemia deaths that occurred among workers with more than 5 years of exposure, the SMR was 2,100.  Exposures were described as less than the recommended standards (25 ppm) for the time period of 1941-1969.  A computer tape containing follow-up information for the Rinsky population through the year 1978 was used in addition to the original Rinsky et al. (1981) data to develop unit risk estimates.  No effort was made to correct for smoking or other potential confounding exposures.

Ott et al. (1978) studied 594 white male workers occupationally exposed to benzene in a chemical manufacturing facility at concentrations ranging from 2 to 25 ppm (8-hour TWA). This group was followed for at least 23 years in a retrospective cohort mortality study.  A retrospective cohort is a group of people, defined by arbitrary criteria as alike in some way, some of whom are known to have experienced particular exposures as well as particular health effects at some time prior to the start of the investigation.  Although three leukemia deaths were observed, the increase was not statistically significant when compared to an unexposed population.

Wong et al. (1983) studied 4,062 male (both white and nonwhite) chemical workers who had been exposed to benzene for at least 6 months between 1946-1975.  The study population was drawn from seven chemical plants, and jobs were categorized with respect to peak exposure.  Subjects with at least 3 days/week exposure (3,036 individuals) were further categorized on the basis of an 8-hour TWA and were compared to controls who held jobs at the same plants for at least 6 months without exposure to benzene.  The range of exposures experienced by these workers was <1 ppm to >50 ppm (8-hour TWAs).  Statistically significant dose-dependent increases in the incidence of leukemia, lymphatic, and hematopoietic cancer (i.e., cancers of the blood forming organs) were found when the data were analyzed in terms of cumulative exposure (i.e., exposure level multiplied by duration of exposure).  The incidence of leukemia was responsible for a majority of the increase, due largely to the fact that the incidence of mortality due to neoplasia in unexposed subjects was lower than expected.

Aksoy et al. (1974) reported effects of benzene exposure among 28,500 Turkish workers employed in the shoe industry who used benzene-containing adhesives.  Mean duration of employment

was 9.7 years (1-15 year range) and mean age was 34.2 years. Peak exposure was reported to be 210-650 ppm. Twenty-six cases of leukemia and a total of 34 leukemias or preleukemias (blood conditions that are thought to precede the onset of leukemia) were observed, corresponding to an incidence of 13/100,000 (by comparison to 6/100,000 for the general population). This represents a statistically significant increase in the incidence of leukemia among the shoe workers. The possibility of concomitant exposure to other agents was not discussed. A follow-up paper (Aksoy 1980) reported eight additional cases of leukemia as well as evidence suggestive of increases in other malignancies in exposed workers.

The leukemogenic (i.e., the ability to induce leukemia) effects of benzene exposure were studied in 748 white males employed from 1940-1949 in the manufacturing of rubber products in a retrospective cohort mortality study (Infante et al. 1977a,b). Statistics were obtained through 1975. A statistically significant increase in the incidence of leukemia was found by comparison to the general U.S. population. The worker exposures to benzene were between 100 ppm and 10 ppm during the years 1941-1945. There was no evidence of solvent exposure other than benzene.

There are many other epidemiologic and case studies that report increased incidence or a causal relationship between leukemia and benzene exposure. In addition, numerous investigators have found significant increases in chromosomal aberrations of bone marrow cells and peripheral lymphocytes from workers with exposure to benzene (IARC 1982).

5.6.1.2 Weight-of-Evidence Judgment of Data and EPA Classification

The weight-of-evidence indicates that benzene is a Group A, known human carcinogen. This is based on sufficient human epidemiologic evidence (Rinsky et al. 1981; Ott et al. 1978; Wong et al. 1983) demonstrating an increased incidence of nonlymphocytic leukemia from occupational inhalation exposure, in addition to supporting animal evidence (Goldstein 1980; NTP 1986; Maltoni et al., 1983) in which there was an increased incidence of neoplasia in rats and mice exposed by inhalation and gavage.

5.6.1.3   Data Sets Used For Unit Risk Estimate

The data sets used to estimate the unit risk[4] for benzene were obtained from a reorganization of the 1981 Rinsky et al. data (followup from 1940 to 1978), Wong et al. (1983), and Ott et al. (1978).  These three studies are summarized in Table 5-8.

The Rinsky data used were from an updated tape that reports one more case of leukemia than was published in 1981.  It should be noted that a recently published paper (Rinsky et al. 1987) reported 2 additional cases of leukemia from the study population but was not used for the current risk estimate.  Updates of other cohorts used in the current EPA assessment are discussed in Section 5.6.3.  Generally, the updates report increased cohort size, improved exposure analyses, and/or alternative methods to analyze the cancer incidence data.

Although the data from Aksoy et al. (1974) and Aksoy (1978) indicated an association of leukemia with benzene, it was decided by EPA that the exposure information was so imprecise that it was not suitable for quantitative estimation.

Selection of the models used in the EPA estimate of unit risk was "a matter of judgement."  The estimates were based on the most extensive and inclusive body of data available that is of acceptable quality, so all three epidemiologic studies were used.  The choice of the studies in which the species (human) and route of exposure (inhalation) most closely corresponded to the environmentally exposed population were given the most weight.  Animal studies were merely used for confirmation purposes.

5.6.1.4 Dose-Response Model Used

The unit lifetime risk estimate was determined by using the relative risk model and the absolute risk model with three different measures of dose (total of six models) to develop 21 maximum likelihood estimates (MLEs).  These 21 MLEs were then used to calculate a geometric mean to determine the unit risk estimate.

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[4]Under an assumption of low-dose linearity, the unit cancer risk is the excess lifetime risk due to continuous constant lifetime exposure to one unit of carcinogen concentration.  Typical exposure units include ppm or ppb in food or water, mg/kg/day by ingestion, or ppm or $\mu g/m^3$ in air (EPA 1986b).

**Table 5-8. Summary of Data Sets Used to Calculate the Unit Risk Factor For Benzene[a].**

| Study | Population Studied/Years of Follow-up | Duration of Exposure | Exposure Level(s) | Effect(s) |
|---|---|---|---|---|
| Rinsky et al. (1981) | 748 Pliofilm® workers (all white males)/ 38 years | At least 24 years | 10-100 ppm (8-hour TWA) | Statistically significant increased incidence of leukemia |
| Ott et al. (1978) | 594 chemical workers (white and nonwhite)/ at least 23 years | Not specified | 2-25 ppm (8-hour TWA) | Increased incidence of leukemia (not statistically significant) |
| Wong et al. (1983) | 44,062 male chemical workers (white and nonwhite)/ 29 years | At least 6 months | <1ppm->50 ppm | Statistically significant increased incidence of leukemia, lymphatic, and hematopoietic cancer |

[a]Various subsets of these studies were used to develop the 21 unit risk factors.

5.6.1.5 Unit Risk Estimates[5]

As stated above, six models and various combinations of epidemiological data sets were used to derive a total of 21 MLEs,with their 95% statistical confidence bounds.  Because the EPA had no basis for choosing one model over another, the geometric mean of these 21 unit risk estimates was taken to obtain a pooled model average estimate, resulting in a maximum likelihood estimate (MLE) unit risk of $2.7 \times 10^{-2}$ for leukemia due to a lifetime exposure of 1 ppm benzene in the air ($8.3 \times 10^{-6}$ $[\mu g/m^3]^{-1}$).

The actual 95% upper bound (UCL) was calculated for each MLE derived with each of the 21 models.  These data are presented in Tables E-1 through E-6 in Appendix E, which were reproduced from (EPA, 1985).  A geometric mean of the UCLs was not calculated.

## 5.6.2  Other Views and Risk Estimates

This section presents alternative views and/or risk assessments for benzene.  These alternative risk assessments are summarized in Table 5-9.

International Agency for Research on Cancer (IARC)

IARC has classified benzene as a Group 1 carcinogen.  A Group 1 carcinogen is defined as an agent that is carcinogenic to humans.  This classification is based on sufficient evidence for carcinogenicity in humans (IARC, 1987).  IARC (1987) based this conclusion on the fact that numerous case reports and follow-up studies have suggested a relationship between exposure to benzene and the occurrence of various types of leukemia.

In addition, IARC (1987) considers the evidence for carcinogenicity to animals to be sufficient.  No unit risk was determined by IARC for benzene.

California Air Resources Board (CARB)

The California Department of Health Services (DHS, 1984) (which provides technical support to CARB) has also determined that there is sufficient evidence to consider benzene a human

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[5]For any dose-response model, one typically obtains risk estimates for various dose levels.  It is possible to obtain maximum-likelihood estimates (MLEs) and upper confidence limits (UCLs) for those risks.  The MLEs represent the best description of the observed data that can be obtained for any given dose-response model.  However, because there are many sources of error that affect the observation of responses (including, but not limited to, random error) it is often desirable to determine upper bounds on the risks.   The UCLs are statistical estimates of those upper bounds; they determine the highest levels of risks associated with specific dose levels that are consistent with the observed responses, the dose-response model, and the level of certainty required by the user.

**Table 5-9. Comparison of Benzene Inhalation Unit Risk Estimates.**

| Source | Tumor Type | Classification | Cancer Unit Risk Estimate $(\mu g/m^3)^{-1}$ | Cancer Unit Risk Estimate $(\mu g/m^3)^{-1}$ MLE |
|---|---|---|---|---|
| EPA (1985) | Nonlymphocytic leukemia in occupational studies | Group A[a] | $6.7 \times 10^{-6}$ – $1.5 \times 10^{-4}$ [b] | $8.3 \times 10^{-6}$ [c] |
| IARC (1987) | Leukemia in occupational studies | Group 1[d] | –[e] | –[e] |
| CARB (DHS 1984) | Leukemia in occupational studies (for lower bound on risk) and preputial gland tumors in mice and rats (for upper bound on risk) | Human Carcinogen | $5.2 \times 10^{-5}$ [f] | $8.3 \times 10^{-6}$ [g] |
| CARB (CAPCOA 1991) | -- | -- | $2.9 \times 10^{-5}$ "best value" | |
| Clement (1988) | Leukemia in occupational studies | –[h] | –[i] | $4.3 \times 10^{-8}$ – $1.1 \times 10^{-6}$ [j] |

[a]Group A = Human Carcinogen
[b]Range of 21 95% UCLs.  Geometric mean not calculated
[c]Geometric mean of 21 MLEs
[d]Group 1 = Human Carcinogen
[e]IARC did not conduct a quantitative risk assessment
[f]Lower bound of cancer risk
[g]Upper bound of cancer risk
[h]Clement did not classify benzene
[i]Clement did not calculate UCLs
[j]Range of MLEs calculated using different assumptions and data

carcinogen.  CARB performed a risk assessment of benzene that was very similar to EPA's risk assessment.  DHS, like EPA, assumed that there is no threshold for benzene-induced carcinogenicity, and that the multistage theory most appropriately describes the phenomenon of benzene-induced carcinogenesis.

The CARB potency factor for benzene is actually a range of potency factors.  For the lower end of the range, DHS calculated a MLE potency estimate for benzene, like EPA had originally done, based on the reevaluation of three epidemiological studies using the linearized multistage model and cumulative exposure averaged over the individual's lifetime (see Appendix F for a lay description of this model).  However, whereas EPA calculated a geometric mean of each of the three study's estimated slopes to obtain one slope factor, DHS used combined input data (i.e., background rate of leukemia, relative risk, and lifetime average exposure level) from the three studies to calculate one slope factor.  As a result, the MLE slope factor calculated by EPA yielded an increase in risk of $2.7 \times 10^{-2}$ due to a continuous lifetime exposure of 1 ppm benzene in the air ($8.3 \times 10^{-6}$ $[\mu g/m^3]^{-1}$) whereas the DHS MLE slope factor corresponds to a lifetime risk of $4.8 \times 10^{-2}$ $(ppm)^{-1}$ ($1.5 \times 10^{-5}$ $[\mu g/m^3]^{-1}$).  CARB chose to use EPA's MLE value of $2.7 \times 10^{-7}$ $ppm^{-1}$ as the lower bound for the benzene cancer potency factor range.

For the upper end of the range, a 95% UCL was calculated based on the most sensitive site in rats and mice, the preputial gland, using the data from the NTP (1983) study.  This data set yielded a risk of $1.7 \times 10^{-1}$ per ppm in air ($5.2 \times 10^{-5}$ $[\mu g/m^3]^{-1}$), which is 3.5-7 times as great as the risk estimated from human mortality data.  Thus, the CARB potency estimate for benzene ranges from $2.7 \times 10^{-2}$ to $1.7 \times 10^{-1}$ $ppm^{-1}$ ($8.3 \times 10^{-6}$ to $5.2 \times 10^{-5}$ $[\mu g/m^3]$).

CARB has also used what is termed as a "best value" for the benzene estimate provided by the California Department of Health Services in conjunction with the California Air Pollution Control Officers Association (CAPCOA, 1991).  The CARB "best value" for benzene is $2.9 \times 10^{-5}$ $(\mu g/m^3)^{-1}$ ($9.4 \times 10^{-2}$ $ppm^{-1}$) which falls within a range of unit risk factors, $0.75 \times 10^{-5}$ to $5.3 \times 10^{-5}$ $(\mu g/m^3)^{-1}$, ($2.4 \times 10^{-2}$ to $1.7 \times 10^{-1}$ $ppm^{-1}$) recommended by DHS for health effects assessments which were prepared for the State's Toxic Air Contamination Program.

## Motor Vehicle Manufacturer's Association (MVMA)

MVMA contracted with Environ (Environ 1987) to evaluate the risk assessment issues in EPA's technical report "Air Toxics Emissions from Motor Vehicles" (Carey 1987).  It is important to note that the Environ document is not actually a risk assessment of benzene; rather, it is a critique of EPA's risk assessment of motor vehicle air toxics.

In a discussion of the possible impact of alternative approaches, Environ (1987) mentioned a risk assessment it performed for the Western Oil and Gas Association, in which it

calculated an estimate of benzene risk that was approximately one-fourth of that developed by EPA. This estimate was based upon the Rinsky et al. (1987) cohort, and assumptions about their exposure as developed by Crump and Allen (1984). No unit risk was determined in this study by Environ for the MVMA.

## American Petroleum Institute

The American Petroleum Institute (API) states that the Yin et al. (1987) study should not be used in evaluating human health risks associated with benzene exposure because of the technical limitations of the study. Technical problems cited by API include exposure to mixtures of chemicals, retrospective benzene exposure measurements, lack of information on other exposures, and no confounding factors (such as smoking) were taken into consideration. API also states that there are problems in the comparison of the chosen exposed and non-exposed cohorts.

API also does not support the conclusion of the most recent data that benzene could be a developmental and reproductive toxicant. API states that its preliminary analysis of these studies indicates that there is a lack of quality data necessary to support this conclusion. API specifically cites the study by Savitz et al. (1989) which reports an elevated risk of still births when fathers were exposed to benzene and specifically finds fault with the exposure methodology. In this study though, Savitz et al. (1989) do discuss the limitations and suggest further evaluation while assuming no definitive relationships.

API has also taken the results of the Lange et al. (1973b) immunological effects study and performed its own analysis. Lange et al. (1973b) indicated a relationship between benzene and an allergic blood disease. API claims that the data in Lange et al. (1973b) indicate non-significant differences between exposed and non-exposed groups.

## Clement Associates, Inc.

Under the sponsorship of the American Petroleum Institute, the Chemical Manufacturers Association, and the Western Oil and Gas Association, Clement Associates, Inc. (Clement 1988) performed a quantitative re-evaluation of the human leukemia risk associated with inhalation exposure to benzene. Clement's risk assessment differed from EPA's in the following ways:

1)   The analysis of risk is based solely on the Rinsky epidemiology cohort, rather than Rinsky, Ott, and Wong. The justification for this was that the Rinsky study was the only one that was not confounded by exposure to other chemicals and had an observed statistically significant dose relationship. Furthermore, the Clement reanalysis made use of three more years of follow-up data on this cohort (Rinsky et al. 1987), and corrected several job code errors that existed in the data used in 1985.

2)   The absolute risk model, rather than a combination of
     the absolute and relative risk models, was used in the
     Clement reanalysis.

3)   The Clement reanalysis selected the weighted cumulative
     form as the most realistic biological latency
     distribution, rather than both a cumulative dose and a
     weighted cumulative dose weighting function.

4)   The Clement reanalysis uses the exact time-dependent
     exposure for each of the 1,740 individuals in the
     cohort as the critical information necessary to
     calculate the transition rate per unit of exposure
     parameter (i.e., the probability that one unit of
     exposure will result in the biological event that leads
     to leukemia).  EPA calculated transition rate by
     relying on an aggregation of data that grouped all
     person-years observed in the epidemiology studies into
     six exposure intervals rather than treating each
     exposed individual separately.

5)   The Clement reanalysis adopts a different definition of
     the types of diseases (i.e., acute leukemia and
     myelodysplastic syndrome/chronic "aplastic" anemia)
     associated with benzene exposure and adjusts background
     rates accordingly.

6)   The Clement reanalysis adds a quadratic model based on
     the hypothesis that two hits (i.e., two molecules of a
     benzene metabolite) are required to induce the
     biological event that leads to leukemia and calculates
     a linear quadratic model[6] as an upper bound on the two-
     hit model. The results of these differences in approach
     are summarized in Table E-7 in Appendix E.

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[6]Dose-response functions are often referred to based on the mathematical
equations that define them.  Many of the equations that are used are polynomials,
which can be expressed in the general form

$$a_0 + a_1*d + a_2*d^2 + ...+ a_k*d^k.$$

Each of the groups of symbols between the plus signs is referred to as a term of
the polynomial.  Polynomials are referred to by their degree, which is the
highest power to which dose, d, is raised.  The equation shown above has degree
k.  Multistage models that have been applied to cancer risk assessment are based
on such polynomial expressions.

A linear-quadratic model is a polynomial-based model that has degree 2.
That is, the polynomial on which a linear-quadratic model is based includes a
term for the background ($a_0$), a term that is linear in dose (dose raised to the
power 1, which is often represented with no exponent, i.e., $d^1$ is the same as d),
and a term with dose raised to the second power ($a_2*d^2$).

A pure quadratic model is similar to the linear-quadratic model in that it
has degree 2.  However, the pure quadratic model dose not have a linear term; it
includes only the background term ($a_0$) and a term with dose raised to the second
power.  One can think of the pure quadratic model as a submodel of the linear-
quadratic model, where the coefficient for the linear term ($a_1$) has been set to
zero.

EPA Rebuttal to Clement (API) Risk Assessment of Benzene

EPA (Chen et al. 1989) raised several issues in response to the Clement (API) risk assessment of benzene. These issues are summarized below:

1) **Use of Rinsky's Cohort as the Sole Data Base.** Chen et al. stated that the Rinsky study lacks adequate exposure information during the early but critical years of employment of the cases. Also, none of the three epidemiological studies used by EPA is considered to be superior to any other.

   Furthermore, it was stated that Clement gave "an incomplete picture of other studies and therefore reduced their usefulness by leaving out important details about those studies that do not support the use of the Rinsky study as the sole data source." Therefore, Chen et al. (1989) does not agree with choosing the Rinsky cohort as the sole data base for the benzene risk assessment.

2) **Differences Between Clement (API) and Rinsky himself in the Use of Rinsky Data Tapes.** Chen et al. (1989) stated that there appears to be some differences between the Rinsky data tapes used by API and the Rinsky data tapes used by Rinsky himself in his 1987 published paper.

3) **Only Certain Types of Leukemia are Induced by Benzene.** Chen et al. (1989) did not agree that acute myelogenous leukemia and aplastic anemia were the only disease end points associated with benzene exposure. They stated that there is also evidence linking acute and chronic forms of lymphocytic leukemia as well as acute nonlymphatic leukemia and multiple myeloma to benzene exposure, and that these should be included in a risk assessment of benzene.

4) **Blood Counts and the Crump-Allen Exposure Estimate.**
Chen et al. (1989) stated that the evidence provided by
Clement to justify the use of the Crump and Allen
(1984) exposure estimate is disputed by Rinsky, and
that both the Rinsky and Crump and Allen exposure
estimates should be considered.  Clement stated that
the Crump and Allen exposure estimate was superior to
Rinsky's because higher blood counts are correlated
with lower exposure estimates, while no correlation was
found using the Rinsky estimate.

5) **Benzene has a Non-Linear and Threshold Dose Effect.**
Clement stated that the Rinsky study showed a strong
non-linearity of leukemia mortality rate with dose
using either the Rinsky or the Crump and Allen exposure
estimates.  EPA's view is that linear low-dose
extrapolation is preferred, unless low dose data and/or
mechanism/metabolism knowledge show otherwise.

6) **Clement's (API's) Model is Superior to EPA's 1985
Model.**  As discussed above, Clement stated that their
model represents an improvement over EPA's 1985 model
because it incorporates latency period data and
individual exposure information.  Chen et al. (1989)
maintains that the way the latency is incorporated in
the model is not appropriate, and that the equation
used by Clement to estimate benzene-induced age-
specific cancer rate is not accurate (see item 7
below).

7) **Problems in the Clement (API) Procedures for Risk
Calculation.**  Chen et al. (1989) stated that the way
the latency is incorporated by API into the Moolgavkar
(MVK) model is both mathematically and biologically
inappropriate because it assumes that one and only one
single tumor cell will eventually lead to leukemia
death.  Furthermore, it is stated by Chen et al. (1989)
that the argument provided in the Clement assessment to
support the use of an absolute risk model over a
relative risk model is not convincing.

## 5.6.3  Recent and Ongoing Research

5.6.3.1 Genotoxicity

Benzene and its metabolites have been shown to cause
clastogenic effects (damages or breaks of the genetic material
that can be observed at the chromosome level) such as sister
chromatid exchange (SCE), micronuclei, and chromosomal
aberrations in both *in vivo* and *in vitro* systems in both humans
and animals.  However, studies attempting to show mutagenic
activity of benzene have generally been negative (Shahin and
Fournier 1978; Lebowitz et al. 1979; Bartsch et al. 1980;
Nestmann et al. 1980; Shimizu et al. 1983; Nylander et al. 1978).
Recent work by Glatt et al. (1989) has shown, using a closed
desiccator system, that benzene is mutagenic in *Salmonella*

*typhimurium* (a type of bacteria) strain TA1535 in the presence of activated microsomal enzymes.  These results suggest that only the metabolites of benzene are mutagenic.

Conflicting results have been obtained regarding the ability of benzene to form DNA adducts *in vivo*.  Although DNA adducts have been demonstrated in *in vitro* experiments with a variety of benzene metabolites, Reddy et al. (1989) have not observed DNA adducts in samples of liver, kidney, bone marrow, and mammary gland obtained from Sprague-Dawley rats following oral administration of benzene (500 mg/kg/day, 5 days/week, for up to 10 weeks).  The only potential adducts identified were observed in isolated rat Zymbal glands.  In contrast, Snyder et al. (1989) observed a peak upon HPLC analysis of bone marrow DNA from rats treated with 1 mL/kg of benzene, 1 time per day for 4 days, with a longer retention time than any of the deoxynucleotide standards, suggesting covalent binding of benzene/benzene metabolite with the DNA.

Recent research has also examined the genotoxicity (i.e., the ability to damage the chromosomes at the DNA level) of the recently identified benzene metabolite, *trans,trans*-muconaldehyde (Latriano et al. 1986).  *Trans,trans*-muconaldehyde has been demonstrated to form stable DNA adducts when reacted with deoxyguanosine monophosphate (Latriano et al. 1989).  Deoxyguanosine monophosphate is a nucleic acid that is one of the building blocks of DNA.  Also, it has been shown to be strongly mutagenic in Chinese hamster V79 cells and weakly mutagenic in bacterial systems (Glatt and Witz 1990).  When administered to mice, *trans,trans*-muconaldehyde increased sister chromatid exchanges (Witz et al. 1990).

Recent work has also demonstrated that 1,4-benzoquinone and 1,2,4-benzenetriol, which are metabolites of benzene, inhibit DNA synthesis in a cell-free DNA synthetic system (Lee et al. 1989).  The inhibitory effect was concluded to be due to inhibition of polymerase $\alpha$ by these metabolites.

Chromosomal aberrations occurring in humans with leukemia thought to be associated with exposure to benzene have been reported.  A recent letter to The Lancet by Lumley et al. (1990) described the case of a 58-year old heavy-goods-vehicle driver who had heavy exposure to gasoline (and thus, benzene) who developed thrombocytopenia, neutropenia, and acute myeloid leukemia.  He was found to have multiple chromosomal abnormalities including deletion of the long arm of chromosome 5, which the authors describe as a cytogenetic hallmark of secondary leukemia.  The authors cite this example of non-random chromosomal changes in individuals with known benzene exposure as useful for early detection of those at risk for developing leukemia.

In a recent study, Irons et al. (1992) tested the effects of benzene metabolites on the growth of myeloid progenitor cells (bone marrow cells that are the precursor to granulocytes and macrophages).  The benzene metabolite, hydroquinone, has been shown in previous studies to cause malignant transformations such as inhibition of microtubule assembly (essential for cell division) and nondisjunctional events (a loss of all or part of chromosomes 5 and 7) in these progenitor cells.  Irons et al. (1992) hypothesized that if agents with leukemogenic potential (such as hydroquinone) have the ability to produce alterations in the regulation of these cells ( i.e., increased growth), the absolute number of dividing progenitor cells would be increased. The increased size of this dividing cell population would serve to increase the probability of malignant transformations occurring.  Actively dividing cells are also more susceptible to transformations due to their nature.

*In vitro* pretreatment of murine (mouse) bone marrow cells with  hydroquinone and the stimulating factor that is required for their differentiation and replication results in an enhancement of granulocyte/macrophage colony formation.  The magnitude of hydroquinone-enhanced colony formation equals or exceeds that described for the synergistic action of other compounds known to cause cell differentiation with the stimulating factor.  The potential of hydroquinone to alter growth response and induce differentiation in a myeloid (bone marrow) progenitor cell population may be important in the pathogenesis of acute myelogenous leukemia secondary to benzene exposure.  Benzene leukemogenesis may result from the dual ability of its metabolites to promote progenitor cell growth and differentiation and also induce cytogenetic changes in replicating cells.  If other leukemogenic agents act similarly, alterations in myeloid progenitor cell differentiation may be important in the pathogenesis of secondary acute myelogenous leukemia in general.

These new studies provide additional support for the clastogenic ability of benzene metabolites and provide new evidence for the potential mutagenic activity of some of these metabolites.  Furthermore, the occurrence of certain chromosomal aberrations in individuals with known exposure to benzene may serve as a marker for those at risk for contracting leukemia.

5.6.3.2  Pharmacokinetics

The tumor diversity observed in different strains and species of rodents has been proposed to be due to the production of a number of potentially carcinogenic metabolites of benzene that may act singly or in combination (although the specific "active" metabolites have not yet been identified) (Huff et al. 1989).

A number of recent studies have examined the effects of dose, dose rate, route of administration, and species on benzene metabolism.  For example, Sabourin et al. (1987) demonstrated that administration of bolus doses $\geq$ 50 mg/kg by oral or

intraperitoneal injection to rats and mice exceeded the metabolic capacity of these rodents and resulted in a portion of the dose being exhaled as benzene and a decrease in conversion to reactive benzene metabolites.  As the dose was increased above 50 mg/kg, proportionately more was exhaled and less converted to benzene metabolites.  With inhalation exposures, a similar phenomenon was observed in rats and mice.  However, mice had a more rapid metabolic rate than rats, resulting in higher metabolite production in mice after an extended inhalation exposure (i.e., 6 hr).  In mice the toxic pathways became saturated, whereas, in rats there was a relative increase in nontoxic pathways as the dose increased.

In addition to the higher metabolic rate in mice than in rats, Sabourin et al. (1988) demonstrated that mice and rats use the various metabolic pathways for benzene to differing degrees.  In mice, detoxification also predominated, but substantial conversion to toxic metabolites was apparent.  In rats, no saturation of toxic pathways was evident with increasing dose rate; however, increases in the mouse exposure level resulted in a shift from toxic metabolic pathways to detoxification pathways (Sabourin et al. 1988).  These results indicate that the net result of exposures to high concentrations (200 ppm by the inhalation route) is to decrease the proportion of toxic metabolites formed relative to the dose administered in both mice and rats, with low level, long duration exposures of mice producing more toxic metabolites.

Age-related differences in benzene pharmacokinetics also appear to occur.  McMahon and Birnbaum (1991) found that the disposition of benzene differed between 3- and 18-month-old male B6C3F1 mice administered as a single oral dose of either 10 or 200 mg/kg benzene.  These differences include increased urinary and fecal elimination, increased expiration of benzene derived $CO_2$, and an effect on the metabolism of benzene to specific metabolites.  While these differences may be due to the physiological effects of aging rather than direct age-related differences in the metabolism of benzene, these results have important implications with respect to the extrapolation of data obtained in young or old animals to young or old humans.

Using information about the relationship of the exposure conditions with the internal dose of various metabolites, computer simulations can be generated to estimate metabolite concentrations after differing exposure regimens (Medinsky et al. 1989) and derive internal doses that may be correlated with observed carcinogenic responses (Bailer and Hoel 1989) for risk assessment.  Recently, Bois and Spear (1991) attempted to correlate circulating levels of phenol and hydroquinone with the onset of cancer in rats and mice using a computer model of benzene metabolism.  No correlation was observed, indicating that other metabolites or combinations of

metabolites may be important in the initiation of cancer following benzene exposure.

Two benzene metabolites that have been shown to interact metabolically are phenol and hydroquinone to produce 1,4-benzoquinone *in vitro* (Eastmond et al. 1987). The observation that phenol and hydroquinone, when administered together in mice, produced a much greater decrease in bone marrow cellularity than did administration of either metabolite alone, suggests that a similar enhancement of the formation of the myelotoxic metabolite, 1,4-benzoquinone, may also occur *in vivo*.

A physiologically based pharmacokinetic model (PBPK) model for benzene has been developed by Travis et al. (1990). PBPK models are designed to allow more accurate prediction of actual internal doses across species. This particular model was developed to quantitatively predict the fate of benzene in mice, rats, and humans following several routes of exposure. One of the advantages to having a highly predictive PBPK model for benzene is that exposure data from benzene-induced cancers in animals may be directly compared to exposure data from human epidemiological studies in terms of metabolized dose, and therefore, route-to-route extrapolations can be made with a higher degree of confidence.

These studies demonstrate that species differ with respect to their ability to metabolize benzene. These differences may be important when choosing an animal model for human exposures and when extrapolating high dose exposures in animals to the low levels of exposure typically encountered in occupational situations. The development of a PBPK model for benzene should help in performing interspecies and route-to-route extrapolations of cancer data. Furthermore, metabolite interactions should be considered in developing PBPK models.

5.6.3.3  Carcinogenicity - Animal Studies

Recent studies examining the carcinogenicity of benzene in rodents have demonstrated that benzene is a potent carcinogen in a number of organs in a variety of species and strains of mice and rats, whether administered orally or by inhalation. In a recent NTP bioassay (Huff 1986), administration of benzene by gavage produced a variety of types of tumors in male and female F344/N rats and B6C3F1 mice. Male rats were administered 0, 50, 100, or 200 mg/kg benzene and female rats and male and female mice were administered 0, 25, 50, 100 mg/kg in corn oil by gavage for 103 weeks. Female rats administered benzene at 25 mg/kg and above caused significantly increased incidences of Zymbal gland carcinoma and at 50 mg/kg and above, squamous cell carcinomas and papillomas of the oral cavity. In male rats, at 100 mg/kg and above, Zymbal gland carcinomas, squamous cell carcinomas (malignant tumors of the skin), and papillomas (benign tumors) of the oral cavity were

significantly increased.  Also in male rats, skin papillomas were increased at 200 mg/kg and above.

In mice, significantly increased incidences of Zymbal gland carcinomas, malignant lymphomas, and alveolar/bronchiolar carcinomas at 50 mg/kg and above were observed.  Harderian gland adenomas increased at 25 mg/kg and above, and squamous cell carcinomas of the preputial gland increases at 50 mg/kg and above were observed in male mice.  At 25 mg/kg and above, malignant lymphomas increased and ovarian granulosa cell tumors (tumor of the ovary), carcinomas of the mammary gland, and alveolar/bronchiolar carcinomas increased at 50 mg/kg and above in female mice.  Zymbal gland carcinomas at 100 mg/kg were also observed in females.  Alveolar tumors are located in the deepest part of the lung in the tissue where air exchange with blood takes place.  Bronchiolar tumors are located in the bronchial tubes in the lungs.  In general, mice were more sensitive to the carcinogenic effects of benzene than were rats.

Similar results were presented by Maltoni et al. (1989). When administered benzene (0, 50, 250 mg/kg or 0, 500 mg/kg) by gavage in olive oil for 104 weeks, benzene-exposed Sprague-Dawley rats had increased incidences of tumors of the Zymbal gland, oral cavity, nasal cavity, skin, forestomach, liver angiosarcomas (malignant tumors in blood vessels in the liver) and marginal increases in carcinomas of the mammary glands, hepatomas (liver tumors), and leukemias.  Wistar rats administered 0 or 500 mg/kg by gavage in olive oil for 104 weeks had increased incidences of carcinomas of the Zymbal gland, oral cavity, and nasal cavity in benzene-exposed animals.  Swiss mice administered 0 or 500 mg/kg by gavage in olive oil for 78 weeks had increased incidences of carcinomas of the mammary gland, lung tumors, and carcinomas of the Zymbal glands in those mice exposed to benzene.  RF/J mice administered 0 or 500 mg/kg by gavage in olive oil for 52 weeks had increased incidences of mammary carcinomas, lung tumors, and leukemias in those mice exposed to benzene.  When adult Sprague-Dawley rats inhaled either 0 or 200 ppm 4 hr/day, 5 days/week for 7 weeks followed by 200 ppm 7 hr/day, 5 days/week for 12 weeks and then 300 ppm 7 hr/day, 5 days/week for 85 weeks, an increased incidence of carcinomas of the Zymbal glands and oral cavity were observed with marginal increases in carcinomas of the nasal cavity, mammary glands, and hepatomas in benzene-exposed rats. Slightly greater numbers of tumors were observed when inhalation exposure at the above concentrations began on day 12 of gestation.

Recently, an increased incidence of myelogenous leukemias (the type of cancer associated with benzene exposure in humans) was reported in mice exposed to benzene by inhalation (Cronkite et al. 1989).  CBA/Ca mice were used in this study.  These mice come from the same stock as a strain (CBA/H) known to have a low incidence of acute myeloblastic leukemia (a type of myelogenous leukemia), but which respond to ionizing radiation with a high incidence of these tumors.  Inhalation of 300 ppm, 6 hr/day, 5 days/week, for 16 weeks significantly decreased survival and increased the incidence of myelogenous neoplasms in male and

female CBA/Ca mice.  Also, an increased incidence of neoplasms
other than hepatic and hematopoietic cancers such as squamous
cell carcinoma, mammary adenocarcinoma (tumors of the mammary
gland), Zymbal and Harderian gland tumors, and papillary
adenocarcinomas of the lung was observed in these mice.  These
tumors (myelogenous neoplasms and other neoplasms) were observed
earlier in benzene-treated animals than in the controls.  Hepatic
neoplasms also appeared sooner in the benzene-exposed mice;
however, both hepatic and lymphomatous neoplasms were
significantly decreased in benzene-treated mice.  At lower
concentrations (100 ppm), an increased incidence of tumors other
than hematopoietic and hepatic neoplasms was also observed
although no significant increase in myelogenous neoplasms was
seen.  Preliminary results indicated that exposure of these mice
to much higher concentrations of benzene (3,000 ppm for 8 days)
did not produce similar increases in mortality or cancer
incidence.  The absence of neoplastic effects at this high dose
is consistent with the much lower hematotoxicity (blood disease)
observed with exposure to 3,000 ppm for 2 days as compared with
exposure to 316 ppm for 19 days (exposures designed to yield
similar total doses of benzene).

These new studies provide additional support for the
carcinogenicity of benzene in animals by both the oral and
inhalation routes and provide the first animal model for the type
of neoplasm identified most closely with occupational exposure,
acute myelogenous leukemia.  Benzene has been shown to be
carcinogenic in both sexes, at multiple sites, in several strains
of rats and mice.

5.6.3.4  Carcinogenicity - Epidemiological Studies

Several studies have become available since the 1985 EPA
carcinogenicity assessment, and have not been considered in the
derivation of the cancer potency factor for benzene.  The study
by Rinsky et al. (1981) has been updated through December 31,
1981 (Rinsky et al. 1987).  An additional two deaths attributable
to leukemia were included in the update, bringing the total
number of leukemia deaths to nine.  The standardized mortality
ratio (SMR) for leukemia calculated in the update was 337 (95%
confidence interval = 154-641).  Also, a significant increase in
multiple myeloma[7] was observed in the updated cohort (SMR=409,
95% confidence interval=110-1047).  Latency for the leukemia
deaths ranged from 5-30 years with seven of the nine deaths
occurring with a latency of <20 years.  In contrast, latency for
all of the cases of multiple myeloma was >20 years.  A matched
case-control analysis was also performed using conditional
logistic regression analysis.  Conditional logistic regression is
used in a case-control study when the cases (i.e., exposed
individuals) and controls (i.e., non-exposed individuals) have

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[7]Myeloma is a tumor originating in the cells of the blood-forming portion
of bone marrow.  Multiple myeloma is a type of cancer characterized by the
infiltration of bone and bone marrow with myeloma cells that form multiple tumor
masses.  This disease is usually progressive and fatal, and is accompanied by
anemia, renal lesions, and high globulin levels in the blood.

been matched (i.e., matched pairs).  It then can provide an unbiased estimate on a number of factors of the relative risk. Although the information reported in the Rinsky et al. (1987) update do not qualitatively change the current EPA risk assessment for benzene (i.e., they support the conclusion that benzene exposure is associated with an increased incidence of leukemia), the analytical methods used in this update, the improved exposure data, and the larger cohort size may impact the quantitative assessment of cancer risk based on this cohort.

The study by Ott et al. (1978) has also been updated (Bond et al. 1986) expanding the cohort size from 594 to 956 and increasing the period of observation to 1940-1982.  An additional death was reported in this update, bringing the total to four leukemia deaths (all of the myelogenous type).  Myelogenous leukemias are diseases where there is unrestrained growth of myelocytes, which are large cells found in the bone marrow that develop into white blood cells.  Although the SMR for leukemia deaths was not significantly elevated, the mortality due to acute myelogenous leukemia was significantly increased.  However, a positive dose-relationship between benzene exposure and leukemia was not observed.

A conditional logistic regression case-control analysis of the Ott et al. (1978) and Bond et al. (1986) studies was performed by the American Petroleum Institute (API) similar to that described in the Rinsky et al. (1987) update.  However, API failed to observe a statistically significant relationship between increasing cumulative benzene exposure and increased risk of leukemia (Peterson 1986).

The study by Wong et al. (1983) has also been updated (Wong 1987).  Two additional leukemias have been added to the cohort, bringing the total to seven.  When compared to workers with no occupational exposure to benzene, those with at least 720 ppm-months of exposure to benzene had a relative risk of 3.93 for lymphatic and hematopoietic cancer.  Workers with <180, 180-719, and ≥720 ppm-months of exposure had a borderline significantly increased incidence of non-Hodgkin's lymphopoietic cancer with increased exposure.

A new retrospective mortality study was published by Yin et al. (1989) of 28,460 benzene-exposed workers from 83 factories in China.  Mortality of workers with at least six months of exposure to benzene between January 1, 1972 and December 31, 1981 was compared with mortality of a similar number of workers from these factories who had not been exposed to benzene.  Significantly increased SMRs for leukemia (SMR=5.74) and lung cancer (SMR=2.31) were observed among exposed males and an increased SMR for leukemia was observed among exposed females.  A higher proportion of acute nonlymphocytic leukemias were observed and a lower proportion of acute lymphocytic leukemias were seen than in the general population.  The risk of leukemia increased with exposure duration up to 15 years and then declined with additional years of exposure.  Cumulative exposure estimates were also performed in this study although measurements of ambient benzene levels

were not complete for all of the subjects.  The cumulative exposure estimates supported the findings by Rinsky et al. (1987) that leukemia was, in many cases, seen in workers with continuous low dose exposure less than 400 ppm-yr of exposure.  Smoking histories were determined in this study and the results demonstrated that smoking had no effect on leukemia mortality. Smoking increased the mortality due to lung cancer, but significantly greater lung cancer mortality was observed in exposed nonsmokers than in nonexposed nonsmokers, suggesting that lung cancer may also be associated with benzene exposure.

The updated studies provide continued evidence of the carcinogenicity of benzene in humans, and incorporation of increased cohort sizes and improved exposure analyses in these studies may strengthen the current cancer risk assessment for benzene.  Furthermore, the observation of significantly increased lung cancer, as well as increased acute myelogenous leukemia, in the new study by Yin et al. (1989), suggests that benzene might be a multisite carcinogen in humans, as has been indicated in animal studies.

Morris and Seifter (1992) hypothesize that the increase in breast cancer incidence observed in urban areas may be due to the increased exposure to aromatic hydrocarbons found in urban pollution.  Aromatic hydrocarbons are capable of inducing breast cancer in animals and benzene is a known cause of leukemia in humans.

Most aromatic hydrocarbons and benzene are readily soluble in fatty tissue (e.g., breast tissue) where they are stored, concentrated, and metabolized in the breast tissue to carcinogenic compounds.  Some of these aromatic hydrocarbons produce electron seeking metabolites which can adduct to the DNA, causing mis-replication which can lead to tumor production. Other metabolites can function in the role of tumor promoter by producing an oxidant through their metabolic detoxification pathways.  These oxidants, oxygen free radicals (activated forms of oxygen), consume glutathione (an anti-oxidant in the cells) that would otherwise protect against tumor promotion.  Some aromatic hydrocarbons can react with cell membrane receptor sites causing oxygen free radicals to peroxidant the polyunsaturated lipids of the cell membrane.  These lipid peroxidases and their degradation by-products cause chromosomal breaks in the related cell and also in remote tissues.  The consequence of long term hydrocarbon exposure is the possibility of an increased pro-oxidant state which destabilizes DNA, causes chromosomal breaks, and allows for initiation and promotion of breast cancer.

In urban communities, there is increased exposure to hydrocarbons due to the use of fossil fuels and, concurrently, there is an increased personal exposure to hydrocarbons.  It is the authors' contention that this low dose, long term exposure to many mammary specific hydrocarbon carcinogens and to the promotional effects of perhaps hundreds of other carcinogenic and non-carcinogenic hydrocarbon metabolites accounts for the urban factor in breast cancer.

## 5.7  Carcinogenic Risk for Baseline and Control Scenarios

Since the benzene unit risk estimate is based on human epidemiology of death data, cancer numbers should be expressed as cancer deaths.  The estimate of cancer deaths may underestimate cancer incidence associated with benzene, since survivorship rates were not included in the supporting studies.  Table 5-10 summarizes the maximum likelihood estimates of annual cancer deaths for all scenarios.  When comparing cancer deaths for the base control scenarios relative to 1990, there is a 39% reduction in 1995, a 50% reduction in 2000, and remains constant at a 50% reduction in 2010.  The reduction in emissions is considerably higher, particularly in the out years.  The projected increase in both population and vehicle miles traveled (VMT) from 2000 to 2010 appears to offset the gains in emissions achieved through fuel and vehicle modifications.

The base control and expanded use scenarios within each year can be directly compared since the same VMT and populations are applied to both.  In 1995, expanding the reformulated fuels program reduces the number of cancer deaths by another 8% from the 1990 base control.  The expanded use of reformulated fuels and the California program in the year 2000 produces another 6% reduction in cancer cases, for both scenarios, when compared to 1990.  Expanded reformulated fuel use in 2010 reduces deaths due to cancer  by 6% relative to 1990 and by approximately 10% for the expanded California standards scenario.  Like the base case comparison, the cancer cases for the control scenarios are similar for 2000 and 2010 despite continued emission reduction, due to the projected population and VMT increase.

## 5.8  Non-Carcinogenic Effects of Inhalation Exposure to Benzene

EPA has no inhalation reference concentration for the noncancer effects of benzene that can be used as a basis for risk assessment.  Benzene's carcinogenic effects serve as the basis for the benzene risk assessment.  Since the focus of this report is on the carcinogenic potential of the various compounds, the noncancer

**Table 5-10. Annual Cancer Death Projections for Benzene.[a,b]**

| Year-Scenario | Emission Factor g/mile | Urban Cancer Deaths | Rural Cancer Deaths | Total Cancer Deaths | Percent Reduction from 1990 | |
|---|---|---|---|---|---|---|
| | | | | | EF | Cancer |
| 1990 Base Control | 0.0882 | 59 | 11 | 70 | – | – |
| 1995 Base Control | 0.0472 | 36 | 7 | 43 | 46 | 39 |
| 1995 Expanded Reformulated Fuel Use | 0.0413 | 31 | 6 | 37 | 53 | 47 |
| 2000 Base Control | 0.0351 | 30 | 5 | 35 | 60 | 50 |
| 2000 Expanded Reformulated Fuel Use | 0.0301 | 26 | 5 | 31 | 66 | 56 |
| 2000 Expanded Adoption of California Standards | 0.0305 | 26 | 5 | 31 | 65 | 56 |
| 2010 Base Control | 0.0285 | 30 | 5 | 35 | 68 | 50 |
| 2010 Expanded Reformulated Fuel Use | 0.0248 | 26 | 5 | 31 | 72 | 56 |
| 2010 Expanded Adoption of California Standards | 0.0228 | 24 | 4 | 28 | 74 | 60 |

[a]Projections have inherent uncertainties in emission estimates, dose-response, and exposure.
[b]The unit risk estimate for benzene is based on human data.  Benzene is classified by EPA as a Group A, known human carcinogen based on sufficient human epidemiologic evidence in addition to supporting animal evidence.

information will be dealt with in a more cursory fashion.  No attempt has been made to synthesize and analyze the data encompassed below.  Also, no attempt has been made to accord more importance to one type of noncancer effect over another.  The objective is to research all existing data, describe the noncancer effects observed, and refrain from any subjective analysis of the data.

The respiratory route is the major source of human exposure to benzene, and much of this exposure is by way of gasoline vapors and automotive emissions (EPA, 1980).  Individuals employed in industries that use or make benzene or benzene-containing products may be exposed to the highest concentrations of benzene, primarily by inhalation.  In 1987, OSHA estimated that approximately 238,000 workers were exposed to benzene in seven major industry sectors, including petrochemical plants, petroleum refineries, coke and chemicals, tire manufacturers, bulk terminals, bulk plants, and transportation via tank trucks (OSHA 1987).  The toxic effects of benzene in humans and other animals following inhalation exposure include central nervous system (CNS), hematological, and immunological effects.  In humans, acute exposure to 20,000 ppm is usually fatal within 5-10 minutes (Gerarde 1960).  Death is preceded by CNS effects such as drowsiness, headache, nausea, staggering gait, delirium, vertigo, tremors, convulsions, and unconsciousness (Cronin 1924; Gerarde 1960; Browning 1965).  In humans, death has been tentatively attributed to asphyxiation, respiratory arrest, CNS depression, or cardiac arrhythmia (Winek and Collum 1971).  Organ hemorrhage was also reported.  An inhalation $LC_{50}$ (the concentration that is lethal to half of the animals exposed by the inhalation route) value for rats was calculated as 13,700 ppm for a 4-hour exposure (Drew and Fouts 1974).

Benzene induces hematological effects in humans and animals.  Early stages of benzene toxicity may be characterized by deficiencies in specific blood elements, resulting in anemia (a reduction in the number of red blood cells), leukopenia (a reduction in the number of white blood cells), or thrombocytopenia (a reduction in the number of blood platelets).  Chronic inhalation exposure to benzene in humans results in pancytopenia, a condition characterized by decreased numbers of circulating erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (blood platelets) (Aksoy and Erdem 1978; Aksoy et al. 1971)[8].  Individuals that develop pancytopenia

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[8]Pancytopenia is the reduction in the number of all three major types of blood cells (erythrocytes, or red blood cells, thrombocytes, or platelets, and leukocytes, or white blood cells).  In adults, all three major types of blood cells are produced in the red bone marrow of the vertebra, sternum, ribs, and pelvis.  The red bone marrow contains immature cells, known as multipotent myeloid stem cells, that later differentiate into the various mature blood cells.  Pancytopenia results from a reduction in the ability of the red bone marrow to produce adequate numbers of these mature blood cells.  Aplastic anemia is a more severe blood disease and occurs when the bone marrow ceases to function, i.e., these stem cells never reach maturity.  The depression in bone marrow function occurs in two stages - hyperplasia, or increased synthesis of blood cell elements, followed by hypoplasia, or decreased synthesis.  As the disease progresses, the bone marrow decreases functioning.  This myeloplastic dysplasia

and have continued exposure to benzene may develop aplastic anemia (pancytopenia associated with fatty replacement of functional bone marrow), whereas others exhibit both pancytopenia and bone marrow hyperplasia, a condition that may indicate a preleukemic state (Aksoy et al. 1974; Aksoy and Erdem 1978).  Similar hematological effects have been reproduced in animals.

Symptoms of immunotoxicity have been reported in workers chronically exposed to benzene at concentrations that ranged from 3.44-53.21 ppm for 1-21 years.  Alterations in serum levels of immunoglobulin (proteins in the blood that are capable of acting as antibodies) and complement (a series of enzymatic proteins in normal serum that, in the presence of a specific stimulus, destroy bacteria and other cells) and indications of benzene-induced autoimmunity and allergy have been observed in benzene-exposed workers whose exposure has been intermediate or chronic (Lange et al. 1973a, 1973b).  Eosinophilia, an indication of an allergic response, has been noted in Turkish workers (Aksoy et al. 1971).  Evidence of a positive leukocyte autoagglutinnin test, associated with decreased granulocyte levels, was suggestive of allergic blood dyscrasia (disease) (Lange et al. 1973b).  The autoagglutinnin test measures the clumping of one's own blood cells.  A positive response indicates that one's own blood cells stimulate an allergic response in the body.  In animals, lymphopenia appears to be the most consistent response to subchronic benzene exposure, and may be seen at exposures as low as 25 ppm (Cronkite et al. 1989).  A dose-response study of short-term inhalation exposure to benzene in mice at levels of 10-30 ppm showed significantly depressed proliferative responses of bone-marrow-derived B cells and splenic T cells in mice (Rozen et al. 1984).  Mice with *Listeria monocytogenes* (a form of bacteria) exposed to intermittent benzene concentrations of 300 ppm resulted in delayed cell-mediated immunity, causing increased bacterial numbers (730% of controls) on day 4 (Rosenthal and Snyder 1985).

The available human data on developmental effects of benzene are inconclusive.  Savitz et al. (1989) conducted an epidemiological study aimed at assessing the effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational age infants.  They used data from National Natality and Fetal Mortality surveys on the probability samples of live births and fetal deaths that occurred in the US in 1980 among married women.  Savitz et al. (1989) found that a high maternal linkage to benzene was predictive of stillbirth risk.  Another significant association was found for paternal exposure to lead and risk of small-for-gestational age.  Despite the limitations inherent in the study design (i.e., lack of exposure data, small size of exposed populations, and possible confounding factors not accounted for), these results suggest that occupational exposure to benzene may be associated with adverse developmental and reproductive outcomes.

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without acute leukemia is known as preleukemia.  The aplastic anemia can progress to AML.

Several animal studies, involving acute inhalation exposure during pregnancy, have shown that exposure to benzene decreased body weight and increased skeletal variants such as missing sternebrae and extra ribs (Murray et al. 1979; Kimmel and Wilson 1973). Alterations in hematopoiesis (growth and development of blood elements) have been observed in the fetuses and offspring of pregnant mice exposed to benzene (Keller and Snyder 1986). Two recent reports have described adverse immunological and hematopoietic effects associated with *in utero* exposure to benzene. One of these studies, Wierda et al. (1989), produced results that suggest that *in utero* exposure of benzene may adversely alter B cell development and responsiveness, and thus, compromise the immune system after birth.

Benzene may impair fertility by causing ovarian atrophy among women occupationally exposed to high levels (levels not specified) of benzene (Vara and Kinnunen 1946). In mice, histopathological changes were observed in ovaries (bilateral cysts) and testes (atrophy/degeneration, decrease in spermatozoa, moderate increase in abnormal sperm forms) following exposure to 300 ppm benzene for 13 weeks (Ward et al. 1985). No studies were located regarding respiratory, hepatic, or renal effects in humans or animals after inhalation exposure to benzene.

Corti and Snyder (1990) reported in a recent abstract that inhalation exposure of female Swiss Webster mice to 10 ppm benzene on gestation days 6-15 resulted in a reduction in the number of erythrocyte progenitor cell colonies in bone marrow cell cultures from female offspring 6 weeks after birth. There was no effect apparent in the male offspring. These results suggest that *in utero* exposure to benzene may adversely affect normal hematopoietic development.

The inhalation reference concentration (RfC) for benzene is currently under review by the EPA RfD/RfC Workgroup (EPA, 1992c). The oral reference dose (RfD) for benzene will be reviewed by the EPA RfD/RfC Workgroup (EPA, 1992c).

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# 6.0 FORMALDEHYDE

## 6.1 Chemical and Physical Properties (EPA, 1991a, 1992)

Formaldehyde is a colorless gas at normal temperatures with a pungent, irritating odor.  It is the simplest member of the family of aldehydes and has the chemical formula HCHO. Formaldehyde gas is soluble in water, alcohols, and other polar solvents.  The chemical and physical properties of pure formaldehyde are presented in Table 6-1.

In the presence of air and moisture at room temperature, formaldehyde readily polymerizes to a solid mixture known as paraformaldehyde.  Another common form of formaldehyde is its cyclic trimer (three formaldehyde molecules forming a ring) known as trioxane ($C_3H_6O_3$).  In aqueous solutions, formaldehyde reacts with water to form methylene glycol.

Pure, dry formaldehyde gas is stable from 25-100°C (77-212°F) and decomposes very slowly up to 300°C (572°F). Polymerization takes place slowly below room temperature but is accelerated by the presence of impurities.  Decomposition of formaldehyde produces carbon monoxide and hydrogen gas.  When catalyzed by certain metals (platinum, copper, or chromia and alumina), formaldehyde decomposition can produce methanol, methyl formate, formic acid, carbon dioxide, and methane.

**Table 6-1.  Chemical and Physical Properties of Pure Formaldehyde.**

| Properties | Values |
|---|---|
| Molecular weight | 30.03 g/mole |
| Melting point | -92.0°C (-133.4°F)a |
| Boiling point at 1 atm. | -19.5°C (-3.1°F) |
| Density at -20°C (-4°F) | 0.8153 g/ml |
| Vapor pressure at -19.5°C | 1 atm. |
| Flash point | 60°C (140°F) at a 40% solution |
| Solubility in water at 25°C | very soluble (up to 55%) |
| Conversions | 1 ppm = 1.23 mg/m$^3$ |

## 6.2 Formation and Control Technology

Formaldehyde is the most prevalent aldehyde in vehicle exhaust and is formed from incomplete combustion of the fuel. Formaldehyde is emitted in the exhaust of both gasoline and diesel-fueled vehicles.  It is not a component of evaporative emissions.

Use of a catalyst has been found to be effective for controlling formaldehyde emissions.  Formaldehyde emissions are controlled to roughly the same extent as total hydrocarbon emissions with a catalyst (Carey, 1987).

## 6.3  Emissions

### 6.3.1  Emission Fractions Used in the MOBTOX Emissions Model

Emission fractions for formaldehyde were developed using vehicle emission test data from various programs (Appendix B2). Formaldehyde emission fractions for different components included in the scenarios are included in Appendix B6.

The formaldehyde TOG emission fraction for LDGVs/LDGTs with three-way catalysts, running on baseline fuel, was based on data from 38 vehicles tested in four studies (Boekhaus et al., 1991a, 1991b, DeJovine et al., 1991, and Auto/Oil, 1990).  The TOG fraction for LDGVs/LDGTs with three-way plus oxidation catalysts, running on baseline fuel, was based on data from 25 vehicles tested in eight studies (Urban, 1980a, 1980b, Sigsby et al., 1987, Stump et al., 1989, 1990, unpublished, Warner-Selph and DeVita, 1989, Boekhaus et al., 1991b, Auto/Oil, 1990).  The TOG fraction for LDGVs/LDGTs with oxidation catalysts, running on baseline fuel, was based on data from 41 vehicles tested in eight studies (Urban, 1980a, Springer, 1979, Sigsby et al., 1987, Smith, 1981, Stump et al., 1989, 1990, Auto/Oil, 1990, Boekhaus et al., 1991a, Warner-Selph and Smith, 1991).  The TOG fraction for LDGVs/LDGTs with no catalysts, running on baseline fuel, was based on data from 11 vehicles tested in four studies (Urban, 1981, Urban 1980a, Sigsby et al., 1987, and Warner-Selph and Smith, 1991).  The LDDV fraction was based on data from 7 vehicles tested in two studies (Springer, 1977 and Springer, 1979).  The HDDV and HDGV non-catalyst fractions were based on 13-mode data from two engines and one engine, respectively, tested in one study (Springer, 1979).  To estimate the three-way fraction for HDGVs, the non-catalyst to three-way fraction for LDGVs/LDGTs was applied to the HDGV non-catalyst fraction.

To calculate TOG fractions for vehicles running on MTBE blends and 10% ethanol, adjustment factors were applied to the baseline emission fractions for each vehicle class/catalyst combination based on average percent change.  The average percent change

numbers for vehicle class/catalyst combinations are contained in Appendix B4.

It should be noted that percent change was calculated on a vehicle by vehicle basis and the average of these percent changes was then calculated for each vehicle class/catalyst combination. When a draft memo was distributed by EPA describing the methodology used to calculate emission fractions for this report (EPA, 1992a), a comment was made in a review prepared by Systems Applications International for the Motor Vehicle Manufacturers Association (MVMA) (Ligocki, 1992) questioning this averaging approach. The review pointed out that if a car had low total mass emissions, but a large change in percent of a toxic, this could result in an overestimate of the effect of this car on the toxic level in the fleet, and an overestimate of the toxic level in reformulated fuel relative to baseline. However, the potential source of error resulting from this averaging technique is diminished by a number of factors, including the fact that data from cars exhibiting unreasonably large changes in toxic levels were discarded. Also, the potential source of error would be expected to affect only formaldehyde and acetaldehyde, since benzene fractions were calculated from equations, and oxygenate level has little effect on 1,3-butadiene. In any case, the MVMA approach is not appreciably more accurate than the EPA approach in predicting actual toxic fractions.

The 15% MTBE and 10% ethanol adjustment factors for LDGVs/LDGTs with various catalyst technologies are summarized in Table 6-2. Note that use of oxygenated fuels increases formaldehyde emissions for all catalyst technologies. These 15% MTBE numbers were estimated using data from Auto/Oil (1991) and DeJovine et al. (1991) for LDGVs/LDGTs with three-way catalysts, Auto/Oil (1991) for LDGVs/LDGTs with three-way plus oxidation and oxidation catalysts, and Warner-Selph and Smith (1991) for vehicles

**Table 6-2. 15% MTBE and 10% Ethanol Emission Fraction Adjustment Factors for Formaldehyde.**

| Vehicle Class | Catalyst Technology | 15% MTBE Adjustment Factor | 10% Ethanol Adjustment Factor |
|---------------|---------------------|----------------------------|-------------------------------|
| LDGV/LDGT | 3-way | 1.6746 | 1.4758 |
| LDGV/LDGT | 3-way + ox | 1.2672 | 1.2288 |
| LDGV/LDGT | oxidation | 2.0244 | 1.2400 |
| LDGV/LDGT | non-cat | 1.5256 | 1.1034 |

with no catalysts. The 10% ethanol numbers were estimated using data from Auto/Oil (1991), Warner-Selph and Smith (1991) and the Colorado Department of Health (1987) for LDGVs/LDGTs with three-

way catalysts, the Colorado Department of Health (1987) for LDGVs/LDGTs with three-way plus oxidation catalysts, and Warner-Selph and Smith (1991) and the Colorado Department of Health (1987) for LDGVs/LDGTs with oxidation catalysts or no catalysts.

Since the average percent change was calculated for 15% MTBE (2.7% weight percent oxygen), and 11.0% MTBE (2.0% oxygen) was assumed for reformulated fuel and California standards components, average percent changes in the formaldehyde TOG fraction from 0 to 15% MTBE were multiplied by 2.0/2.7, the ratio of oxygen contents by weight. For HDGVs with three-way catalysts and with no catalysts, the same 15% MTBE and 10% ethanol adjustment factors were assumed as for LDGVs/LDGTs with the same catalyst technologies.

### 6.3.2  Emission Factors for Baseline and Control Scenarios

The fleet average formaldehyde emission factors as determined by the MOBTOX emissions model are presented in Table 6-3. When comparing the base control scenarios relative to 1990,the emission factor is reduced by 43% in 1995, by 61% in 2000, and by 66% in 2010. The expansion of reformulated fuel use in 1995 actually increases the emission factor, resulting in a 39% reduction relative to 1990. In 2000, the expanded control scenarios increase the emission factor slightly, when compared to the 2000 base control. In 2010, there is similarly little or no change from the 2010 base control for the expanded control scenarios.

### 6.3.3  Nationwide Motor Vehicle Formaldehyde Emissions

The nationwide formaldehyde metric tons are presented in Table 6-4. Total metric tons are determined by multiplying the emission factor (g/mile) by the VMT determined for the particular year. The VMT, in billion miles, was determined to be 1793.07 for 1990, 2029.74 for 1995, 2269.25 for 2000, and 2771.30 for 2010. When comparing the base control scenarios relative to 1990, the metric tons are reduced by 36% in 1995 and by 45% in 2000. Even though the emission factor continues to decrease from 2000 to 2010, this is more than offset by the large increase in VMT. As a result, metric tons in 2010 actually increase relative to 2000.

### 6.3.4 Other Sources of Formaldehyde

The onroad motor vehicle contribution to ambient formaldehyde levels contains both direct (primary) and secondary formaldehyde formed from photooxidation of VOC. It appears that roughly 33% of formaldehyde emissions may be attributable to motor vehicles. Section 6.5.2 contains a complete explanation of how this number is determined.

**Table 6-3. Annual Emission Factor Projections for Formaldehyde.**

| Year-Scenario | Emission Factor g/mile | Percent Reduction from 1990 |
|---|---|---|
| 1990 Base Control | 0.0412 | – |
| 1995 Base Control | 0.0234 | 43 |
| 1995 Expanded Reformulated Fuel Use | 0.0251 | 39 |
| 2000 Base Control | 0.0162 | 61 |
| 2000 Expanded Reformulated Fuel Use | 0.0166 | 60 |
| 2000 Expanded Adoption of California Standards | 0.0168 | 59 |
| 2010 Base Control | 0.0140 | 66 |
| 2010 Expanded Reformulated Fuel Use | 0.0143 | 65 |
| 2010 Expanded Adoption of California Standards | 0.0138 | 67 |

**Table 6-4. Nationwide Metric Tons Projection for Formaldehyde.**

| Year-Scenario | Emission Factor g/mile | Metric Tons |
|---|---|---|
| 1990 Base Control | 0.0412 | 73,874 |
| 1995 Base Control | 0.0234 | 47,496 |
| 1995 Expanded Reformulated Fuel Use | 0.0251 | 50,946 |
| 2000 Base Control | 0.0162 | 36,762 |
| 2000 Expanded Reformulated Fuel Use | 0.0166 | 37,670 |
| 2000 Expanded Adoption of California Standards | 0.0168 | 38,123 |
| 2010 Base Control | 0.0140 | 38,798 |
| 2010 Expanded Reformulated Fuel Use | 0.0143 | 39,630 |
| 2010 Expanded Adoption of California Standards | 0.0138 | 38,244 |

Formaldehyde is produced in the U.S. by 13 chemical companies in 46 locations encompassing 18 states (EPA, 1991a). Formaldehyde is used in the manufacture of four major types of resins: urea-formaldehyde, melamine-formaldehyde, phenol-formaldehyde, and polyacetal resins.  These resins are used in a wide variety of products, such as plywood, particle board, and counter tops.  Formaldehyde is also used as a raw material in several synthetic organic chemical production processes, in the production of solid urea (used as a fertilizer, a protein supplement for animal feed, and in plastics), and in the production of ureaform fertilizers.

In addition, formaldehyde is produced as a by-product in the following types of processes:  combustion (mobile, stationary, and natural sources), petroleum refinery catalytic cracking and coking, phthalic anhydride production, asphaltic concrete production, and atmospheric photooxidation of unburned hydrocarbons.

In an attempt to determine the effects of actual formaldehyde exposure, an analysis was conducted by the EPA Office of Mobile Sources (EPA, 1987a) to determine the cancer risk attributable to indoor and outdoor sources of formaldehyde. The analysis consisted of three parts: (1) estimation of the U.S. population distribution and amount of time spent in each of several environments, (2) estimation of the formaldehyde concentrations in the various environments, and (3) estimation of unit risks.

This analysis determined that the largest single source of risk is the home environment, which accounted for 60 percent of the most likely number of malignant and benign tumors.  The uncertainty in the formaldehyde concentrations experienced in this environment and the entire analysis is high. This is not an unexpected result as the nation, on average, spends nearly two-thirds of its time in non-mobile homes.  The high exposure scenarios (mobile homes, high office exposures, high industrial exposures) which had high concentrations, accounted for just slightly more than ten percent of all tumors due to the small population involved.  Mobile sources were calculated to only account for two to six percent of the total risk.

## 6.4 Atmospheric Reactivity and Residence Times

### 6.4.1 Gas-Phase Chemistry of Formaldehyde

As a result of its structure, formaldehyde has a high degree of chemical reactivity and good thermal stability.  Formaldehyde is thus capable of undergoing a wide variety of chemical reactions.  The major mechanisms of destruction in the atmosphere are reaction with hydroxyl radicals and photolysis.

Formaldehyde is present in emissions but is also formed by the atmospheric oxidation of virtually all reactive organic species.  As a result, it is ubiquitous in the atmosphere.

The processes involved in transformation and residence times were previously discussed in Section 5.4 with the same information concerning benzene.  For a more detailed explanation of the various parameters involved in these processes, please refer to Section 5.4.  The information that follows on transformation and residence times has been mainly excerpted from a report produced by Systems Applications International for the EPA (Ligocki et al., 1991).

Since formaldehyde is formed by the oxidation of methane and biogenic hydrocarbons, it is ubiquitous in the atmosphere.  The chemical system of NO and formaldehyde is the minimum system needed to generate urban-like photochemical ozone in air.  This property has lead to the use of formaldehyde/NO smog chamber experiments for testing the inorganic reactions needed in smog mechanisms.  On a per-carbon basis, formaldehyde has also been identified as the most important smog precursor in urban atmospheres (Smylie et al., 1990).  Furthermore, formaldehyde is perhaps the most common secondary product from the atmospheric oxidation of all organic compounds.

## 6.4.1.1 Formation

Formaldehyde is formed from the atmospheric oxidation of many types of natural and anthropogenic (human produced) organic compounds.  In remote areas, the slow oxidation of methane and the rapid oxidation of biogenic hydrocarbons such as isoprene produces a background concentration of about 0.6 ppb of formaldehyde during daylight hours (NRC, 1981).  In urban areas, the oxidation of olefins such as ethene ($C_2H_4$) and propene ($C_3H_6$), and aromatics, such as toluene and xylene, produce formaldehyde. Dodge (1990) showed that the most important precursors for formaldehyde production are ethene, olefins, and higher aldehydes.  Production of formaldehyde in the reaction of ethene with OH is particularly efficient because each mole of ethene reacts to produce 1.56 moles of formaldehyde.  The atmospheric oxidation of methanol also produces formaldehyde.

## 6.4.1.2 Gas Phase Reactions

The reactions of formaldehyde with the OH radicals are responsible for a part of the destruction of formaldehyde in the atmosphere, while the reactions with $HO_2$, oxygen atoms, $O_3$, and Cl are not important in the ambient atmosphere.

An important destruction and radical production pathway is found in the photolysis of formaldehyde in the atmosphere.  Three factors determine the rate of photolysis of a chemical species in the atmosphere (Jeffries and Sexton, 1987).  The first factor is the amount of sunlight of a particular wavelength passing through the atmosphere at a given time.  The second factor is the ability

of the chemical to absorb radiation.  The third factor is the
tendency of the molecule to form a particular set of products
after it has absorbed a photon.  The product of these three
factors, integrated over the range of wavelengths of light
present in the atmosphere, determines the photolysis rate for a
given reaction.

A key property of formaldehyde photochemistry is its
photolysis to form radical products.  Under many conditions, the
radicals from formaldehyde photolysis are the most important net
source of smog generation.  In addition, these radicals determine
the chemical residence time of other toxic species.  Formaldehyde
absorbs UV radiation from below 290 nm to about 340 nm.  Two
pathways of photolysis are widely recognized:  one pathway
produces two relatively stable products, molecular hydrogen ($H_2$)
and carbon monoxide (CO), whereas the other pathway produces two
radicals, the formyl radical (HCO) and a hydrogen atom (H).  Both
of these radicals react quickly with atmospheric oxygen ($O_2$) to
give hydroperoxyl radicals ($HO_2$) and CO.

## 6.4.1.3 Reaction Products

The oxidation of formaldehyde by OH proceeds primarily by
H-atom abstraction, forming an HCO radical which rapidly reacts
with atmospheric $O_2$ to form CO and $HO_2$ radicals.  Production of
formic acid (HCOOH) in the HCHO + OH reaction has been measured
and found to account for only 2 percent of the product yield
(Yetter et al., 1989).  The HCHO + $HO_2$ reaction does produce
formic acid; however, the rapid back-reaction precludes this from
being a major formaldehyde transformation pathway.  Therefore,
the dominant carbon-containing product from all atmospheric
formaldehyde reactions, including both photolysis pathways, is
carbon monoxide.

## 6.4.2 Aqueous Phase Chemistry of Formaldehyde

In contrast to benzene and 1,3-butadiene, formaldehyde is
quite soluble in water because it rapidly hydrates in solution to
form a glycol ($CH_2(OH)_2$).  Formaldehyde is readily incorporated
into clouds and rain, and is an important species in cloud
chemistry.  The product of the aqueous-phase oxidation of
formaldehyde is formic acid.

Formaldehyde is also interesting because of its
participation in sulfur chemistry within clouds.  Aqueous
formaldehyde reacts with aqueous $SO_2$ (S(IV)) to form the stable
adduct hydroxymethanesulfonate (HMS) (Munger et al., 1984).  This
reaction has been proposed to stabilize aqueous S(IV) against
oxidation to sulfate (McArdle and Hoffmann, 1983).

Formaldehyde is formed in the aqueous phase by the oxidation of methanol (Jacob, 1986), and by the oxidation of HMS (Martin et al., 1989).  However, the rate of in-cloud formation of formaldehyde is negligible relative to the rate of gas-phase formation.

## 6.4.3 Formaldehyde Residence Times

Residence times for formaldehyde were calculated by considering gas-phase chemical reactions with OH, $NO_3$, and $HO_2$, photolysis, in-cloud chemical reaction with OH, and wet and dry deposition.  The reaction of aqueous formaldehyde with aqueous $SO_2$ was not considered.  Although this reaction is fast and may be important to cloud chemistry as a whole, it does not destroy formaldehyde but merely binds it up as an adduct.

The results of the residence time calculation for formaldehyde are presented in Table 6-5.  During the daytime, under clear-sky conditions, the residence time of formaldehyde is determined roughly equally by its photolysis and reaction with OH, leading to calculated residence times on the order of a few hours under summer, daytime, clear-sky conditions.  The summer, daytime residence times for formaldehyde presented in Table 6-5 are comparable to a half-life of 2.6 h (equal to a residence time of 3.8 h) previously estimated for formaldehyde under polluted urban conditions (NRC, 1981).  The residence time of formaldehyde in the atmosphere has also been estimated by EPA to range from 0.1 to 1.2 days (Cupitt, 1980), in good agreement with the values presented in Table 6-5.

In the presence of clouds, approximately 10 to 30 percent of the daytime chemical destruction of formaldehyde and 20 to 90 percent of the nighttime chemical destruction of formaldehyde was estimated to occur in clouds.  The presence of clouds would also be expected to decrease the formation rate of formaldehyde; thus, cloud cover may actually decrease formaldehyde concentrations despite the predicted increase in residence time.

At night, formaldehyde is destroyed slowly because of its relatively slow rate of reaction with $NO_3$.  The reaction of formaldehyde with $HO_2$ may be important at night under low $NO_3$ conditions, because the concentration of $HO_2$ radicals does not decrease at night as rapidly as does OH.  However, since this reaction is reversible, the calculated residence time will be an upper bound.  For the cases in which this reaction might be important, the residence times calculated with and without the $HO_2$ reaction are presented in Table 6-5 as a range of possible residence times.

Dry deposition may also be important as a removal mechanism for formaldehyde.  Residence times due to dry deposition were estimated to range from 90 h under winter, nighttime conditions to

**TABLE 6-5.** Atmospheric residence time calculation for formaldehyde. All times are in hours unless otherwise noted.

| | Los Angeles | | St. Louis | | Atlanta | | New York | |
|---|---|---|---|---|---|---|---|---|
| | July | Jan | July | Jan | July | Jan | July | Jan |
| Clear sky – day | 3 | 10 | 2 | 13 | 2 | 10 | 3 | 17 |
| Clear sky – night | 20-60[*] | 90 | 30-250[*] | 90 | 20-70[*] | 80 | 20-110[*] | 90 |
| Clear sky – avg | 4 | 20 | 3-4[*] | 30 | 4 | 20 | 5 | 40 |
| Cloudy – day | 5 | 20 | 4 | 20 | 3 | 19 | 6 | 30 |
| Cloudy – night | 14-30[*] | 70 | 14-30[*] | 70 | 6-8[*] | 70 | 18-50[*] | 80 |
| Cloudy – avg | 7 | 30 | 6 | 40 | 4 | 30 | 9 | 50 |
| Rainy – day | --[**] | 3 | 3 | 0.8 | 2 | 1.6 | 3 | 0.8 |
| Rainy – night | --[**] | 1.4 | 3 | 0.3 | 3 | 0.7 | 3 | 0.5 |
| Rainy – avg | --[**] | 2 | 3 | 0.4 | 2 | 0.9 | 3 | 0.6 |
| Monthly Climatological Average | 5 | 18 | 4 | 18 | 4 | 14 | 7 | 17 |

[*]Range of values obtained with and without $HCHO + HO_2$ reaction (see text).
[**]Not calculated since July rainfall is zero for Los Angeles (Table 2-1).

800 h for summer, nighttime conditions. For the cases considered here, dry deposition was a minor removal mechanism except under winter, nighttime conditions. However, the deposition rate of formaldehyde to water surfaces is much greater than the deposition rate used in this calculation, and may be important to consider for urban areas located near oceans or major lakes and rivers.

Under wintertime conditions, the photolysis rate is not decreased by as large a factor as the OH radical concentration. Therefore, in the absence of precipitation, photolysis determines the winter, daytime formaldehyde residence time. Wet deposition, particularly under wintertime conditions, is an extremely effective removal mechanism for formaldehyde. Residence times for formaldehyde during winter rainy conditions range from fractions of an hour in colder climates to a few hours in warmer climates. Wet deposition accounts for roughly half of the monthly average removal of formaldehyde during the wintertime. It should be emphasized that this calculation assumes that the partitioning of formaldehyde in rain holds for all forms of precipitation. For colder climates where January precipitation is primarily in the form of snow, this assumption may not be appropriate.

As with benzene and 1,3-butadiene, the differences in formaldehyde residence time between cities within a season were not as large as the difference between seasons. The summer residence times are short in most cases, whereas the winter residence times are greater than one day in most cases. Thus, formaldehyde as well as 1,3-butadiene must be considered to be persistent in wintertime. Unlike the other two species, however, the effect of this longer winter residence time is difficult to assess for formaldehyde because of the importance of secondary formation. Rates of formation of formaldehyde will be roughly an order of magnitude slower in the wintertime. Thus, it is difficult to predict whether ambient concentrations of formaldehyde will increase or decrease in winter.

The major uncertainties in the residence time calculation for formaldehyde include the factor-of-two uncertainty in the OH radical concentration and the uncertainties in the deposition velocity. The uncertainty in the photolysis rate has only a minor effect on the overall uncertainty. The uncertainties associated with the $NO_3$ concentration and the $NO_3$ rate constant are less important for formaldehyde than for 1,3-butadiene because the $NO_3$ reaction with formaldehyde is much slower than the corresponding 1,3-butadiene reaction.

## 6.4.4 Limited Urban Airshed Modeling Results for Formaldehyde

The Urban Airshed Model (UAM) has been previously discussed in Section 5.4. Please refer to this section for details about

the model, its inputs, and modifications.  Much of the
information below has been excerpted from reports conducted for
EPA by Systems Applications International (SAI) (Ligocki et al.,
1991, 1992).

Formaldehyde is an existing UAM species.  The simulations
included three formaldehyde species; one each for mobile and
stationary-source primary formaldehyde and one for secondary
formaldehyde.  Secondary formaldehyde is that produced by
atmospheric reactions.  The full radical and product chemistry of
formaldehyde was retained, with the only change being that all
formaldehyde production was assigned to the secondary species
"FORM".  Since formaldehyde is a product of the photooxidation of
virtually all atmospheric organic compounds, it was not possible
within the scope of this study to track secondary formaldehyde
formed from mobile-source precursors.

St. Louis

A time series plot of formaldehyde concentrations in the St.
Louis urban area is presented in Figure D-2 in Appendix D.
Mobile-source and stationary-source primary formaldehyde species
concentrations remain below 1 ppb throughout the simulation,
whereas secondary formaldehyde increases to more than 5 ppb in
the afternoon.  The UAM simulation showed that formaldehyde
concentrations were about twice as high in the simulation with
chemistry as they were in the inert simulation, indicating that
formaldehyde is formed more rapidly than it is destroyed in urban
areas in the summertime.  The concentration of formaldehyde would
be expected to decrease in the wintertime due to a decrease in
photolysis activity on formaldehyde precursors.

The contribution of mobile-source precursors to the
secondary formaldehyde concentrations can be estimated by
examining the mobile vs. stationary emissions of formaldehyde
precursors.  For formaldehyde, the simulation demonstrated that
the component of the concentration due to primary formaldehyde
emissions is small (20 percent) relative to the component due to
secondary formation in the atmosphere.  The fraction of this
secondary formaldehyde which formed from mobile-source precursors
is not known, but based on emissions of important formaldehyde
precursors, it appears to be 25-50 percent.

The comparison of simulated concentrations with ambient
measured concentrations showed good agreement for formaldehyde.

The formaldehyde photolysis rates used in the UAM for this
study were the higher (and currently accepted) values rather than
those used in the Carbon Bond Mechanism-IV (CBM-IV).  Besides the
effect which changing the photolysis rate would have on
formaldehyde concentrations, there is the potential for secondary
effects on other species concentrations, such as 1,3-butadiene,

because the formaldehyde photolysis is a source of radicals and,
ultimately, ozone.  A sensitivity study was conducted in which
the formaldehyde photolysis rate was increased by an additional
30%. The results from this simulation (with the base-case initial
and boundary concentrations) showed, as expected, the higher
photolysis rate caused a decrease in the predicted formaldehyde
concentrations during the afternoon.  This decrease was roughly
10% of the formaldehyde concentration.  Because the higher
formaldehyde photolysis rate caused increased production of
reactive radicals, the 1,3-butadiene concentration decreased by
about 3% in the mid-afternoon in this simulation as compared to
the base case.

## Houston and Baltimore-Washington Area Simulations

Simulations for the summer Baltimore-Washington area episode
(Ligocki et al., 1992) resulted in both increases and decreases
in ambient formaldehyde with use of federal reformulated
gasoline, with increases due to increased primary formaldehyde in
near-source areas, and decreases due to decreased secondary
formaldehyde in downwind areas.  Overall, the increases and
decreases in simulated ambient formaldehyde concentration
approximately cancel out.  Use of California reformulated
gasoline resulted in a decrease in secondary formaldehyde nearly
three times as large as in federal reformulated gasoline
scenarios, with similar primary formaldehyde increases.  Maximum
daily average formaldehyde concentration for the 1988 base
scenario was 9.3 ppb.  Motor vehicle-related formaldehyde
accounted for about 35% of total formaldehyde emissions.  Motor
vehicle-related formaldehyde also accounted for about 10% of
total simulated ambient formaldehyde on day 2 and 15% on day 3,
based on the 1995 no motor vehicle scenario.  75 to 80 percent of
this formaldehyde was secondary.

Summer Baltimore-Washington area simulations were in fairly
good agreement with UATMP data for formaldehyde in the Baltimore
part of the domain, but UAM-Tox overpredicted formaldehyde in the
Washington part of the domain (although the overprediction was
lower than for UAM).

In the winter 1988 base scenario, the maximum daily average
formaldehyde concentration was 10.2 ppb, slightly higher than in
summer.  However, simulated concentrations throughout most of the
domain were lower.  Simulations for the winter Baltimore-
Washington area episode resulted in slight increases in ambient
levels of formaldehyde with the use of reformulated gasoline, on
the order of 1-2 percent, with a primary formaldehyde increase
and a secondary formaldehyde decrease.  Motor vehicle-related
formaldehyde emissions accounted for about 43% of total
formaldehyde emissions.  Motor vehicle primary formaldehyde
emissions were about 30 percent higher with reformulated gasoline
use.  Motor-vehicle related formaldehyde accounted for about 12%

of the maximum simulated concentration, based on the 1995 no motor vehicle scenario.  Comparison of simulated concentrations with measured concentrations in the Washington part of the modeling domain indicate that the model may underpredict winter formaldehyde concentrations.

For the summer 1987 base scenario in Houston, the maximum daily average formaldehyde concentration was 23.4 ppb.  Motor vehicle-related formaldehyde accounted for about 19% of total formaldehyde emissions in the 1987 base scenario, and 6% of the maximum simulated concentration, based on the 1995 no motor vehicle scenario.  Simulations for the summer Houston episode predicted slight increases in the simulated daily average concentration throughout most of the domain with use of reformulated gasoline.  Comparison of simulated concentrations with measured concentrations suggest the model may overpredict formaldehyde concentrations in Houston.

## 6.5  Exposure Estimation

### 6.5.1  Annual Average Exposure Using HAPEM-MS

The data presented in Table 6-6 represent the results determined by the HAPEM-MS modeling that was described previously in Section 4.1.1.  These numbers have been adjusted to represent the increase in VMT expected in future years.

The HAPEM-MS exposure estimates in Table 6-6 represent the 50th percentiles of the population distributions of exposure, i.e., half the population will be above and half below these values.  High end exposures can also be estimated by using the 95th percentile of the distributions.  According to the HAPEM-MS sample output for benzene, the 95th percentile is 1.8 times higher than the 50th percentile for urban areas, and 1.2 times high for rural areas.  Applying these factors to the exposure estimates in Table 6-6, the 95th percentiles for urban areas range from 1.03 $\mu g/m^3$ for the 2010 expanded California standards scenario to 2.25 $\mu g/m^3$ for the 1990 base control scenario.  The 95th percentiles for rural areas range from 0.37 to 0.82 $\mu g/m^3$, respectively.

### 6.5.2  Comparison of HAPEM-MS Exposures to Ambient Monitoring Data

As stated in section 4.1.2, four national air monitoring programs/databases contain data on formaldehyde.  The Aerometric Information Retrieval System (AIRS), the Toxic Air Monitoring System (TAMS), the Urban Air Toxic Monitoring Program (UATMP), and the National Ambient Volatile Organic Compounds Data Base (NAVOC) all have a significant amount of data for formaldehyde.  The urban exposure data for formaldehyde from all four databases are summarized in Table 6-7.

The AIRS data base contains data on formaldehyde for 1987
and 1988 (AIRS User's Guide Volume I-VII, 1989).  The location
and number of the sites varies between the two years.  Referring
back to the summary table in section 4.1.2, 14 sites monitored

**Table 6-6.    Annual Average HAPEM-MS Exposure Projections for Formaldehyde.**

| Year-Scenario | Urban Exposure µg/m$^3$ | Rural Exposure µg/m$^3$ |
|---|---|---|
| 1990 Base Control | 1.25 | 0.68 |
| 1995 Base Control | 0.78 | 0.42 |
| 1995 Expanded Reformulated Fuel Use | 0.83 | 0.45 |
| 2000 Base Control | 0.58 | 0.31 |
| 2000 Expanded Reformulated Fuel Use | 0.60 | 0.32 |
| 2000 Expanded Adoption of California Standards | 0.60 | 0.33 |
| 2010 Base Control | 0.58 | 0.31 |
| 2010 Expanded Reformulated Fuel Use | 0.59 | 0.32 |
| 2010 Expanded Adoption of California Standards | 0.57 | 0.31 |

**Table 6-7.  Air Monitoring Results for Formaldehyde.**

| Program | Years | Ambient Data[a] $\mu g/m^3$ | Estimated Motor Vehicle Contribution[b] $\mu g/m^3$ |
|---------|-------|-----------------|-----------------------------------|
| AIRS | 1988 | 3.26 | 1.08 |
|  | 1987 | 3.43 | 1.13 |
| UATMP | 1989 | 2.61 | 0.86 |
|  | 1990 | 5.18[c] | 1.71 |
| TAMS | 1987–89 | 2.15 | 0.71 |
| NAVOC | 1987 | 4.00 | 1.32 |

[a]Caution should be taken in comparing these numbers.  The methods of averaging the data are not consistent between air monitoring databases.  The sampling methodology is also inconsistent.

[b]The ambient data are adjusted to represent the motor vehicle contribution to the ambient concentration, which for formaldehyde is estimated to be 33%, based on emissions inventory apportionment and modeling.

[c]The 1990 UATMP is the only program which accounted for ozone interference in the measurement method.

formaldehyde in 1987 and 16 sites monitored it in 1988.  All the
cities where the monitoring sites were located are listed below.

                 Birmingham, AL              Miami, FL
                 Jacksonville, FL            Atlanta, GA
                 Chicago, IL                 St. Louis, MO
                 Louisville, KY              Baton Rouge, LA
                 Dearborn, MI                Detroit, MI
                 Port Huron, MI              Lansing/E. Lansing, MI
                 Cleveland, OH               Dallas, TX
                 Houston, TX                 Burlington, VT

The average level of formaldehyde for 1987 (averaged equally by
the number of sites) was 2.79 ppb.  In 1988, the average was 2.65
ppb.
Because the number of sites differs from year to year and the
number of samples taken at the various sites varies greatly, it
is misleading to make direct comparisons between these two
numbers.  However, these numbers do provide a general idea of the
average amount of formaldehyde being emitted in a year.

     Looking at the AIRS data on a site by site basis for 1987,
Cleveland, Ohio had the highest average level of formaldehyde
among the 14 sites sampled (4.72 ppb) at a site located in a
central, urban, commercial area.  Six samples were taken at this
site.  Miami, Florida had the lowest average level of
formaldehyde in 1987 (1.43 ppb) with six samples taken in an
urban commercial area.  In 1988, Louisville, Kentucky had the
highest average reading of formaldehyde (5.03 ppb) with 20
samples taken at a downtown urban commercial area.  Port Huron,
Michigan had the lowest average reading (1.20 ppb) with 19
samples taken in a suburban residential area.

     Referring to the table in section 4.1.2., ten sites in the
Toxics Air Monitoring System (TAMS) monitored formaldehyde in the
following 4 cities.

                      Boston (3 sites)
                      Houston (3 sites)
                      Chicago (3 sites)
                      Seattle/Tacoma (1 site)


The period of time took place in various time periods between
1987 and 1989.  The overall average for the 10 sites was 1.75
ppb.  Because of the varying time intervals, it may be misleading
to make direct comparisons between the four cities involved, but
the measurements do give a general indication of the amount of
formaldehyde being emitted.

     One of the three TAMS sites in Chicago recorded the highest
amount of formaldehyde (2.27 ppb)  Chicago also had the highest

measurement of formaldehyde averaged from all three of the sites located there (2.13 ppb).  One of the sites in Houston had the lowest level of formaldehyde (1.23 ppb).  Although it only had one site, Seattle/Tacoma had the lowest overall average of formaldehyde (1.54 ppb).  Boston had the next lowest average with three sites (1.56 ppb).

The Urban Air Toxics Monitoring Program (UATMP) monitored the twelve cities listed below.

| | |
|---|---|
| Baton Rouge, LA | Miami, FL |
| Chicago, IL | Pensacola, FL |
| Camden, NJ | St. Louis, MO |
| Dallas, TX | Sauget, IL |
| Ft. Lauderdale, FL | Washington, D.C. |
| Houston, TX | Wichita, KS |

Washington, D.C. and Wichita, Kansas each had two monitoring sites, while the other 10 cities each had one monitoring site. At least 28 samples were collected at each site, except for Pensacola, Florida (7 samples).  The comparatively larger number of samples taken in UATMP makes the data more reliable.  The overall average formaldehyde level for all the samples was 2.13 ppb.

Averaged together, the two sites in Washington, D.C had the highest level of Formaldehyde ((3.77 + 3.09)/2 = 3.43 ppb). Twenty-eight samples were collected at one site and thirty were collected at the other site.  Also averaged together, the two sites in Wichita, Kansas had the lowest level of formaldehyde ((1.46 + 1.40)/2 = 1.43 ppb).

In the 1990 Urban Air Toxics Monitoring Program (UATMP), 354 measurements of formaldehyde were taken at 12 sites.  These sites were in the cities listed below.

| | |
|---|---|
| Baton Rouge, LA | Chicago, IL |
| Camden, NJ | Houston, TX |
| Orlando, FL | Pensacola, FL |
| Port Neches, TX | Sauget, IL |
| Toledo, OH | Washington, D.C. |
| Wichita, KS | |

The highest average was 6.44 $\mu g/m^3$ (7.92 ppb) at an urban commercial site in Washington, D.C..  Thirty samples were collected at this site.  The lowest average was 1.83 $\mu g/m^3$ (1.49 ppb) at a suburban residential site in Houston, Texas. Twenty-six samples were collected at this site.  The overall average of the averages for each site was 5.18 $\mu g/m^3$ (4.21 ppb).  Ozone was removed from the ambient air collected in this program through the use of an ozone denuder.  The use of an ozone denuder in the sampling system resulted in higher, but more accurate, reported

formaldehyde concentrations.  Only the 1990 UATMP data will be used for the comparisons in this study.

The National Ambient Volatile Organic Compound (NAVOC) program only had one monitoring site in Philadelphia, Pennsylvania for formaldehyde.  Thirty-six samples were collected and averaged equally.  This resulted in an average of 3.25 ppb of formaldehyde.

HAPEM-MS assumes that the dispersion and atmospheric chemistry of formaldehyde is similar to CO.  This assumption is not valid for a reactive compound like formaldehyde, which is both destroyed and formed in the atmosphere.  For formaldehyde, HAPEM-MS would overestimate the primary (i.e., directly emitted) concentration in the atmosphere, since formaldehyde is more reactive than CO.  On the other hand, HAPEM-MS would not account for, and thus underestimate, the secondary (i.e., atmospherically formed) formaldehyde, since HAPEM-MS does not account for atmospheric transformation.  Since these two factors offset one another to some extent, it is possible that the HAPEM-MS results could still provide a reasonable estimate of the formaldehyde exposure from motor vehicles.  Also, HAPEM-MS offers the advantage of being able to project future formaldehyde levels, based on emission data.

To test the reasonableness of using the HAPEM-MS modeling results, the HAPEM-MS results for 1990 are compared to ambient monitoring results for recent years.  In order to make this comparison, the motor vehicle contribution to total ambient formaldehyde needs to be estimated.  This requires first estimating the fractions of total ambient formaldehyde due to primary and secondary formaldehyde, and then estimating the motor vehicle contribution to primary and secondary formaldehyde.

The Five-City Study (EPA, 1989) and the UAM-Tox atmospheric modeling studies conducted by SAI (Ligocki et al., 1991, 1992) attempted to apportion the formaldehyde in the atmosphere into primary and secondary contributions.  The Five City Study estimated that primary formaldehyde emissions account for about 40% of the total ambient formaldehyde.  The UAM-Tox modeling studies determined that the concentration due to primary emissions is small, about 20%, relative to secondary formation of formaldehyde.  The mid-point of these studies, 30%, was chosen to represent the contribution of primary formaldehyde emissions. Therefore, 70% was chosen to represent the contribution of secondary formaldehyde.

These studies also attempted to apportion a fraction of secondary formaldehyde formation in the atmosphere to motor vehicles.  The Five City Study determined that motor vehicles are responsible for 35% of total VOC which contributes to secondary formaldehyde production.  The St. Louis modeling study (Ligocki

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et al., 1991) stated that the fraction of secondary formaldehyde formed from motor vehicle precursors is not known, but based on emissions of important formaldehyde precursors, it appears to be 25 to 50%. Based on this information, it was then estimated that motor vehicles account for approximately 35% of the secondary formaldehyde.

The 1987 EPA Air Toxics Report (Carey, 1987) attributed approximately 28% of the primary formaldehyde emissions to motor vehicles. This percentage is based on 1985 emissions data.

By using the numbers described above, the portion of formaldehyde in the ambient air that is attributable to motor vehicles was determined to be 33%. The fractions are: 30% primary formaldehyde in the ambient air of which 28% is from motor vehicles and 70% secondary formaldehyde in the ambient air of which 35% is due to motor vehicles. The calculation is as follows:

.30(.28) + .70(.35) = 33% of total ambient formaldehyde from
(primary) (secondary)    motor vehicles

or:  8.4% + 24.5% = 33%

This estimate is higher than the estimates in the Houston and Baltimore-Washington Area UAM-Tox simulations (Ligocki et al., 1992). In Baltimore-Washington, motor vehicle-related formaldehyde accounted for about 10% of total simulated ambient formaldehyde on day 2 and 15% on day 3, while in Houston, motor vehicle- related formaldehyde accounted for about 19% of total simulated ambient formaldehyde. The estimate of 33% will be used in this study to represent the nationwide average percentage of ambient formaldehyde attributable to motor vehicles, while acknowledging the apparent area-to-area variations and the possibility that this may overestimate the motor vehicle contribution. Using this estimate, two approaches are used to compare the HAPEM-MS and the air monitoring results. The first approach attempted to adjust the HAPEM-MS number upward to account for secondary formaldehyde. If it is assumed that motor vehicles contribute 33% to ambient formaldehyde, 8.4% primary and 24.5% secondary (as determined in the equation above), then the ratio of secondary to primary is 2.92:1. If the primary formaldehyde is 1.25 µg/m$^3$ (from HAPEM-MS) then the secondary is 2.92×1.25 or 3.65 µg/m$^3$. When added to the primary formaldehyde result of 1.25 µg/m$^3$, the total is 4.90 µg/m$^3$ formaldehyde attributable to motor vehicles. This is inconsistent with the ambient monitoring data presented in Table 6-7 and thus was not used.

The second approach was to adjust the ambient air monitoring data to estimate the motor vehicle portion. This method applied the 33% formaldehyde from motor vehicles to each of the air monitoring results. This is presented as part of Table 6-7. Since the only program that accounted for the interference of ozone was the 1990 UATMP, only that ambient data will be used for this comparison. The resulting 1990 UATMP level is 1.71 $\mu g/m^3$. When the adjustment factor of 0.622 for the ambient motor vehicle levels, that was determined in Section 5.5.2 is applied, this exposure level becomes 1.06 $\mu g/m^3$. The HAPEM-MS 1990 base control exposure level of 1.25 $\mu g/m^3$ must be multiplied by a factor of 0.848 to reduce it to 1.06 $\mu g/m^3$ to agree with the ambient data. All analysis based on the HAPEM-MS ambient motor vehicle levels will have this factor applied. Adjusted urban, rural, and nationwide exposures are found in Table 6-8.

Any formaldehyde exposures projected by HAPEM-MS itself should be viewed with caution. The adjusted HAPEM-MS exposure estimates attempt to account for both primary and secondary formaldehyde; however, these estimates are based only on changes in primary emissions of formaldehyde. The reactivity of motor vehicle VOC emissions is likely to change with technology and fuel changes. Changes in the reactivity of these emissions, which would result in changes to secondary formaldehyde levels, cannot be accounted for by HAPEM-MS.

## 6.5.3  Short-Term Microenvironment Exposures

The primary emphasis for formaldehyde exposure will be exposure in microenvironments that are enclosed, increasing the exposure to tailpipe emissions. These microenvironments include in-vehicle and parking garage exposure. The information contained in Table 6-9 is excerpted from two studies that have measured microenvironment exposures to formaldehyde. These two studies are the In-Vehicle Air Toxics Characterization Study in the South Coast Air Basin (Shikiya et al., 1989) and Air Toxics Microenvironment Exposure and Monitoring Study (Wilson et al., 1991). See the information in Section 4.2 for more details about the methodology, and Section 5.5.3 for a description of the studies.

Maximum microenvironment exposure levels of formaldehyde related to motor vehicles were determined in these studies to range from 4.9 $\mu g/m^3$ from exhaust exposure at a service station to 41.8 $\mu g/m^3$ from parking garage exposure. This compares to ambient levels of 2.15 to 4.0 $\mu g/m^3$ determined through air monitoring studies and presented in Table 6-7. Since for the majority of the population these are short-term acute exposures to formaldehyde, the concern would be with non-cancer effects. No RfC has been developed by EPA though formaldehyde is a known irritant for the eyes, nose, and upper respiratory system at levels of 123 $\mu g/m^3$, and become widespread at concentrations near

$3.7 \times 10^3$ µg/m$^3$ in humans. Exposures greater than $3.7 \times 10^3$ µg/m$^3$ are generally intolerable for more than short periods.  Sensitive humans may detect effects at lower concentrations.  Please see Section 6.8 for more information on non-cancer effects.

Due to more stringent fuel and vehicle regulations, short-term exposure to formaldehyde in these microenvironments is expected to decrease in future years.

**Table 6-8.      Adjusted Annual Average HAPEM-MS Exposure Projections for Formaldehyde.**

| Year-Scenario | Exposure ($\mu g/m^3$) | | |
|---|---|---|---|
| | Urban | Rural | Nationwide |
| 1990 Base Control | 1.06 | 0.57 | 0.95 |
| 1995 Base Control | 0.66 | 0.35 | 0.58 |
| 1995 Expanded Reformulated Fuel Use | 0.70 | 0.38 | 0.62 |
| 2000 Base Control | 0.49 | 0.27 | 0.42 |
| 2000 Expanded Reformulated Fuel Use | 0.51 | 0.27 | 0.44 |
| 2000 Expanded Adoption of California Standards | 0.51 | 0.28 | 0.44 |
| 2010 Base Control | 0.49 | 0.27 | 0.42 |
| 2010 Expanded Reformulated Fuel Use | 0.50 | 0.27 | 0.46 |
| 2010 Expanded Adoption of California Standards | 0.49 | 0.26 | 0.42 |

**Table 6-9.  Microenvironment Exposure to Formaldehyde ($\mu g/m^3$).**

| Scenarios | In-Vehicle | | Service Station | | Parking Garage | | Office Building | |
|---|---|---|---|---|---|---|---|---|
| | Mean | Max. | Mean | Max. | Mean | Max. | Mean | Max. |
| SCAQMD Study[a] (Shikiya et al., 1989) | 15.4 | 35.4 | -- | -- | -- | -- | -- | -- |
| SCAQMD Study[b] (Wilson et al., 1991) | -- | -- | -- | 4.9 | -- | 41.8 | -- | 44.2 |

[a]The estimated sampling time period was 1.5 hours/round-trip.
[b]The measurements from this study are five minute levels.


## 6.6  Carcinogenicity of Formaldehyde and Unit Risk Estimates

### 6.6.1  Most Recent EPA Assessment

The information presented in Section 6.6.1 was obtained from EPA's Assessment of Health Risks to Garment Workers (EPA, 1987a), the Integrated Risk Information System (IRIS) (EPA, 1992b), the Motor Vehicle Air Toxics Health Information (Clement, 1991), as well as the primary sources cited in these documents.  The carcinogenicity risk assessment for formaldehyde was last updated on IRIS in January 1992, and contains data published through 1987.  The 1991 version of the formaldehyde risk assessment on IRIS does not contain any information that is not included in the 1987 risk assessment.  The Office of Toxic Substances (OTS) prepared a formaldehyde risk assessment update in September 1990 (EPA 1990a, external review draft).  This document is not yet final, and thus does not yet represent official Agency policy with regard to the risk assessment of formaldehyde.  EPA's Science Advisory Board has reviewed this document, and has requested additional analyses.  Therefore, the results presented in the OTS assessment are likely to change.  Nevertheless, new issues discussed in this 1990 risk assessment update will be summarized in Section 6.6.2.  Section 6.6.3 summarizes recent and ongoing research not included in the 1987 EPA risk assessment for formaldehyde.  Some of this recent and ongoing research is discussed in the 1990 risk assessment, but is not yet part of the official Agency risk assessment for formaldehyde.

6.6.1.1  Description Of Available Carcinogenicity Data

Genotoxicity

    Mutagenic activity of formaldehyde has been demonstrated in
viruses, *Escherichia coli, Pseudomonas fluorescens, Salmonella
typhimurium* (all three are bacteria), and certain strains of
yeast, fungi, *Drosopohila* (fruit fly), grasshopper, and mammalian
cells (Ulsamer et al., 1984).  Formaldehyde has been shown to
cause gene mutations, single strand breaks in DNA, DNA-protein
crosslinks, sister chromatid exchanges, and chromosomal
aberrations.  Formaldehyde produces *in vitro* transformation in
BALB/c 3T3 mouse cells, BHK21 hamster cells and C3H-10TI/2 mouse
cells, enhances the transformation of Syrian hamster embryo cell
by SA7 adenovirus, and inhibits DNA repair (Consensus Workshop on
Formaldehyde, 1984).

Animal Data

    According to EPA (1987b), the principal studies indicating
formaldehyde may cause cancer in animals are Kerns et al. (1983)
(the Chemical Industry Institute of Toxicology [CIIT] study),
Albert et al. (1982) (the NYU study), Sellakumar et al. (1985),
and Tobe et al. (1985).  The carcinoma response in animals was
similar for the four studies but the benign tumor response
differed among the studies.  EPA (1987b) concluded that there was
"sufficient" evidence of carcinogenicity of formaldehyde in
animals by the inhalation route based on increased incidence of a
rare type of malignant cancer (i.e., squamous cell carcinoma) in
rats and mice and in both sexes.

    In the CIIT study, Fischer 344 rats and B6C3F1 mice
(120/sex/group) inhaled 0, 2, 5.6 or 14.3 ppm formaldehyde,
6 hours/day, 5 days/week, for 24 months followed by 6 months of
recovery (Kerns et al., 1983).  Animals were sacrificed at
6 months, 12 months, and 18 months, while at 24 and 27 months,
the number of animals sacrificed was unclear from the report.
The study was terminated at 30 months.  For the rats, mortality
was significantly increased in the 14.3 ppm exposed animals after
12 months and in the 5.6 ppm exposed males after 17 months.  At
the end of the study period, squamous cell carcinomas in nasal
cavities were reported in 51 of 117 male rats and 52 of
115 female rats at the high dose and in 1 of 119 male rats and 1
of 116 female rats at the intermediate dose.  No tumors were
observed at 0 or 2 ppm formaldehyde exposure.  Polypoid adenomas
(benign tumors) of the nasal mucosa were also seen in rats at all
doses in a significant negative dose-related trend, although the
incidence was significant only at 2 ppm formaldehyde.  In the
B6C3F1 mice, squamous cell carcinomas were observed in only two
of the males exposed to 14.3 ppm formaldehyde.  Although this
increase was not significant, the occurrence of this carcinoma

type in mice was considered to be formaldehyde-related because this cancer is rare in mice.

In the Tobe study, male Fischer 344 rats who were exposed to 0 (methanol only), 0.3, 2, 3.3 or 15 ppm formaldehyde in aqueous solution methanol, 6 hours/day, 5 days/week for 28 months (Tobe et al., 1985).  At the end of the 15-month exposure period, mortality in the high dose group was 88% while mortality was 60% in controls.  Mortality was 32% in the low-dose group at 28 months.  Squamous cell carcinomas occurred in 14 of 27 high-dose rats surviving past 12 months.  No polypoid adenomas were observed but benign nasal papillomas were evident in formaldehyde-exposed animals.

Moreover, in the NYU study, after Sprague-Dawley rats inhaled 0 (air) or 14.2 ppm formaldehyde, 6 hours/day, 5 days/week, for a lifetime, there was a statistically significant elevation of the squamous cell carcinoma in 38 of 100 rats (Albert et al., 1982).  Papilloma or polyps were detected in 10 of 100 exposed rats.  The study was limited because only one exposure level was tested.

Sellakumar et al. (1985) exposed male Sprague-Dawley rats, 6 hours/day, 5 days/week for lifetime to 10 ppm HCl and to 14 ppm formaldehyde.  The HCl and formaldehyde were administered simultaneously and separately, with an equal number of rats receiving an air control.  HCl was administered to determine if tumor response was enhanced by an additional irritant effect or by the combining of formaldehyde and HCl to form bis-(chloromethyl)ether (BCME).  Groups receiving formaldehyde alone or with HCl showed an increase in nasal squamous cell carcinomas; those without formaldehyde were free of carcinomas and other tumors, although rhinitis and hyperplasia were of comparable incidence.

Two other chronic inhalation studies examined the carcinogenicity of formaldehyde in upper and lower airways (Dalbey et al., 1982; Horton et al., 1963).  However, nasal tissues were not systematically examined which limited the usefulness of these studies.  Horton et al. (1963) exposed C3H mice to coal tar aerosol and/or formaldehyde at 40, 80, and 160 ppm for 1 hour/day, 3 days/week, for 35 weeks (4 weeks for the 160 ppm group).  The study was limited because of insufficient animals surviving the first year, individual exposures were short, and complete histopathology was not reported.  Dalbey (1982) exposed male Syrian golden hamsters (88-132/group) to 10 ppm formaldehyde, 5 days/week, for a lifetime.  Results showed that there was no evidence of carcinogenic activity following exposure to 10 ppm formaldehyde in animals although survival was reduced relative to controls.  EPA (1987a) found that the pathology evaluation in the study was less rigorous compared to

the Kerns et al. (1983) study and the study was limited because only one dose was tested.


Rusch et al. (1983) carried out a 6-month toxicity study in 6 male cynomolgus monkeys, 40 F344 rats, and 20 Syrian golden hamsters with 22 hours/week exposure to three levels of formaldehyde with corresponding controls.  The highest dose tested was 2.95 ppm.  The short duration of the assay, the small sample sizes, and, possibly, the low concentrations tested, limited the sensitivity of the assay to detect tumors.  In the highest dose group in both rats and monkeys, incidences of squamous metaplasia/hyperplasia of the nasal turbinates were significantly elevated.

Furthermore, several recently published drinking water studies provide additional suggestive evidence that formaldehyde is carcinogenic following oral exposure as well.  The tumor-promoting potential of formaldehyde in mouse skin, rat trachea, and rat stomach has been also recently been demonstrated.  The recent carcinogenicity studies referred to above are summarized in Section 6.6.3.3.

Human Data

EPA reviewed only cohort or case-control studies because these studies yielded the best qualitative information for evaluating causality.  There was a total of 28 studies but many of them had limitations that could potentially influence the conclusions, and therefore will not be addressed in this section. Of these studies, 11 were of chemical or industrial workers and 7 were of medically-related professionals (e.g., morticians, pathologists).  The other 10 were case-control studies examining workers with sinonasal cavity and pharyngeal cancers.  Only six studies had enough data to evaluate exposure-response effects; these are the studies that will be reviewed in this section.  Of these six, two cohort studies (Blair et al., 1986, 1987; Stayner et al., 1988) and one case-control study (Vaughan et al., 1986) were well conducted and specifically designed to detect small to moderate formaldehyde-associated human risks.  These three studies were discussed in the IRIS cover sheet. According to EPA, weaknesses inherent in the human studies in general included: 1) inference of formaldehyde levels from industrial hygiene data, 2) concurrent exposures to other chemicals which prevented determination of specific exposure levels, 3) small sample size for cohorts, 4) small number of site-specific deaths, and  5) insufficient follow-up.

Blair et al. (1986) conducted the largest occupational exposure study that has been published to date (see Section 6.6.3.4 for more details on the followup).  They reported a significant increase in lung and nasopharyngeal cancer in a

cohort study at 10 industrial sites. The authors concluded that there was little evidence showing an association between lung cancer and formaldehyde exposure because the risk did not increase with exposure intensity or cumulative exposure. The observation of nasopharyngeal tumors support similar findings in animals. EPA considered the lung and nasopharyngeal cancer mortality data "meaningful" despite the lack of significant trends. EPA also believed that misclassification of exposure and categorization of deaths into 4 exposure levels (although not specified by EPA 1987a) may account for the lack of a dose-response relationship.

A cohort study by Stayner et al. (1985) found buccal cavity tumors in formaldehyde-exposed garment workers. The SMR was highest in workers with the longest duration of employment (exposure) and follow-up period (latency). There were no other details reported.

A significant association was reported between nasopharyngeal cancer and people living 10 years or more in a "mobile home" built in the 1950's to 1970's (Vaughan et al., 1986). The walls and flooring in mobile homes are generally made out of plywood or some sort of wood composite material that contains urea-formaldehyde resins or adhesives. Exposure to formaldehyde in residents of mobile homes occurs when the formaldehyde in these resins and adhesives offgas as the material ages.

The studies by Olsen et al. (1984), Hayes et al. (1986), and Hardell et al. (1982) reported significant excesses of sinonasal cancer in individuals exposed to both formaldehyde and wood-dust. However, only the first two studies controlled for wood-dust exposure. The detection limits in both studies exceeded corresponding expected excesses in the incidence of sinonasal tumor and, therefore, no significant excesses were likely to have been observed (EPA, 1987a). Acheson et al. (1984) compared excess mortalities due to lung cancer in one of six formaldehyde resin producing plants in England. Only borderline significance was observed. The authors concluded that the increases in mortality from lung cancer were not related to exposure since the elevation was not statistically significant when compared with local lung cancer rates. However, EPA (1987b) believed that the risk was sufficiently increased to enable this study to be used for corroboration. Other studies, Pattanen et al. (1985), Bertazzni et al. (1986), and Blair et al. (1986, 1987) also indicated that lung cancer also may be associated with occupational exposure to formaldehyde. The risk associated with sinonasal cancer appeared to be specific for the histologic type, squamous cell carcinoma. The relative risks observed for upper respiratory tract cancers in all the reviewed studies ranged from just above 1.0 (a risk of 1.0 implies no association between exposure and disease) to 3.0, depending on the site.

There were 19 studies that indicated the possibility that observed leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure; however, the biological support for these findings has not yet been demonstrated.

## 6.6.1.2 Weight-of-Evidence Judgment of Data and EPA Classification

EPA has classified formaldehyde as a Group B1, probable human carcinogen under its Guidelines for Carcinogen Risk Assessment. This is based on limited epidemiological evidence and sufficient evidence of carcinogenicity in animal studies. In addition, this evidence is supported by mutagenic activity in various *in vitro* test systems.

The CIIT inhalation study (Kerns et al., 1983) in rats is considered the primary study for estimating unit risk. The study was well designed, well conducted, multiple doses (4 exposure levels) were included, and sufficient animals were tested. The malignant tumor data (i.e., squamous cell carcinoma in nasal cavity) in the Kerns et al. (1983) study were used for estimating risk since the response in treated rats was definite and unequivocal in both males and females and there was an increasing dose-related trend. Furthermore, similar malignant tumor types were evident in all rat and mouse inhalation studies with formaldehyde exposure. EPA also believes that the appearance of benign tumors in the Kerns et al. (1983) study contributes to the qualitative weight-of-evidence that formaldehyde may pose a carcinogenic hazard.

The other animal inhalation studies had limitations that prevented their use for quantitative risk assessment. Data from Sellakumar et al. (1985), the NYU (Albert et al. 1982) and Tobe et al. (1985) studies were also considered by EPA for unit risk estimates. The Tobe et al. (1985) study gave supportive evidence in the same strain of rats but was not used for primary risk estimation because a tumor response was observed only at the high dose. The Albert et al. (1982) study was considered less appropriate because it contained only one nonzero exposure concentration. The Kerns et al. (1983) study also suggests carcinogenicity at the high dose but the response was limited or not significant.

A degree of uncertainty was due to the different responses of animals to formaldehyde exposure. Only the rats showed statistically significant numbers of neoplasms. The mice only had two carcinomas (Tobe et al., 1985), but the response was complicated by the fact that mice were able to reduce their breathing rate to a greater extent than rats. According to EPA, the mice with tumors received 14.3 ppm formaldehyde, a dose that approximates that which rats received at 5.6 ppm. Thus, on a "dose" received basis, the rats and mice may be equally sensitive to formaldehyde.

The epidemiological data had limited exposure information, insufficient sample size, and concurrent exposures for risk estimate determination.

6.6.1.3  Data Sets Used For Unit Risk Estimates

The consequences of inhalation exposure to formaldehyde has been studied in rats, mice, hamsters, and monkeys.  The principle evidence comes from positive studies in both sexes of two strains of rats (Kerns et al., 1983; Albert et al., 1982; Tobe et al., 1985) and males of one strain of mice (Kerns et al., 1983), all showing squamous cell carcinomas.  The primary data set is the squamous cell carcinomas of the nasal turbinates in Fischer 344 rats from the CIIT study (Kerns et al., 1983).  This data set used to calculate the cancer risk estimate for formaldehyde is summarized in Table 6-10.

Three epidemiological studies are also used as supporting evidence.  Two cohort studies (Blair et al., 1986, 1987; Stayner et al., 1988) and one case-control study (Vaughan et al., 1986a,b) were well-conducted and specifically designed to detect small to moderate increases in formaldehyde-associated human risks.  These were discussed previously in Section 6.6.1.1b. Primates and rats have been shown to respond similarly to formaldehyde exposure with
respect to the development of nasal tumors.  In any case, ppm is considered equivalent across species, so a species scaling factor was needed.

6.6.1.4  Dose-Response Model Used

Since low level exposure can not be measured in animal or human studies, several models are possible for low-dose extrapolation.  Data were inconsistent regarding a linear or nonlinear relationship between formaldehyde exposure and carcinogenicity.  Because of the absence of biological evidence on the mechanism of action for formaldehyde, the linearized multistage procedure was chosen as the default model as specified by EPA guidelines (see Appendix F for a complete explanation), although various other models were presented for comparative purposes.  They found that only the one-hit model produced higher risk estimates (about 10-fold higher).

6.6.1.5  Unit Risk Estimates

The inhalation unit cancer risk is $1.3 \times 10^{-5}$ $(\mu g/m^3)^{-1}$ or $1.6 \times 10^{-2}$ $(ppm)^{-1}$ based on squamous cell carcinoma in F344 rats. The unit risk should not be used if the air concentration exceeds 800 $\mu g/m^3$.  The major contributor to the uncertainty in the risk estimate using the multistage model is due to the steep dose response observed in the CIIT study.  There was a 50-fold increase in the number of tumors compared to a 2.5-fold increase

in the dose level; 0 tumors at 2 ppm, 2 at 5.6 ppm, and 103 at 14.5 ppm.  Other uncertainties are the marked nonlinearity of the response and the different responses observed in the tested animals.

**Table 6-10. Summary of Data Set Used to Calculate Unit Risk Estimate for Formaldehyde.**

| Source | Test Animal | Tumor Type | Administered Dose (ppm) | Human Equivalent Dose (mg/kg/day) | Tumor Incidence |
|---|---|---|---|---|---|
| Kerns et al. (1983)[a] | F344 rats, male and female, combined | Squamous cell carcinoma | 0 | 0 | 0/156 |
| | | | 2 | 2 | 0/159 |
| | | | 5.6 | 5.6 | 2/153 |
| | | | 14.3 | 14.3 | 94/140 |
| Kerns et al. (1983)[b] | F344 rats, male and female, combined | Squamous cell carcinoma | 0 | 0[c] | 0/156 |
| | | | 2 | 15.3 | 0/159 |
| | | | 5.6 | 70.8 | 2/153 |
| | | | 14.3 | 318 | 94/140 |

[a]Data set used in EPA 1987b cancer risk assessment
[b]Data set used in EPA 1990 cancer risk assessment
[c]Delivered dose expressed as pmol/mg/DNA/day calculated using rat DPX data and   adjusted for average daily dose

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There is a wide range between MLE and upper bound estimates of risk (ranging from 1-5 orders of magnitude) at different exposure levels showing the statistical uncertainty of the estimates that were generated from highly non-linear data. For example, using the 1987 unit risk, at an exposure level of 3 ppm (3,685 $\mu g/m^3$) for 36 hours/week for 40 years (typical occupational exposure conditions), the upper bound estimate of lifetime cancer risk is $6 \times 10^{-3}$ and the maximum likelihood estimate of risk is $6 \times 10^{-4}$, whereas a 10-year exposure to 0.07 ppm (86 $\mu g/m^3$) formaldehyde (believed to be the home/environment background upper limit in conventional homes), the upperbound estimate of risk is $1.0 \times 10^{-4}$ and the maximum likelihood estimate of risk is $6.0 \times 10^{-11}$. However, the predictive power of the model is not significantly disturbed by slight perturbations of the data.

## 6.6.2  Other Views and Unit Risk Estimates

This section presents alternate views and/or risk assessments for formaldehyde. These are summarized in Table 6-11.

Office of Toxic Substances 1991 Formaldehyde Draft Report

The OTS (EPA, 1991b) risk assessment for formaldehyde concluded that recent animal studies confirm the previous findings of an increased incidence of squamous cell carcinomas of the nasal cavity in rats exposed by inhalation and a steep dose-response curve. In addition, the distribution of nasal tumors in rats has been better defined; the findings suggest that not only regional exposure but also local tissue susceptibility may be important for the distribution of formaldehyde-induced neoplasms. Many of the recent studies used in EPA (1991b) are discussed in Section 6.6.3.

In the OTS risk assessment update concerning the epidemiological data, it was concluded that when the risk assessment is examined in context of the previously reviewed studies, the human studies released since 1987 support the conclusions drawn by EPA in its 1987 document and do not alter the evaluation that 'limited' evidence exists for an association between formaldehyde and human cancer. Collectively, however, the data do not conclusively demonstrate a causal relationship.

The 1991 update goes on to describe that recent epidemiological studies provide additional evidence that "modest" increases in nasopharyngeal and nasal cavity and sinus cancer risks, and possibly in lung cancer risks, have been observed among various occupational subgroups. However, the evidence for an association between lung cancer and occupational formaldehyde is tenuous. The recent epidemiological studies referred to above are summarized in Section 6.6.3.4.

The OTS update also concurred with the weight-of-evidence evaluation presented in the 1987 risk assessment.  Based on

**Table 6-11.    Comparison of Formaldehyde Inhalation Unit Risk Estimates.**

| Source | Classification | Cancer Unit Risk Estimate $\mu g/m^3)^{-1}$ Upper Bound[a] |
|---|---|:---:|
| EPA (1987) | Group B1[b] | $1.3 \times 10^{-5}$ |
| EPA (1991b) | Group B1 | $6 \times 10^{-7}$ [c] |
| | | $8 \times 10^{-6}$ [d] |
| IARC (1987) | Group 2A[e] | $-$[f] |
| CARB (1992b) | Probable Human Carcinogen | $6.0 \times 10^{-6}$ |
| OSHA (1987) | Potential Occupational Carcinogen | $2.64 \times 10^{-2}$ [g] |

[a]MLEs have not been presented because EPA does not generally compare MLEs based on animal data because of the high variability associated with these numbers.  Therefore, they are of little value.
[b]Group B1 = Probable Human Carcinogen
[c]Calculated using monkey DPX data
[d]Calculated using rat DPX data
[e]Group 2A = Probable Human Carcinogen
[f]IARC did not conduct a quantitative risk assessment
[g]Upper bound estimates calculated for risk to 100,000 workers exposed to 1 ppm for 45 years.  It should be noted that OSHA used the maximum likelihood estimate, and not the upper bound, for regulatory purposes.

sufficient animal evidence (mainly nasal cancers in rats and mice), limited human evidence associating nasal and nasopharyngeal cancer with formaldehyde exposure, and other key evidence including structure-activity considerations, the known genotoxic activity of formaldehyde, and the ability of formaldehyde to injure cells and affect cell division, OTS concurred that formaldehyde should be classified as a probable human carcinogen (Group B1).

The OTS updated risk assessment calculated new cancer unit risks for formaldehyde. However, the data set used as the basis for the unit risks is the same as that used by EPA in 1987; squamous cell carcinomas of the nasal turbinates in Fischer 344 rats from the CIIT study (Kerns et al., 1983). The data set used to calculate the cancer risk estimate for formaldehyde is summarized in Table 6-9.

In the OTS update, EPA chose to continue with the linearized multistage model to calculate the new unit risk estimates because there is insufficient evidence, especially with respect to mechanism, to warrant a departure from this model.

These unit risk estimates have been modified in the 1991 OTS update to reflect new information regarding dose-rate effects and the use of DNA binding data as an intracellular dosimeter for formaldehyde.

Since the 1987 risk assessment, data have become available regarding nasal DNA binding of formaldehyde in the form of DNA-protein cross-links (DPX), and the quantitation of these DPX levels (see Section 6.6.3.2 for a discussion of DPX). OTS concluded that these new data support the use of DPX as an internal measure of formaldehyde dose, and has used the data of Casanova et al. (1989) in F344 rats and Heck et al. (1989) in Rhesus monkeys to calculate internal formaldehyde doses to be used in the revised risk assessment. Specifically, the rat DPX data were input into the linearized multistage model, and the risk to humans was then calculated by applying monkey DPX data to the resulting equation because it was believed that the actual risk to humans lies somewhere between the risk estimates derived using only the rat or the monkey DPX data. The modified unit risk estimates also used a different method to adjust the calculated delivered doses to average daily doses to be input into the linearized multistage model. Generally, experimental exposure rates are multiplied by a factor of 5/7 and 6/24 (to reflect the fact that exposure only occurred for 6 hours/day, 5/days/week) to convert to continuous lifetime daily average exposure. In the case of formaldehyde, OTS considered this to be inappropriate. There is evidence to support the hypothesis that dose rate (or the concentration of formaldehyde reaching the target tissue) is more critical in determining the severity of the toxic effects, such as cell proliferation and histological

changes, than average exposure concentration. Therefore, OTS adjusted the DPX-derived dose levels by a factor of only 5/7 because this approach acknowledges the importance of a possible dose-rate effect by not averaging the exposure and expected DPX over the course of 24 hours. Tumor incidences were not induced by a continuous exposure regiment, and these tumor incidences should be linked as nearly as possible with the exposure levels which caused them.

Based on the results of many pharmacokinetics studies, EPA has concluded that most of the objections expressed in the expert panel's report have been adequately addressed and that the use of DPX as the surrogate dose for risk estimates appears appropriate with the following reservations. The DPX data were obtained following a single exposure to formaldehyde (acute), whereas the carcinogenic bioassay was a chronic (2-year) study. The different exposure conditions may have little effect on DPX yields at low concentrations, where the normal morphology of the nose is unaltered by exposure, but it may have a major effect at high concentrations. This is due to the proliferation of the squamous cells which may have very different metabolic abilities, formaldehyde uptake, and detoxifying mechanisms than the epithelial cell examined in the DPX experiments. Indeed, recent studies at CIIT on the formation of DPX in rats exposed subchronically to 15 ppm of formaldehyde indicate that such effects can occur (Casanova and Heck, 1991).

Another reservation regarding the use of DPX is that the role of DPX, if any, in the induction of nasal cancer is not completely understood. This problem is relatively insignificant if DPX are used only as a dosimeter, and the linearized multistage model is used to estimate risk. However, it could become more important if the DPX were given a specific mechanistic role in a biologically-based model.

A final reservation is that the current DPX data should not be used to make assumptions about species differences in sensitivity (response) since the necessary mechanistic information is lacking.

The resulting modified unit risk factors (UCL) calculated by OTS are $6 \times 10^{-7}$ $(\mu g/m^3)^{-1}$ ($7 \times 10^{-4}$ [ppm]$^{-1}$) using the monkey-based DPX data and $8 \times 10^{-6}$ $(\mu g/m^3)^{-1}$ ($1 \times 10^{-2}$ [ppm]$^{-1}$) using the rat-based DPX data. The MLE's are $8.1 \times 10^{-8}$ $(\mu g/m^3)^{-1}$ ($1 \times 10^{-4}$ [ppm]$^{-1}$) and $8.1 \times 10^{-6}$ $(\mu g/m^3)^{-1}$ ($1 \times 10^{-2}$ [ppm]$^{-1}$), respectively. The unit risk estimate calculated using the rat DPX data is lower than that calculated in EPA (1987a) presented above by an approximately 25-fold difference, 4-fold of which is due to the difference in continuous exposure correction used and 6-fold of which is due to the use of the rat

DPX data.  The risk estimate calculated using the monkey DPX data is approximately 9 times lower than the 1987 risk estimate.[1]

## International Agency for Research on Cancer (IARC)

IARC has classified formaldehyde as a Group 2A carcinogen. A Group 2A carcinogen is defined as an agent that is *probably* carcinogenic to humans.  This classification is based on limited evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in animals (IARC 1982, 1987).

IARC reviewed the available human data and concluded that these studies do provide some evidence that occupational exposure to formaldehyde is associated with an excess of various forms of cancer.  Cancers that occurred in excess in more than one study are:  Hodgkin's disease, leukemia, and cancer of the buccal cavity and pharynx (particularly nasopharynx), lung, nose, prostate, bladder, brain, colon, skin, and kidney (IARC 1982b, 1987c).  However, in many of these studies, actual exposure to formaldehyde is unknown.

IARC concluded that the available animal data provide sufficient evidence of the carcinogenicity of formaldehyde. These data consist of inhalation studies in one strain of mice and two strains of rats.  No unit risk estimate was determined by IARC.

## Motor Vehicle Manufacturer's Association (MVMA)

MVMA contracted with Environ Corporation to 1) describe the means for conducting an assessment that incorporates all scientific information pertinent to the question of risk for formaldehyde (Environ, 1986); and 2) to evaluate the risk assessment issues in EPA's technical report "Air Toxics Emissions from Motor Vehicles" (Environ, 1987).  It is important to note that neither document is actually a risk assessment of formaldehyde, i.e., no alternative unit risk estimates were developed; rather, they are critiques of existing risk assessments (the 1986 document critiques OSHA's 1985 risk assessment of formaldehyde [50 FR 50412-40499], and the 1987 document critiques EPA's risk assessment of motor vehicle air toxics (Carey, 1987) and descriptions of elements that should be considered in a comprehensive risk assessment of formaldehyde.

Environ (1986) points out that any risk assessment of formaldehyde must take into consideration the following issues:

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[1]The MLEs calculated in the 1991 updated risk assessment have been presented here, but it is explicitly stated in this document that EPA does not generally compare MLEs based on animal data because of the high variability associated with these numbers.  Therefore, they are of little value.

(a) the mechanism of action of formaldehyde
(b) the relationship between the magnitude and duration of exposure to formaldehyde and the 'target-site dose' of the proximate carcinogen
(c) the relative importance of the genotoxic activity of formaldehyde compared to its other biological effects in determining risk
(d) the shape of the dose-response curve at dose levels below the experimental range
(e) the relationship between risk in rodents and risk in humans.

With regard to mechanism of action and its role in risk assessment, Environ (1986, 1987) describes several mechanisms that have been proposed to account for the carcinogenic effects of formaldehyde.  These include:

(1) Chemistry and metabolism.  This takes into account the nonlinear relationship between the concentration of formaldehyde in the air and the level of DNA adducts to establish a relationship between dose and response.

(2)  Physiological effects.  Animals exposed to high levels of formaldehyde reduce their rate and depth of breathing, thus resulting in a reduction of inhaled dose.  In addition, formaldehyde reduces the protective flow of mucus over the surface of the nasal passages (nasal epithelium), thus resulting in the slower removal of dissolved proportions of inhaled formaldehyde.  This information should be used to adjust the dose used in modeling the dose-response relationship to more accurately reflect the target-site dose.[2]
(3)  Effect on proliferation of respiratory epithelium.  High concentrations of formaldehyde have been shown to cause cellular degeneration and abnormal stimulation of cell replication that attempts to replace the dead cells (regenerative hyperplasia) of the nasal epithelium.  This effect may contribute to the carcinogenic action of formaldehyde.  This proliferation does not occur at exposure levels below 6 ppm, therefore, this mechanism would not likely contribute to carcinogenesis at low levels.

Environ agrees with EPA and OSHA that the data set that provides the best estimate of the relationship between dose and response for formaldehyde is the CIIT rat study (Kerns et al.,

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[2]OTS, in their updated risk assessment for formaldehyde (EPA 1990), acknowledges that these two mechanisms (reduced respiration rate and mucociliary clearance), may alter the dose of formaldehyde that reaches the target tissue. However, they concluded that not enough is known to quantitate the amount that these two mechanisms may alter the actual delivered dose of formaldehyde.

1983).  However, Environ (1986) cautions that all data sets
should be used to provide a range of risk estimates to provide a
better indication of the uncertainty of the estimates.

Environ (1986, 1987) contends that EPA's and OSHA's use of
the linearized multistage model for low dose extrapolation
overestimates the carcinogenic risk of formaldehyde.  They
suggest that there is some evidence to indicate that formaldehyde
may be a threshold carcinogen.  This, together with the fact that
the dose-response data for formaldehyde are not linear, led
Environ to conclude that linear extrapolation of responses that
occur following exposure to high doses to predict responses at
low doses may not be entirely valid.  They suggest that if a
model that better fits the data is used, for example, a non-
linearized multistage model (i.e., a five-stage or six-stage
model) or a Weibull model, then the predicted risks at low dose
levels are orders-of-magnitude lower than those predicted using
the linearized multistage model.

California Air Resources Board (CARB)

CARB (1992b), like EPA and IARC, has concluded that
formaldehyde is a probable human carcinogen.  CARB (1992b) has
performed an assessment of the carcinogenic risk of formaldehyde
using the CIIT rat data (Kerns et al., 1983) in the linearized
multistage model.  However, their assessment differs from EPA
(1987a) in the following two ways:

(1)    The present approach uses the rate of binding of
       formaldehyde to DNA in the nasal lining of the rat, in
       order to characterize the dose rate.  The EPA in its
       1987 risk assessment decided to use administered dose
       (inhalation exposure) rather than estimated tissue dose
       for risk estimation purposes because their reviewers
       did not consider the tissue data then available for
       their assessment to be adequate.

(2)   The present approach uses three different scaling
      factors to extrapolate the equivalent dose rate from
      rats to humans.  EPA (1987a) did not specifically
      discuss the issue of scaling to extrapolate from
      rodents to humans for formaldehyde.

The UCL for unit risk for lifetime exposure calculated by
CARB (1992b) using the methods and assumptions described above is
$7.0 \times 10^{-3}$ ppm$^{-1}$ ($6.0 \times 10^{-6}$ [$\mu g/m^3$]$^{-1}$).  The two differences in
methodology (i.e., target-site dose and scaling factor) result in
a doubling of the upper confidence limit (UCL) on the unit risk
calculated by EPA.  CARB (1992b) did not calculate MLEs for
formaldehyde.  CARB also calculated a range of UCL for unit risks
based on the three scaling factors and two measures of exposure

to formaldehyde by inhalation. This range is $0.3\times10^{-3}$ ppm$^{-1}$ to $40\times10^{-3}$ ppm$^{-1}$ ($0.25\times10^{-6}$ to $33\times10^{-6}$ [µg/m$^3$]$^{-1}$).

Occupational Safety and Health Administration (OSHA)

OSHA published a final rule for occupational exposure to formaldehyde in 1987, in which they concluded that formaldehyde should be regarded as a "potential occupational carcinogen" (OSHA, 1987). The 1987 final rule differs only slightly from the 1985 proposed rule mentioned above. With regard to the adequacy of the available human data, in the 1985 proposed rule, OSHA has not relied on the epidemiologic results to assess risk of lifetime exposure of workers to formaldehyde. However, in 1987, OSHA stated that the evidence regarding human risk of exposure to formaldehyde has become substantial.

OSHA has also selected the CIIT rat study (Kerns et al., 1983) as the basis for its risk assessment for formaldehyde. OSHA, like EPA and CARB, selected the linearized multistage model to calculate lifetime risk of exposure to formaldehyde. Unlike CARB, OSHA chose not to use a scaling factor and also chose not to use the pharmacokinetic model relating DNA-formaldehyde adducts to external exposure dose to estimate target-site dose. OSHA (1987) concluded that the pharmacokinetic model, as it presently exists, is greatly limited by the scarcity of data identifying DNA protein- formaldehyde cross-links, and it cannot be presumed to predict overall human cancer risk resulting from long-term repeated exposures to formaldehyde.

As a result of the data set and low-dose extrapolation model chosen, and the assumptions made with regard to scaling and correct estimation of dose, OSHA (1987) calculated the following lifetime risk of cancer per 100,000 workers:

| Exposure level (ppm) | Maximum Likelihood Estimate (MLE) | Upper Confidence Limit (UCL) |
|---|---|---|
| 3 | 71 | 834 |
| 2 | 11.4 | 534 |
| 1 | 0.6 | 264 |
| 0.5 | 0.03 | 132 |
| 0.1 | 0.001 | 26 |

Universities Associated for Research and Education in Pathology (UAREP)

This panel reviewed the same body of literature (UAREP, 1988) as IARC (1987c) and EPA (1987) using a metanalysis approach. The UAREP panel commented only on the determination of causality. Unlike the IARC and EPA, the UAREP panel did not attempt to

categorize the epidemiological evidence other than whether causality could be established.  The panel concluded that a causal relationship has not been established for cancer at any site.  In addition, the panel noted that if such a causal relationship exists, the excess risk must be small.  The panel noted elevated risks in nasopharyngeal cancer with formaldehyde exposure in several studies, and concluded that the evidence for causality was weak.  With respect to observed excesses in nasal cavity and sinus cancers and any formaldehyde exposures, several studies suggest an approximate doubling of the risk, while other studies could not exclude an elevation of the size.  Overall, the panel concluded that the presence or absence of an association could not be firmly established.  With respect to lung cancer, the panel thought the evidence was not consistent and did not indicate a causal association with formaldehyde exposure.

For sites which are not directly in contact with formaldehyde, the panel stated that the rapid metabolism of formaldehyde makes it unlikely that formaldehyde is the agent responsible for increased brain tumors observed in the group that used formalin.  For the excesses in leukemia observed in several studies of anatomists, embalmers, and pathologists, the panel concluded that socioeconomic factors influencing diagnosis may explain the elevations observed in these groups.

"Epidemiological Evidence on the Relationship Between Formaldehyde Exposure and Cancer" (Blair et al. 1990b)

Blair et al. (1990b) performed a metanalysis on essentially the same body of literature as reviewed by IARC (1987c), UAREP (1988), and EPA (1987) with the addition of more recent findings, either published or in press.  From this analysis, the authors found excesses in deaths due to cancers of the nasal cavities, nasopharynx, lung, and brain, and due to leukemia.  The investigators believed that a causal role for formaldehyde was most probable for cancers of the nasopharynx and, to a lesser extent, the nasal cavities.  Blair et al. (1990b) derived their support for the conclusion from statistically significant increases in nasal cavity cancer risk, from the apparent specificity of the association with squamous cell carcinoma, and from histological changes in the nasal mucosa seen in industrial studies which correspond to those observed in the rat.

The investigators further concluded that the excesses in lung cancer were difficult to interpret due to inconsistencies among studies and lack of trends with either level or duration of exposure.  In addition, the excesses of leukemia, brain, and colon cancer observed among professionals were most likely not related to formaldehyde since similar excesses were not observed among the industrial workers.

<u>"Quantitative Cancer Risk Estimation for Formaldehyde"</u> (Starr, <u>1990)</u>

Starr (1990) calculated cancer risks based on the DPX (DNA protein cross-link) experiments of Casanova et al. (1989) in rats, and of Heck et al. (1989) in monkeys.  Using the linear multistage model, Starr fit a "three-stage" model using rat DPX levels interpolated from the DPX experiment to correspond to the bioassay exposures of Kerns et al. (1983).  Predicted risks corresponding to 0.1, 0.5, and 1.0 ppm formaldehyde in air, based on the DNA-binding data for both rats and monkeys are reproduced in the table above.  Starr also did not address the non-nasal DPX observed in monkeys in making his calculations.  Starr concluded that point estimates of human risk (also called maximum likelihood estimates, or MLEs) based on DPX in monkeys were lower than those based on airborne concentrations to rats (the basis of EPA's 1987 unit risk), by as much as 1,500,000-fold.

**Comparison of Risk Estimates form Starr (1990), Upper Bounds and Point (Maximum Likelihood) Estimates[a]**

| Air Conc. (ppm) | Upper Bound and (MLE) Estimates of Risk From Several Formaldehyde Exposure Measures | | |
|---|---|---|---|
| | Rat/1983[b] | Rat/1989[c] | Monkey/1989[d] |
| 0.1 | 2 E-4[e] (3 E-7) | 7 E-5 (2 E-9) | 8 E-6 (2 E-12) |
| 0.5 | 8 E-4 (3 E-5) | 4 E-4 (3 E-7) | 4 E-5 (3 E-10) |
| 1.0 | 2 E-3 (3 E-4) | 1 E-3 (6 E-6) | 1 E-4 (1 E-8) |

[a]  Continuous lifetime average exposure adjustment not used.
[b]  Kern et al. (1983) exposure concentrations (ppm).
[c]  DNA-protein cross links (pmol/mg DNA) from Casanova et al. (1989).
[d]  Using the 1989 rat DNA=binding data for the dose-response relationship, and the Heck et al (1989) DNA-protein cross-links for delivered dose at 0.1, 0.5, and 1.0 ppm.
[e]  $2\ E\text{-}4 = 2 \times 10^{-4}$

Starr calculated a MLE risk of $3 \times 10^{-7}$ based on the air concentration of 0.1 ppm administered to rats, while the corresponding MLE human risk based on monkey DPX was $2 \times 10^{-12}$. The differences between upper bounds on risk were less dramatic, the largest difference being 25-fold between an upper bound rat dosimetry-based risk of $2 \times 10^{-4}$ and upper bound monkey dosimetry-based risk of $8 \times 10^{-6}$ at an air concentration of 0.1 ppm.

### 6.6.3  Recent and Ongoing Research

#### 6.6.3.1  Genotoxicity

   Recent studies on the genotoxicity of formaldehyde have
demonstrated the covalent binding and induction of DNA strand
breaks, induction of chromosomal aberrations *in vitro*, co-
mutagenesis of formaldehyde and x-rays in *Drosophila*,
cytotoxicity and mutagenicity in human lymphocytes and *Salmonella*
and sister chromatid exchange in anatomy students exposed to
embalming solution (Bogdanffy et al., 1987; Casanova and Heck,
1987; Casanova et al., 1989; Craft et al., 1987;  Crosby, 1988;
Dresp and Bauchinger, 1988; Dowd et al., 1986; Ecken and Sobels,
1986; Liber et al., 1989; Heck and Casanova, 1987; Heck et al.,
1989; Schmid et al., 1986; Snyder and Van Houten, 1986; Yager et
al., 1986).  These studies have been reviewed by EPA (1990a) and
it was concluded that they added nothing new or substantially
different to what was written in EPA (1987a) regarding the
genotoxic effects of formaldehyde.

#### 6.6.3.2  Pharmacokinetics

   Recent work on the pharmacokinetics of formaldehyde has
focused on the validation of measurement of DNA-protein adducts
(DPX) as internal dosimeters of formaldehyde exposure.  In other
words, the binding of DNA to protein to which formaldehyde is
bound to form a separate entity that can be quantified may serve
as a means to measure the amount of formaldehyde that is present
inside a tissue.  An internal dosimeter for formaldehyde exposure
is desirable because the inhaled concentration of formaldehyde
may not reflect actual tissue exposure levels.  The difference in
inhaled concentration and actual tissue exposure level is due to
the action of multiple defense mechanisms (such as the protection
of underlying cells by the mucociliary apparatus) that act to
limit the amount of formaldehyde that reaches cellular DNA.  At
issue is the rebuttal by EPA and the Science Advisory Review
Board (summarized in EPA 1987a) of the assertion that DPX
measurements could be used in quantitative cancer risk
assessments as an indication of intracellular dose (Starr and
Buck, 1984).  The rebuttal was based on EPA and the Science
Advisory Review Board's belief that inadequate evidence was
presented demonstrating that the method used to measure DPX was
valid, the measurement of DPX as an intracellular dosimetric
marker was adequate, and the results obtained in acute studies
that measured DPX could be extrapolated to the chronic exposure
situation.

#### 6.6.3.3  Carcinogenicity - Animal Studies

   Recent studies examining the carcinogenicity of formaldehyde
in animals have further studied the characteristics of nasal

tumor induction as a result of inhalation of formaldehyde.
Morgan et al. (1986) mapped the specific location of the nasal
squamous cell carcinomas that were observed in rats in the study
by Kerns et al. (1983). The authors proposed that in addition to
regional exposure, local tissue susceptibility may be an
important determinant for distribution of formaldehyde-induced
neoplasms.

In the CIIT study (Kerns et al., 1983), nasal tumors were
induced by formaldehyde at concentrations that also induced
severe degenerative, hyperplastic, and metaplastic changes in the
nasal epithelium, suggesting that cytotoxicity and/or increased
cell proliferation may have had a role in tumor induction.
Recent studies by Woutersen et al. (1989) and Feron et al. (1988)
and an ongoing study by Monticello and Morgan (1990) support the
association between cytotoxicity and cell proliferation and tumor
induction at exposures of 10 to 20 ppm, 6 hours/day, 5 days/week
at exposures ranging from 4 weeks to 28 months. The study by
Woutersen et al. (1989) more directly examined the effect of
tissue damage on the tumorigenic response of formaldehyde. These
authors found that external sources of damage to the nasal
epithelium could enhance the tumorigenic response of Wistar rats
to formaldehyde.

One explanation for the increase in tumor induction in areas
of tissue damage proposes that nasal defense mechanisms may be
irreparably damaged in such areas. For example, the mucociliary
apparatus has been proposed to trap and remove formaldehyde in
the mucus layer before it has a chance to reach underlying cells
(Zwart et al., 1988). The tissue damage may prevent adequate
functioning of the mucociliary apparatus. Both *in vitro* and *in
vivo* studies (Morgan et al., 1983, 1986) have shown that there is
a clear dose-dependent effect of formaldehyde on the mucociliary
apparatus of the rats. In addition to tissue damage, exposure to
high concentrations of formaldehyde has been suggested to
interfere with the protective function of mucus. A recent study
by Bogdanffy et al. (1987) examined [14C]-formaldehyde binding to
nasal mucus from rats and a human volunteer and found the
formaldehyde bound to albumin within the mucus. These authors
postulated that formaldehyde binding to mucus may alter the
physical characteristics of mucus and lead to mucostasis. This
would allow formaldehyde to penetrate to the submucosal cell
layer. In humans, nasal mucociliary function was inhibited by
exposure to 0.3 ppm formaldehyde for 1 to 5 hours (Anderson and
Molhave, 1983). It is also known that formaldehyde at levels
below 1 ppm can be detected in the olfactory region of the human
nose, indicating that formaldehyde is not completely removed by
the mucus layer, even at low concentrations.

Another explanation for the increase in tumor induction in
areas of tissue damage is that cytotoxicity may increase cell
proliferation thereby increasing the amount of single-stranded

DNA available for damage by formaldehyde.  Alternatively, cytotoxicity may in some way promote the carcinogenic response in formaldehyde-initiated cells.

Cell proliferation in response to formaldehyde has been observed in human tissues and the monkey, as well as in the rat. In studies by Klein-Szanto et al. (1989) and Ura et al. (1989) human tracheobronchial epithelia were transplanted into deepithelialized rat tracheas.  A concentration-dependent proliferative response similar to that observed in the rat was observed when the tracheas were exposed *in vivo* to devices that slowly released formaldehyde.  Exposure of monkeys to 0 or 6 ppm of formaldehyde for 1 or 6 weeks resulted in an 18-fold increase in cell proliferation in formaldehyde exposed animals (Monticello et al., 1989).

Although increased cell proliferation has been observed in a number of studies in which nasal tumors have been induced, stimulation of cell proliferation does not appear to be sufficient to cause tumors.  For example, in the study by Monticello and Morgan (1990), although proliferation and inflammation were observed at the same doses at which carcinogenicity was observed, proliferation and inflammation were not observed only at those sites at which tumors developed. Also, Zwart et al. (1988) found that exposure of formaldehyde produced patterns of cell proliferation that were not consistent with carcinogenic patterns.  For example, after 3 days of exposure to 3 ppm, increases in cell proliferation were observed in regions with a high tumorigenic response; but, after 13 weeks the proliferation in these areas was slightly less than in controls.  These acute (Swenberg et al., 1983; Zwart et al., 1988) and chronic (Monticello and Morgan, 1990) studies have demonstrated that there is a correlation between cytotoxicity and cell proliferation induced by formaldehyde in the rat nasal epithelium and that the cell proliferation rate is concentration-dependent.

The role of concentration versus total dose (i.e., the total dose that an animal receives is the exposure concentration multiplied by the duration of exposure) in the response of respiratory tissue to formaldehyde was examined in two studies by Wilmer et al. (1987, 1989).  In both studies the Wistar rats were exposed to formaldehyde on a continuous and intermittent basis and the response appeared to be more dependent on concentration than on total dose.

A number of recent studies have also examined the carcinogenic potential of formaldehyde by the oral route. Exposure of rats to 0.2% formaldehyde (0.001 to 0.25%) in the drinking water produced squamous cell papillomas in the forestomach (Takahashi et al., 1986) and an increase in gastric neoplasms (squamous cell carcinomas, adenocarcinomas, and

leiomyosarcomas [a tumor of the smooth muscle tissue]) (Soffritti et al., 1989). A slight increase in leukemia was also observed in treated animals, but the significance of this finding was not addressed. In contrast, no increase in tumors was observed in Wistar rats exposed to formaldehyde (0.002 to 0.5%) in the drinking water (Til et al., 1989; Tobe et al., 1989) but hyperplasia and inflammation of the forestomach and glandular stomach were reported. These results provide suggestive evidence of carcinogenicity of formaldehyde by the oral route.

A number of recent studies have also examined the tumor promotion potential of formaldehyde. Using rat tracheal explants, Cosma and Marchok (1987) examined the effects of formaldehyde, benzo[a]pyrene, and the combination of these agents on the induction of carcinogenesis. Tracheal explants are tracheal cells taken from a rat and grown in tissue culture outside of the animal. Carcinogenicity was quantified as the number of growth altered populations observed per tracheal explant. Formaldehyde treatment (0.2%) twice weekly for 4.5 months by itself produced only 0.25 altered populations per explant, benzo[a]pyrene produced 2.37 altered populations per explant, and pretreatment with benzo[a]pyrene followed by formaldehyde treatment produced 7.83 populations per explant, indicating the tumor promotion potential of formaldehyde. Also, in a skin painting experiment by Iversen (1986), hr/hr Oslo strain mice were treated with 51.2 µg of the tumor initiator dimethylbenz[a]anthracene (DMBA). Nine days later, a group of these mice was treated with 200 µl of 10% formaldehyde twice a week for 60 weeks. Although the incidence of tumors was similar in DMBA treated animals both with and without formaldehyde treatment (approximately 38%), the time of appearance of the tumors was significantly reduced in those mice treated with both the formaldehyde and DMBA. However, a later experiment using SENCAR mice (bred for maximal sensitivity to carcinogens) found no change in tumor induction when mice that had been pretreated with 51.2 µg of DMBA were treated twice weekly with 4% formaldehyde (Iversen, 1988). Thus, in some tissues formaldehyde may have tumor promoting potential.

6.6.3.4  Carcinogenicity - Epidemiological Studies

Since the 1987 EPA carcinogenicity assessment, a limited number of new epidemiologic studies and reanalyses of previous studies have been published. Many of the reanalyses have examined the results of the largest study that has been published to date (Blair et al., 1986, 1987). This study examined the mortality experience of 26,561 workers employed in a total of 10 plants known to use formaldehyde. The estimated 8-hour time-weighted-average exposure to formaldehyde fell into five categories: trace, <0.1 ppm, 0.1-0.5 ppm, 0.5-<2.0 ppm, and >2.0 ppm based on job category. Blair et al. (1986, 1987) reported that workers exposed to >0.1 ppm formaldehyde had an elevated

rate of lung cancer; but, that no increase in lung cancer incidence could be correlated with increases in exposure. Also, these authors reported that workers with exposure to both formaldehyde and particulates had a dose-related elevated rate of nasopharyngeal cancer.

The increase in nasopharyngeal cancer was reanalyzed by Collins et al. (1988) and was reported to be confined to only one of the 10 plants studied. Also, the dose-related increase in nasopharyngeal cancer originally reported by Blair et al. (1986, 1987) was not seen if only those workers with simultaneous exposure to particulates and formaldehyde were considered. Blair et al. (1986, 1987) had grouped exposure to formaldehyde and particulates irrespective of whether the exposures had occurred simultaneously. Although Collins et al. (1988) indicated that these data showed a lack of an association between formaldehyde exposure and increased incidence of nasopharyngeal cancer, EPA (1990a) reevaluated the data using a Poisson trend statistic and found a significant trend for increased nasopharyngeal cancer with increasing formaldehyde exposure.

Robins et al. (1988) reanalyzed the lung cancer data using a method developed to correct for the existence of a healthy worker effect. These authors confirmed the lack of an association between lung cancer and increased formaldehyde exposure. Sterling and Weinkam (1988 1989) also reanalyzed the lung cancer data from Blair et al. (1986 1987) using methods that would reduce the influence of a healthy worker effect. This included using a time-integrated exposure score and comparison of internal high and low exposure groups. The report published in 1988 contained calculation errors and was amended in 1989. The 1989 paper reported a significant increase in the odds ratio (OR)[3] for lung cancer in those over age 40 (40-55 yr, OR = 11.10, 95% CI[4] = 6.45 to 1926; 55+ yr, OR = 67.44, 95% CI = 35.59 to 127.59). A significant increase in the odds ratio for lung cancer for hourly workers was also observed (OR = 1.61, 95% CI = 1.12 to 2.31). Also, a significant trend for increased lung cancer incidence was reported with increased cumulative exposure, although none of the cumulative exposure levels was associated with a significant increase in lung cancer incidence (<0.1 ppm-yr, OR = 1.0; 0.1-0.5 ppm-yr, OR = 1.21, 95% CI = 0.84 to 1,74; 0.5-2 ppm-yr, OR = 1.19, 95% CI = 0.78 to 1.83; 2+ ppm-yr, OR = 1.56, 95% CI = 0.95 to 2.56).

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[3]The odds ratio (OR) is an estimate of the relative risk (RR). It is a measure of association between the characteristic and disease in a case-control study. Relative risks (i.e., odds ratios) that are >1 imply an association between the characteristic and the disease.

[4]The confidence interval (CI) is the investigator's assurance that the sample selected is one of 95% (for a 95% confidence interval) of all samples that will provide a correct statement based on the interval.

Blair et al. (1990) disputed the results reported by Sterling and Weinkam (1989) based on the observation that Sterling and Weinkam had grouped all respiratory cancer deaths rather than examining only lung cancer deaths.  However, reanalysis using only lung cancer deaths lowered the calculated risks, but did not affect the overall conclusions of Sterling and Weinkam. Further analysis of the association between lung cancer and formaldehyde exposure by Blair et al. (1990) revealed that lung cancer mortality was elevated in workers with formaldehyde and particulate exposure from the production of resin and molding compounds and that exposure to melamine, urea, phenol, or wood dust in these operations may have accounted for the increases in lung cancer that were attributed to formaldehyde exposure.

Two new case control studies reported the cancer mortality of persons occupationally exposed to formaldehyde.  In the study by Gerin et al. (1989), an elevated odds ratio of 2.3 (95% CI = 0.9 to 6.0) was determined for persons with adenocarcinoma of the lung and long-duration, high exposure to formaldehyde.  The odds ratio appeared to increase between those with long-duration low level exposure (OR = 0.8, 95% CI = 0.3 to 1.3), those with long-duration, medium level exposure (OR = 0.8, 95% CI = 0.4 to 1.6), and those with long-duration high level exposure, but this was not statistically analyzed.  In the study by Roush et al. (1987), an odds ratio of 2.3 (95% CI = 0.9 to 6.0) was determined for persons with nasopharyngeal cancer and occupational exposure to formaldehyde at high levels 20 years prior to death.  The odds ratio was statistically significant for those persons over 68 years of age (OR = 4.0, 95% CI = 1.3 to 12.0).  No such increase was observed for persons with sinonasal cancer and occupational exposure to high levels of formaldehyde 20 years prior to death (OR = 1.5, 95% CI = 0.6 to 3.1).

Another case-control study (Partanen et al., 1990) examined possible associations between formaldehyde and respiratory cancer of 136 respiratory cancers among 7307 male Finnish woodworkers. These men were employed in jobs in particleboard, plywood, construction carpentry, furniture manufacturing, and glue manufacturing plants, and in sawmills.  After accounting for a minimum latency period of 10 years, smoking, and vital status at the time of data collection, an elevated odds ratio for respiratory cancer (OR = 1.4, 90% CI = 0.4 to 4.1) was found with exposure to cumulative formaldehyde (either dustborne or as gas) (≥3 ppm-months).  When further analyzing upper respiratory cancer and lung cancer separately, the odds ration for upper respiratory cancer becomes OR = 2.4 and that of lung cancer OR = 0.9. Partanen et al. (1990) believed these results are compatible either with chance or with a weak elevated risk mainly due to cancers of the upper respiratory organs.

Hayes et al. (1990) conducted a proportional mortality ratio (PMR) study of embalmers and funeral directors in the U.S.

Statistically significantly elevated proportions of deaths were
found from a variety of causes, specifically cancers of the
nasalpharyngeal, colon and lymphatic and hematopoietic systems.
There was also a significant increase in ischemic heart disease.
The authors believed the apparent elevated proportions of death
due to nasalpharyngeal cancer and leukemia were consistent with
previous observations in formaldehyde-exposed industrial cohorts
and other studies of professionals.

Other related studies examining cancer mortality among
workers exposed to formaldehyde include a population-based case
control study by Linos et al. (1990) that observed an increase in
follicular non-Hodgkin's lymphoma and acute myeloid leukemia
among embalmers and funeral directors.  Also, Malker et al.
(1990) found a significant increase in nasopharyngeal cancer in
workers in fiberboard plants and among book binders (both are
subject to formaldehyde exposure).  A study of 9.365 leather
tannery workers reported 1 death due to squamous cell carcinoma
of the nasal cavity (0.4 expected) and attributed the death to 18
years of exposure to a variety of chemicals, including chrome and
formaldehyde (Stern et al. 1987).

Histochemical analyses of biopsies taken from nasal tissues
of workers exposed to formaldehyde revealed precancerous lesions.
Holmstrom et al. (1989) observed significant changes in the
middle turbinate of workers exposed to well-defined levels of
formaldehyde.  However, similar changes were not observed in
nasal tissues of workers exposed to formaldehyde and wood dust.
Boysen et al. (1990) also found a significant increase in the
degree of metaplasia in the nasal cavity of workers exposed to
formaldehyde.

These new studies support the previous conclusion by EPA
(1987a) that limited evidence of an association between
formaldehyde exposure and nasopharyngeal and, possibly lung,
cancer in humans exists.  No definitive causal relationships are
demonstrated in the new studies.

## 6.7  Carcinogenic Risk for Baseline and Control Scenarios

Table 6-12 summarizes the annual cancer incidences for all
the scenarios.  When comparing cancer incidence for the base
control scenarios relative to 1990, there is a 36% reduction in
1995, a 52% reduction in 2000, and 50% in 2010, which is actually
an increase when compared to 2000.  The reduction in emissions
are considerably higher, particularly in the out years.  The
projected increase in both population and vehicle miles traveled
(VMT) from 2000 to 2010 appears to offset the gains in emissions
achieved through fuel and vehicles modifications.

From Table 6-12 it can also be observed that the expanded use scenarios provide no decrease in the cancer cases and, in one scenario, the cancer cases increase slightly.  This is generally due to the fact that increased use of oxygenates in gasoline will increase formaldehyde emissions.  The HAPEM-MS exposure model estimates exposure based on direct emissions of formaldehyde.  As discussed in Section 6.5.2, however, the use of oxygenates in gasoline is expected to change the reactivity of the emissions. It is probable that secondary (i.e., atmospherically formed) formaldehyde could be reduced with the use of oxygenates.  As a result, the cancer risk estimates given in Table 6-11 should be considered conservative estimates.

Please note that the cancer unit risk estimate for formaldehyde is based on animal data and is considered an upper bound estimate for human risk.  True human cancer risk may be as low as zero.

**Table 6-12.  Annual Cancer Incidence Projections for Formaldehyde.[a,b]**

| Year-Scenario | | Emission Factor g/mile | Urban Cancer Cases | Rural Cancer Cases | Total Cancer Cases | Percent Reduction from 1990 | |
|---|---|---|---|---|---|---|---|
| | | | | | | EF | Cancer |
| 1990 | Base Control | 0.0412 | 37 | 7 | 44 | – | – |
| 1995 | Base Control | 0.0234 | 24 | 4 | 28 | 43 | 36 |
| 1995 | Expanded Reformulated Fuel Use | 0.0251 | 25 | 5 | 30 | 39 | 32 |
| 2000 | Base Control | 0.0162 | 18 | 3 | 21 | 61 | 52 |
| 2000 | Expanded Reformulated Fuel Use | 0.0166 | 19 | 3 | 22 | 60 | 50 |
| 2000 | Expanded Adoption of California Standards | 0.0168 | 19 | 3 | 22 | 59 | 50 |
| 2010 | Base Control | 0.0140 | 19 | 3 | 22 | 66 | 50 |
| 2010 | Expanded Reformulated Fuel Use | 0.0143 | 20 | 4 | 24 | 65 | 45 |
| 2010 | Expanded Adoption of California Standards | 0.0138 | 19 | 3 | 22 | 67 | 50 |

[a]Projections have inherent uncertainties in emission estimates, dose-response, and exposure.
[b]Cancer incidence estimates are based on upper bound estimates of unit risk,  determined from animal studies.  EPA has classified formaldehyde as a Group B1, probable human carcinogen based on limited epidemiological evidence and sufficient evidence in animal studies.

## 6.8 Non-carcinogenic Effects of Inhalation Exposure to Formaldehyde

Since the focus of this report is on the carcinogenic potential of the various compounds, the noncancer information will be dealt with in a more cursory fashion. No attempt has been made to synthesize and analyze the data encompassed below. Also, no attempt has been made to accord more importance to one type of noncancer effect over another. The objective is to research all existing data, describe the noncancer effects observed, and refrain from any subjective analysis of the data.

Irritation of the eyes (lacrimation and increased blinking) and mucous membranes is the principal effect of exposure to low concentrations (0.05-2.0 ppm) of formaldehyde observed in humans (NRC, 1981). Other human upper respiratory effects associated with acute formaldehyde exposure include a dry or sore throat, and a tingling sensation of the nose. These effects are frequently seen following exposure to 1-11 ppm (NRC, 1981). Sensitive humans may detect effects at lower concentrations (CARB, 1991b). Tolerance to eye and upper airway irritation may develop after 1-2 hours exposure, but symptoms may return if exposure is resumed following an interruption (NRC, 1981). Nasal mucocillary clearance system effects (loss of cilia, keratosis, mild dysplasia) have been reported in humans at concentrations of 0.1 ppm (Edling et al., 1985), and following chronic exposure to undetermined concentrations (NRC, 1981). Forty percent of formaldehyde-producing factory workers reported nasal symptoms such as rhinitis, nasal obstruction, and nasal discharge following chronic exposure (Wilhelmsson and Holmstrom, 1987). In persons with bronchial asthma, the upper respiratory irritation caused by formaldehyde can precipitate an acute asthmatic attack, sometimes at concentrations below 5 ppm (Burge et al., 1985); formaldehyde exposure may also cause bronchial asthma-like symptoms in nonasthmatics (Hendrick et al., 1982; Nordman et al., 1985). However, it is unclear whether asthmatics are more sensitive than nonasthmatics to formaldehyde's effects (EPA, 1990a). Lower airway irritation, characterized by cough, wheezing, and chest tightness, has been reported often in people chronically exposed to 5-30 ppm formaldehyde, and has been observed in concentrations below 1 ppm (EPA, 1987a). However, acute exposure did not cause lower airway symptoms in medical students in an anatomy laboratory (Uba et al., 1989). Neither lower airway irritation (cough, chest symptoms, and dyspnea [labored or difficult breathing]) nor decrements in pulmonary functioning were more frequently reported among asthmatics than among nonasthmatics (Uba et al., 1989). Formaldehyde concentrations exceeding 50 ppm may cause severe lower respiratory tract reactions, in which not only the airways, but also the alveolar tissue is involved. This acute injury includes pneumonia, bronchial inflammation, pulmonary edema, and, at concentrations exceeding 100 ppm, death may occur in sensitive individuals (NRC, 1981). Pulmonary effects, as measured by pulmonary function tests, have not been reported consistently across studies. Overall, chronic decrements in lung function do not appear to be associated with formaldehyde exposure (Witek et al., 1987; Sauder et al., 1987), although small transient

decreases have been noted (Sauder et al., 1986; Horvath et al., 1988).

Immune stimulation may occur following formaldehyde exposure, although conclusive evidence is not available.  Patterson et al. (1986) demonstrated the presence of IgE antibodies against formaldehyde-human serum albumin conjugates and human serum albumin (HSA).  IgE (immunoglobulin gamma E) is a protein antibody produced by cells of the lining of the respiratory and intestinal tract. It appears that formaldehyde is capable of inducing respiratory tract allergy, but data are lacking on induction concentrations (Burge et al., 1985; Nordman et al., 1985).  Central nervous system effects such as dizziness, apathy, inability to concentrate, and sleep disturbances have been reported in a variety of studies following inhalation exposure in humans (EPA, 1987a).  However, in general, formaldehyde's effect on the CNS is not clearly defined (Consensus Workshop, 1984).

With regard to the developmental toxicity of formaldehyde, menstrual disorders were reported among 47.5% of women occupationally exposed to formaldehyde vapors from urea-formaldehyde resins, with dysmenorrhea (pain in association with menstruation) being the most common disorder (Shumilina, 1975). There have been several animal inhalation studies conducted to assess the developmental toxicity of formaldehyde.  The only exposure-related effect noted in a study conducted by Martin (1990) observed a decrease in maternal body weight gain at the high-exposure level but no adverse effects on reproductive outcome or the fetuses that could be attributed to treatment were noted.  In another study conducted by Sallenfait et al. (1989), reduced fetal weight was noted following exposure of pregnant Sprague Dawley rats to 20 or 40 ppm formaldehyde on gestations days 6-20.  No effects on embryonic or fetal lethality, or in the external, visceral, or skeletal appearance of the fetuses were noted.  In Ulsamer et al. 1984, other effects such as increased duration of gestation and body weight of offspring, microscopic changes in the liver, kidneys, and other organs of fetuses from exposed dams, and decreased levels of nucleic acid in the testes of exposed males have been reported.

Acute and subchronic inhalation exposure of various laboratory animals to low (<1 ppm) or moderate (10-50 ppm) concentrations of formaldehyde vapor is known to cause increased airway resistance, decreased sensitivity of the nasopalatine nerve (a nerve that innervates both the nose and the palate), irritation of the eyes and respiratory system, and changes in the hypothalamus (a part of the brain that is important in controlling certain metabolic activities such as maintenance of water balance, sugar and fat metabolism regulation of body temperature and secretion of hormones).  Exposure to high concentrations (>100 ppm) of formaldehyde vapor can cause salivation, acute dyspnea, vomiting, cramps, and death (CIR, 1984).  Subchronic and chronic inhalation exposure in experimental animals has resulted in a variety of nasal cavity lesions, including dysplasia (abnormal development of tissue) and squamous metaplasia (conversion of one kind of tissue into a form that is not normal for that tissue) of respiratory epithelium,

purulent or seropurulent rhinitis (an inflammation of the nasal tissue characterized by discharges that contain pus or serum and pus), interstitial inflammation of the lungs (CIR, 1984), reduced weight gain, reduced liver weights, and lesions of the kidney, liver, cerebral cortex, and respiratory tract (EPA, 1985c). Rusch et al., (1983) determined a NOAEL for squamous metaplasia and rhinitis of 1.0 ppm for rats and monkeys, although the study duration was not specified.  Effects on the liver (decreased liver weights, histological changes) and kidney (vasodilation in a part of the renal cortex that is near the renal medulla) effects were also seen in animals following subchronic inhalation exposure (Rusch et al., 1983; Feldman and Bonashevskaya, 1971). In animals, formaldehyde has been shown to affect the firing rate of certain nerves in the nasal sensory system (EPA, 1987a).  At high concentrations, formaldehyde has been reported to cause cerebral acid proteinase activity in rats in one study and decrease in cerebral RNA concentration, together with decreases in the succinate dehydrogenase and acid proteinase activities, in another (Consensus Workshop, 1984).

A range of predicted responses for upper respiratory and eye irritation risk, for a given formaldehyde concentration is obtained when seven studies are examined comparatively (Bender et al., 1983; Hanrahan et al., 1984; Horvath et al., 1988; Kulle, 1985; Liu et al., in press; Anderson and Molhave, 1984; Ritchie and Lehnen, 1987).  Caution must be taken in inferring the results in EPA (1987) and in this data to the general population. Limitations in these studies at the present prevent the inference of eye and upper respiratory risks.  None of the studies reviewed in this document and in EPA (1987) provide adequate data to precisely quantify general population risks for eye and upper respiratory effect associated with a specific formaldehyde concentration.  Nevertheless, these studies document eye and upper respiratory tract effects at levels previously identified , 0.1 ppm to 3.0 ppm.  Even though the prevalence of exposure can not be precisely estimated for a given formaldehyde concentration, these studies support the conclusion that the number of individuals responding in a population will increase with increasing formaldehyde concentration.

An inhalation reference concentration (RfC) is not available for formaldehyde at this time.  EPA (1992b) has derived an oral reference dose (RfD) of $2\times10^{-1}$ mg/kg/day, based on reduced weight gain and histopathology in rats following a 2-year drinking water study (Til et al., 1989).  An uncertainty factor of 100 and a no-observed-adverse-effect level (NOAEL) of 15 mg/kg/day in male rats were used to derive the RfD.

A recent study by Krzyzanowski et al. (1990) analyzed the relation of chronic respiratory symptoms and pulmonary function to indoor formaldehyde exposure in a sample of children and adults in Tucson, Arizona.  The average concentration of formaldehyde, measured in 202 households, was 26 ppb (32 μg/m$^3$). In only a few cases did the formaldehyde exceed 90 ppb (111 μg/m$^3$), with a maximum value of 140 ppb (172 μg/m$^3$).  The data were collected from 298 children and 613 adults.

In children, the prevalence rates of chronic respiratory symptoms were not related to the formaldehyde exposure (considered in three categories:  below 40 ppb, 41-60 ppb, and over 60 ppb).  However, the diseases diagnosed by a doctor, asthma and chronic bronchitis in children 6-15 years of age, were more prevalent in  houses with formaldehyde levels of 60-120 ppb (74-148 µg/m$^3$) than in those children less exposed.  This is especially evident in children also exposed to environmental tobacco smoke.  The effects in asthmatic children exposed to formaldehyde below 50 ppb (62 µg/m$^3$) were greater than in healthy ones.  The effects in adults were less evident:  decrements in expiratory flow rates due to formaldehyde over 40 ppb (49 µg/m$^3$) were seen only in the morning, and mainly in smokers.  This childhood data are considered signs of developmental toxicity since the definition of developmental    toxicity includes children up to the time of puberty.

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## 7.0  1,3-BUTADIENE

### 7.1 Chemical and Physical Properties (EPA, 1989; 1992)

1,3-Butadiene is a colorless, flammable gas at room temperature with a pungent, aromatic odor, and a chemical formula $C_4H_6$ ($CH_2$:$CHCH$:$CH_2$).  Table 7-1 summarizes 1,3-butadiene's chemical and physical properties.  1,3-Butadiene is insoluble in water, slightly soluble in methanol and ethanol, and soluble in organic solvents such as benzene and ether.  1,3-Butadiene is also structurally related to known carcinogens.

Because of its reactivity, 1,3-butadiene is estimated to have a short atmospheric lifetime.  The actual lifetime depends upon the conditions at the time of release.  The primary removal mechanisms are through chemical reactions with hydroxyl radicals and ozone.  Therefore, factors influencing 1,3-butadiene's atmospheric lifetime, such as the time of day, sunlight intensity, temperature, etc., also include those affecting the availability of hydroxyl radicals and ozone.

Table 7-1.  Chemical and Physical Properties of 1,3-Butadiene.

| Properties | Values |
|---|---|
| Molecular weight | 54.09 g/mole |
| Melting point | -108.91°C (-164.04°F) |
| Boiling point | -4.41°C (24.06°F) |
| Density at 20°C (68°F) | 0.6211 g/cm$^3$ |
| Vapor pressure at 20°C | 1.2 atm. |
| Flash point | -105.0°C (-157.0°F) |
| Solubility in water at 20°C | 0.735 g/L |
| Conversions at 25°C (77°F) | 1 ppm (by volume) = 2.21 mg/m$^3$<br>1 mg/m$^3$ = 0.45 ppm (by volume) |

### 7.2 Formation and Control Technology

1,3-Butadiene is formed in vehicle exhaust by the incomplete combustion of the fuel and is assumed not to be present in vehicle evaporative and refueling emissions.  As a rule, refiners try to minimize the level of 1,3-butadiene in gasoline and diesel fuel because it tends to readily form a varnish which can be harmful to engines (EPA, 1989).  Therefore, the majority of gasoline and diesel fuel should have no significant 1,3-butadiene content.

1,3-Butadiene emissions appear to increase roughly in proportion to hydrocarbon emissions.  Since hydrocarbons are decreased by the use of a catalyst on a motor vehicle, 1,3-butadiene emissions are expected to decrease proportionally.


## 7.3  Emissions

### 7.3.1  Emission Fractions Used in the MOBTOX Emissions Model

Actual vehicle emissions were used to develop 1,3-butadiene emission fractions.  Because 1,3-butadiene decays rapidly in the Tedlar bags used to collect emissions samples, exhaust speciation analyses often underestimate 1,3-butadiene emissions.  This is especially true of older studies.  Thus, although 1,3-butadiene emissions data from many studies were available (Appendix B2), it was decided to use data from one study with a very large number of vehicles, recently conducted by CARB (1991), in which deterioration of 1,3-butadiene was strictly controlled, and emission fractions were adjusted to account for time lag between sample collection and sample analysis.  This study also tested more typical in-use vehicles, rather than low mileage vehicles as in other studies.  1,3-Butadiene emission fractions for different programs included in modeling components are included in Appendix B6.  For vehicles with three-way catalysts, 1,3-butadiene emission fractions from the Auto/Oil study were somewhat lower than emission fractions from the CARB data (overall, about 15%).  This may indicate that later model vehicles, with more efficient catalysts, have lower 1,3-butadiene fractions.  Thus, with fleet turnover, 1,3-butadiene fractions in motor vehicle emissions may drop.  Also, it should be noted that most 1,3-butadiene emissions occur during cold starts, and use of heated catalysts in future years will reduce these cold start emissions (see Ford Motor Company comments in Appendix I).

CARB measured 1,3-butadiene mass emissions for 55 LDGVs/LDGTs with three-way catalysts or three-way plus oxidation catalysts, 7 LDGVs/LDGTs with oxidation catalysts, 16 LDGVs/LDGTs with no catalysts, 2 LDDVs, and 1 HDDV.  CARB then calculated THC fractions and converted these fractions to TOG fractions using conversion factors.  CARB's THC fraction was converted to a TOG fraction using the conversion factors in Table 3-7, rather than the CARB conversion factors.  The resultant TOG fractions for vehicles running on baseline fuel are listed in Appendix B5.  CARB calculated an average emission fraction for three-way catalyst and three-way plus oxidation catalyst LDGV/LDGT combined.  Since only 7 of the 55 vehicles from the combined category had three-way plus oxidation catalysts, the average emission fraction was applied to the three-way catalyst category.  For LDGVs/LDGTs with three-way plus oxidation catalysts, it was assumed that TOG fractions for this category would be the same as for oxidation catalysts.  CARB also did not measure 1,3-butadiene emissions for HDGVs.  It was assumed the fraction for HDGVs with

three-way catalysts was the same as for LDGVs with three-way catalysts, and that the fraction for HDGVs with no catalysts was the same as for LDGVs with no catalysts.

No 1,3-butadiene data were available for oxygenated fuels from the CARB study.  To calculate TOG fractions for vehicles running on MTBE blends and 10% ethanol, adjustment factors were applied to the baseline emission fractions for each vehicle class/catalyst combination.  To calculate an appropriate adjustment factor, percent of 1,3-butadiene in exhaust was compared for baseline and oxygenated blends (Appendix B4).  This comparison was performed for 15% MTBE and 10% ethanol.  The average percent change (expressed as a fraction) was added to 1, representing baseline emissions with gasoline, and the baseline 1,3-butadiene fractions then multiplied by the resultant factor. The 15% MTBE and 10% ethanol adjustment factors for LDGVs/LDGTs with various catalyst technologies are summarized in Table 7-2. The 15% MTBE numbers were estimated using data from Auto/Oil (1990) and DeJovine et al. (1991) for LDGVs/LDGTs with three-way catalysts, Auto/Oil (1991) for LDGVs/LDGTs with three-way plus oxidation and oxidation catalysts, and Warner-Selph and Smith (1991) for LDGVs/LDGTs with no catalysts.  The 10% ethanol numbers were estimated using data from Auto/Oil (1990) and Warner-Selph and Smith (1991) for LDGVs/LDGTs with three-way catalysts, and Warner-Selph and Smith (1991) for LDGVs and LDGTs with oxidation catalysts or no catalysts.  Due to a lack of data, the adjustment factor for LDGVs/LDGTs with three-way plus oxidation catalysts was assumed to be equal to the one for LDGVs/LDGTs with oxidation catalysts.

**Table 7-2.  15% MTBE and 10% Ethanol Emission Fraction Adjustment Factors for 1,3-Butadiene.**

| Vehicle Class | Catalyst Technology | 15% MTBE Adjustment Factor | 10% Ethanol Adjustment Factor |
|---|---|---|---|
| LDGV/LDGT | 3-way | 0.9798 | 0.8812 |
| LDGV/LDGT | 3-way + ox | 0.9873 | 0.9375 |
| LDGV/LDGT | oxidation | 1.1790 | 0.9375 |
| LDGV/LDGT | non-cat | 1.2382 | 1.1233 |

Since the average percent change was calculated for 15% MTBE (2.7% weight percent oxygen), and 11.0% MTBE (2.0% oxygen) was assumed for reformulated fuel and California standards components, average percent changes in the 1,3-butadiene TOG fraction from 0 to 15% MTBE  were multiplied by 2.0/2.7, the

ratio of oxygen contents by weight for reformulated gasoline and 15% MTBE.  For HDGVs with three-way catalysts and with no catalysts, the same 15% MTBE and 10% ethanol adjustment factors were assumed as for LDGVs/LDGTs with the same catalyst technologies.

## 7.3.2  Emission Factors for Baseline and Control Scenarios

The fleet average 1,3-butadiene emission factors as determined by the MOBTOX emissions model are presented in Table 7-3.  When comparing the base control scenarios relative to 1990, the emission factor is reduced by 40% in 1995, by 54% in 2000, and by 57% in 2010.  The expansion of reformulated fuel use in 1995 provides no net reduction in the emission factor, relative to 1990.  In 2000 and in 2010, the expansion of reformulated fuel usage and the California standards reduces the emission factor by another 2 to 3% over the base control from the respective year.

## 7.3.3  Nationwide Motor Vehicle 1,3-Butadiene Emissions

The nationwide 1,3-butadiene metric tons are presented in Table 7-4.  Total metric tons are determined by multiplying the emission factor (g/mile) by the VMT determined for the particular year.  The VMT, in billion miles, was determined to be 1793.07 for 1990, 2029.74 for 1995, 2269.25 for 2000, and 2771.30 for 2010.  When comparing the base control scenarios relative to 1990, the metric tons are reduced by 32% in 1995 and by 42% in 2000.  Even though the emission factor continues to decrease from 2000 to 2010, this is more than offset by the large increase in VMT.  As a result, metric tons in 2010 actually increase relative to 2000.

## 7.3.4 Other Sources of 1,3-Butadiene

Mobile sources account for approximately 94% of the total 1,3-butadiene emissions (EPA, 1989).   The remaining 1,3-butadiene emissions (6%) come from stationary sources related to industries producing 1,3-butadiene and those industries that use 1,3-butadiene to produce other compounds.

Of the 6% attributable to stationary 1,3-butadiene sources, 73.8% is produced by the styrene-butadiene copolymer (rubber and latex) industry.  Another 25.8% of the 1,3-butadiene emissions are produced by the industries manufacturing polybutadiene, neoprene rubber, acrylonitrile-butadiene-styrene resin, nitrile rubber, and adiponitrile, the raw material for nylon 6,6 production.  There are also miscellaneous producers/users that account for only a small percentage of the total stationary source emissions.  The final 0.4% is produced by the manufacturing of 1,3-butadiene itself.  Of the 11 producers of 1,3-butadiene, 9 are located in Texas, and 2 in Louisiana (EPA, 1989).

**Table 7-3. Annual Emission Factor Projections for 1,3-Butadiene.**

| Year-Scenario | Emission Factor g/mile | Percent Reduction from 1990 |
|---|---|---|
| 1990 Base Control | 0.0156 | – |
| 1995 Base Control | 0.0094 | 40 |
| 1995 Expanded Reformulated Fuel Use | 0.0093 | 40 |
| 2000 Base Control | 0.0071 | 54 |
| 2000 Expanded Reformulated Fuel Use | 0.0069 | 56 |
| 2000 Expanded Adoption of California Standards | 0.0069 | 56 |
| 2010 Base Control | 0.0067 | 57 |
| 2010 Expanded Reformulated Fuel Use | 0.0064 | 59 |
| 2010 Expanded Adoption of California Standards | 0.0062 | 60 |

**Table 7-4. Nationwide Metric Tons Projection for 1,3-Butadiene.**

| Year-Scenario | Emission Factor g/mile | Metric Tons |
|---|---|---|
| 1990 Base Control | 0.0156 | 27,972 |
| 1995 Base Control | 0.0094 | 19,080 |
| 1995 Expanded Reformulated Fuel Use | 0.0093 | 18,877 |
| 2000 Base Control | 0.0071 | 16,112 |
| 2000 Expanded Reformulated Fuel Use | 0.0069 | 15,658 |
| 2000 Expanded Adoption of California Standards | 0.0069 | 15,658 |
| 2010 Base Control | 0.0067 | 18,568 |
| 2010 Expanded Reformulated Fuel Use | 0.0064 | 17,736 |
| 2010 Expanded Adoption of California Standards | 0.0062 | 17,182 |

Approximately 59% of the mobile source 1,3-butadiene
emissions (56% of total 1,3-butadiene emissions) can be
attributed to onroad motor vehicles, with the remainder
attributed to nonroad mobile sources.  This figure is based on
the average of an EPA estimate and a California Air Resources
Board estimate (CARB, 1991).

Analysis of EPA data indicated that about 46% of mobile
source 1,3-butadiene emissions (43% of total 1,3-butadiene
emissions) can be attributed to onroad motor vehicles, with the
remainder attributable to nonroad mobile sources.  This figure is
based on a number of crude estimates and assumptions.  First, it
was estimated that about 70% of mobile source VOCs are
attributable to onroad vehicles (Section 5.3.4).  This VOC split
was adjusted by onroad and nonroad 1,3-butadiene fractions to
come up with the estimate of 46% of mobile source 1,3-butadiene
from on-road motor vehicles.  For onroad vehicles, 1,3-butadiene
was estimated to be 0.61% of exhaust.  This is a 1990 fleet
average toxic fraction, with fractions in Appendix B2, weighted
using 1990 VMT fractions.  For nonroad vehicles, 1,3-butadiene
was estimated to be 1.3% of exhaust, based on the NEVES report
(EPA, 1991).

The CARB study cited above indicated that, in California, of
about 96% of 1,3-butadiene estimated to come from mobile sources,
71% could be attributed to onroad motor vehicles, and the
remainder to other mobile sources.  Thus, by averaging the EPA
estimate and the CARB estimate, an estimated contribution of 59%
of mobile source 1,3-butadiene emissions from onroad motor
vehicles was derived.

## 7.4 Atmospheric Reactivity and Residence Times

### 7.4.1 Gas Phase Chemistry of 1,3-Butadiene

The processes involved in transformation and residence times
were previously discussed in Section 5.4.  For a more detailed
explanation of the various parameters involved in these processes
please refer to Section 5.4.  The information that follows on
transformation and residence times has been mainly excerpted from
a report produced by Systems Applications International for the
EPA (Ligocki et al., 1991).

The structure of 1,3-butadiene ($C_4H_6$) is a straight-chain
molecule with two conjugated double bonds ($H_2C=CH-CH=CH_2$).
Species
containing double bonds are referred to as "alkenes" or
"olefins".  These double bonds represent extremely active sites
for atmospheric oxidation.  In contrast to the slow rate of
reaction of benzene in the atmosphere, 1,3-butadiene reacts quite
rapidly with the hydroxyl radical, ozone and nitrate radical.
Furthermore, the oxidation of 1,3-butadiene produces two species
which are themselves toxic, formaldehyde and acrolein ($C_3H_4O$).

Acrolein and
its oxidation products are powerful lacrimators (compounds which
cause eye irritation).  Concern for the high atmospheric
reactivity of compounds such as 1,3-butadiene and their
undesirable products such as acrolein lead to early regulations
limiting the olefin content of gasoline (e.g., Rule 66 by the Los
Angeles Air Pollution Control District in 1966).

7.4.1.1 Gas Phase Reactions

       There are three chemical reactions of 1,3-butadiene which
are important in the ambient atmosphere: reaction with OH,
reaction with $O_3$, and reaction with $NO_3$.  All of these reactions
are rapid, indicating that 1,3-butadiene will be transformed
rapidly in the atmosphere.  The reaction of 1,3-butadiene with
the oxygen radical and with $NO_2$ do occur in the atmosphere, but
because their concentrations are much lower than OH and $O_3$, these
reactions are not important in the ambient atmosphere.

7.4.1.2 Reaction Products

       The atmospheric oxidation of 1,3-butadiene by OH proceeds
primarily by addition across the double bonds.  Olefins generally
react to form two aldehyde products, one from each side of the
original double bond.  Therefore, the major products from
1,3-butadiene are formaldehyde (from the terminal carbon) and
acrolein (from the internal carbon).  These products would be
expected, at least to some extent, from any of the atmospheric
reactions of this diolefin, although the mechanism and products
from the $O_3$ reaction are not completely understood.  An exception
is the reaction of 1,3-butadiene with $NO_3$.  This reaction
apparently proceeds primarily by addition, producing
approximately 60% nitrates, with the yield of formaldehyde and
acrolein only 12% (Barnes et al., 1990).

       Formaldehyde has many sources in the atmosphere.  The
production of formaldehyde from the oxidation of 1,3-butadiene
would not be expected to be a significant portion of the total
secondary formaldehyde production.  However, 1,3-butadiene can be
considered to be the major precursor species for atmospheric
acrolein production.

**7.4.2 Aqueous Phase Chemistry of 1,3-Butadiene**

       The aqueous solubility of 1,3-butadiene is very low, an
order of magnitude smaller than that of benzene.  Incorporation
of 1,3-butadiene into clouds and rain will not be an important
process due to the low solubility of 1,3-butadiene despite the
relatively rapid reaction with OH radical.

**7.4.3 1,3-Butadiene Residence Times**

       Residence times for 1,3-butadiene were calculated by

considering only gas-phase chemical reactions with OH, $NO_3$, and $O_3$. Due to the low solubility of 1,3-butadiene, wet deposition and in-cloud chemical destruction are not important processes for 1,3-butadiene, and were not considered in the calculations. The importance of dry deposition for 1,3-butadiene depends upon the value assumed for the reactivity parameter. For these calculations, 1,3-butadiene was assumed to be unreactive on surfaces; if this assumption is valid then its deposition velocity will be negligibly small.

The results of the residence time calculations for 1,3-butadiene are presented in Table 7-5. During the daytime, the residence time of 1,3-butadiene is determined primarily by its reaction with OH radical, with a small contribution from the reaction with $O_3$. The residence time of 1,3-butadiene under summer, daytime, clear-sky conditions is one hour or less for all four cities. The residence time of 1,3-butadiene has previously been estimated at 4 hours under clean, background atmospheric conditions (Cupitt, 1987). The shorter residence times estimated here are a result of the higher oxidant concentrations predicted for urban areas.

At night, the rapid reaction of 1,3-butadiene with $NO_3$, and to a lesser extent $O_3$, leads to residence times of 0.5-6 h under clear-sky conditions. In fact, for Los Angeles, the summer, clear-sky residence time for 1,3-butadiene is estimated to be shorter at night than it is during the daytime. These relatively short residence times for 1,3-butadiene even at night indicate that there is very little possibility of carryover of 1,3-butadiene concentrations from one day to the next during the summertime under clear-sky conditions. Under cloudy-sky conditions, summer nighttime residence times were estimated to be 6-15 h. These are long enough to allow for the possibility of day-to-day carryover.

Daytime residence times for different cities within a given season varied by factors of 2-3, whereas nighttime residence times varied by much larger factors. As with benzene, the difference between summer and winter conditions was large at all sites, with winter residence times 10-30 times greater than summer residence times.

Under wintertime conditions, the residence time of 1,3-butadiene was estimated to be in the range of 12-2000 h. Although daytime residence times during the winter are still relatively short, residence times at night can be very long because of the extremely low $NO_3$ concentrations. Behavior of 1,3-butadiene is therefore very different in the winter than it is during the summer. Significant day-to-day carryover of 1,3-butadiene concentrations is possible in the winter, particularly under cloudy-sky conditions.

The major uncertainties in the residence time calculations for 1,3-butadiene are most likely the nighttime $NO_3$ concentrations and
the $NO_3$ reaction rate.  Concentrations of $NO_3$ are highly variable,

**TABLE 7-5.** Atmospheric residence time calculation for 1,3-butadiene. All times are in hours unless otherwise noted.

|  | Los Angeles | | St. Louis | | Atlanta | | New York | |
|---|---|---|---|---|---|---|---|---|
|  | July | Jan | July | Jan | July | Jan | July | Jan |
| Clear sky – day | 0.8 | 5 | 0.5 | 7 | 0.6 | 7 | 1.0 | 14 |
| Clear sky – night | 0.4 | 16 | 6 | 200 | 0.6 | 5 | 1.1 | 1600 |
| Clear sky – avg | 0.6 | 8 | 2 | 17 | 0.6 | 6 | 1.0 | 40 |
| Cloudy – day | 1.7 | 10 | 1.2 | 16 | 1.2 | 16 | 2 | 30 |
| Cloudy – night | 6 | 90 | 15 | 400 | 7 | 90 | 11 | 2000 |
| Cloudy – avg | 2 | 20 | 2 | 40 | 1.8 | 30 | 3 | 80 |
| Monthly Climatological Average | 0.8 | 11 | 2 | 30 | 1.0 | 12 | 1.7 | 50 |

often peaking shortly after sunset and then decreasing rapidly by
midnight (Platt et al., 1980).  In addition, the $NO_3$ reaction
rate is only known to within a factor of two.  Therefore,
although the daytime residence times are accurate to about a
factor of two, nighttime residence times are certain only to
within an order of magnitude.

**7.4.4 Limited Urban Airshed Modeling Results for 1,3-Butadiene**

The Urban Airshed Model (UAM) has been previously discussed
in Section 5.4.  Please refer to this section for details about
the model, its inputs, and modifications.  Much of the
information below has been excerpted from reports conducted for
EPA by Systems Applications International (SAI) (Ligocki et al.,
1991, 1992).

1,3-Butadiene was treated explicitly in the UAM-Tox.  Mobile
and stationary emissions of 1,3-butadiene were tagged separately
and carried through the simulation as distinct species.  The gas
phase reactions discussed previously were added to the chemistry
subroutines.  Because the focus of the study was on destruction
of the toxic species rather than on the subsequent chemistry of
their reaction products, no products were included in the UAM
modifications for 1,3-butadiene.

St. Louis Simulation

In the St. Louis simulation, the high reactivity of
1,3-butadiene is demonstrated by the large deviation of the
reactive and inert 1,3-butadiene curves in Figure D-3 located in
Appendix D.  By mid-afternoon, the concentration predicted in the
absence of chemistry would be 0.4 ppb, versus 0.05 ppb for the
simulation which included chemistry.  Thus, the afternoon
concentration of 1,3-butadiene was reduced by 90 percent due to
atmospheric reactions.  The two curves approach each other again
after sunset, when the 1,3-butadiene concentration reached its
highest value of the simulation.  These results suggest that
human exposure to 1,3-butadiene during the summertime will be
limited to areas near sources.  According to Table 7-5,
1,3-butadiene is destroyed relatively rapidly even at night, so
little or no carryover of 1,3-butadiene concentration to the
following day would be expected.  The concentration of
1,3-butadiene would be expected to be greater in the wintertime
due to the less active photochemistry.

The comparison of simulated concentrations with ambient
measured concentrations showed good agreement for 1,3-butadiene.

Baltimore-Washington and Houston Area Simulations

Simulations for the summer Baltimore-Washington area episode
(Ligocki et al., 1992) resulted in little change in ambient
concentrations of 1,3-butadiene with the use of federal

reformulated gasoline.  Use of California reformulated gasoline
also had little impact on ambient concentrations of 1,3-
butadiene.  Maximum daily average 1,3-butadiene concentration for
the 1988 base scenario was 0.95 ppb.  Motor vehicle-related 1,3-
butadiene emissions accounted for about 23% of total 1,3-
butadiene emissions, based on the 1995 no motor vehicle scenario.
This motor vehicle emission estimate is lower than the 56%
estimate obtained in Section 7.3.4 for motor vehicles.  The
Ligocki et al. (1992) study suggests that a reason for this
discrepancy could be the inclusion of more types of area source
toxic emissions in the UAM-Tox inventory than had been considered
previously.  Also, the nonroad contribution to mobile source 1,3-
butadiene could be underestimated.  Summer Baltimore-Washington
area simulations were in very good agreement with UATMP data
throughout the domain.

     In the winter 1988 base scenario, the maximum daily average
1,3-butadiene concentration was 2.57 ppb, about 3 times higher
than in summer.  A major reason for this is slower reactive decay
of 1,3-butadiene in winter.  Motor vehicle-related 1,3-butadiene
accounted for 29% of total 1,3-butadiene emissions.  Reformulated
gasoline use had very little effect on winter 1,3-butadiene
ambient concentrations.

     For the summer 1987 base scenario in Houston, the maximum
daily average 1,3-butadiene concentration was 33.2 ppb.  This
high level was due to the single largest point source of 1,3-
butadiene emissions in the United States.  However, the model may
have significantly overestimated the magnitude of this
concentration.  Throughout the rest of the modeling domain,
concentrations were around 2 ppb.  Motor vehicle-related 1,3-
butadiene accounted for 16% of total 1,3-butadiene emissions,
based on the 1995 no motor vehicle scenario.  Motor vehicle-
related 1,3-butadiene contributed less to overall 1,3-butadiene
in Houston than in the Baltimore-Washington area, due to the
large impact of point sources in Houston.  Simulations for the
summer Houston episode predicted little effect on maximum daily
average concentration of 1,3-butadiene with reformulated
gasoline.

## 7.5  Exposure Estimation

### 7.5.1  Annual Average Exposure Using HAPEM-MS

     The data presented in Table 7-6 represent the results
determined by the HAPEM-MS modeling that was described previously
in Section 4.1.1.  These numbers have been adjusted to represent
the increase in VMT expected in future years.

     The HAPEM-MS exposure estimates in Table 7-6 represent the
50th percentiles of the population distributions of exposure,
i.e., half the population will be above and half below these

values.  High end exposures can also be estimated by using the 95th

**Table 7-6.     Annual Average HAPEM-MS Exposure Projections for 1,3-Butadiene.**

| Year-Scenario | Exposure (µg/m$^3$) | | |
|---|---|---|---|
| | Urban | Rural | Nationwide |
| 1990 Base Control | 0.48 | 0.26 | 0.42 |
| 1995 Base Control | 0.31 | 0.17 | 0.28 |
| 1995 Expanded Reformulated Fuel Use | 0.31 | 0.17 | 0.27 |
| 2000 Base Control | 0.26 | 0.14 | 0.23 |
| 2000 Expanded Reformulated Fuel Use | 0.25 | 0.13 | 0.22 |
| 2000 Expanded Adoption of California Standards | 0.25 | 0.13 | 0.22 |
| 2010 Base Control | 0.28 | 0.15 | 0.25 |
| 2010 Expanded Reformulated Fuel Use | 0.27 | 0.14 | 0.24 |
| 2010 Expanded Adoption of California Standards | 0.26 | 0.14 | 0.23 |

percentile of the distributions.  According to the HAPEM-MS sample output for benzene, the 95th percentile is 1.8 times higher than the 50th percentile for urban areas, and 1.2 times high for rural areas.  Applying these factors to the exposure estimates in Table 7-6, the 95th percentiles for urban areas range from 0.45 µg/m$^3$ for the 2000 expanded reformulated gasoline and California standards use scenarios to 0.86 µg/m$^3$ for the 1990 base control scenario.  The 95th percentiles for rural areas range from 0.16 to 0.31 µg/m$^3$, respectively.

## 7.5.2  Comparison of HAPEM-MS Exposures to Ambient Monitoring Data

As stated in section 4.1.2, four national air monitoring programs/databases contain data on air toxics and the data for 1,3-butadiene is found in only three.  The Aerometric Information Retrieval System (AIRS), the Urban Air Toxic Monitoring Program (UATMP), and the National Ambient Volatile Organic Compounds Data Base (NAVOC) all have data for 1,3-butadiene.  The urban exposure data for 1,3-butadiene from the three databases are found in Appendix C and summarized in Table 7-7.

In the 1988 Aerometric Information Retrieval System (AIRS), 18  measurements of 1,3-butadiene were taken at 3 sites.  These sites were in the cities listed below.

        Louisville, KY                    Houston, TX
        Burlington, VT

The highest average was 2.45 µg/m$^3$ (1.11 ppb) at an suburban residential site in Houston, Texas.  Six samples were collected at this site.  Houston, Texas does possess areas with high point source concentrations and, coupled with the fact that the location of the monitor is difficult to ascertain in relation to the point sources, the decision was made to exclude the 6 samples from Houston from the final average ppb for the entire program. The second highest average was 1.04 µg/m$^3$ (0.47 ppb) at a urban commercial site in Burlington, Vermont.  Six samples were collected at this site.  The lowest average was 0.97 µg/m$^3$ (0.44 ppb) at a urban industrial site in Louisville, Kentucky.  Six samples were also collected at this site.  The overall average of the averages for each site was 1.48 µg/m$^3$ (0.67 ppb).  The removal of the 6 Houston samples changes the ambient mean level from 1.48 µg/m$^3$ (0.67 ppb) to 1.01 µg/m$^3$ (0.46 ppb).

In the 1990 Aerometric Information Retrieval System (AIRS), 101  measurements of 1,3-butadiene were taken at 7 sites.  These sites were in the cities listed below.

        Detroit, MI                       Houston, TX
        Arlington County, VA              Henrico County, VA
        Hampton, VA                       Hopewell, VA
        Roanoke, VA

**Table 7-7. Air Monitoring Results for 1,3-Butadiene.**

| Program | Years | Ambient Data[a] $\mu g/m^3$ | Estimated Motor Vehicle Contribution[b] $\mu g/m^3$ |
|---------|-------|-----------------------------|----------------------------------------------------|
| AIRS | 1988 | 1.01 | 0.56 |
| | 1990 | 0.47 | 0.26 |
| | 1991 | 0.22 | 0.12 |
| UATMP | 1989 | 0.46 | 0.26 |
| | 1990 | 0.31 | 0.17 |
| NAVOC | 1987 | 0.75 | 0.42 |

[a]Caution should be taken in comparing these numbers. The methods of averaging the data are not consistent between air monitoring databases. The sampling methodology is also inconsistent.

[b]The ambient data are adjusted to represent the motor vehicle contribution to the ambient concentration, which for 1,3-butadiene is estimated to be 56%, based on emissions inventory apportionment.

The highest average was 1.58 μg/m$^3$ (0.72 ppb) at an suburban
residential site in Houston, Texas.  Four samples were collected
at this site.  Due to the reasons cited above, the four samples
from Houston, Texas were excluded from the final average ppb for
the entire program.  The second highest average was 0.73 μg/m$^3$
(0.33 ppb) at an urban commercial site in Detroit, Michigan.
Nineteen samples were collected at this site.  The lowest average
was 0.29 μg/m$^3$ (0.13 ppb) at a suburban residential site in
Hopewell, Virginia.  Sixteen samples were also collected at this
site.  The overall average of the averages for each site (minus
Houston, Texas) was 0.47 μg/m$^3$ (0.21 ppb).

     In the 1991 Aerometric Information Retrieval System (AIRS),
117  measurements of 1,3-butadiene were taken at 6 sites.  These
sites were in the cities listed below.

          Detroit, MI                  Arlington County, VA
          Henrico County, VA           Hampton, VA
          Hopewell, VA                 Roanoke, VA

The highest average was 0.27 μg/m$^3$ (0.12 ppb) at suburban
residential sites in Henrico County and Roanoke, Virginia.
Twenty-one and fourteen samples were collected, respectively, at
each site.  The lowest average was 0.13 μg/m$^3$ (0.06 ppb) at a
suburban residential site in Hopewell, Virginia.  Sixteen samples
were collected at this site.  The overall average of the averages
for each site was 0.22 μg/m$^3$ (0.10 ppb).

     In the 1989 Urban Air Toxics Monitoring Program (UATMP), 160
measurements of 1,3-butadiene were taken at 14 sites.  These
sites were in the cities listed below.

          Baton Rouge, LA              Chicago, IL
          Camden, NJ                   Dallas, TX
          Fort Lauderdale, FL          Houston, TX
          Miami, FL                    Pensacola, FL
          St. Louis, MO                New Sauget, IL
          Washington, D.C.             Wichita, KS

The highest average was 1.33 μg/m$^3$ (0.60 ppb) at a suburban
residential site in Houston, Texas.  Thirty-four samples were
collected at this site.  The lowest average was 0.11 μg/m$^3$ (0.05
ppb) at a suburban industrial site in Pensacola, Florida.  Only
seven samples were collected at this site.  The overall average
of the averages for each site was 0.46 μg/m$^3$ (0.21 ppb).

     In the 1990 Urban Air Toxics Monitoring Program (UATMP), 349
measurements of 1,3-butadiene were taken at 12 sites.  1,3-
Butadiene was identified in 106 of the samples.  These sites were
in the cities listed below.

```
        Baton Rouge, LA                  Chicago, IL
        Camden, NJ                       Houston, TX
        Orlando, FL                      Pensacola, FL
        Port Neches, TX                  Sauget, IL
        Toledo, OH                       Washington, D.C.
        Wichita, KS
```

The highest average was 24.51 µg/m$^3$ (11.09 ppb) at a suburban
residential site in Port Neches, Texas.  Twenty-eight samples
were collected at this site.  Port Neches, Texas does possess
areas with high point source concentrations and, coupled with the
fact that the location of the monitor is difficult to ascertain
in relation to the point sources, the decision was made to
exclude the 28 samples from Port Neches from the final average
ppb for the entire program.  The second highest average was 1.04
µg/m$^3$ (0.47 ppb) at a suburban residential site in Houston,
Texas.  Twenty-eight samples were collected at this site. The
lowest average was 2.73 µg/m$^3$ (0.06 ppb) that was measured at
five different sites.  The overall average of the averages for
each site was 2.25 µg/m$^3$ (1.02 ppb).  The removal of the 28 Port
Neches samples changes the ambient mean level from 2.25 µg/m$^3$
(1.02 ppb) to 0.31 µg/m$^3$ (0.14 ppb).

     In the 1987 National Ambient Volatile Organic Compound
Database (NAVOC), 9 measurements of 1,3-butadiene were taken at 6
sites.  These sites were in the cities listed below.

```
        Bakersfield, CA                  Concord, CA
        Fremont, CA                      Richmond, CA
        San Jose, CA                     Stockton, CA
```

The highest average was 1.33 µg/m$^3$ (0.60 ppb) at an urban site in
Fremont, California.  Two samples were used for the average at
this site.  The lowest average was 0.55 µg/m$^3$ (0.25 ppb) also at
an urban site in San Jose, California.  Two samples were also
used for the average for this site.  The overall average of the
averages for each site was 0.75 µg/m$^3$ (0.34 ppb).

     HAPEM-MS assumes that the dispersion and atmospheric
chemistry of 1,3-butadiene is similar to CO.  This assumption
would appear not to be valid for a reactive compound like 1,3-
butadiene, which is transformed in the atmosphere.  To test the
reasonableness of the HAPEM-MS modeling results, the HAPEM-MS
results for 1990 are compared to ambient monitoring results for
recent years.  Before comparing the HAPEM-MS results to the
ambient data, the ambient monitoring data must be adjusted to
represent the amount that is attributed to mobile sources.  The
data derived from emission inventories estimate that 56% of the
ambient 1,3-butadiene can be apportioned to motor vehicles.  The
numbers in the second column of Table 7.7 are 56% of the ambient
levels and thus represent estimated motor vehicle levels.

     The motor vehicle apportionment of the ambient monitoring

data, presented in Table 7-7, ranges from 0.12 to 0.56 µg/m$^3$.
When the adjustment factor of 0.622 that was determined in
Section 5.5.2 is applied, this range becomes 0.08 to 0.35 µg/m$^3$.
The HAPEM-MS 1990 base control level of 0.48 µg/m$^3$ lies above
this range.  Since the unit risk estimate for 1,3-butadiene is an
upper bound estimate, the upper end of the ambient range is used
to calculate cancer incidences.  The HAPEM-MS 1990 base control
level must be multiplied by a factor of 0.73 to agree with the
upper end of the ambient data.  All analysis based on the HAPEM-
MS ambient motor vehicle levels will have this factor applied.
Adjusted urban, rural, and nationwide exposures are found in
Table 7-8.

       In an ambient monitoring study conducted by the California
Air Resources Board (CARB, 1992a) 20 monitoring sites were
established throughout the State of California to assess 1,3-
butadiene levels.  The range of the averages of the six basins
detailed in this study was 0.49 to 0.93 µg/m$^3$ (0.22 to 0.42 ppb).
When this range is adjusted for the motor vehicle contribution
and integrated exposure it becomes 0.17 to 0.32 µg/m$^3$ (0.08 to
0.15 ppb).  The upper end of this range compares favorably with
the adjusted HAPEM-MS exposure number.

       The degree of confidence in the air monitoring programs,
especially the Urban Air Toxics Monitoring Program (UATMP),
appears to be high.  The UATMP analyzed 1,3-butadiene using gas
chromatography/ multiple detector (GC/MD).  The GC/MD compound
identifications were confirmed by analyzing about 15% of the 1989
UATMP samples by gas chromatography/mass spectrometer (GC/MS).
The GC/MS samples confirmed 94.1% of all the compound
identifications resulting from the initial analysis.  UATMP also
determined the level of confidence in its 1,3-butadiene
identification analysis.  The precision (percent coefficient of
variation, % CV) was calculated for the compound response ratio
in the sample and the compound response ratio in the standard.
It was determined that approximately 22% of the samples were
within ±20% CV, while 60% were below the 0.10 ppbv detection
limit (EPA, 1990).

       As demonstrated in the section above, it is very clear that
there is a need for better ambient data and exposure methodology
for all the pollutants examined in this study.  An individual's
annual exposure could be very different then the one number
presented in this study due to geographic and temporal variation
inherent in exposures.  Actual exposure estimates need to take
this into account.

## 7.5.3  Short-Term Microenvironment Exposures

       The primary emphasis for 1,3-butadiene exposure will be
exposure in microenvironments that are enclosed, increasing the
exposure to tailpipe emissions.  These microenvironments include

**Table 7-8.   Adjusted Annual Average HAPEM-MS Exposure
Projections for 1,3-Butadiene.**

| Year-Scenario | Exposure ($\mu g/m^3$) | | |
|---|---|---|---|
| | **Urban** | **Rural** | **Nationwide** |
| 1990 Base Control | 0.35 | 0.19 | 0.30 |
| 1995 Base Control | 0.23 | 0.12 | 0.20 |
| 1995 Expanded Reformulated Fuel Use | 0.23 | 0.12 | 0.20 |
| 2000 Base Control | 0.19 | 0.10 | 0.16 |
| 2000 Expanded Reformulated Fuel Use | 0.18 | 0.09 | 0.16 |
| 2000 Expanded Adoption of California Standards | 0.18 | 0.09 | 0.16 |
| 2010 Base Control | 0.20 | 0.11 | 0.18 |
| 2010 Expanded Reformulated Fuel Use | 0.20 | 0.10 | 0.17 |
| 2010 Expanded Adoption of California Standards | 0.19 | 0.10 | 0.16 |

in-vehicle and parking garage exposure, though, actual exposure
information is only available for in-vehicle exposure.  This
information is taken from the Commuter's Exposure to Volatile
Organic Compounds, Ozone, Carbon Monoxide, and Nitrogen Dioxide
(Chan et al., 1989), which focused on the driver's exposure to
VOC's in the Raleigh, NC area.  See the information in Section
4.2 for more details about the methodology, and Section 5.5.3 for
a description of the study.

The in-vehicle exposure level of 1,3-butadiene was
determined in this study to have a mean of 3.0 $\mu g/m^3$ and a
maximum measured level of 17.2 $\mu g/m^3$.  Exterior to the vehicle,
the mean was determined to also be 3.0 $\mu g/m^3$ with a maximum level
of 6.9 $\mu g/m^3$.  This compares to ambient levels of 0.31 to 1.48
$\mu g/m^3$ determined through air monitoring studies and presented in
Table 7-7.  Since for the majority of the population these are
short-term acute exposures to 1,3-butadiene, the concern would be
with non-cancer effects.  Health information for non-cancer
effects is very limited and no RfC has been developed by EPA.
Inhalation of 1,3-butadiene is mildly toxic in humans at low
concentrations (data on actual levels are not conclusive) and may
result in a feeling of lethargy and drowsiness.  At very high
concentrations, 1,3-butadiene causes narcosis leading to
respiratory paralysis and death.  Please see Section 7.8 for more
information on non-cancer effects.

Due to more stringent fuel and vehicle regulations, short-
term exposure to 1,3-butadiene in microenvironments is expected
to decrease in future years.


## 7.6  Carcinogenicity of 1,3-Butadiene and Unit Risk Estimates

### 7.6.1     Most Recent EPA Assessment

The information presented in Section 7.6.1 was obtained from
the EPA document Mutagenicity and Carcinogenicity Assessment of
 1,3-Butadiene (EPA, 1985), EPA's Integrated Risk Information
System (IRIS) (EPA, 1992), the Motor Vehicle Air Toxics Health
Information (Clement, 1991), as well as the primary sources cited
in these documents.  The carcinogenicity risk assessment for 1,3-
butadiene was last updated on IRIS in January 1992, and contains
data published through 1991.  However, with the exception of a
change in absorption factor (used to calculate the target dose)
based on new pharmacokinetic data, the 1992 version of the 1,3-
butadiene risk assessment on IRIS is based on the same study as
the 1985 risk assessment.  EPA's Office of Research and
Development has just recently started the process to review the
1,3-butadiene risk assessment.  Section 7.6.3 summarizes recent
and ongoing research not included in the 1985 EPA risk assessment
for 1,3-butadiene.

7.6.1.1   Description of Available Carcinogenicity Data

Genotoxicity

     Three studies have shown 1,3-butadiene to be mutagenic for
*Salmonella typhimurium* upon addition of mammalian hepatic (liver)
homogenates for metabolism (de Meester et al., 1978, 1980;
Poncelet et al., 1980).  The weight of evidence available
suggests that 1,3-butadiene is a promutagen in bacteria; its
mutagenicity depends on metabolic activation by hepatic
homogenates prepared from chemically induced animals.  No whole-
animal mutagenicity studies have been reported.

     Pharmacokinetic and various types of toxicity studies
indicate that the carcinogenic effects of 1,3-butadiene can be
attributed to the metabolites 3,4-epoxybutene and/or 1,2,3,4-
diepoxybutane.  These metabolites, which are potent alkylating
agents (chemically react with DNA), have been shown to be
mutagenic and carcinogenic (Lawley and Brookes, 1967; Ehrenberg
and Hussain, 1981).  The metabolite, 3,4-epoxybutene, is a
direct-acting mutagen in bacteria, and induces sister chromatid
exchanges and chromosomal aberrations in mice (de Meester et al.,
1978; Voogd et al. 1981, Hemminki et al., 1980).

     1,2:3,4-Diepoxybutadiene is a bifunctional alkylating agent,
and as such it can form cross-links between two strands of DNA.
It is mutagenic in bacteria (Voogd et al., 1981, Wade et al.,
1979), fungi (Olszewska and Kilbey, 1975; Luker and Kilbey,
1982), and the germ cells of *Drosophila* (Sankaranarayanan, 1983;
Sankaranarayanan et al., 1983).  It also induces DNA damage in
cultured hamster cells and in mice (Perry and Evans, 1975; Conner
et al., 1983), is clastogenic in fungi and cultured rat cells
(Zaborowski et al., 1983; Dean and Hodson-Walker, 1979), and
produces chromosome damage/breakage in *Drosophila* germ cells
(Zimmering, 1983).

     Under certain conditions, such as during rubber curing, 1,3-
butadiene can dimerize (two molecules bonding together).  The
dimer was not mutagenic in the Salmonella preincubation assay in
the presence of liver homogenates from chemically induced rats or
hamsters (NTP, 1985).  In contrast, the metabolites of the dimer
are mutagenic or clastogenic in various in vitro bacterial and
animal cell systems as a base-pair substitution mutagen (Murray
and Cummins, 1979; Simmon and Baden, 1980; Truchi et al., 1981;
Voogd et al., 1981).  Therefore, the evidence indicates that 3,4-
epoxybutene, diepoxybutane, and other mono- and diepoxide
metabolites are mutagens/clastogens in microbes and animals.

Animal Data

     In a chronic study conducted by the National Toxicology
Program (NTP, 1984), B6C3F1 mice (50/sex/group) were exposed via
inhalation to 0, 625, and 1,250 ppm 1,3-butadiene, 6 hours/day, 5

days/week.  Because of excessive deaths, primarily due to
lymphoma, among treated animals, mice were sacrificed after 60-61
weeks instead of the planned lifetime exposure (2 years).
Histopathologic examination revealed an increased frequency of
primary tumors at both exposure levels.  These tumors included
hemangiosarcomas (malignant tumors in the blood vessels) that
were found primarily in the heart, alveolar/bronchiolar adenomas
and carcinomas, and lymphomas.  The incidence of acinar cell
carcinoma (mammary) and granulosa cell tumor (layer cells located
in the ovary) or ovarian carcinomas were increased in females in
the high-dose group.  According to EPA (1985), NTP conducted an
audit of the study and reported that some genetic variation was
observed during 1981 in the male C3H parents of the mice used in
this study.  The effect of genetic nonuniformity in the hybrid
mice on the study was unknown, but the results were considered
valid because of the use of matched concurrent controls.  More
recent work by NTP is discussed in Section 7.6.3.

     In a two-year study conducted by Hazleton Laboratories
Europe, Ltd. (1981) (later published as Owen et al., 1987, see
Section 7.6.3.2) Charles River CD rats (110/sex/group) inhaled 0,
1,000, and 8,000 ppm 1,3-butadiene, 6 hours/day, 5 days/week, for
111 weeks (males) and 105 weeks (females).  The authors reported
significant increases in both common and uncommon tumors.  There
was an increase in multiple mammary gland tumors in females for
all treatment groups, thyroid follicular adenoma and carcinoma in
the high-dose females, and Leydig cell (cells located in the
testicles believed to be responsible for secreting testosterone)
adenoma and carcinoma in the high-dose males.  The report did not
include detailed histopathological evaluations and did not
perform independent data quality evaluation (EPA, 1985).
Therefore, uncertainty about the number of tissues examined
limited the usefulness of animal-to-human extrapolation.  In
addition, the higher butadiene dimer (the combination of two
butadiene molecules) content of the material for rats might
contribute to the difference in the effective dose, although its
effect on the study results is unknown (EPA, 1985).  The
incidence of tumors in hormonal-dependent tissues was greater in
rats, although it may have been masked by early deaths in mice.

Human Data

     There were several epidemiological studies evaluating
mortality due to cancer in workers exposed to 1,3-butadiene.
These study results were inconsistent and limited because of
concurrent occupational exposures to other contaminants, usually
styrene (potential carcinogen and leukemogen), and the lack of
adequate exposure data on 1,3-butadiene concentrations.

     Excess mortalities were reported in 6,678 male workers in a
rubber tire manufacturing plant in Akron, Ohio (McMichael et al.,
1974; 1976).  During a 9-year follow-up period from 1964-1972,
statistically significant increases in deaths were due to stomach

and prostate cancer, lymphosarcoma, and leukemia, as well as
diabetes mellitus and arteriosclerosis.  The 1968 U.S. male
population was used as the standard population.  An age-
standardized risk ratio of 6.2 for lymphatic and hematopoietic
cancer was calculated for workers with at least 5 years of
exposure.  To further evaluate the cancer-specific deaths,
McMichael et al. (1976) conducted a case-control study which
indicated that certain cancers were significantly elevated in
certain job classifications and with at least 5 years of
exposure.  Levels of exposure to 1,3-butadiene were not
quantified.

        In a historic prospective cohort study, increased incidence
of lymphatic and hematopoietic cancers were reported in 8,938
males in the rubber manufacturing plant during 1964-1973
(Andjelkovich et al., 1976).  Data were collected from company
records, life insurance death claims, and bureaus of vital
statistics.  The increased mortality ratios were evaluated in
relation to work areas by using the entire cohort as a reference
group.  EPA (1985) concluded that the study was limited because
of the uncertainty regarding the duration that a subject worked
in a specific job department (i.e., estimated duration ranged
from 10% to 100% of employment) and the use of 1968 mortality
data which may have underestimated expected deaths.  Furthermore,
the levels of exposure were not quantified.

        Checkoway and Williams (1982) evaluated the same group of
rubber manufacturing workers as the McMichael et al. (1976) case-
control study.  The objective of this study was to quantify
exposure and to relate it to hematologic measurements.  Air
sampling of the plant and blood samples from the subjects were
taken in May 1979.  Time-weighted averages of 20.03 and 13.67 ppm
were determined for 1,3-butadiene and styrene, respectively.  No
association was found between hematologic values and 1,3-
butadiene exposure.  Because the study was cross-sectional,
excess cancer risk was not expected to be identified since
subjects who may have developed cancers and left the job force
were not available for evaluation.  The study was also limited
because air sampling could not be used to generalize past
exposure levels.  Furthermore, concurrent exposure to more than
one potentially toxic chemical renders it impossible to associate
any adverse health effects that may be seen with exposure to a
particular chemical.

        A retrospective cohort mortality study was conducted on two
rubber plants in Texas by Meinhardt et al. (1982).  The time-
weighted average exposures of butadiene were 1.24 and 13.5 ppm
for the two plants.  Subjects were also concurrently exposed to
styrene and benzene.  Deaths due to lymphatic and hematopoietic
cancers and lymphatic leukemia were exhibited, although they were
not statistically significant.  Results showed borderline
significance for the subcohort employed during the batch process
of the

production process.  This finding may have been biased by uncertainty in the number of deaths and/or factors in choosing the study group (EPA, 1985).

There were no excess mortalities in a retrospective cohort mortality study involving 8 styrene-butadiene rubber plants (Matanoski et al., 1982).  None of the SMRs were statistically significant.  According to EPA, information on the employees was gathered from company records; however, this study evaluated less than 50% of the population of the 8 plants and may have underestimated the number of deaths.

7.6.1.2  Weight-of-Evidence Judgment of Data and EPA Classification

1,3-Butadiene is classified by EPA as a Group B2, probable human carcinogen using EPA's Proposed Guidelines for Carcinogen Risk Assessment (EPA, 1984).  This classification was based on sufficient evidence from two species of rodents and inadequate epidemiologic evidence, as described in Section 7.6.1.1 above.

The mouse inhalation study by NTP (1984) was considered the primary study for calculating the cancer risk estimate of 1,3-butadiene (EPA, 1985).  It was the most appropriate choice because the study was well-conducted and tumors were observed in animals of both treatment groups.  The rat bioassay (Hazleton Laboratories, 1981) had deficiencies that limited its use as the primary data set for animal-to-human extrapolation.  According to EPA, the quality of the study and its results have not been peer-reviewed or published (this study has since been published as Owen et al., 1987, see Section 7.6.3.2), the histopathology report was not available, and the calculated slope factors for male and female rats were limited from a modeling standpoint since it had only one effective dose.  In spite of the fact that this study has been published, EPA still considers it inadequate for risk assessment because of reporting problems, and because the pharmacokinetic analysis in Owens et al. (1987) is considered by EPA to indicate that the effective doses were the same for both treatment groups.

The human studies were not used for determining unit risk because there were inadequate data on the carcinogenicity of 1,3-butadiene, a lack of exposure information, and concurrent exposures to several other possible carcinogens (i.e., styrene) to the workers.  However, EPA did conduct quantitative estimates based on mouse-to-man extrapolation to predict human responses in several epidemiologic studies.  Comparisons were hampered by scarcity of information concerning actual exposures, age distributions, and work histories.  Considering the uncertainties in the human exposure data, the estimate based on animal extrapolation is consistent and the best that can be achieved.

7.6.1.3    Data Sets Used For Unit Risk Estimates

    A summary of the data set used to calculate the cancer unit
risk estimate for 1,3-butadiene (EPA, 1985) is presented in Table
7-9.  EPA used both male and female mouse data sets from the NTP
(1984) study in determining the unit cancer risk estimates.
Animals with at least one of the statistically significant
increased tumors or tumors considered unusual were included in
the data set.  The data set had an adequate number of animals per
treatment group and the estimates across species for females were
relatively close which supports the confidence of the slope
factor.
However, only high doses were tested so the true shape of the
dose-response curve at low environmental levels is not known.

7.6.1.4    Dose-Response Model Used

    The low-dose linear multistage extrapolation model was used
for calculating the unit risk estimate (see Appendix F for a
description of the linearized multistage model), although
alternative models were discussed but found inappropriate by EPA.
This model gave a conservative estimate while the other models
result in a lower risk estimate.

    Because 1,3-butadiene is considered a partially soluble
vapor, the average dose/day is proportional to the $O_2$ consumption
and is proportional to two-thirds of the weight and also to gas
solubility in body fluids (expressed as absorption coefficient).
All three factors listed above must be utilized when determining
average dose/day.  In the absence of experimental information,
the absorption fraction is assumed to be the same for all
species.  In
order to convert to internal dose in animals, EPA used the
absorption study by Bond et al. (1986) which reported 20%
absorption of 1,3-butadiene following inhalation exposure in rats
and mice.

    Because mice were exposed to 1,3-butadiene for a less-than-
lifetime duration, an adjustment was made for extrapolation from
the 60-61 weeks in the NTP mouse study to two full years
(lifetime exposure).

7.6.1.5    Unit Risk Estimates (UCL and MLE)

    The upper-limit unit risks were $3.4 \times 10^{-1}$ $ppm^{-1}$ ($3.8 \times 10^{-4}$ $[\mu g/m^3]^{-1}$) for male mice and $1.9 \times 10^{-1}$ $ppm^{-1}$ ($2.1 \times 10^{-4}$ $[\mu g/m^3]^{-1}$) for
female mice using a 20% absorption rate at low exposures.  The
geometric mean of unit risks was $2.5 \times 10^{-1}$ $ppm^{-1}$ ($2.8 \times 10^{-4}$ $[\mu g/m^3]^{-1}$)
for the two mouse unit risks (EPA, 1992).  Calculating geometric
means of several unit risk estimates is standard EPA policy to
derive a single unit risk estimate.  However, the unit risk
should not be used if air concentrations exceed 16 $\mu g/m^3$.  The
maximum likelihood estimate

(MLE) of unit risk based on several tumor types observed in male

**Table 7-9.      Summary of Data Set Used to Calculate Unit Risk Estimate for 1,3-Butadiene.**

| Source | Test Animal | Tumor Type | Administered Dose (ppm) | Internal Dose (mg/kg/day) | Tumor Incidence |
|---|---|---|---|---|---|
| NTP (1984) | B6C3F1 mice | Hemangiosarcomas of the heart, lymphomas, and alveolar/ bronchiolar adenomas/ carcinomas | 0 | 0 | 2/50 (male) 4/48 (female) |
| | | | 625 | 18.4 | 43/49 (male) 31/48 (female) |
| | | | 1250 | 27.8 | 40/45 (male) 45/49 (female) |

and female mouse NTP data for a 1 ppm continuous lifetime exposure in the air is $2.5×10^{-2}$ ($2.8×10^{-5}$ [$\mu g/m^3$]$^{-1}$).

The unit risk estimates in EPA (1985) were different from those reported in EPA (1992) because the values were calculated using the absorption data from the 1985 NTP absorption study which reported an absorption rate of 54% in mice and rats. Therefore, according to EPA (1985), calculations from the NTP (1985) study resulted in an inhalation unit risk estimate of $9.1×10^{-1}$ (ppm)$^{-1}$ ($1.0×10^{-3}$ [$\mu g/m^3$]$^{-1}$) for males and $4.5×10^{-1}$ (ppm)$^{-1}$ ($5.0×10^{-4}$ [$\mu g/m^3$]$^{-1}$) for females with a geometric mean of $6.4×10^{-1}$ (ppm)$^{-1}$ ($7.2×10^{-4}$ [$\mu g/m^3$]$^{-1}$).  In this case, the unit risk was not to be used if the air concentration exceeded 40 $\mu g/m^3$ since the slope factor may differ from that stated at higher concentrations.

## 7.6.2    Other Views and Risk Estimates

This section presents alternate views and/or risk assessments for 1,3-butadiene.  These alternate risk assessments are summarized in Table 7-10.  All alternate risk assessments are expressed as UCLs; no MLEs are presented.

International Agency for Research on Cancer (IARC)

IARC has classified 1,3-butadiene as a Group 2A carcinogen. A Group 2A carcinogen is defined as an agent that is *probably* carcinogenic to humans.  This classification is based on limited evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in animals (IARC, 1992).

IARC reviewed the available human data and concluded that these studies do provide some evidence that occupational exposure to 1,3-butadiene is associated with an excess of leukemias and lymphomas.  However, these data are considered by IARC to be limited because concomitant exposure to other potentially carcinogenic agents (e.g., styrene and benzene) preclude any definitive causative link to be drawn between exposure to 1,3-butadiene and cancer.

IARC concluded that the available animal data provide sufficient evidence of the carcinogenicity of 1,3-butadiene. These data consist of inhalation studies in mice and rats conducted by NTP (1984) and Hazleton Laboratories Europe, Ltd. (Owen et al., 1987).  Details of these studies were mentioned previously in Section 7.6.1.1.  No unit risk was determined by IARC.

California Air Resources Board (CARB)

CARB (1992a,b) has performed an assessment of the carcinogenic risk of 1,3-butadiene using both the mouse (NTP, 1984; Melnick et al., 1990) and rat (Owen et al., 1987) data in

the linearized multistage model.  As EPA did, total significant tumor incidences

**Table 7-10.    Comparison of 1,3-Butadiene Unit Risk Estimates and Calculated Doses for an Extra Lifetime Cancer Risk of $1 \times 10^{-6}$.**

| Source | Tumor Types | Classification | Cancer Unit Risk Estimate $(\mu g/m^3)^{-1}$ | Dose $(\mu g/m^3)$ For a Cancer Risk of $1 \times 10^{-6}$ |
|---|---|---|---|---|
| OSHA (1990)[b] | Pooled female mouse tumors, multiple types[c] | Human Carcinogen | $5.8 \times 10^{-6}$ | $1.7 \times 10^{-1}$ |
| | Pooled female mouse hemangiosarcomas | | $2.7 \times 10^{-6}$ | $3.7 \times 10^{-1}$ |
| | Pooled female rat tumors[d] | | $7.5 \times 10^{-6}$ | $1.3 \times 10^{-1}$ |
| EPA (1985) | Pooled male and female mouse tumors | Group B2[e] | $7.2 \times 10^{-4f}$ | $1.4 \times 10^{-3}$ |
| | Pooled male rat tumors | | $4.7 \times 10^{-4}$ | $2.1 \times 10^{-3}$ |
| | Pooled female rat tumors | | $6.2 \times 10^{-4}$ | $1.6 \times 10^{-3}$ |
| ICF (1986) | Male mouse lymphomas | – | $3.4 \times 10^{-3}$ | $2.9 \times 10^{-4}$ |
| | Female mouse liver tumors | | $2.6 \times 10^{-4}$ | $3.8 \times 10^{-3}$ |
| Turnbull et al. (1990) (Environ) | Pooled male rat tumors[g] | – | $5.9 \times 10^{-7}$ | $1.7 \times 10^{+0}$ |
| | Pooled female rat tumors[h] | | $5.1 \times 10^{-7}$ | $2.0 \times 10^{+0}$ |
| EPA (1992) | Pooled female mouse data | Group B2 | $2.8 \times 10^{-4}$ | $3.5 \times 10^{-3}$ |

**Table 7-10. Continued.**

| Source | Tumor Type | Classification | Cancer Unit Risk Estimate $(\mu g/m^3)^{-1}$ | Dose $(\mu g/m^3)$ For a Cancer Risk of $1 \times 10^{-6}$ |
|---|---|---|---|---|
| Hattis and Watson (1987) | Male rat-total tumors | - | $1.1 \times 10^{-7}$ | $9.3 \times 10^{+0}$ |
| | Female rat-total tumors | | $1.3 \times 10^{-6}$ | $7.6 \times 10^{-1}$ |
| | Male mice-total tumors | | $2.3 \times 10^{-5}$ | $4.5 \times 10^{-2}$ |
| | Female mice-total tumors | | $1.7 \times 10^{-5}$ | $6.0 \times 10^{-2}$ |
| IARC (1992) | Multiple tumors | Group 2A[i] | - | - |
| CARB (1992b) | Total rat tumors (less mammary fibroadenomas and uterine tumors) | - | $4.4 \times 10^{-6}$ | $2.3 \times 10^{-1}$ |
| CARB (1992b) | Total mouse tumors | - | $1.7 \times 10^{-4}$ | $6.0 \times 10^{-3}$ |

[a]MLEs are not presented because they were not always calculated by the various organizations. Furthermore, EPA dose not generally compare MLEs based on animal data because of the high variability associated with these numbers. Therefore, they are of little value.
[b]Source: Grossman and Martonik, 1990. Based on estimates of extra risk per 10,000 for a lifetime occupational exposure. The following assumptions were made: absorption at low doses is 54%, adult body weight is 70 kg, adult breathing rate is 10 $m^3$/8-hour day, exposure is for 250 days/year for 45 years of a 74 year lifetime.
[c]Incidence of lymphoma excluded from pooled tumor incidence.
[d]High-dose group dropped from the analysis.
[e]Group B2 = Probable Human Carcinogen
[f]UCLs is the geometric mean of the UCLs estimated from the male mouse data and the female mouse data.
[g]Incidence of Zymbal gland carcinoma excluded from pooled tumor incidence.
[h]Incidence of mammary fibroadenoma excluded from pooled tumor incidence.
[i]Group 2A = Probable human carcinogen.

for each species and sex were used instead of individual site-specific tumor incidences because CARB believed that tumors which rapidly resulted in animal mortality may have masked the development of tumors at other, possibly more sensitive sites.

CARB concluded that, for use in risk assessment, the quality of the Melnick et al. (1990) is superior to that of the rat data. The primary reasons for this conclusion are: 1) the use of lower, more relevant dose levels in the Melnick et al. (1990) study; 2)the use of five dose levels in the Melnick et al. (1990) study, compared to two in the rat study; 3) the presence of two mouse studies; 4) the fact that the rat study has not been replicated; 5) the consistency in sites of carcinogenicity between the two mouse
studies; 6) the greater detail in the available mouse data which allows in-depth analysis; and 7) suggestions from limited epidemiological observations that 1,3-butadiene exposure may be associated in humans with lymphatic and hematopoietic cancers, effects that were seen in mice. The continuous internal dose (i.e., the dose of butadiene that is retained in the animal) was considered by CARB to be the best estimate of delivered dose (i.e., the dose of butadiene that is actually available at target tissue sites) available. The continuous internal doses were derived from the applied external doses using the data of Bond et al. (1986).

CARB calculated the theoretical human risk associated with a continuous lifetime exposure to butadiene ($q_1^*$, 95% UCL) as $1.7 \times 10^{-4}$ $[\mu g/m^3]^{-1}$ based on the mouse inhalation study of Melnick et al. (1990). The risk based on the mouse data is comparable to EPA's current unit risk of $2.8 \times 10^{-4}$ $[\mu g/m^3]^{-1}$, which is a geometric mean of the unit risks derived from the male and female mouse data sets (EPA, 1992, see Section 7.6.1.5).

CARB also fit the data to various other models. They concluded that the data gave better fits to the linearized multistage model or the GLOBAL 86 version of the linearized

multistage model than to the other models. They concluded that the mouse provides the best estimate for the upper bound for plausible excess cancer risk to humans.

Based on the findings of 1,3-butadiene-induced carcinogenicity and the results of the risk assessment, CARB finds that, at ambient concentrations, 1,3-butadiene is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

Occupational Safety and Health Administration (OSHA)

OSHA contracted with ICF/Clement (ICF/Clement, 1986) to conduct a risk assessment on 1,3-butadiene to be used as rule-

making support in setting a revised occupational exposure standard for this chemical.  ICF/Clement's risk assessment differed from EPA (1985) only by the data set used, and the final adjusted doses used in the risk assessment.  ICF/Clement expressed dose in parts per million, employed the linearized multistage model for low-dose extrapolation, adjusted for less-than-lifetime exposure, and adjusted the experimental dose for absorption.  This adjustment differed from that used by EPA (1985) and was done using a line generated by plotting a log-log scale based on data reported in EPA (1985) that indicated retention of 1,3-butadiene is inversely related to dose.  As in the EPA (1985) risk assessment, the data from the NTP (1984) mouse bioassay were used to calculate the unit risk for 1,3-butadiene.  However, EPA used pooled tumor incidence data for mice, whereas ICF/Clement used site-specific individual tumor data.  ICF/Clement claimed that the multistage model is based on the observation that cancer is a progressive disease that develops in stages.  Data are available suggesting that the number of stages or the stage at which a particular carcinogen acts may vary among different organ systems in the body. Therefore, ICF/Clement concluded that the use of pooled tumor data is not well-justified on theoretical grounds, even though EPA felt differently when it developed a potency factor for 1,3-butadiene.  The results of these analyses for the worst case (male mouse lymphoma) and best case (female mouse liver tumors), as compared to those calculated by EPA are presented in Table 7-10.

OSHA also conducted its own risk assessment of 1,3-butadiene (Grossman and Martonik, 1990).  In this risk assessment, experimental dose was measured in milligrams per kilogram per day and adjusted for absorption (method not specified).  The risks were derived using both pooled tumor and site-specific tumor incidence data for both mice (NTP, 1984) and rats (Owen et al., 1987), using the multistage model.  The results of these analyses, as compared to those performed by EPA (1985), ICF/Clement (1986), CARB (1991), and Environ (see section below) are presented in Table 7.10.

Chemical Manufacturer's Association (CMA)

CMA contracted with Environ Corporation to perform an independent assessment of the potential risk to workers from exposure to 1,3-butadiene (Turnbull et al., 1990).  Environ's risk assessment departed from that of EPA (EPA, 1985) with regard to the data set used and the low dose extrapolation models employed.  However, like EPA, (1985), they measured dose in milligrams per kilogram per day and adjusted the experimental dose of 1,3-butadiene for retained dose, assuming an absorption of 54%, regardless of dose.  EPA (1992) has since revised their calculation of the unit risk by assuming a 20% absorption rate at low exposures as per Cote and Bayard (1990) (see discussion in Section 7.6.1.5).  Environ disagreed with the choice of the mouse

data from the NTP (1984) study as the basis for the unit risk for a number of reasons (Environ, 1987).

In an attempt to address some of the perceived uncertainties with the NTP (1984) mouse data listed in Environ 1987, Environ employed the following procedures.  Separate extrapolations were conducted based on tumor-bearing animals having any of the tumors that showed a significant increase in incidence in one or both of the treated groups, and on the same animals except those that developed lymphoma.  To account for the less-than-lifetime exposure duration in the mouse study, the Hartley-Sielken general product model was used.  The results of these calculations are summarized in Table 7-10.

Environ also calculated unit risks on the rat data from the Hazleton Laboratories Europe, Ltd. study (Owen et al., 1987) using three different low-dose extrapolation models.  However, the tumor incidences from this study that were used by Environ differed from those used by EPA for unexplained reasons.  The results of the unit risk estimates resulting from the use of the multistage model only are presented in Table 7-10.

The results of these analyses generally predicted lower risks than those predicted by EPA, and indicate that mice appear to be at a greater risk (by a factor of 5-fold to 40-fold) than rats.  Environ noted that some of this species difference (3-fold to 5-fold) may be due to differences in metabolism, and that mice metabolize 1,3-butadiene to the carcinogenic epoxide derivatives at a higher rate than rats (though not mentioned by Environ in its analysis, this species difference could reflect decreased elimination of reactive intermediates in mice as compared to rats).  In addition, Environ predicted the lifetime risk to humans using several exposure levels based on all of the risk estimates derived above.  This risk was then used to calculate the expected number of extra deaths from lymphopoietic cancer and compared them to the actual number of deaths observed in the Matanoski et al. (1982) cohort.  This exercise led to the conclusion that these risks were inconsistent with the observations made in occupational studies, i.e., the animal risks (particularly those based on the mouse data) overpredicted the risk to humans.  However, it should be noted that the revised risk estimate for butadiene cited in EPA (1992) that incorporates a new absorption factor results in the prediction of 40% less excess cancer cases (Cote and Bayard, 1990).  Therefore, the conclusions of Turnbull et al. (1990) with regard to overpredicting the risk to humans exposed to butadiene may no longer be valid.

Hattis and Wasson (1987)

Hattis and Wasson (1987) developed a pharmacokinetic/mechanism-based model for butadiene in an attempt to further refine the estimate of the "effective" dose for 1,3-

butadiene to be used in risk assessment.  This model estimates
the effective dose "as the total amount of butadiene that
eventually undergoes at least the first step of metabolic
activation to 3,4-epoxy-1-butene".  Development of this model
required an estimation of the octanol/water partition coefficient
from chemical structural information and a water/air partition
coefficient from aqueous solubility information as a function of
temperature so that tissue/blood and blood/air partition
coefficients could be estimated.  Contrary to previous
assumptions that butadiene was metabolized only in the liver, the
model was structured to allow butadiene metabolism throughout the
"vessel-rich group" (kidneys, viscera, and brain) in addition to
the liver.  Finally, maximal metabolic rates for humans were
scaled using general metabolic rates -- (body weight)$^{.75}$.  Using
their model, Hattis and Wasson (1987) calculated rodent
metabolized doses that were 2-4.5 times the absorbed doses used
in earlier (i.e., EPA [1985] and Environ [1987]) risk
assessments.  This larger metabolized dose effectively reduces
the apparent carcinogenic potency of butadiene as compared to the
earlier risk assessments.  Another factor that reduces the
carcinogenic risk of butadiene is the fact that this model
predicts that net absorption will represent only about 11-15% of
the butadiene reaching the alveoli over an 8-hour period, and
only 8-10.5% of total inhaled butadiene.

Risk assessments conducted prior to Hattis and Wasson's work
assumed 50% of total inhaled butadiene would be absorbed by
humans at low doses.  (However, in the most current EPA
assessment [1992], an absorption factor of 20% is used, see
discussions above).  This difference results in a further
reduction of human delivered dose, and therefore, risk.  Hattis
and Wasson (1987) also differed from the EPA (1985) and Environ
(1987) risk assessments in the manner in which they treated tumor
incidence.  Rather than add up the tumor-bearing animals at all
sites with statistically significant tumor increases before
calculating risk, they calculated separate risks from each
individual site and then added up the overall expected risks from
all of the sites at the end.[1]  The effect of such an approach is
most likely to overestimate the risk.  The UCLs calculated using
the effective doses estimated with their model as compared to the
UCLs calculated by EPA, CARB, ICF/Clement, OHSA, and Environ are
summarized in Table 7-10.

National Institute for Occupational Safety and Health (NIOSH)

NIOSH (Dankovic et al., 1991) developed a quantitative risk

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[1]While it is appropriate and acceptable to consider each tumor separately,
model each response, and then combine the probabilities at the end to arrive at
an overall expected risk, it is not correct to simply add the individual tumor
risks.  It is correct to add the individual risks together and then subtract out
the product of the risks to arrive at the overall risk, and this is most likely
what Hattis and Wasson (1987) actually did, as evidenced by the numbers presented
in their table.

assessment of 1,3-butadiene based on the NTP bioassay in B6C3F$_1$ mice of Melnick et al. (1990). The risk assessment utilized the data from the published report as well as the data on the time of death and tumor status of each individual mouse in the study. The NIOSH study also chose to use exposure concentration instead of internal dose and the Weibull time-to-tumor model to determine their risk estimate.

Excess risk estimates were derived from fitting the one-stage, two-stage, and three-stage Weibull time-to-tumor models to the seven individual tumor types observed in the male mice, and to the nine individual tumor types observed in the female mice. Overall, the estimate yielding the largest extrapolated human risks at low exposure concentrations, that is, the most sensitive site, was the female mouse lung. Based on this site, the projected excess risk for a person occupationally exposed to 2 ppm 1,3-butadiene, for an entire working lifetime, is estimated to be 597 cases of cancer per 10,000 ($5.97 \times 10^{-2}$), or approximately 6 per 100.

Caution must be taken in comparing this number to the previously stated risk estimates summarized in Table 7-10. The risk estimates in Table 7-10 are based on a 70 year lifetime exposure to 1 μg/m$^3$ of 1,3-butadiene whereas, the NIOSH risk estimate is based on a working lifetime exposure of 2 ppm ($4.42 \times 10^3$ μg/m$^3$) 1,3-butadiene.

## 7.6.3    Recent and Ongoing Research

### 7.6.3.1   Genotoxicity

Two new studies were published after the EPA assessment that supported the observation that metabolites of 1,3-butadiene are genotoxic (Gervasi et al., 1985; Sharief et al., 1986). The study by Gervasi et al. (1985) observed that 1,2:3,4-diepoxybutane is a potent mutagen in the *S. typhimurium* mammalian microsome assay. Gervasi et al. (1985) also demonstrated that the potency of 1,2:3,4-diepoxybutane in this assay correlated well with the alkylating ability of this compound using nicotinamide as a substrate. Sharief et al. (1986) examined the *in vivo* genotoxicity of another 1,3-butadiene metabolite, 1,2-epoxybutene-3. A single intraperitoneal injection of 1,2-epoxybutene-3, at doses as low as 25 mg/kg, produced a significantly increased frequency of sister chromatid exchange (SCE) and chromosomal aberrations in bone marrow cells of C57B1/6 mice.

At the time of the EPA assessment (EPA, 1985), no *in vivo* studies of the genotoxicity of 1,3-butadiene were available for review. A number of inhalation studies have since been completed that examine the genotoxic effects of 1,3-butadiene exposure. For example, exposure of rats and mice to concentrations of 1,3-butadiene ranging from 10 to 10,000 ppm for 6 hr/day for 2 days

produced no increase in the frequency of micronucleus (MN) induction or SCE in bone marrow of Sprague-Dawley rats, but significantly increased the frequency of MN and SCE in bone marrow of B6C3F1 mice at doses as low as 100 ppm (Choy et al., 1986; Cunningham et al., 1986).[2]  No increase in MN or SCE was observed in the B6C3F1 mice at 50 ppm.  Exposure of B6C3F1 mice to concentrations of 1,3-butadiene ranging from 6.25 to 625 ppm for a somewhat longer period (6 hr/day, 5 days/week, for 2 weeks) revealed significant increases in SCE at 6.25 ppm, MN at 62.5 ppm, and chromosomal aberrations at 625 ppm in bone marrow (Tice et al., 1987).  Chromosomal aberrations were predominantly chromatid-type breaks and exchanges.  Increases in MN in peripheral blood were observed at doses of 1,3-butadiene as low as 6.25 ppm following longer-term exposure (for 6 hr/day, 5 days/week, for 13 weeks) (Jauhar et al., 1988).  The potent genotoxicity of 1,3-butadiene in the mouse compared with the absence or low level of such effects in rats are consistent with the relative carcinogenic effects in these two species.

The strain specificity of the genotoxic effects in the mouse was tested by comparing chromosomal damage in B6C3F1 mice with that seen in NIH Swiss mice (Irons et al. 1987a).  After a single 6-hour exposure to 1,250 ppm 1,3-butadiene, a high frequency of chromosomal aberrations, chromatid breaks, and chromatid and isochromatid gaps were seen in both strains of mice.[3]  The NIH Swiss mouse does not possess murine leukemia virus, indicating that the genotoxicity of 1,3-butadiene is not dependent on the presence of this virus.  However, the virus may play a role in the expression of murine leukemogenesis in the B6C3F1 strain.

Exposure of B6C3F1 mice and Wistar rats to ($^{14}$C)-1,3-butadiene (approximately 700 ppm for 4-7 hours) resulted in covalent binding of the radioactivity to liver nucleoproteins (a combination of a nucleic acid and a protein that is found in cell nuclei) and DNA in both species (Kreiling et al., 1986a).  The alkylation of nucleoproteins was approximately twice as high in mice as in rats.  The degree of alkylation was proportional to the different rates of metabolism of 1,3-butadiene in these two species.  In contrast, the incorporation of radioactivity into DNA was approximately equal in both mice and rats.  It is unclear to what extent the incorporation of radioactivity in DNA represented alkylation of nucleosides or metabolic incorporation into nucleosides.  However, an alkylation product of guanine, 7-

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[2]Micronuclei are formed after cell division when pieces of chromosomes do not get included within either nucleus of the newly formed cells.  Sister chromatid exchange occurs when pieces of DNA break off and reattach to another piece of DNA.  An increased frequency of micronuclei or SCE indicates chromosome breakage.

[3]A chromatid gap is a short missing region of DNA in one strand of a dividing chromosome.  An isochromatid gap is a short missing region of DNA in one strand of an abnormally dividing (i.e., two strands break instead of each of the strands separating intact) chromosome.

(1-hydroxy-3-buten-2-yl) guanine was identified in mouse liver DNA after inhalation exposure to 1,3-butadiene (Laib and Kreiling, 1987).

A dominant lethal study in CD-1 mice was performed following inhalation exposure of males to concentrations of 1,3-butadiene ranging from 200 to 5,000 ppm for 6 hr/day for 5 days (Hackett et al., 1988b).  A significant increase in intrauterine deaths was observed in females bred with males exposed to 1,000 ppm but not in females bred with males exposed to 5,000 ppm.

Cytogenetic monitoring of 1,3-butadiene rubber workers was reported in an abstract by Zhou et al. (1986).  No significant increase in chromosomal aberrations or SCE in peripheral lymphocytes was observed when a group of 30 styrene-butadiene workers were compared with matched controls.  Sex, age, and smoking status were considered in the analysis.  However, 1,3-butadiene exposure levels were not measured and workers may have been exposed to toluene.

7.6.3.2    Pharmacokinetics

1,3-Butadiene is a carcinogen in both rats and mice, with mice being substantially more sensitive than rats (Csanády and Bond, 1991a).  In the development of the pharmacokinetic model by CIIT, both *in vitro* and *in vivo* studies have demonstrated that 1,3-butadiene is metabolized by cytochrome P-450 to 1,2-epoxy-3-butene (butadiene monoepoxide, BMO).  Further metabolic activity may transform BMO to two other metabolites, 1,2-epoxy-3,4-butanediol and diepozybutane (DEB).  All three epoxides can potentially interact with DNA (Bryant and Osterman-Golkar, 1991).  Not all of the metabolites of 1,3-butadiene have been identified yet, and those that have been identified, there has been limited pharmacokinetic testing.

Differences in the pharmacokinetics of 1,3-butadiene in mice and rats have been more closely examined in recent studies in an effort to explain the differences in the carcinogenic potency of 1,3-butadiene in these two species.

Many studies (Bond et al., 1986, 1987, 1988; Deutschmann and Laib, 1989; Kreiling et al., 1986b, 1987, 1988; Schmidt and Loeser, 1985, 1986; Jelitto et al., 1989) suggest that differences in species carcinogenicity susceptibility may be related to differences in 1,3-butadiene metabolism.  When compared to the rat, mice have both a higher rate of 1,2-epoxybutene-3 synthesis and presence of DNA adducts, as well as a limited ability to detoxify this metabolite.

A physiologically-based, pharmacokinetics model for 1,3-butadiene exposure in rats and mice, based on the conversion of 1,3-butadiene to 1,2-epoxybutene-3, was developed by Hattis and Wasson (1987) utilizing blood butadiene concentrations as

described by Bond et al. (1986) and metabolic rates as described by Kreiling et al. (1986b). For this model, blood/air and tissue/air partition coefficients were estimated from structural and solubility information. According to this model, however, differences in pharmacokinetics failed to account for the differences in carcinogenicity of 1,3-butadiene in these two species.

Recent data from Csanády and Bond (1991b) indicate that the maximum rates of 1,3-butadiene metabolism in liver microsome isolated from humans, B6C3F$_1$ mice, and Sprague-Dawley rats (all male) are in the ratio of approximately 3:3:1. However, the investigators found that the key ratio that governs metabolic rates at low concentrations was 5-fold greater in mouse liver than in human liver. This means that the mouse produces more in the way of potential adduct forming metabolite (BMO), and thus is considered a more susceptible species. Csanády and Bond (1991b) also report that B6C3F$_1$ mouse lung microsomes are much more active than human lung microsomes in metabolizing 1,3-butadiene to BMO, with the key metabolic ratio in the mouse lung being approximately 6-fold greater than in the human lung.

In a recent presentation by CIIT (Recio et al., 1991) the *in vivo* mutagenicity of 1,3-butadiene was assessed in lung, liver, and bone marrow using a transgenic mutagenicity assay. It was found that the overall activation (by oxidation) of 1,3-butadiene to BMO was significantly higher for mice, especially in the lung. The detoxification of BMO (by hydrolysis) is slower in the mouse than in the rat or the human; thus, this correlates with the higher carcinogenicity sensitivity of mice than rats to 1,3-butadiene.

7.6.3.3   Carcinogenicity - Animal Studies

Additional information regarding the carcinogenicity of 1,3-butadiene in animals has been presented since the EPA mutagenicity and carcinogenicity assessment of 1,3-butadiene was performed in 1985. For example, another long-term inhalation study of 1,3-butadiene in B6C3F1 mice was initiated. The need for another mouse carcinogenicity study arose because the study that was originally evaluated in the EPA assessment demonstrated a strong multiple-organ carcinogenic response to 1,3-butadiene at exposure concentrations of 625 and 1,250 ppm (Huff et al., 1985), but clear dose-response relationships were not established and the study was terminated after 60 weeks of exposure because of reduced survival due to fatal tumors. Therefore, a study that examined lower exposure concentrations (6.25-625 ppm) was initiated. Preliminary results from that study through week 65 were reported (Melnick et al., 1988, 1989a, 1989b). After 65 weeks of exposure, 73/90 males and 80/90 females exposed to 625 ppm have died. The primary lesion observed in these animals was lymphocytic lymphoma. This was more prevalent in the males than in females. Other types of cancer observed in the high-dose

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animals included hemangiosarcoma of the heart, squamous cell
neoplasms in the forestomach, alveolar-bronchiolar neoplasms,
adenoma of the Harderian gland, mammary gland adenocarcinoma, and
granulosa cell neoplasms of the ovary.  Elevated incidences of
these neoplasms were also seen at 200 ppm 1,3-butadiene.
Alveolar-bronchiolar neoplasms of the lung in females were
increased above the incidence in controls at all concentrations
of 1,3-butadiene tested.

     As part of this study, three groups of animals were also
exposed for limited periods of time to study the relationship
between exposure levels and duration of exposures on butadiene-
induced carcinogenicity.  The groups consisted of male mice
exposed to 625 ppm for either 13 weeks or 26 weeks and mice
exposed to 312 ppm for 52 weeks.  The animals were then held
until 65 weeks from the start of exposure.  By week 65 of the
study, the incidence of lymphocytic lymphoma in animals exposed
to 625 ppm for 26 weeks (60%) was twice that observed in animals
exposed to 625 ppm for 13 weeks (30%), but was much greater than
the incidence in animals exposed to 312 ppm for 52 weeks (6%).
Thus, the multiple of the exposure concentration times the
exposure duration did not predict the incidence of lymphocytic
lymphoma in these mice.  However, this study revealed that the
early incidence of fatal lymphocytic lymphoma in the high-dose
animals appeared to limit the expression of tumors at other
sites.  Substantially higher levels of some tumor types were
observed in the dose group with low levels of lymphatic lymphoma
than in the dose group with high levels of lymphatic lymphoma.
For example, a much higher incidence of hemangiosarcoma of the
heart was observed in mice exposed to 312 ppm for 52 weeks (30%)
than in mice exposed to 625 ppm for 26 weeks (10%).  Other tumor
types observed at a higher incidence in mice that survived 45-65
weeks that were not observed in the NTP study because of early
deaths due to lymphatic lymphoma include squamous cell neoplasms
of the forestomach, alveolar-bronchiolar neoplasms, Harderian
gland adenomas, adenocarcinomas of the mammary gland, granulosa
cell neoplasms of the ovary, and hepatocellular neoplasms.  This
study is significant in that it demonstrated that:  (1) exposure
to lower levels of 1,3-butadiene than those used in the study
that served as the basis for the EPA risk assessment allows the
expression of neoplasms at other sites because of a lower number
of early mortalities; (2) a clearer dose response relationship
for 1,3-butadiene-induced lymphocytic lymphomas was obtained
using the lower exposure levels because of increased survival;
and, (3) the multiple of exposure duration and concentration does
not predict the incidence of lymphocytic lymphomas.  These
findings are relevant to the current EPA assessment of 1,3-
butadiene carcinogenicity because they demonstrate that the
induction of neoplasms in mice at multiple sites (i.e., some that
were not considered in the current assessment) occurs at lower
concentration levels than those used to derive the cancer potency
factor.

A study characterizing the lymphomas observed in B6C3F1 mice exposed to 1,250 ppm 1,3-butadiene for 28 to 45 weeks reported that the lymphomas consisted of well-differentiated lymphoblasts of T-cell origin (i.e., cells that develop into lymphocytes that subsequently migrate to the thymus gland) with variable but elevated levels of murine leukemic virus antigens (virus proteins found in mice that cause leukemia) (Irons et al., 1986c). In order to test the role of the endogenous retrovirus (i.e., a type of virus that is known to cause cancer), murine leukemic virus, in the development of the thymic lymphoma/leukemia in B6C3F1 mice, NIH Swiss mice (which do not express the retrovirus) were exposed to 1,3-butadiene under identical conditions as the B6C3F1 mice (Irons et al., 1989). This study revealed that B6C3F1 and NIH Swiss mice exposed to 1,250 ppm 6 hours/day, 5 days/week, for 1 year had similar increases in chromosomal aberrations and micronuclei in bone marrow and micronuclei in the peripheral blood, but NIH Swiss mice had a much lower incidence of lymphoma (14%) than did the B6C3F1 mice (57%). The tumors in both strains were morphologically similar, but the lymphoblasts in NIH Swiss mice did not have surface antigens for the murine leukemic virus. These results demonstrate that expression of the retrovirus is not entirely responsible for the incidence of lymphoma. However, the murine leukemic virus may influence the incidence of the lymphoma in B6C3F1 mice.

The carcinogenicity study in rats that was reviewed in the EPA carcinogenicity assessment but was available only as an unpublished report from Hazleton, has been published (Owen et al., 1987). This report (Owen et al., 1987) contains the same information as the Hazleton report that is summarized in the EPA carcinogenicity assessment. In summary, the data suggested treatment related increases in mammary gland, thyroid, and testicular tumors. The authors proposed that the carcinogenic effect was likely an indirect effect mediated through the endocrine system rather than through the production of reactive intermediates.

7.6.3.4  Carcinogenicity - Epidemiological Studies

The results of another epidemiologic study of 1,3-butadiene-exposed workers have been reported since the original EPA assessment (EPA, 1985). This study examined the mortality of 2,586 workers employed for at least 6 months between 1943 and 1979 at a 1,3-butadiene manufacturing facility (Downs et al., 1987). Data regarding exposure levels were not available, but workers were divided according to 4 qualitative exposure categories based on employment records. The categories of exposure were:  low exposure, routine exposure (included process workers), nonroutine exposure (intermittent exposure; maintenance workers), and unknown exposures. The overall mortality of the workers was significantly below the U.S. national average (standardized mortality ratio (SMR) = 80). However, the SMR for lympho- and reticulo-sarcoma of the whole cohort was

significantly greater than the U.S. national average (SMR = 235; 95% CI = 101 to 463).  Lympho- and reticulosarcoma are malignant diseases of the lymphatic system and the reticuloendothelial system, respectively.  The reticuloendothelial system are cells scattered throughout the body that have the power to ingest particulate matter.  When calculated by exposure category, the routine exposure group had significant increases in lymphohematopoietic and kidney cancer and the nonroutine exposure group had a significantly increased rate of leukemia when compared to the U.S. national average.  These rates of cancer were elevated when compared to the local cohort, but were not statistically significant.  Limitations of this study included an unreliable designation of race, lack of worker histories, and the observations that nearly half of the cohort worked at the facility for less than 5 years and that many workers had spent time working at neighboring styrene-butadiene rubber plants.

An update of the Downs et al. (1987) study and updates of two studies originally contained in the EPA 1985 assessment have also been published.  In the update of the study by Downs et al. (1987), the workers' mortality experience through 1985 was examined (Divine, 1990).  One additional death from lymphosarcoma had occurred since the previous analysis by Downs et al. (1987).  Findings were similar to those reported in the 1987 study.  Excess mortality due to lymphatic and hematopoietic cancers were seen primarily in those occupational categories with the greatest known exposure to 1,3-butadiene, in those with less than 10 years of employment, and in those employed during World War II.

In the update of the study by Matanoski and Schwartz (1987), followup of workers was improved and extended through 1982 (Matanoski et al., 1990).  The cohort in the update was restricted to 12,100 workers by limiting employees from the one Canadian plant to those who had worked 10 years or more or who had reached age 45 during employment.  Overall mortality in these workers was less than the U.S. national average (SMR = 81).  The only significant increase in mortality observed in the workers was in arteriosclerotic heart disease among black employees compared to the U.S. national average (SMR = 1.48, 95% CI: 1.23-1.76).  The workers were subdivided according to the job held the longest.  The categories of employment included production, utilities, maintenance, and a combination of all others.  Significant increases in mortality were observed among the production workers.  Combined race data showed a significant increase in other lymphatic malignancies (SMR = 2.60, 95% CI: 1.19-4.94) and blacks had significant increases in all lymphopoietic cancers (SMR = 5.07, 95% CI: 1.87-11.07) and in leukemia (SMR = 6.56, 95% CI: 1.35-19.06).  Whites had elevated mortality due to lymphatic (SMR = 2.30, CI: 0.92-4.73) and hematopoietic (SMR = 1.10, CI: 0.58-1.87) malignancies, but the increase was not statistically significant.  This study is somewhat limited in that the race designation of approximately 15% of the workers was unknown but was assumed to be white.

A nested case-control study of the lymphopoietic neoplasms from the cohort of butadiene workers studied by Matanoski and Schwartz (1987) was conducted by Santos-Burgoa (1988). The 59 cases of lymphopoietic neoplasms were matched to controls based on plant, age, hire date, duration of work, and survival to the death date of the case. Exposures to 1,3-butadiene for the cases and controls were estimated through a ranked job exposure matrix which was multiplied by the duration of exposure to yield estimates of cumulative exposure. In a matched analysis based on a categorization of exposure above and below the geometric mean, a statistically significant odds ratio of approximately 2.0 (OR = 2.0) for all lymphopoietic neoplasms and OR = 9.0 for leukemia was calculated for butadiene exposure. Both types of analysis that were performed in this study showed a significant trend for leukemia with cumulative butadiene exposure, but not for all lymphopoietic neoplasms.

An occupational epidemiological pilot study was conducted (Ward et al., 1992) to evaluate the effects of 1,3-butadiene exposure on the frequencies of lymphocytes containing mutations at the hypoxanthine guanine phophoribosyl transferase (hprt) locus in workers in a 1,3-butadiene production plant. Seven workers from areas of the plant where the highest exposures to 1,3-butadiene occur were compared to four workers from plant areas where 1,3-butadiene exposures were low. In addition, four workers from the investigating laboratory were also studied as outside controls. All the subjects were non-smokers. An air sampling survey indicated that average 1,3-butadiene levels in the high exposures area were about 3.5±7.5 ppm while they were 0.03±0.03 in the low exposure area. The low-exposed controls and the outside controls mean variant frequencies, 1.19 and 1.03 respectively, were not significantly different, but the mean frequency of mutant lymphocytes in the seven exposed subjects (4.09) was significantly higher when compared to the means of the eight controls. The observation of an elevated mean in the exposed subjects indicates that exposures occurring in areas where higher concentrations of 1,3-butadiene have been documented were sufficient to induce higher frequencies of somatic cell mutants. Additional studies are being conducted to confirm the effects that have been observed.

## 7.7  Carcinogenic Risk for Baseline and Control Scenarios

Table 7-11, summarizes the annual cancer incidences for all the scenarios. When comparing cancer incidence for the base control scenarios relative to 1990, there is a 31% reduction in 1995, a 42% reduction in 2000, and a 33% reduction in 2010 which is actually an increase when compared to 2000. The reduction in emissions are considerably higher, particularly in the out years. The projected increase in both population and vehicle miles traveled (VMT) from 2000 to 2010 appears to offset the gains in emissions achieved through fuel and vehicles modifications.

From Table 7-11 it can also be observed that the expanded use scenarios provide little additional reduction in the cancer cases.

**Table 7-11.  Annual Cancer Incidence Projections for 1,3-Butadiene. [a,b]**

| Year-Scenario | Emission Factor g/mile | Urban Cancer Cases | Rural Cancer Cases | Total Cancer Cases | Percent Reduction from 1990 | |
|---|---|---|---|---|---|---|
| | | | | | EF | Cancer |
| 1990 Base Control | 0.0156 | 258 | 46 | 304 | – | – |
| 1995 Base Control | 0.0094 | 177 | 32 | 209 | 40 | 31 |
| 1995 Expanded Reformulated Fuel Use | 0.0093 | 175 | 32 | 207 | 40 | 32 |
| 2000 Base Control | 0.0071 | 149 | 27 | 176 | 54 | 42 |
| 2000 Expanded Reformulated Fuel Use | 0.0069 | 145 | 26 | 171 | 56 | 44 |
| 2000 Expanded Adoption of California Standards | 0.0069 | 146 | 26 | 172 | 56 | 43 |
| 2010 Base Control | 0.0067 | 173 | 31 | 204 | 57 | 33 |
| 2010 Expanded Reformulated Fuel Use | 0.0064 | 164 | 30 | 194 | 59 | 36 |
| 2010 Expanded Adoption of California Standards | 0.0062 | 158 | 28 | 186 | 60 | 39 |

[a]Projections have inherent uncertainties in emission estimates, dose-response, and exposure.
[b]Cancer incidence estimates are based on upper bound estimates of unit risk, determined from animal studies.  1,3-Butadiene is classified by EPA as a Group B2, probable human carcinogen based on sufficient evidence in two rodent studies and inadequate epidemiologic evidence.

Please note that the cancer unit risk estimate for 1,3-butadiene is based on animal data and is considered an upper bound estimate for human risk. True human cancer risk may be as low as zero.


## 7.8  Non-Carcinogenic Effects of Inhalation Exposure to 1,3-Butadiene

Since the focus of this report is on the carcinogenic potential of the various compounds, the noncancer information will be dealt with in a more cursory fashion. No attempt has been made to synthesize and analyze the data encompassed below. Also, no attempt has been made to accord more importance to one type of noncancer effect over another. The objective is to research all existing data, describe the noncancer effects observed, and refrain from any subjective analysis of the data.

1,3-Butadiene is used primarily as a monomer in the production of rubber and plastics (Chemical and Engineering News, 1986). It is also found in automobile exhaust (CARB, 1991). Although no human data on the metabolism of 1,3-butadiene exist, animal studies indicate that this chemical is rapidly absorbed following inhalation (Hattis and Wasson, 1987). Inhalation of 1,3-butadiene
is mildly toxic in humans at low concentrations (not otherwise specified) and may result in a feeling of lethargy and drowsiness. At very high concentrations, 1,3-butadiene causes narcosis leading to respiratory paralysis and death. The first signs of toxicity observed in humans are central nervous system symptoms including blurred vision, nausea, paresthesia (a sense of numbness, prickling, or tingling), and dryness of the mouth, throat, and nose, followed by fatigue, headache, vertigo, decreased blood
pressure and pulse rate, and unconsciousness (Sandmeyer, 1981). Retrospective epidemiological studies indicate the possibility of higher than normal mortality rates from cancer and certain cardiovascular diseases, mainly chronic rheumatic and arteriosclerotic heart diseases, among middle-aged rubber workers (McMichael et al., 1974, 1976). Workers exposed to unknown concentrations of 1,3-butadiene during the manufacture of rubber complained of irritation of the eyes, nasal passages, throat, and lungs (Wilson, 1944). An increased rate of emphysema among rubber workers was reported by McMichael et al. (1976). No human studies on the renal, hepatic, or immunological effects of inhaled 1,3-butadiene were located in the available literature.

An $LC_{50}$ of 129,000 ppm in rats after 4 hours of exposure and an $LC_{50}$ of 122,000 ppm in mice after 2 hours of exposure were reported (Shugaev, 1969), indicating that 1,3-butadiene is only mildly acutely toxic. After chronic exposure to 1,250 ppm 1,3-butadiene, mice exhibited respiratory changes such as chronic inflammation of the nasal cavity, fibrosis, cartilaginous

metaplasia, osseous metaplasia, and atrophy of the sensory epithelium (NTP, 1984).  No histopathological cardiovascular lesions were found in mice following subchronic exposure (Crouch et al., 1979) or rats (Owen et al., 1987) following chronic exposure to 1,3-butadiene; however, NTP (1984) observed endothelial hyperplasia in the hearts of mice after 61 weeks of exposure.  In a chronic study, high incidences of liver necrosis and epithelial hyperplasia in the forestomach of mice were found at 625 ppm (LOAEL) (NTP, 1984), but no nonneoplastic gastrointestinal lesions were found in rats exposed chronically (Owen et al., 1987) or mice exposed subchronically (NTP, 1984). Macrocytic-megaloblastic anemia was observed in mice exposed to 1,250 ppm butadiene for 6-24 weeks (Irons et al., 1986a, 1986b). Bone marrow damage was expressed as reduced numbers of red blood cells, decreased hemoglobin concentration and hematocrit, and increased mean corpuscular volume of circulating erythrocytes. Decreases in red blood cell counts and hemoglobin concentrations were reported in male mice after an intermediate duration exposure of at least 62.5 ppm (Melnick et al., 1989b).  However, other studies found no hematological effects in animals following subchronic and chronic exposure to high exposure concentrations of 1,3-butadiene (Carpenter et al., 1944; Crouch et al., 1979; Owen et al., 1987).

   1,3-Butadiene appears to be a developmental toxicant.  When exposed to concentrations up to 8,000 ppm of 1,3-butadiene during gestation days 6-15, depressed body weight gain among dams was observed at all concentrations, and fetal growth was significantly decreased in the 8,000 ppm group.  Major skeletal abnormalities (wavy ribs, irregular rib ossification) were observed in the 1,000 and 8,000 ppm groups (Irvine, 1981).  In studies conducted by NTP (Morrissey et al., 1990), pregnant Sprague Dawley rats exposed to 1,000 ppm 1,3-butadiene by inhalation on gestation days 6-15 exhibited depressed body weight gain, but there was no evidence of developmental toxicity in their offspring.  In contrast, male and female fetuses of mice similarly exposed exhibited reduced weight at levels of 40 ppm and higher, and 200 ppm and higher, respectively.

   Melnick et al. (1990) reported that testicular atrophy was observed in male B6C3F1 mice exposed to 625 ppm 1,3-butadiene for 65 weeks, and ovarian atrophy was observed in female B6C3F1 mice exposed to ≥20 ppm for 65 weeks.  A concentration-related increase in the incidence of sperm-head abnormalities occurred in mice after exposure to 1,000 and 5,000 ppm of 1,3-butadiene for 6 hours/day for 5 days (Hackett et al., 1988a).  Dominant lethality (i.e., a gene mutation that must only occur in one copy of the gene to result in death of the offspring) in mice was also observed during the first 2 postexposure weeks after the males were exposed to 200, 1,000 or 5,000 ppm (Hackett et al., 1988b), suggesting that more mature cells (spermatozoa and spermatids) may be altered by 1,3-butadiene exposure.

CARB used the two-year inhalation studies with mice (Huff et al., 1985; Melnick et al., 1988, 1989a, 1989b; Miller, 1989) exposed to 0, 6.25, 20, 62.5, 200, and 625 ppm 1,3-butadiene to establish a LOAEL. These studies were designed as cancer bioassays. Gonadal atrophy was observed at a high incidence in exposed animals of both sexes at levels of 200 ppm and above, but not in any of the control animals. In the later study, using the entire dose range, levels of 6.25 ppm and higher also produced gonadal atrophy in females. Thus, a NOAEL was not established in these studies, but a LOAEL of 6.25 ppm was observed. In contrast, the Hazelton rat bioassay (Owen et al., 1987) did not report any reproductive effects even at 8000 ppm level.

Neither an inhalation reference concentration (RfC) nor an oral reference dose (RfD) is available for 1,3-butadiene at this time.

## 7.9  References for Chapter 7

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