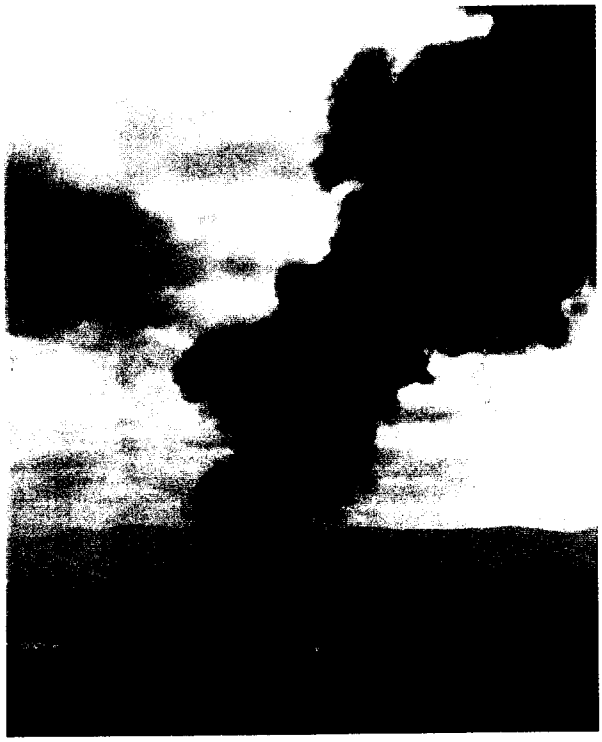
REPORT TO THE LEGISLATURE

TIRE FIRE SMOKE: MAJOR CONSTITUENTS AND POTENTIAL FOR PUBLIC HEALTH IMPACTS



May 2002

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Tire Fire Smoke: Major Constituents and Potential for Public Health Impacts

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1.0 Executive Summary

A number of tire fires have occurred in the United States and elsewhere over the years. There have been major tire fires at Panoche, Tracy and Westley within the last few years in California. The latest major tire fire occurred in September 1999 in Westley, California. Approximately five million tires caught fire and burned for 36 days. The California State Legislature subsequently requested a report from the Office of Environmental Health Hazard Assessment (OEHHA) that identified the major chemical constituents of smoke from burning tires, the toxicity of those chemicals, and the potential effects on human health from exposure to smoke from tire fires. This report will not discuss site remediation or potential ground water contamination issues from tire fires. The Integrated Waste Management Board, Department of Toxic Substances Control and the State Water Resources Board have expertise in these areas.

Currently, there are limited data available to evaluate the constituents of tire fire smoke and the potential health effects of exposure. The United States Environmental Protection Agency has sponsored studies to identify the major chemical constituents of tire smoke. These studies involve igniting chunks of tires in a laboratory, collecting the smoke and then identifying the chemicals that can be measured. Combustion generates thousands of different chemical constituents and many of these are not readily identifiable using current analytical techniques. In addition, toxicology studies must be available in order to estimate the potential health effects of exposure to a chemical that is identified from the source testing. However, toxicological studies are not available for the majority of chemicals identified in source testing. Only eight of the 78 chemicals identified in the source tests have health values for acute or chronic endpoints.

We have taken two approaches to provide information on potential health impacts of exposure to tire fire smoke. The first is to identify chemicals known to occur in tire fire smoke and describe what is known about the toxicity of those chemicals. Although, identification of individual constituents provides useful information this approach does have limitations. Not all identified constituents have been tested for toxicological properties. Furthermore, without information on concentrations to which people are exposed, it is not possible to state with certainty what health effects might result. The second approach is to consider the information available on exposure to the entire mixture (smoke). This second approach has important limitations also. Information on exposure to tire fire smoke is limited so exposure to other types of smoke must be used instead. The use of both approaches gives the best available picture of tire fire smoke toxicity.

All smoke contains toxic chemicals, different types of smoke can vary in the proportions of individual toxic constituents and toxicant classes. However, there is enough similarity between smoke types to make comparisons useful. Each tire contains about 2 gallons of oil that is similar to heating oil. Therefore tire fire smoke is probably most like an uncontrolled oil fire. Tire fire smoke is particularly irritating probably in part because sulfur dioxide is generated from the sulfur in tires.

There are a number of irritating chemicals that have been identified or are also most certainly present in tire fire smoke such as sulfur dioxide, xylenes, aldehydes, toluene, and styrene. Respirable small particles composed of a carbon core with numerous chemicals attached are also a major component of smoke. Some smoke constituents (e.g. irritants and small particles) are known to trigger asthma attacks in people with preexisting asthma. Stanislaus County data on clinic visits and phone calls seems to indicate that asthmatics did experience exacerbation of symptoms. People who have been exposed to tire fire smoke, for example at the Westley tire fire, have reported symptoms that would result from exposure to irritants. Forest fire smoke and second-hand tobacco smoke exposure have also been associated in a number of studies with exacerbation of asthma.

As noted above, tire fire smoke contains many tiny particles small enough to be inhaled into the deep lung. Those particles small enough to be inhaled into the lung are referred to as PM_{10} because they are 10 μm (10 millionths of a meter) or less in diameter. PM_{10} is known to cause increased emergency admissions to hospitals for patients with lung and heart disease. Each 10 $\mu g/m^3$ increase in 24 hour average PM_{10} concentration has been associated with a 1% increase in daily mortality in epidemiological studies conducted in a number of cities, primarily in elderly people who have pre-existing heart and/or lung disease. In London in the early 1950's, there were days when the PM_{10} concentrations were extreme (several thousand $\mu g/m^3$) and thousands of people died.

A concern of many people is the possibility of contracting cancer because of exposure to tire fire smoke. Tire fire smoke contains a number of known cancer-causing chemicals (carcinogens). The major carcinogens of concern are the polycyclic aromatic hydrocarbons (PAHs), a large group of fused six carbon ring structures that are formed with virtually all types of combustion sources to a greater or lesser extent. These combustion sources include, for example, wood burning, automobile and diesel engines and tobacco smoke. Tire fire smoke contains more PAHs than other commonly encountered types of smoke such as wood smoke. In addition to the PAHs, the carcinogens benzene and 1,3-butadiene are present in tire fire smoke. These two chemicals are common in vehicular exhaust. To put the risks in perspective, the chances of developing some kind of cancer over a lifetime are about 1 in 5. The assumption with carcinogens is that there is no threshold and that each exposure can cause some increased risk. Many regulatory agencies consider cancer risks below 1 in a million, or 10 in a million, and infrequently 100 in a million to be below a level of public health concern. The USEPA conducted a cancer risk assessment of the Everett, Washington tire fire. They concluded that the cancer risks from PAH exposure were not large. The risk from exposure to other carcinogens in tire fire smoke such as benzene and 1,3-butadiene are likely to be small relative to everyday exposure to these chemicals from other combustion sources.

Monitoring data indicate that tire fires emit trace quantities of polychlorinated dibenzo-p-dioxins and dibenzofurans, commonly known as dioxins. Although these compounds are in general initially emitted into the air, the major source of dioxin exposure to the public turns out to be through consumption of animal fat and not through

breathing contaminated air. This is because dioxins have a long environmental half life and are deposited onto vegetation. Animals consume contaminated vegetation and accumulate dioxins in their fat. When contaminated animal fat is consumed dioxins are in turn stored in human fat and slowly accumulate in most people over a lifetime. They are very slowly eliminated from the body.

The levels of dioxins found in air at some distance downwind from a tire fire are several times greater than the normal airborne levels. However, the amount of dioxins inhaled during the days to weeks that many tire fires burn is not likely to be a significant contribution to the total exposure of an individual relative to normal ongoing exposures. Dioxins are carcinogenic and have noncancer health effects as well. Any additional exposure from breathing tire smoke is undesirable but not likely to be a source of significant individual exposure relative to other sources.

PAHs and dioxins are at least partially associated with particles in the air and so can be deposited onto vegetation, including food crops. Monitoring at tire fires indicates that some surface contamination can occur especially in close proximity to tire fires. The amounts deposited a kilometer or more away from a tire fire would probably not represent a significant exposure for people consuming the crops. Metals are present in tires as a significant fraction of the total weight and could potentially be deposited onto crops since they are also in the form of particles in the atmosphere. However, the source test data from USEPA does not indicate that tire fires release significant quantities of metals into the air. The available ambient air monitoring data also indicate that public exposure to airborne metals, as the result of a tire fire is not likely to be significant.

It is true that public exposure to tire fire smoke will cause some increased risk of cancer. There is reason for concern because smoke from burning tires is about 16 times more mutagenic than residential wood smoke and about 8 times more mutagenic than open burning of plastic on a weight basis. However, it is useful to compare the exposures to these chemicals commonly experienced from other sources of combustion with the levels that have been measured during tire fires. The levels of carcinogens detected at monitoring stations, for example at the Westley tire fire, did not exceed levels commonly found in Modesto prior to the tire fire. The carcinogens measured included PAHs, benzene, and 1,3-butadiene. The favorable meteorology and prompt extinguishing of the oil part of the tire after one week played a role in reducing emissions and thus influenced the monitoring results at Westley. The increased risk of cancer experienced by fire fighters also provides useful insight. Firefighters are exposed to smoke during their entire working lives and according to some studies do experience an increased risk of cancer. The exposure that firefighters receive is much greater than public exposure over a period of days to weeks. It is unlikely that exposure to tire fire smoke will result in a significant increased cancer risk to the public.

The most significant public health risk from exposure to tire fire smoke appears to be to people with asthma, heart or lung disease who are particularly affected by exposure to irritating components of smoke including PM_{10}. The elderly with these diseases are particularly at risk. Children may be somewhat more vulnerable than healthy adults

because they breath more on a body weight basis, are more active and spend more time outdoors, all of which increases their exposure to airborne contaminants including particulate matter. Tire fires produce large quantities of smoke and depending on meteorological conditions, concentrations of irritating smoke constituents including particulate matter concentrations could become extreme. Extreme levels of particulate matter were not reached in the Westley tire fire, according to monitoring data but levels during the fire were above the state health standard of 50 $\mu g/m^3$ (24 hour average) for a number of days. Twenty-four hour average levels of PM_{10} detected during the tire fire ranged from 10.5 to 180.5 $\mu g/m^3$. In addition, on several days the Federal standard of 150 $\mu g/m^3$ (24 hour average) was exceeded. The Federal standard is not considered by California to be health protective (OEHHA and CARB, 2000a). The average PM_{10} concentration for the permanent Modesto monitoring site at I Street for 1997 (prior to the tire fire) was 32.3 $\mu g/m^3$ and the maximum value was 119 $\mu g/m^3$ (California Air Resources Board, 2001). It is important to note that monitors at a tire fire may not necessarily be located where short-term or daily average maximum concentrations would have occured.

In summary, tire fire smoke contains irritating chemicals, particulate matter and carcinogens. The acute health effects of exposure result from the irritating compounds and include eye, nose and throat irritation, exacerbation of asthma and respiratory conditions and potential exacerbation of pre-existing heart disease. The effects seen would obviously depend on the concentrations to which people are exposed. Irritation and exacerbation of asthma apparently occurred during the Westley tire fire. The available scientific information on tire fire smoke constituents and studies of exposure to other types of smoke point to the need to control tire disposal so as to avoid tire fires. In addition, the data point to the need to rapidly extinguish any tire fires that do occur. Extinguishing the oil part of the Westley tire fire at the end of the first week reduced the volume of smoke by a large percentage and the entire fire was extinguished after 36 days. If meteorological conditions had not been favorable and the fire had not been rapidly extinguished, more severe and more wide spread respiratory and cardiovascular health effects might have occurred.

The lack of toxicological studies on combustion product chemicals is a serious data gap when evaluating the health impacts of exposure to tire fire smoke. In particular there is a need for studies to better characterize the irritating properties of these chemicals. These chemicals are commonly found in urban air due to controlled and uncontrolled combustion sources such as automobiles, trucks and wood burning. Such research would also aid in understanding the effects of urban air pollution. Research studies are needed on the effects of short-term high exposures to particulates so that better public health recommendations can be developed. Research is also needed on ways to establish clean air shelters so that sensitive subpopulations can be protected when smoke concentrations become excessive. These research studies would be useful for protecting public health during tire fires. The studies would also be useful for protecting the public from forest fire smoke exposure, which is likely to be more common. In addition, research into understanding risks from additional PAHs might help clarify the relative importance of exposure to this class of compounds.

2.0 Introduction

This report is prepared in response to a mandate from the California State Legislature. SB-876 (statutes 2000, chaptered 2000; Public Resources Code, Chapter 838) requires "...preparation of a report by the Office of Environmental Health Hazard Assessment in consultation with the State Air Resources Board, the Integrated Waste Management Board, and the State Department of Health that includes, at a minimum, the major chemical constituents of smoke from burning tires, the toxicity of those chemicals, and the potential effects on human health from exposure to smoke from the tire fires. The report shall be submitted to the Governor, the Legislature and the board by December 21, 2001." (SB-876). The report addresses the risk from airborne toxicants and not issues associated with the cleanup of a site after the tire fire is extinguished, such as potential ground water contamination from site runoff.

Combustion of a complex fuel like tires is known to generate many thousands of chemicals. Analytical techniques are not readily available to identify all of the chemicals generated. However, source tests have identified many chemicals, and use of these data provides information on the major chemicals of concern. In Chapter 3, known individual chemical constituents of tire smoke are presented. The USEPA conducted source tests by igniting tires in a laboratory collecting the smoke and analyzing the constituents. In addition, monitoring for a select group of chemicals has been conducted at various accidental tire fires. The California Air Resources Board (CARB) conducted monitoring at the 1999 Westley tire fire. These data are also presented.

We have taken two approaches to provide information on potential health impacts of exposure to tire fire smoke. The first is to identify chemicals known to occur in tire fire smoke and describe what is known about the toxicity of those chemicals. Although, identification of individual constituents provides useful information this approach does have limitations. Not all identified constituents have been tested for toxicological properties. Furthermore, without information on concentrations to which people are exposed, it is not possible to state with certainty what health effects might result. The second approach is to consider the information available on exposure to the entire mixture (smoke). This second approach has important limitations also. Information on exposure to tire fire smoke is limited so exposure to other types of smoke must be used instead. The use of both approaches gives the best available picture of tire fire smoke toxicity.

Exposure to airborne toxic chemicals can occur by several different routes (Chapter 4). Breathing in the chemicals is usually the most important way that exposure occurs. Inhalation is also the only way that significant public exposure to gaseous chemicals can occur. However, a few of the chemicals exist partially or wholly as particles. These chemicals can be deposited onto soil, crops and into surface waters. Exposure to these chemicals can occur by incidental ingestion of contaminated soil, drinking contaminated water, and eating contaminated produce, dairy products or livestock. In addition, contact with contaminated dirt can result in chemicals being

absorbed through the skin. A nursing mother who is exposed to certain toxic chemicals an also pass the chemicals to the baby through her milk. A discussion of the hazards from tire fire smoke needs to consider all the ways that people can be exposed. Limited sampling data are available from vegetation in the proximity of tire fires including the Westley tire fire.

Toxicity from chemical exposure is often divided into three main categories: noncancer acute, noncancer chronic and carcinogenicity (Chapter 4). Both acute and chronic noncancer toxicity are considered to have a threshold or air concentration below which toxicity does not occur. Cancer health effects are not considered to have a threshold, although cancer risks below a certain level are not considered to be of significance. Thus for all three types of health effects there can be air concentrations of chemicals where significant health impacts would not expected in the general population. All three types of toxicity need to be considered for public exposure to tire fires, because chemicals that can cause each type of health effect are present in tire fire smoke. However, because exposures to the smoke are of relatively short duration (compared to a lifetime), the most important health impacts are likely to be acute health impacts.

For some chemicals inducing noncancer health effects, including those that occur with short term and long term exposure to chemicals, regulatory agencies have developed Reference Exposure Levels which represent an air concentration below which health effects are not expected occur at least in the majority of the population. The monitoring information from some distance away from the tire fires can be compared to these Reference Exposure Levels to give an idea if the typical public exposure concentrations are below a level that health effects would occur.

Chapter 4 discusses the toxicity of the chemicals that have been identified in Chapter 3. OEHHA has developed or endorsed health values for noncancer acute RELs, noncancer chronic RELs and cancer unit risk factors. These are presented along with the critical organs that are affected by the chemicals. Many of the chemicals found in tire fire smoke are irritants. Even though these individual chemicals might be below a level of concern identified with the acute health values or Reference Exposure Level, the combined action of so many irritants clearly had an impact at the Westley tire fire and other tire fires. Eye, nose, and throat irritation can occur from the irritant effects of smoke. Some of the irritants in smoke can cause asthma attacks in individuals with preexisting asthma conditions. Asthma attacks are potentially lethal.

The dark smoke from tire fires contains particulate matter that has its own toxicity apart from the individual chemicals. Tire fires generate huge amounts of particulate matter as can be seen from the source testing. The portion of particulate matter of most concern is the size fraction that can be inhaled deeply into the lung that is 10 μm or less in diameter, often referred to as PM_{10}. Particulate matter has been found to have major health impacts in epidemiological studies. Each increase of 10 μg/m has been associated with a 1% increase in daily mortality primarily among elderly people with pre-existing heart and lung disease. Increased PM_{10} concentrations are also associated with increased hospital admissions for asthma and heart and lung disease. Measured particulate matter

concentrations in the proximity of the Westley tire fire (Appendix B), for example were well above a level of concern on a number of days. Health data collected by Stanislaus County are consistent with an increase in asthma attacks.

As noted above, we considered the health effects of exposure to the entire mixture (smoke). Smoke from tire fires has some unique properties. For example, it is a particularly irritating smoke, and contains more polycyclic aromatic hydrocarbons (PAHs) than sources such as wood smoke (USEPA, 1997). PAHs are the principle cancer causing chemicals found in tire fire smoke. However, there are no direct toxicological or epidemiological studies that evaluate health effects of tire fire smoke. Tire fire smoke exposure has enough in common with some of the risks of exposure to forest fire smoke and smoke from urban fires to warrant discussion of some of the human health studies available from these types of exposures. In response to public concern, an assessment of cancer risk from exposure to tire fire smoke following the Everett, Washington tire fire was conducted by USEPA. While they concluded that the cancer risks were not large, such risk assessments are difficult to interpret because of the short-term nature of the exposure. Cancer potency factors are based on the assumption of long-term exposure.

The serious health threat from tire fires is likely to be the exposure to irritating chemicals and PM_{10}. This exposure can worsen asthma symptoms in those with preexisting asthma. Epidemiological evidence indicates that patients with preexisting lung or heart conditions are also at risk from PM_{10}. In addition, a study on public exposure to forest fire smoke found an increase in emergency room visits for asthma and respiratory conditions. Although tire fire smoke contains a higher amount of the cancer causing PAHs than wood smoke, other evidence suggests that public exposure to tire smoke is not likely to result in significant excess cancer risk. The risk assessment from the Everett, Washington tire fire indicates that cancer risks were not great. The monitoring data for PAHs from the Westley tire fire were similar to levels found in urban areas such as Modesto before the fire. Urban firefighters who are exposed to smoke all their working lives do show an increase in cancer risk in some studies. However, the exposure that firefighters receive is almost certainly much greater than public exposure from an individual tire fire.

3.0 Major Chemical Constituents of Smoke.

3.1 Identification of Constituents of Smoke Using USEPA Source Testing.

Source testing has been conducted by the USEPA for open burning of chunk tires, defined as from one sixth to one fourth of a whole tire (USEPA, 1997). Emissions from tire pieces of this size are likely to be similar to open accidental burning of whole tires. Individual compounds are identified from the collected emissions. Tables 1-6 show the various chemicals that have been identified in tire fire smoke; values are reported in terms of g/kg of chunk tire. The various tables represent different classes of chemicals. The USEPA divided the chemicals into volatile and semivolatile classes. Although the chemicals listed as semivolatile are less volatile than those listed as volatile, most of the semivolatile chemicals are likely to exist mostly as gases at moderate environmental

temperatures. Many of the polycyclic aromatic hydrocarbons (PAHs) in Table 5 are cancer-causing chemicals. These chemicals are classified together because of their common toxicology. Table 12 presents PAH data from the plume from the Reinhardt tire fire (Frederick county, Virginia). This data can be used to give an idea of the relative amounts of PAHs present in the smoke coming directly off an accidental fire.

The source tests are the best available information on the individual chemical constituents of tire fire smoke but there are uncertainties in extrapolation of the data to accidental tire fires. Accidental mass tire fires go through distinct combustion phases with differing amounts of oxygen and different combustion temperatures. In the later stages of an accidental tire fire that is allowed to burn out or almost burn out, such as the Panoche and Tracy tire fires, the concentration of metals such as zinc will become greater as the combustible components volatilize or are consumed. This may mean that emissions of metals like zinc increase in the later stages. Available oxygen and combustion temperatures are major factors in determining the quantity and chemical composition of the smoke. The number of tires on fire and the geometry of the tire pile may also influence combustion conditions (Table 15). The USEPA (1997) source test data are probably more characteristic of the early vigorous relatively high temperature phases of accidental tire fires. Individual tire fires also may have unique characteristics. For example, the Westley tire fire pyrolitic oil drained from the bottom of the tire fire and the burning oil was extinguished about one week after the tire fire started. This drastically changed the quantity of smoke, and may have altered the chemical composition of the smoke.

The presence of a particular toxic chemical in the source test does not by itself indicate that the public at some distance away will necessarily be exposed, or that any health consequences will occur. Health consequences of exposure to a toxic chemical depend both on the concentration and the duration of exposure. The source tests are useful in indicating the toxic chemicals likely to be of most concern and the best candidates for air monitoring at locations where the public may be exposed. The primary purpose of monitoring at accidental tire fires is to inform public health decisions, such as whether to shelter in place or evacuate.

3.2 Constituents Monitored at Accidental Tire Fires.

The available air concentration monitoring data from a number of accidental tire fires are summarized by USEPA (1997) in Tables 8, 9, 10 and Appendix B. Tables 5 and 6 present the range of air concentrations monitored at a number of tire fires at distances of less than to more than 1000 feet, respectively. There is a large variability in the monitored concentrations even though monitors were placed downwind. Different meteorological conditions including thermal inversions, wind direction and speed contribute to the variability. There is also wide variability in the number of tires on fire at each tire site (Table 13) and overall combustion conditions. There is variability in distance of the monitors from the fire with measurements only being separated into two categories. Monitoring from the Westley tire fire is presented in Appendix B. Monitoring data from the Tracy tire fire is presented in Appendix F. The variation in

monitoring data reflects the variability in measurements taken at a single site. The California Air Resources Board points out that monitoring data at the Westley tire may have detected PM_{10} from non-tire fire activities and forest fire smoke from fires to the north may have influenced measurements (Appendix B). The variability in the USEPA (1997) data and the Westley tire fire data point out the difficulties of generalizing about population exposure to tire fire smoke.

The smaller array of chemicals monitored compared to the number of chemicals detected in the source tests not only reflects judgments as to the chemicals most likely to cause public health problems but also other factors. Field equipment may not be capable of detecting the generally lower concentration of chemicals as the atmosphere dilutes them. There is little point in monitoring chemicals for which toxicity data are not available because without this data public health impacts cannot be assessed. Unfortunately, only eight of the 78 chemicals identified in the source tests have health values for acute or chronic endpoints (see Tables 1-3).

4.0 Toxicity of Some of the Individual Chemicals in Tire Fires.

4.1 Introduction

The health effects from chemicals can be divided into roughly three categories, acute noncancer toxicity, chronic noncancer toxicity, and carcinogenicity (causing cancer). Some chemicals cause both acute and chronic noncancer, and/or cancer health effects. Understanding these three categories is useful because the health values used to assess public health impacts fall into these three categories. Exposure to cancer causing chemicals (carcinogens) can increase the risk of developing cancer. Some of the airborne chemicals in tire fire smoke can cause an increased risk of lung cancer. Some chemicals in tire fire smoke can cause acute health effects with exposures over a short period of time, such as one hour. For example, there are many chemicals in tire fire smoke that cause irritation to the respiratory tract, eyes and nose. These chemicals have the potential for very serious health impacts because they can trigger asthma attacks in individuals with preexisting asthma. Tire fires are notoriously difficult to put out and therefore exposure can occur over a period of weeks, months, or even years. Exposure to tire fire chemicals can potentially cause subchronic noncancer health effects when exposure occurs over these longer time periods. Most of the chemicals identified in the source test do not have acute or chronic RELs or cancer unit risk factors. The toxicological data required to generate health values for public exposure are not always or even usually available. Most toxicological testing for individual chemicals has been directed toward drugs, food additives and pesticides because law requires it. Tables 3, 5A, 6A, 7A, 8, 9, 10, and 11 contain health values for chemicals identified in source tests, monitored at accidental tire fires or likely to be present in tire fire smoke. It should be noted that emissions factors such as in Tables 1, 2, 3, 4, 5, 6 and 7 cannot be linked to public exposure and risk without the use of air dispersion modeling. In addition, short-term monitoring data cannot be construed to be representative of long-term exposures, and thus the utility of such measurements for assessing chronic health effects or cancer risk is limited.

Analysis of the individual toxic components of tire fire smoke is an approach to characterizing the toxicity of the mixture that provides valuable information. The most toxic individual components can be selected for monitoring at accidental tire fires. Public health recommendations can be tailored to protect against the most serious threats to public health. Limitations include lack of toxicological data on identified constituents and a large number of unidentified combustion products. Health effects from multiple chemical exposure may be additive, greater than additive or less than additive. This can lead to overestimation or underestimation of risk. Emissions at accidental tire fires may be different than source testing results depending on available oxygen, stage of the accidental tire fire and other factors. For example, metal emissions could increase in tire fires as the more volatile components are consumed.

4.2 Chemicals with Known Acute Toxicity.

For both acute and chronic noncancer health effects there is considered to be an exposure level or air concentration (threshold) below which health effects are not expected, even in sensitive individuals. Health standards for acute health effects have been developed for various exposure times ranging from one hour to twenty-four hours. The California Office of Environmental Health Hazard Assessment (OEHHA) has developed a number of Reference Exposure Levels (RELs) for acute (mostly 1 hour) exposures to air toxics. The acute REL is the concentration in air at or below which acute noncancer health effects are not expected to occur following a one-hour exposure (OEHHA, 1999a). The acute REL is expressed in μg of chemical per cubic meter of air ($\mu g/m^3$). Identification of the actual level or threshold at which health effects would first start to occur for the diverse human population is not possible due to limitations in existing toxicological data. Therefore, one or more ten-fold safety factors are commonly applied to concentrations where no toxicological effects or minimal toxicological effects are found in animal studies or occasionally human studies, helping to ensure the REL is set at a concentration below where health effects will occur. The better the toxicology data for a particular compound is, the more likely the REL will be close to the actual threshold for health effects in the general population. It is important to note that a chemical with a relatively low acute REL may or may not be highly toxic because the REL may reflect toxicity, or the quality and uncertainty of the toxicological data, or both.

The potential for public health impacts from exposure to a chemical with the potential to cause acute health effects is estimated using a hazard index approach. A one-hour concentration of a toxic chemical in ($\mu g/m^3$) can be divided by the acute REL ($\mu g/m^3$) to give the Hazard Index. A Hazard Index of one or less indicates that health effects would not be expected in the general population, even in sensitive individuals. A Hazard Index greater than 1 does not mean that health effects will actually occur in the exposed population, but as the hazard index increases above one the likelihood of acute health effects increases.

OEHHA is not aware of one-hour chemical concentration monitoring data from tire fires (with the exception of PM_{10} levels at one Westley tire fire monitoring site).

There is no acute REL for PM_{10}, although there is a 24-hour average Ambient Air Quality Standard for PM_{10}.

Some of the chemicals identified in the source testing of tire fires (Table 1 and 2) are acute irritants. These include xylene, styrene, toluene, and phenol (Table 3). Although the simple aldehydes such as acrolein and formaldehyde have not been identified in tire fire source testing, these compounds have been identified in wood smoke (Materna et al., 1992) and are almost certainly present in tire fire smoke. These compounds cause severe respiratory irritation and may exacerbate asthma (OEHHA, 1999a). Sulfur dioxide has not been identified in the source testing but is almost certainly present in tire fire smoke because of the high sulfur content of tires. Sulfur dioxide is irritating at low concentrations and can cause decreases in lung function and exacerbation of asthma symptoms in asthmatics (OEHHA, 1999a).

Although these toxic chemicals were not individually present above the acute RELs in the available limited monitoring data, their combined impacts undoubtedly contribute to the irritating properties of tire smoke. Furthermore, the monitoring data only give a specific snapshot in time. The concentrations to which the public is exposed vary with wind speed and direction, and other factors. Thus irritating effects of smoke exposure reported during fires are likely to occur when the plume is blown into a populated area. There are also likely to be many more irritating chemicals present in tire fire smoke, notably other aldehydes that have not been studied toxicologically.

There are other health endpoints such as nervous system and developmental effects listed for chemicals found in tire fire smoke. These effects would occur at relatively high concentrations, probably considerably higher than the public is likely to be exposed to over a short period of time.

Carbon monoxide is capable of displacing oxygen from the blood; thus, it results in hypoxia (an insufficiency of oxygen) in the tissues. Carbon monoxide was monitored at the Westley tire fire (Appendix B) and found to be well below the acute REL (OEHHA, 1999A). Based on monitoring data near forest fires, carbon monoxide exposure has not been found to result in health effects to the public near forest fires (USEPA, 2001a).

4.3 Chemicals with Known Subchronic or Chronic Toxicity.

The time period for exposure for subchronic and chronic health effects to occur is less well defined than for acute exposures and is dependent on the chemical. Subchronic exposures lie between acute exposures and chronic exposures. Subchronic health effects may occur following weeks to a few years of exposure depending on the chemical and the type of health effect. OEHHA has developed a number of chronic RELs for air toxics. These are designed to be compared to annual averages of chemicals, as the underlying assumption is fairly long exposures (OEHHA and USEPA have defined the period of exposure for chronic RELs to be 8 years). The chronic RELs are developed using human or animal studies with chronic exposure durations (OEHHA, 2000). Similar

to the development of acute RELs, safety factors are used for developing chronic RELs. Similar procedures are used by the USEPA (IRIS, 2001) in developing the Reference Exposure Concentrations or RfCs. A chronic hazard index can be calculated by dividing the annualized average air concentration by the chronic REL to give a chronic Hazard Index. Health effects are not expected to be seen in the general population with a Hazard Index of one or less. The likelihood of health effects increases as the Hazard Index becomes progressively greater than 1. More information on the health effects of the individual chemicals and the development of the chronic RELs for the chemicals found in tire fire smoke may be found in Appendix A.

There are some chemicals identified in source testing (Tables 1,2 and 3) and monitoring at greater and less than 1000 feet from tire fires (Tables 8 and 9) that are known to cause health effects with subchronic or chronic exposure. These include benzene, toluene, styrene, methylene chloride, chloroform, ethyl benzene, xylenes and lead. The chemicals with the most potential to cause health effects are benzene, toluene, styrene and xylene because they are clearly present in higher concentrations based on the monitoring data. Some monitoring levels were above the chronic REL. However, it is unlikely that long-term average air concentrations at any given location would remain above the chronic REL long enough that chronic health effects would occur. The potential noncancer health effects that could occur from chronic exposure to benzene, toluene, styrene, and xylene include adverse reproductive, developmental, and central nervous system effects, and eye and respiratory irritation. The irritating effects of these chemicals are the most likely subchronic health effects at most tire fires. Respiratory irritation can occur with both acute and chronic exposure.

4.4 Cancer Causing Chemicals (Carcinogens)

Unlike acute and chronic noncancer health effects, the assumption with cancer causing chemicals is that there is no identifiable dose or air concentration at which health effects will not occur. However, cancer risks below 1×10^{-6} (one chance in a million), often 1×10^{-5} (one chance in one hundred thousand; used in Proposition 65 significant risk determinations) and, in limited cases, 1×10^{-4} (one chance in ten thousand) are considered to be below a level of significance as a matter of policy by various state and federal agencies. Cancer unit risk factors are numerical indicators of the increased risk of cancer from breathing 1 μg of a particular chemical per cubic meter of air over 70 years (OEHHA, 1999b). The units for cancer unit risk factors are $(\mu g/m^3)^{-1}$. The larger the unit risk factor is, the more potent the carcinogen is. To estimate cancer risk, the annualized average air concentration is multiplied by the unit risk factor to derive a unitless probability of cancer. Cancer risk from a mixture of chemicals is usually considered to be additive. The cancer unit risk factors and cancer risk estimation methods are based on long-term exposures to carcinogens, and are not readily applicable to use for short-term exposures, such as that occurring during a fire. The effects of breathing a higher amount of a carcinogenic chemical over a period of weeks to months may not be the same as breathing the same amount spread over a lifetime. It is therefore difficult to know with any certainty the cancer risks from breathing carcinogenic chemicals from a tire fire over

periods of days to months. Appendix A contains information on the studies used for deriving the cancer unit risk factors.

As a rule, significant cancer risks will occur at much lower airborne concentrations of chemicals than acute or chronic health impacts but are generally considered to result from long-term exposure. Cancer is a particularly serious and life threatening health impact. It is difficult to assess cancer risks when dealing with emergencies such as tire fires. The methods used to assess risk are all based on long-term exposure. Major known carcinogens present in tire fires have typically been selected for monitoring. Tire fires, as well as other uncontrolled sources of combustion, are particularly rich sources of polycyclic aromatic hydrocarbons (PAHs) (USEPA, 1997). In the U.S.EPA source tests, PAHs were present in tire fire smoke at levels about 800 times higher than wood smoke. Short-term exposure to PAHs from tire smoke, however, may not be significant compared to daily low-level cumulative exposures from other common combustion sources such as auto, truck, and bus exhaust, environmental tobacco smoke, and fireplace wood smoke. In Table 10, we provide information on the concentrations of PAHs in the plume of the Rhinehart tire fire. We also provide the unit risk factors for some of the PAHs where available. It should be noted that it is not appropriate to calculate cancer risk from the concentrations presented in the table because the monitoring was conducted for a short-time and is not representative of chronic exposure, and the data are not necessarily representative of concentrations to which people were exposed.

There is a large array of PAHs, many of which have not undergone carcinogenicity testing. Unit risk factors are available for some PAHs from testing in rodent cancer bioassays. PAHs, when inhaled or ingested, can cause lung and possibly other cancers. We have included information on the individual cancer potency factors for PAHs and other carcinogens in Appendix A.

Lead is a carcinogenic metal identified in source testing (Table 7) at relatively low levels. The Air Resources Board monitored for airborne metals during the Westley tire fire (Appendix B) and found concentrations similar to urban air. Stanislaus County (Appendix C) monitored metals on vegetables. Metal levels within the limitations of detection limits were normal in the vegetable samples. Benzene and 1,3-butadiene are also fairly potent carcinogens and emitted in relatively large amounts in tire fires. Both of these volatile organic compounds are ubiquitous air pollutants that do not bioaccumulate. Exposures to these carcinogens, which are components of vehicular exhaust, would of course depend on wind direction and other factors, and may or may not be different than typical exposures from auto exhaust. Since the exposures to these carcinogens in tire fire smoke generally are relatively short, an assessment of cancer risk is difficult.

Another class of cancer-causing chemicals is the dioxins. These chemicals are potent carcinogens produced in small quantities in tire fires. In addition, this class of compounds has significant bioaccumulative potential and long environmental half-lives. Formation of dioxins during tire combustion is quenched by the presence of sulfur in tires

(Antony et al. 2001), and thus tire fires are not a major source of dioxins relative to fires burning chlorinated chemicals or plastics. Dioxins were measured at the Hagersville, Ontario tire fire both in the air downwind of the fire (Table 12) and in vegetation close to the fire (Steer et al., 1994). The concentrations detected in the air were about ten times less at 3 km as compared with 1 km. As the fire was brought under control the air levels declined. Dioxins and furans were about 10 times higher at 1 km from the fire than they were at 3 km. The February 24/25 sample, taken a couple of days before the fire was extinguished on February 27th, was similar to typical background concentrations found in North America. It should be noted that the Hagersville, Ontario tire fire was considerably larger than some other tire fires, including the Westley tire fire (Table 13). Contamination of foliage was confined to within about 500 m around the Hagersville fire.

4.5 PM_{10} Toxicity

The source monitoring results indicate that large amounts of PM_{10} are generated from the open combustion of tires. (Particles are what you see as smoke.) PM_{10} is particulate matter that is 10 μm or less in diameter. Particles of this size readily penetrate into the deep lung. Numerous studies have found severe health impacts from PM_{10} exposure. The effects include a 1% increase in daily mortality rates for each increase of 10 $\mu g/m^3$ in 24-hour measurements (Dockery and Pope, 1994), primarily in elderly people with pre-existing heart and lung disease. In addition there are well-documented increases in serious illness, as measured by such end points as hospital admissions for asthma and heart and lung conditions, associated with exposure to PM_{10}. The studies that have identified PM_{10} health effects have been conducted in cities in California and all over the world. PM_{10} in cities is a combination of particles from combustion sources as well as other sources, and may have somewhat different properties than tire fire generated PM_{10}. However, there is no reason to believe tire fire particulate would be less toxic. Monitored PM_{10} levels have been used as a surrogate measure of smoke for forest fire studies.

PM_{10} health effects are probably the most serious potential risk from tire fires. PM_{10} levels exceeding the state standard of 50 $\mu g/m^3$ (24-hour average) were measured on a number of days at the Westley tire fire, and measurements exceeding the Federal standard of 150 $\mu g/m^3$ (24 hour average) were measured on a few days. The average PM_{10} concentration for the permanent Modesto monitoring site at I Street for 1997 (prior to the tire fire) was 32.3 $\mu g/m^3$ and the maximum value was 119 $\mu g/m^3$ (California Air Resources Board, 2001). PM_{10} exposure can vary considerably over the course of a day depending on the meteorological conditions. The elderly are the most sensitive subpopulation affected by PM_{10}, in part because of a greater incidence of preexisting heart and lung disease. Children may be more vulnerable than healthy adults because they breathe more on a body weight basis, are more active and spend more time outdoors and are thus exposed to more airborne contaminants including particles than adults. The effects of short-term high exposures (1 hour) to PM_{10} are not clearly understood, since most epidemiological studies have relied on 24-hour average measurements. Such short-term high exposures to the public are likely at tire fires as the wind and other

meteorological factors change. More information on PM_{10} health effects can be found in Appendix A.

PM_{10} measurements using a TEOM device were available on an hourly basis at the Westley truck stop. The public health recommendations (Appendix D) developed by OEHHA, the Department of Health Services, and the Stanislaus County Health Officer were based on PM_{10} levels. The PM_{10} health effects were the most serious health impacts that OEHHA and the Department of Health Services expected during the Westley tire fire based on the health literature and previous monitoring data. The assumption was that recommendations to protect the public against PM_{10} exposure and health effects would be sufficient to protect against other health impacts.

5.0 Studies of Health Effects from Smoke Exposure.

Another approach to characterizing the toxicity of tire fire smoke is to evaluate studies of exposure to the entire mixture. There are no toxicological or epidemiological studies of tire fire smoke but there are studies on exposure to other types of smoke. Smoke may vary in the proportion of individual constituents but valuable insights can be gained by studies on other types of smoke.

Various groups have studied the effects of exposure to different types of smoke. Studies on exposure to whole smoke avoid some of the difficulties of assessing the effects of exposure to the individual components of smoke. Smoke varies considerably in the proportions of toxic components, which depend on the material being burned. There are some epidemiological studies of the effects of exposure to smoke on firefighters. Although the composition smoke that firefighters are exposed to will vary considerably depending on the materials being consumed, these studies are useful in giving at least an approximate idea of the risk to the public from exposure to tire fire smoke. In addition, exposure to secondhand tobacco smoke has been linked to a variety of health effects in epidemiological studies.

5.1 Cancer Risk from Exposure to Smoke.

Lung cancer is considered an occupational disease for fire fighters in California. There have been several studies of cancer incidence among firefighters. Demers et al. (1993) studied a cohort of 2,447 Seattle fire fighters for 16 years using a population-based tumor registry. The incidence of various cancers, including lung, was compared with local county rates and rates in policemen. Police would presumably be exposed to less smoke than firefighters. Demers et al. (1993) found a significant increase in prostate cancer relative to the rates in the general male population, but the rates in the policemen were the same as in the firefighters. No increased incidence of lung cancer was found in firefighters relative to policemen or the local county population.

Hansen (1990) conducted a historical cohort study of 886 Danish firefighters and 47,694 civil servants in other professions. The comparison group for the firefighters was chosen to resemble the firefighters in terms of work related demands on physical strength

and fitness, social class, geographic distribution and stability of employment in part to help control for smoking. The investigator concludes that bias from different smoking patterns in the two groups was probably not great. She found a small increased mortality from all types of cancer in firefighters from 30 to 49 years of age relative to the control group. The investigator also found about a three-fold increase in the incidence of lung cancer in firefighters ages 60 to 74 relative to the control group. This is a large relative risk, particularly given the number of subjects in the study. Firefighters are exposed to smoke throughout their working lives. Firefighters are exposed to smoke from a variety of burning substances including wood, plastics, paints, and chemicals. Although they do wear protective gear when entering buildings, often protective gear is not worn during the clean up period after the active part of the fire is extinguished (Morse et al., 1992). The exposure of firefighters to smoke over a working lifetime is likely to be much greater than public exposure to smoke from a single tire fire even given the availability of protective equipment.

Sama et al. (1990) studied cancer incidence among Massachusetts firefighters from 1982 to 1986. This study was a case control analysis using cancer registry data. These investigators found an increased incidence of melanoma and bladder cancer when firefighters were compared to the general population. When firefighters were compared to policemen, an increased incidence of bladder cancer was found. Other studies of firefighters have been done with similar mixed results.

DeMarini et al. (1994) measured the mutagenicity of tire fire smoke and smoke from a number of other types of fires both controlled and uncontrolled. A bacterial test system called the Ames test was used. Mutagenicity is not the same as carcinogenicity, however many carcinogens test positive in the Ames test including PAHs. The Ames test can also give an indication of relative mutagenicity. DeMarini et al. (1994) found that smoke from open tire burning was 16 times more mutagenic than residential wood smoke and 8 times more mutagenic than open burning of plastic on a weight basis. The particulate fraction from tire fire smoke contained the vast majority of the mutagenic activity relative to the semivolatile organic fraction. Most of the mutagenic activity is accounted for by the PAHs in the tire fire smoke. These studies indicate carcinogenicity of tire fire smoke is of potential concern and that air monitoring and mitigation of smoke exposure at tire fires is prudent.

5.2 Noncancer Risks from Exposure to Smoke.

Liu et al. (1992) measured lung function in 63 wildland firefighters before and after a season of active firefighting. They found an increase in airway responsiveness and a decrease in three measures of lung function: FVC, FEV_1 and FEF_{25-75} after a season of firefighting. The authors state that these effects may disappear over the 5-6 months that seasonal firefighters are not exposed to smoke. Municipal firefighters have been found to have a decline in FEV_1 about 2.5 times that of retired firefighters (Tepper et al., 1991). Municipal firefighters are exposed to smoke year around. These effects could be potentially more serious to member of the general population with asthma, chronic obstructive lung disease, emphysema or heart disease.

Reinhardt et al. (2000) studied smoke exposure among firefighters at prescribed burns in the Pacific Northwest. Firefighters reported an increase in eye and nose irritation, cough, phlegm and wheezing. Wildfire smoke exposure has also been associated with shortness of breath, and with headaches, dizziness and nausea lasting up to several hours. Reinhardt et al. (2000) identified the chief inhalation hazards to be carbon monoxide, aldehydes, benzene, and respirable particulate matter (PM 3.5).

Exposure to secondhand tobacco smoke (ETS) has been linked to a variety of adverse health effects (NCI, 1999). Acute exposure can cause exacerbation of asthma and increased risk of ear and respiratory infections in children. In addition, eye and nasal irritation are commonly reported effects among nonsmokers exposed to ETS. These acute effects are reasonable to consider as potential effects of exposure to tire fire smoke. Chronic exposure to ETS has been associated with induction of asthma, chronic cough, phlegm and wheezing, and impacts on lung function growth in children, as well as increased risk of cancers and heart disease in nonsmokers. However, the chronic health effects are not particularly useful in comparing general population exposure to tire fire smoke.

6.0 Exposure.

6.1 Inhalation and Noninhalation.

Exposure can be defined as the way the chemical enters the body. The most significant way that the public is exposed to tire fire smoke is through inhalation of toxic gaseous chemicals or particles. Public exposure can also potentially occur by ingestion of contaminated soil, surface waters, produce and meats. In addition, if a nursing mother is exposed by inhalation or by ingestion of contaminated food or water, certain fat-soluble toxic chemicals, such as dioxins, can be ingested by an infant via mother's milk. Skin contact with contaminated soil can result in absorption of toxic chemicals through the skin, although this pathway is a minor contributor to risk with chemicals that originate in the air.

6.2 Factors affecting Exposure.

Exposure to an individual from a tire fire is affected by many factors. Physical activity and activity patterns as well as the amount of time spent indoors can influence exposure. The person may be more or less exposed at work or school. Exposure can vary with distance from the fire because the smoke tends to be dispersed and diluted with distance. Meteorological conditions such as thermal inversions, wind direction and speed can have a major impact on air concentrations. The number of tires on fire will affect the quantity of emissions. Thus it is difficult to characterize a "typical" individual exposure or to know what a particular individual's exposure may have been.

7.0 Potential Effects On Human Health From Exposure To Smoke From Tire Fires.

7.1 Noncancer Health Effects.

There is no "typical" tire fire. Health effects would vary from one tire fire to the next because the quantity and quality of the smoke would vary. In addition, exposure can vary tremendously among tire fires and even different time points at the same tire fire, for reasons that have been described. Individual sensitivity within the general population is known to vary widely. The general population includes the elderly, the sick, children, pregnant women and infants all of who may be more sensitive to the effects of chemicals. Even within a subgroup such as young healthy males, there is wide genetic diversity affecting vulnerability to pollutants.

The monitoring data as well as epidemiological and toxicological data allow a determination of the most likely health effects that will be seen in the exposed population at tire fires. A number of individual chemicals present in tire fire smoke according to the source tests are highly irritating. These chemicals irritate the eyes, nose, and throat, and may trigger asthma attacks in people with pre-existing asthma. Clearly these types of health effects could be expected with exposure to tire fire smoke.

The data on smoke from forest fires indicates that there is an increase in visits to emergency rooms for asthma and other respiratory conditions during smoky conditions. The literature on PM_{10} indicates that there is a 1% increase in daily mortality with every 10 $\mu g/m^3$ increase in 24-hour particulate matter concentrations. The deaths are for the large part seen in those with preexisting cardiovascular or respiratory disease, including emphysema, chronic obstructive pulmonary disease, and asthma. The elderly are disproportionately afflicted with heart and lung disease, and are therefore a vulnerable subpopulation.

The data collected by Stanislaus County during the Westley tire fire are consistent with public exposure to irritating smoke (Appendix D). Coughing, sore throat, headache, runny nose, difficulty in breathing, congestion, burning nose, dizzy, itchy eyes, watery eyes, tight chest, and nasal irritation comprise a large majority of the symptoms of the patients seen during the tire fire. A third of the people who called the county nurse had been previously diagnosed with asthma. Since about 7% of the California population has asthma, the fact that a third of the calls were from asthmatics are an indication that asthmatics may have been more impacted than those without asthma.

Daily PM_{10} monitoring available from the Westley tire fire indicates that PM_{10} levels were unhealthy for several days, rising above the federal PM_{10} level, and above the state level for most of the time that the fire burned. Concentrations higher than the Federal standard were common in the South Coast air basin in the 1970's and 80's. The state PM_{10} standard is exceeded fairly regularly in almost all areas of California. Forest fires that filled the Central Valley with smoke are likely to have contributed to high PM_{10} levels detected on October 16-17 (Appendix B).

A tire fire occurring under a low level meteorological inversion that trapped PM_{10}, allowing levels to rise into the thousands of $\mu g/m^3$ could kill large numbers of people, if the population of a large city were exposed to such levels. Such inversions occur in the Central Valley of California trapping fog in the winter.

7.2 Cancer Health Effects.

Significant cancer risk to the public from exposure to tire fire smoke at a single tire fire does not appear likely from monitoring data and indirect evidence. The USEPA (Appendix E) conducted a cancer risk assessment following the Everett, Washington tire fire. The assessment was based on monitoring data and air modeling. It concluded that the maximum risk ranged from 1×10^{-4} to 1×10^{-6} for the four most highly exposed individuals. Risks were characterized as considerably less for most people. The estimation of cancer risk from short-term exposure, such as is often the case with tire fires, is not really appropriate because carcinogenicity modeling assumes long-term (chronic) exposure.

Another indication of the cancer risk from tire fires is the monitoring of PAHs at the Westley tire fire. PAHs above the detection limit were found on 9/30 and 10/1 at the Westley-Livingston monitoring station. PAHs were monitored for 26 days at the Westley-Livingston site and PAHs were detected on 3 days (Appendix B). A total of 15 measurements of individual PAHs above the detection limit were measured. Nine of these measurements were above the average levels measured in Modesto in 1997 before the tire fire, and six of these measurements were lower than the average values measured in Modesto in 1997.

At the Patterson High School site, PAHs were monitored for a total of 9 days and PAHs were detected on all 9 days. A total of 44 measurements on individual PAHs on the 9 days monitored at Patterson High School were above the limit of detection. PAHs above the detection limit were found at Patterson High School on 10/6, 10/7, 10/8, 10/13, 10/14, 10/15, 10/18, 10/19, and 10/20. Seventeen of the 44 measured concentrations were above the average individual PAH levels measured in Modesto in 1997. The remainder were below the average levels in Modesto. None of the measurements exceeded the maximum levels detected in Modesto in 1997. Although comparison of a yearly average with the shorter monitoring times has its scientific limitations, it is an indication that PAH concentrations in at least two locations were not very different from what would be found in an urban area in the San Joaquin Valley (Table 14).

PAHs are found in varying quantities in wood smoke, diesel exhaust, gasoline exhaust, cigarette smoke, and in smoke from virtually anything else that burns. The PAHs found in Modesto are not surprising and may be considerably higher in areas more dependent on wood for heat.

Benzene levels in Modesto in 1997, before the tire fire, averaged 0.46 ppb and the maximum detected was 2.2 ppb. Benzene levels were monitored at the Westley-

Livingston site during the Westley tire fire. The maximum value detected was 2.88 ppb. The rest of the values detected at Westley-Livingston were a little above or below the average Modesto value for 1997. Typical benzene concentrations in the South Coast air basin are now around 1 ppb. 1,3-Butadiene levels detected in at Westley-Livingston were in all cases below the maximum level detected in Modesto in 1997 and in all but one case below the average Modesto level. The levels of benzene and 1,3-butadiene detected during at the Westley tire fire at the one monitoring site are not different from typical urban exposures.

The Westley tire fire is not necessarily "typical" for all tire fires. The oil part of the tire fire was extinguished after one week, probably reducing the PAHs emissions considerably. The meteorology was also generally favorable to widespread dispersal and dilution of pollutants, thus reducing exposure.

The studies on firefighters are a rough indication of the magnitude of risk from exposure to smoke. Firefighters are exposed to many different types of smoke that may be more or less carcinogenic than tire fire smoke. The occupational exposure of firefighters to the carcinogens in smoke over a working lifetime is likely to be much greater than the public exposure from a single tire fire. In general, studies have not detected an increase in cancer rates. However, one study has found about a three fold increased risk of lung cancer for firefighters toward the end of their careers.

The air monitoring results at the Hagersville fire indicate that air concentrations of dioxins were elevated above background. Dioxins are products of combustion emitted from many sources of combustion. They are relatively long-lived in the environment both in the air and the soil. They are deposited on vegetation that is subsequently consumed by domestic animals. Therefore, most people receive the bulk of their exposure to dioxins through consuming animal fat in their diets, not from breathing dioxins in the air (USEPA, 2001b). The amount of dioxins inhaled over a period of days to weeks downwind of a tire fire are not likely to be very great compared to the amount a person normally takes in through diet. It should be noted that existing body burdens of dioxins are considered unacceptable by regulatory agencies and that therefore sources need to be controlled. The contribution of tire fires to general environmental levels of dioxins that will ultimately end up in the human diet, is probably not major but is still undesirable.

The dioxins detected on trees in close proximity of the Hagersville, Ontario fire were associated with an oily residue. Consumption of dioxin contaminated pasture by food animals could present a potential risk to humans consuming the meat or milk from food animals, but the limited area of contamination indicates that the actual risk from this pathway is likely to be small.

PAH exposure can occur through inhalation and also through ingestion of contaminated soil, leafy vegetables, and exposed vegetables such as tomatoes. Mcliveen (1990a; 1990b) monitored PAHs in the evergreen foliage around the Hagersville tire fire.

The fire occurred in the winter so crops were not available for sampling. Heavy PAH contamination of foliage was found in close proximity to the Hagersville, Ontario fire in which almost fourteen million tires burned. Low level contamination was found up to several kilometers away. In contrast, no contamination of vegetables was found when sampling was conducted in close proximity to a smaller fire (4,000 tires) at Kingsville, Ontario (Gizyn, 1990). The cancer risk from consuming produce contaminated from PAHs at reasonable distance from a tire fire is likely to be very small.

8.0 Summary and Data Gaps.

The available scientific information on tire fire smoke constituents and studies of exposure to other types of smoke point to the need to control tire disposal so as to avoid tire fires. In addition, the data point to the need to rapidly extinguish any tire fires that do occur.

The most serious health impacts from exposure to tire fire smoke appears to be effects on those with preexisting cardiovascular disease or respiratory conditions such as asthma. These health impacts include worsening of these conditions and a possible increase in the death rate. The rest of the population is likely to experience eye and respiratory irritation. The public health recommendations developed by the Department of Health Services, OEHHA and the Stanislaus county health department during the Westley Tire specifically suggested measures to reduce exposure for these groups.

The lack of toxicological studies on combustion product chemicals is a serious data gap when evaluating the health impacts of exposure. In particular there is a need for human studies to better characterize the irritating properties of these chemicals. These chemicals are commonly found in urban air due to controlled and uncontrolled combustion sources such as automobiles, trucks and wood burning. Such research would also aid in understanding the effects of urban air pollution. Research studies are needed on the effects of short term high exposures to particulates so that better public health recommendations can be developed. Research is also needed on ways to establish clean air shelters so that sensitive subpopulations can be protected when smoke concentrations become excessive. Clean air shelters could be existing structures with good filtration or existing structures with added filtration. These research studies would be useful for protecting public health during tire fires (which will hopefully be very rare in California). The studies would also be useful for protecting the public from forest fire smoke exposure, which is likely to be more common. In addition, research into understanding risks from additional PAHs might help clarify the relative importance of exposure to this class of compounds.

TABLE 1. OPEN BURNING EMISSIONS: VOLATILE ORGANICS [a,b] (LABORATORY SIMULATION,CHUNK TIRES)[1]

Compound	Exhaust Conc.	Exhaust Emission Factor (mass/mass tire)	
	mg/m^3	mg/kg	lbs/ton
Benzaldehyde	0.260	299.2	0.5984
Benzene	1.910	2,156.3	4.3126
Benzodiazine	0.017	13.7	0.0274
Benzofuran	0.049	25.1	0.0502
Benzothiophene	0.014	26.3	0.0526
1,3-Butadiene	0.152	308.4	0.6168
Cyclopentadiene	0.081	48.6	0.0972
Dihydroindene	0.013	40.6	0.0812
Dimethyl benzene (xylene)	0.413	779.7	1.559
Dimethyl hexadiene	0.008	28.3	0.0566
Dimethyl methyl propyl benzene	ND	ND	ND
Dimethyl dihydroindene	0.007	22.0	0.0440
Ethenyl benzene(styrene)	0.678	941.8	1.88
Ethenyl cyclohexane	0.006	26.2	0.0524
Ethenyl dimethyl benzene	0.014	7.2	0.014
Ethenyl methyl benzene	0.016	14.1	0.0282
Ethenyl dimethyl cyclohexane	ND	ND	ND
Ethenyl methyl benzene	0.129	221.6	0.4432
Ethyl benzene	0.182	460.8	0.9216
Ethyl methyl benzene	0.120	334.5	0.6690
Ethynyl benzene	0.322	190.0	0.3800
Ethynyl methyl benzene	0.562	530.6	1.061
Heptadiene	0.009	25.4	0.051
Isocyanobenzene	0.341	348	0.696
Limonene	0.011	27.5	0.055
Methyl benzene (toluene)	0.976	1,606	3.21
Methyl cyclohexane	0.005	21.1	0.420
Methyl hexadiene	0.021	71.3	0.143
Methyl indene	0.138	316	0.632
Methyl naphthalene	0.287	312	0.624
Methyl thiophene	0.006	5.5	0.011
Methyl ethenyl benzene	0.027	55.7	0.111
Methyl methylethenyl benzene	0.046	98.0	0.196
Methyl methylethyl benzene	0.041	111	0.222
Methyl methylethyl cyclohexane	ND	ND	ND
Methyl propyl benzene	ND	ND	ND
Methylene indene	0.038	48.5	0.097
Methylethyl benzene	0.045	135	0.270
Naphthalene	1.29	1,130	2.26
Pentadiene	0.077	164	0.388
Phenol	0.002	0.5	0.001
Propyl benzene	0.026	72.4	0.145
Tetramethyl benzene	ND	ND	ND
Thiophene	0.023	54.6	0.109
Trichlorofluoromethane	0.158	57.6	0.115
Trimethyl benzene	0.022	46.9	0.0938
TOTALS	**8.53**	**11,182**	**22.364**

Concentrations determined using system responses to toluene. [a] These data are averaged over six sets of VOST tubes taken over 2 days. [b]
ND = None detected.
[1] USEPA, 1997

TABLE 2. OPEN BURNING EMISSIONS: SEMI-VOLATILE ORGANICS (LABORATORY SIMULATION, CHUNK)[1]

Compound	Exhaust Conc.	Exhaust Emission Factor (mass/mass tire)	
	mg/m^3	mg/kg	lbs/ton
1-Methyl naphthalene	0.292	330.7	0.6614
1,1' Biphenyl, methyl	0.013	11.1	0.0222
1H fluorene	0.187	210.3	0.4206
2-Methyl naphthalene	0.314	350.7	0.7014
Acenaphthylene	0.580	633.8	1.267
Benzaldehyde	0.218	244.1	0.4482
Benzisothiazole	ND	ND	ND
Benz(b)thiophene	0.050	44.2	0.0884
Biphenyl	0.186	209.5	0.4190
Cyanobenzene	0.199	223.7	0.4474
Dimethyl benzene (xylene)	0.254	305.0	0.6100
Dimethyl Naphthalene	0.034	41.1	0.082
Ethyl benzene	0.181	205.2	0.4104
Ethyl dimethyl benzene	ND	ND	ND
Ethynyl benzene (styrene)	0.254	275.8	0.5516
Hexahydro-azepinone	0.062	75.1	0.150
Indene	0.462	503.4	1.007
Isocyano- naphthalene	0.011	9.4	0.019
Limonene	0.047	56.1	0.112
Methyl benzaldehyde	ND	ND	ND
Methyl benzene (Toluene)	1.105	1,212.2	2.4244
Methyl indene	0.093	111.8	0.02360
Methyl methylethyl Benzene	0.107	127.9	0.2558
Methylethyl benzene	0.040	48.3	0.0966
Naphthalene	1.578	1,697.9	3.3958
Phenanthrene	0.173	183.7	0.3674
Phenol	0.330	365.9	0.7318
Propenyl naphthalene	0.027	23.5	0.0470
Propenyl methyl Benzene	ND	ND	ND
Propyl benzene	ND	ND	ND
Styrene	0.605	659.9	1.320
Tetramethyl benzene	ND	ND	ND
Trimethyl benzene	ND	209.4	0.4188
Trimethyl Naphthalene	ND	ND	ND
TOTALS	**7.593**	**8,369.7**	**16.739**

ND - None detected.
[1] USEPA, 1997

TABLE 3. AVAILABLE CALIFORNIA HEALTH VALUES FOR CHEMICALS IDENTIFIED IN OPEN BURNING EMISSIONS: VOLATILE AND SEMIVOLATILE ORGANICS [a,b] (LABORATORY SIMULATION,CHUNK TIRES)[1]

Compound	Acute REL[2]	Target Organ	Chronic REL[3]	Target Organ	Unit Risk Factor[4]
	$\mu g/m^3$		$\mu g/m^3$		$(\mu g/m^3)^{-1}$
Benzene	1300	Reproductive; Developmental	60	Hematopoietic system; development; nervous system	2.9×10^{-5}
1,3-Butadiene			20	Reproductive	1.74×10^{-4}
Dimethyl benzene (xylene)	22,000	Eye; Respiratory irritation	700	Nervous System; Respiratory System	
Ethenyl benzene (styrene)	21,000	Eye; Respiratory irritation	900	Nervous System	
Ethyl benzene			2,000	Developmental; alimentary system; kidney; endocrine	
Methyl benzene (toluene)	37,000	Central Nervous System; Eye; Respiratory irritation	300	Nervous system; Respiratory system; development	
Naphthalene			9	Respiratory system	
Phenol	5800	Respiratory system, eyes	200	Alimentary system, circulatory system; kidney; nervous system	

[1] USEPA, 1997
[2]OEHHA, 1999a
[3]OEHHA, 2000b
[4]OEHHA, 1999b

TABLE 4. OPEN BURNING: TOTAL ORGANICS EMISSION SUMMARY (LABORATORY SIMULATION)[1]

Organic Component		Exhaust Conc.	Exhaust Emission Factor (mass/mass tire)	
		mg/m^3	mg/kg	lbs/ton
Volatile		8.53	11,182	22.364
Semi-Volatile		3,514.6	9,792.0	19.584
Particulate		4,048.0	11,223.5	22.4470
TOTALS		**7,571.1**	**32,197.5**	**64.3950**

[1] USEPA, 1997

TABLE 5. OPEN BURNING: PAH EMISSIONS (LABORATORY SIMULATION-CHUNK)[1]

Compound	Exhaust Conc.	Exhaust Emission Factor (mass/mass tire)	
	mg/m^3	mg/kg	lbs/ton
Acenaphthylene	0.802	861.3	1.722
Acenaphthene	0.282	290.3	0.5806
Fluorene	0.243	260.5	0.5210
Phenanthrene	0.225	237.5	0.4750
Anthracene	0.053	56.3	0.113
Fluoranthene	0.324	338.7	0.6774
Pyrene	0.030	33.8	0.0676
Benz(a)anthracene	0.076	82.2	0.164
Chrysene	0.068	70.8	0.142
Benzo(b)fluoranthene	0.064	69.4	0.139
Benzo(k)fluoranthene	0.069	74.3	0.149
Benzo(a)pyrene	0.08	84.8	0.170
Dibenz(a,h)anthracene	0.001	1.1	0.0022
Benzo(g,h,i)perylene	0.060	66.0	0.132
Indeno(1,2,3-cd)pyrene	0.049	51.6	0.103
TOTALS	**3.212**	**3,394.5**	**6.7890**

[1] USEPA, 1997

TABLE 5A. AVAILABLE CALIFORNIA HEALTH VALUES FOR CHEMICALS IDENTIFIED IN OPEN BURNING: PAH EMISSIONS (LABORATORY SIMULATION-CHUNK)[1]

Compound	Unit Risk Factor $(\mu g/m^3)^{-1}$
Benz(a)anthracene	1.1×10^{-4}
Chrysene	1.1×10^{-5}
Benzo(b)fluoranthene	1.1×10^{-4}
Benzo(k)fluoranthene	1.1×10^{-4}
Benzo(a)pyrene	1.1×10^{-3}
Dibenz(a,h)anthracene	1.2×10^{-3}
Indeno(1,2,3-cd)pyrene	1.1×10^{-4}

[1] OEHHA, 1999b

TABLE 6. OPEN BURNING: PARTICULATE EMISSIONS (LABORATORY SIMULATION-CHUNK)[1]

Sample	Exhaust Conc. (mg/m^3)	Emission Factor (mass/mass tire)	
		mg/kg	lbs/ton
Organic Particulate Filter	93	97,100	1,940
Metal Particulate Filter	111.55	105,000	210
PM_{10} Filter[a]	444.14	113,500	227.0

N/ A = not analyzed.
The PM sampling filter became heavily loaded during the initial part of each run. The results are biased high due to higher burning rates that occurred during this portion of the run.
[1] USEPA, 1997

TABLE 6A. CALIFORNIA AND FEDERAL 24-Hour PM_{10} STANDARDS

CA PM_{10} Standard ($\mu g/m^3$)	Federal PM_{10} Standard ($\mu g/m^3$)
50	150

TABLE 7. OPEN BURNING: METALS EMISSIONS (LABORATORY SIMULATION- CHUNK)[1]

Metal	Exhaust Conc.	Exhaust Emission Factor (mass/mass tire)	
		mg/kg	lbs/ton
Aluminum	ND	ND	ND
Antimony	ND	ND	ND
Arsenic	ND	ND	ND
Barium	ND	ND	ND
Calcium	0.0079	8.54	0.0171
Chromium	ND	ND	ND
Copper	ND	ND	ND
Iron	ND	ND	ND
Lead	0.0004	0.47	0.0094
Magnesium	0.0012	1.26	0.00252
Nickel	ND	ND	ND
Selenium	ND	ND	ND
Sodium	0.0084	9.51	0.0190
Titanium	ND	ND	ND
Vanadium	ND	ND	ND
Zinc	0.0409	31.17	0.06234

[1] USEPA, 1997 ND = Not detected.

TABLE 7A. AVAILABLE CALIFORNIA HEALTH VALUES FOR CHEMICALS IDENTIFIED IN OPEN BURNING: METALS EMISSIONS (LABORATORY SIMULATION- CHUNK)[1]

Metal	Acute REL	Target Organ	Chronic REL	Target Organ	Unit Risk Factor
	$\mu g/m^3$		$\mu g/m^3$		$(\mu g/m^3)^{-1}$
Arsenic	1.9×10^{-1}	Reproductive/ Developmental	0.03	Developmental; Cardiovascular; Nervous	3.3×10^{-3}
Lead					4.2×10^{-2}
Nickel	6.0×10^{0}	Respiratory System; Immune Response	0.05	Respiratory System; Hematopoietic System	2.6×10^{-4}

ND = Not detected.
[1]OEHHA, 1999b

TABLE 8. OPEN BURNING: AMBIENT CONCENTRATIONS <305 m (1000 FT) DOWNWIND[1]

Analyte	N[2]	No. Fires Where Meas. Taken	Concentrations (µg/m³)						Acute REL[6]	Target Organ	Chronic REL[7]	Target Organ	Unit Risk Factor[8]
			Median	90% LCL[3]	90% UCL[3]	A[4]	90th Pcnt[5]	Max	µg/m³		µg/m³		(µg/m³)⁻¹
Benzene	101	21	121	33	525	17	6,375	79,693	1300	Reproductive; Developmental	60	Hematopoietic system; development; nervous system	2.9×10^{-5}
Toluene	94	21	220	38	527	16	3,766	206,753	37,000	Central Nervous System; Eye; Respiratory irritation	300	Nervous system; Respiratory system; development	
Styrene	86	14	85	20	174	15	2,320	2,705	21,000	Eye; Respiratory Irritation	900	Nervous system	
Xylenes	41	9	17	ND	607	11	1,424	3,809 5	22,000	Eye; Respiratory irritation	700	Nervous system; Eyes	
m,p-Xylene	30	6	76	1	282	9	912	999			700	Nervous system; Eyes	
o-Xylene	49	10	35	1	109	12	336	564			700	Nervous system; Eyes	
Methylene chloride	39	10	8	ND	89	10	565	836			400	Cardiovascular system; nervous system	
Chloroform	33	9	42	ND	197	9	533	1,085			300	Alimentary; kidney; development	5.3×10^{-6}

TABLE 8. OPEN BURNING: AMBIENT CONCENTRATIONS <305 m (1000 FT) DOWNWIND[1] (CONT.)

Analyte	N[2]	No. Fires Where Meas. Taken	Concentrations (µg/m³)						Acute REL[6]	Target Organ	Chronic REL[7]	Target Organ	Unit Risk Factor[8]
			Median	90% LCL[3]	90% UCL[3]	A[4]	90th Pcnt[5]	Max	µg/m³		µg/m³		(µg/m³)⁻¹
Ethyl benzene	57	12	49	ND	204	12	502	1,477			2000	Developmental; alimentary system (liver); kidney; endocrine system	
Trichloroethene (trichloroethylene)	45	11	ND	ND	41	11	425	881 5			600	Nervous System; Eyes	2.0×10^{-6}
1,1,2-Trichloroethane	33	7	ND	ND	82	9	316	542					1.6×10^{-5}
1,1,1-Trichloroethane	43	12	ND	ND	10	11	39	817					
1,1-Dichloroethane	26	10	ND	ND	ND	8	16	42					
Chlorobenzene	33	11	ND	ND	ND	9	2	11			1000	Alimentary system; kidney; reproductive system	
Trichloroethane	17	7	ND	ND	1	7	1	1 5					
Carbon tetrachloride	31	10	ND	ND	ND	9	ND	44	$1.9 \times 10^{+3}$	Reproductive/ Developmental ; Nervous; Alimentary tract	40	Alimentary System;Development; Nervous System	4.2×10^{-5}
Tetrachloroethene (perchloroethylene)	28	9	ND	ND	ND	9	ND	ND	$2 \times 10^{+4}$	Central Nervous System; Eye; Respiratory system			5.9×10^{-6}

[1] Monitoring Data from USEPA, 1997
[2] n = number of measurements
[3] The 90 percent confidence limits lower and upper as determined for the median.
[4] Where a is the number of data values from the median to the upper and to the lower 90 percent confidence limits.
[5] The analytes in this table are arranged in order of 90th percentile (except for the o-xylene isomer).
[6] OEHHA, 1999a
[7] OEHHA, 2000b
[8] OEHHA, 1999b
[8] OEHHA, 1999b
ND = Not detected.

TABLE 9. OPEN BURNING: AMBIENT CONCENTRATIONS >305 m (1000 FT) DOWNWIND[1]

Analyte	N[2]	No.Fires Where Meas. Taken	Concentrations (µg/m^3)						Acute REL[6]	Target Organ	Chronic REL[7]	Target Organ	Unit Risk Factor[8]
			Median	90% LCL[3]	90% UCL[3]	a[4]	90th Pcnt[5]	Max	µg/m^3		µg/m^3		(µg/m^3)$^{-1}$
Styrene	45	5	1	ND	16	11	554	2,705	21,000	Eye; Respiratory Irritation	900	Nervous system	
Ethyl benzene	18	5	3	ND	172	7	172	1,390			2000	Developmental; alimentary system (liver); kidney; endocrine system	
Toluene	45	10	5	1	37	11	156	634	37,000	Central Nervous System; Eye; Respiratory irritation	300	Nervous system; Respiratory system; development	
Benzene	47	10	4	ND	29	11	67	524	1300	Reproductive; Developmental	60	Hematopoietic system; development; nervous system	2.9×10^{-5}
Xylene	20	4	ND	ND	ND	7	4	20 [5]	22,000	Eye; Respiratory irritation	700	Nervous system; Eyes	
M,p-Xylene	28	3	2	1	9	9	14	999	22,000	Eye; Respiratory irritation	700	Nervous system; Eyes	
o-Xylene	38	6	1	1	5	10	13	521	22,000	Eye; Respiratory irritation	700	Nervous system; Eyes	
Chlorobenzene	29	5	1	ND	1	9	1	1			1000	Alimentary system; kidney; reproductive system	

TABLE 9. OPEN BURNING: AMBIENT CONCENTRATIONS >305 m (1000 FT) DOWNWIND (CONTINUED)

Analyte	N[2]	No.Fires Where Meas. Taken	Concentrations (µg/m^3)						Acute REL[6]	Target Organ	Chronic REL[6]	Target Organ	Unit Risk Factor[7]
			Median	90% LCL[3]	90% UCL[2]	A[4]	90th Pcnt[5]	Max	µg/m^3		µg/m^3		(µg/m^3)$^{-1}$
1,1,1-Trichloroethane	30	5	1	ND	1	9	1	7					
Trichloroethane	34	4	1	ND	1	10	1	3 [5]					
Carbon tetrachloride	8	4	ND	ND	ND	4	ND	ND					
Trichloroethene (trichloroethylene)	6	4	ND	ND	18	3	ND	18 [5]			600	Nervous System; Eyes	2.0×10^{-6}
1,1-Dichloroethane	7	3	ND	ND	ND	3	ND	ND					1.6×10^{-6}
1,1,2-Trichloroethane	6	2	ND	ND	ND	3	ND	ND					1.6×10^{-5}
Chloroform	3	3	ND	ND	ND	1	ND	ND			300	Alimentary; kidney; development	5.3×10^{-6}
Methylene chloride	14	3	ND	ND	ND	6	ND	660	1.4×10^{4}		400	Cardiovascular system; nervous system	1.0×10^{-6}
Tetrachloroethene (perchlorethylene)	8	4	ND	ND	ND	4	ND	ND	$2 \times 10^{+4}$	Central Nervous System; Eye; Respiratory system			5.9×10^{-6}

[1] Monitoring Data from USEPA, 1997
[2] n = number of measurements
[3] The 90 percent confidence limits lower and upper as determined for the median.
[4] Where a is the number of data values from the median to the upper and to the lower 90 percent 3 confidence limits.
[5] The analytes in this table are arranged in order of 90th percentile (except for the o-xylene isomer). Pcnt = percentile 4 Contains mixed isomers. 5
ND = Not detected.
[6] OEHHA, 1999a
[7] OEHHA, 2000b
[8] OEHHA, 1999b

TABLE 10. PAH PLUME CONCENTRATIONS – RHINEHART TIRE FIRE[1]

PAH	Concentration ($\mu g/m^3$)*	Limit of Detection(μg)	Unit Risk Factor $(\mu g/m^3)^{-1}$
Naphthalene	461	5	
Acenaphthylene	ND	7	
Acenaphthene	9	1	
Fluorene	26	0.5	
Phenanthrene	54	0.2	
Anthracene	35	0.3	
Fluoranthene	16	0.005	
Pyrene	11	0.1	
Benz(a)anthracene	6	0.005	1.1×10^{-4}
Chrysene	18	0.10	1.1×10^{-5}
Benzo(b)fluoranthene	1	0.003	1.1×10^{-4}
Benzo(k)fluoranthene	1	0.005	1.1×10^{-4}
Benzo(a)pyrene	3	0.005	1.1×10^{-3}
Dibenz(a,h)anthracene	ND	0.05	1.2×10^{-3}
Benzo(g,h,I)perylene	ND	0.05	
Indenopyrene	3	0.02	1.1×10^{-4}
TOTAL PAHs	**644**	--	

[1] Monitoring Data from USEPA, 1997
*Sample duration = 405 min.
ND - Not detected
Sampling Method: Zefluor filter + ORBD 43 sorbent; flow rate 1.0 LPM.
Analytical Method: HPLC with UV detection.

Table 11 Aldehydes Present in Smoke from Wildland Fires[1]

Aldehyde	Acute REL ($\mu g/m^3$)	Endpoint	Chronic REL ($\mu g/m^3$)	Endpoint	Unit Risk Factor $(\mu g/m^3)^{-1}$
Formaldehyde	94	Eye Irritation	3	Respiratory System	6.0×10^{-6}
Acetaldehyde			9	Respiratory System; Eyes	2.7×10^{-6}
Furfural					
Acrolein	0.19	Eye Irritation	0.06	Respiratory System; Eyes	

[1]Materna et al., 1992

Table 12 Ambient Air PCDD (Dioxins) and PDCF (Furans) International Toxic Equivalents Downwind of the Hagersville Tire Fire (pg/m^3)[1]

Date (1990)	Days after fire Started	1 km Downwind			3 km Downwind		
		Dioxin	Furan	Total	Dioxin	Furan	Total
Feb 19/20	8/9	0.34	2.2	2.5	0.039	0.23	0.27
Feb 20/21	9/10	0.18	1.4	1.6	0.03	0.13	0.16
Feb 21/22	10/11				0.037	0.2	0.24
Feb 23/24	12/13	0.095	0.66	0.76	0.014	0.032	0.046
Feb 24/25	13/14	0.01	0.012	0.022			
Feb 26/27	15/16	0.029	0.093	0.12			

1 Adapted from Steer et al., 1995
(Fire was extinguished on February 26

Table 13 Tire Fire Incident Characteristics[1]

Incident Location	# of Tires at Site	% of Tires Burned	# of Tires Burned	Burn Duration (Days)	Site Size (Acres)	Fire Size (Acres)	Pile Height (Feet)	Pile Config.
Fairbanks, TX	NA	NA	NA	NA	50	2	12	NA
Norfolk, VA	NA	NA	NA	26	5	NA	NA	NA
Batesville, AR	NA	NA	NA	NA	NA	NA	NA	NA
Danville, PA	NA	NA	NA	NA	NA	NA	NA	NA
Jonesville, NC	20	NA	NA	4	NA	NA	NA	NA
Tacoma, WA	1,000	NA	NA	NA	NA	NA	NA	NA
Chadbourn, NC	90,000	100	90,000	1	NA	NA	7	Enclosure
Spencer, MA	200,000	NA	NA	5	12	NA	10	Shallow pit
Minden, IA	300,000	98	294,000	2	NA	NA	30	Pit
Wawina, MN	500,000	65	325,000	3	2	1	15	Random Flat Piles
Wakefield, VA	625,000	60	375,000	3	4	3	10	Pit
Webber, UT	700,000	NA	NA	5	2	NA	30	Heaps
Andover, MN	800,000	50	400,000	2	NA	NA	17	Random Flat Piles
Everett, WA	1,000,000	75	750,000	60	NA	NA	10	Wind Rows
St Amable, Quebec	2,000,000	45	900,000	3	55	55	65	Wind Rows
Level Cross, NC	3,000,000	60	1,800,000	14	7	7	9	Heaps
Belchertown, MA	4,250,000	NA	NA	40	NA	NA	NA	NA
Winchester, VA	5,000,000	NA	NA	270	NA	5	NA	NA
Catskill, NY	5,000,000	NA	NA	NA	NA	NA	NA	NA
Danville, NH	5,000,000	NA	NA	14	NA	NA	NA	Heaps
Somerset, WI	6,000,000	33	2,000,000	5	25	20	5	Conical Heaps
Hagersville, Ontario	14,000,000	99	13,860,000	17	12	12	20	Heaps
Choperena (Panoche), CA						4		
Tracy, CA	2,500,000	NA	NA	860	NA			Heaps
Westley, CA	5,000,000	NA	NA	36	30	15		Heaps

1 Adapted from USEPA, 1993. Panoche, Tracy and Westley tire fire data added

Table 14 Comparison of Average Monitored PAH Concentrations at the Westley Tire Fire with Modesto 1997 Annual Average Daily Concentrations ($\mu g/m^3$)[1]

PAH	Westley-Livingston	Patterson High School.	Modesto Average	Modesto Maximum
Benzo (b) fluoranthene	0.18	0.42	0.270	3.3
Benzo (k) fluoranthene	0.12	0.11	0.115	1.30
Benzo (a) pyrene	0.12	0.18	0.191	2.20
Dibenz (a,h) anthracene	0.11	0.03	0.034	0.25
Benzo (g,h,i) perylene	0.15	0.29	0.543	5.00
Indeno (1,2,3-cd) pyrene	0.18	0.31	0.293	3.10

[1]The nondetect values were averaged using the one half the detection limit.
Data from Appendix B

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Appendix A
Toxicology Profiles for Some Chemicals Found in Tire Fire Smoke.
[Compilation of Profiles from Existing OEHHA Documents (Except Dioxins)]

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Acrolein

Acute Toxicity Summary in Air Toxics "Hot Spots" Risk Assessment Guidelines Part I: Technical Support Document. The Determination of Acute Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA. March 1999.

Chronic Toxicity Summary in Air Toxics "Hot Spots" Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA.

ACROLEIN

CAS Registry Number: 107-02-8

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**0.19 µg/m³**
Critical effect(s)	eye irritation in healthy human volunteers
Hazard Index Target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994)

Description	colorless liquid
Molecular formula	C_3H_4O
Molecular weight	56.1
Density	0.843 g/cm^3 @ 20°C
Boiling point	53°C
Melting point	-87°C
Vapor pressure	220 mm Hg @ 20°C
Flashpoint	-26°C
Explosive limits	2.8% - 31% by volume
Solubility	soluble in ethanol, diethyl ether, and up to 20% w/v in water
Odor threshold	0.5 ppm
Metabolites	glycidaldehyde, acrylic acid
Conversion factor	1 ppm in air = 2.3 mg/m³ @ 25° C

III. Major Uses or Sources

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water-treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1985). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein.

IV. Acute Toxicity to Humans

Exposure to 1 ppm (2.3 mg/m³) for 5 minutes causes lacrimation and irritation of the eyes, nose, and throat (IARC: Fassett, 1962). At a concentration of 7 mg/m³, acrolein causes severe lacrimation and irritation of the mucous membranes of the respiratory tract (Prentiss, 1937). A 10-minute exposure to 350 mg/m³ acrolein was lethal (Prentiss, 1937). A case report of respiratory failure and death in individuals exposed to vapors from overheated frying pans containing fat and food items implicated acrolein as the principal toxicant (Gosselin *et al.* 1979).

The lowest observed adverse effect level (LOAEL) for eye irritation in healthy human volunteers is exposure to 0.14 mg/m³ (0.06 ppm) acrolein for five minutes (Darley *et al.*, 1960).

Prolonged treatment of cancer patients with cyclophosphamide can result in hemorrhagic cystitis. The bladder toxicity is due to the formation of acrolein as a metabolite and may be prevented by co-administration of 2-mercaptoethane sulfonate (Brock *et al.*, 1979).

There is inadequate direct evidence for carcinogenicity of acrolein in experimental animals or in humans (IARC, 1985). However, a metabolite of acrolein, the reactive epoxide glycidaldehyde, has been shown to be mutagenic and carcinogenic in mice and rats. Therefore, acrolein has been designated a Group C substance, with possible human carcinogenic potential (U.S.EPA, 1987).

Predisposing Conditions for Acrolein Toxicity

Medical: Persons with pre-existing eye, skin, respiratory, allergic, asthmatic or heart diseases might be at increased risk due to acrolein exposure. Individuals with cystic fibrosis or asthma should be excluded from acrolein exposure (Reprotext, 1999).

Chemical: Cancer patients treated with cyclophosphamide could be at increased risk because acrolein is a metabolite of cyclophosphamide (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The LC_{50} for inhalation of acrolein in rats is 300 mg/m³ for a 30-minute exposure (Fassett, 1963). An LC_{50} of 152 mg/m³ is reported in mice for a 6-hour exposure (Philippin *et al.*, 1970). An LC_{50} of 58 mg/m³ for a four-hour exposure is reported for hamsters (Kruysse, 1971). No mortality was observed in 8 rats exposed to 100 mg/m³ acrolein for 30 minutes, although heavy lacrimation and nasal secretion were reported (NTIS, 1981). An initial 35% decrease in liver alkaline phosphatase (AP) activity, followed by a 200% increase in AP activity over controls, was seen in rats exposed to 10 mg/m³ for 24 hours (NTIS, 1981). In guinea pigs, exposure to 39.6 mg/m³ for 1 hour resulted in no changes in respiratory rate, minute volume, or airway resistance (NTIS, 1981).

Roemer *et al.* (1993) exposed Male Sprague Dawley rats by inhalation to 0, 0.2 or 0.6 ppm acrolein for 6 h per day on one or three successive days. Nasal and tracheal epithelial and free lung cells were analyzed for proliferative responses using 5-bromodeoxyuridine (BrdU) labeling to identify DNA synthesizing cells. A single exposure to acrolein increased the DNA synthesizing cells 3-fold. After three exposures the increase was distinctly lower. All sites analyzed showed approximately the same concentration/response pattern. Since significant changes in cell proliferation were detected at 0.2 ppm acrolein, it is a LOAEL for this experiment.

Acrolein depletes glutathione (GSH) and other free thiol groups both in vitro and in vivo (WHO, 1992). Exposure of rats to a concentration of 11.4 mg/m³ for 3 hours caused irreversible depletion of GSH in the nasal mucosa. In addition, ^{14}C-labeled acrolein has been shown to bind irreversibly to sulfhydryl groups on cytochrome P450 in rats (WHO, 1992). The binding of

acrolein to sulfhydryl groups is localized to the area of contact (e.g., nasal membranes or lung epithelium), and is not a systemic effect (WHO, 1992).

VI. Reproductive or Developmental Toxicity

In rats, acrolein can induce teratogenic and embryotoxic effects when administered directly into the amniotic fluid, or when added to cultured rat embryos (ReproText, 1999; Slott and Hales, 1986). Additionally, acrolein injected into chicken embryos resulted in embryotoxicity and some teratogenic effects at moderate to high doses (0.001-0.1 mg/egg) (Chhibber and Gilani, 1986). However, intravenous exposure to 3 mg/kg in pregnant rabbits showed no developmental effects in the offspring (WHO, 1992). Based on this latter study, the World Health Organization (1992) concluded that human exposure to acrolein was unlikely to affect the developing embryo.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.09 ppb (0.19 μg/m³)

Study	Darley *et al.*, 1960
Study population	36 healthy human volunteers
Exposure method	5 minute exposures to 0.06 ppm; carbon-filter respirators worn during exposure
Critical effects	subjective reports of eye irritation
LOAEL	0.06 ppm
NOAEL	not observed
Exposure duration	5 minutes
Extrapolation to 1 hour	$C^n * T = K$, where n = 1 (Ten Berge *et al.*, 1986)
Extrapolated 1 hour concentration	0.005 ppm (5 ppb)
LOAEL uncertainty factor	6
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	0.09 ppb (0.19 μg/m³)

Only volunteers without a prior history of chronic upper respiratory or eye problems were included in the study. Subjects wore carbon-filter respirators during exposure, so that only the eyes were exposed to the test mixture. There is significant uncertainty in this calculation because of the lack of a NOAEL and the short exposure duration (5 min) in the study.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Forty-six human subjects (21 male and 25 female) were exposed to 0.3 ppm (0.69 mg/m³) acrolein for 1 hour (Weber-Tschopp *et al.*, 1977). Effects included significant irritation of the eyes, nose, and throat. A decrease in respiratory rate of 10% was evident in 47% of the subjects

after 10 minutes of exposure. Based on this information the National Academy of Sciences decided that the previous EEGL of 0.2 ppm was not sufficiently protective, and it was changed to 0.05 ppm (0.115 mg/m^3). The NAS-EEGL for acrolein was determined by an expert panel and the details governing the selection of a margin of safety are not presented by NAS. Lack of data on 1-hour exposures of humans to lower concentrations of acrolein prevented NAS from deriving a definitive EEGL for a 1-hour exposure. Therefore, no recommendation can be made.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

LC_{50} data in mice, guinea pigs, rabbits, and rats ranged from 8-25 ppm (18.4 - 57.5 mg/m^3) acrolein (Carpenter *et al.*, 1949; Pattle and Cullumbine, 1956; Kruysse, 1971). Based on these animal lethality studies, a value of 3 ppm (6.9 mg/m^3) was chosen by AIHA as the life-threatening level (AIHA, 1989). The methodology employed by AIHA to develop the margin of safety for the ERPG-3 for acrolein is not presented in the ERPG document. NIOSH (1995) lists a revised IDLH of 2 ppm based on several reports of acute inhalation toxicity in healthy humans for exposure periods of 10 minutes or less to 1.8-8 ppm acrolein. There is no formal protocol for its derivation and no consideration of sensitive subpopulations. Therefore, no recommendation can be made for a level protective against life-threatening effects.

VIII. References

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CHRONIC TOXICITY SUMMARY

ACROLEIN

(2-propenal, acraldehyde, allyl aldehyde, acryl aldehyde)

CAS Registry Number: 107-02-8

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.06 μg/m^3** (0.03 ppb)
Critical effect(s)	Histological changes in nasal epithelium in rats
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless or yellow liquid with piercing, disagreeable odor
Molecular formula	C_3H_4O
Molecular weight	56.1 g/mol
Density	0.843 g/cm^3 @ 20°C
Boiling point	53°C
Melting point	–88°C
Vapor pressure	220 torr @ 20°C
Odor threshold	160 ppb (370 μg/m^3) (Amoore and Hautala, 1983)
Solubility	Soluble in ethanol, diethyl ether, and up to 20% w/v in water
Conversion factor	1 ppm = 2.3 mg/m^3 @ 25° C

III. Major Uses or Sources

Acrolein is principally used as a chemical intermediate in the production of acrylic acid and its esters. Acrolein is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1985). Combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats contribute to the environmental prevalence of acrolein (IARC, 1985). Acrolein is a byproduct of fires and is one of several acute toxicants which firefighters must endure. It is also formed from atmospheric reactions of 1,3-butadiene. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 54,565 pounds of acrolein (CARB, 2000).

IV. Effects of Human Exposure

Information regarding the chronic toxicity of acrolein to humans is scarce (IPCS, 1992). Acutely acrolein acts primarily as an irritant to the eyes and respiratory tract. The LOAEL for eye irritation is 0.06 ppm (0.14 mg/m^3) acrolein for five minutes (Darley *et al.*, 1960). In this study, 36 healthy human volunteers were exposed to 0.06 ppm (0.14 mg/m^3) for 5 minutes. Only volunteers without a prior history of chronic upper respiratory or eye problems were included in the study. Subjects wore carbon-filter respirators during exposure, so that only the eyes were exposed to the test mixture. Subjects reported a significant incidence of eye irritation in a questionnaire following the exposure.

V. Effects of Animal Exposure

Male Fischer-344 rats were exposed for 6 hours/day, 5 days/week for 62 days to acrolein at concentrations of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3) (Kutzman, 1981; Kutzman *et al.*, 1985). Each group of 24 animals was assessed for pulmonary function immediately prior to the end of the experiment. Pulmonary function tests (PFT) included lung volumes, forced respiratory capacity, pulmonary resistance, dynamic compliance, diffusing capacity of carbon monoxide, and multi-breath nitrogen washout. At the end of the experiment, animals were killed and histopathological changes in the lung were recorded. Eight additional rats were designated for histopathology and 8 rats were used for reproductive testing only. All analyses were performed post-exposure for 6 days to minimize the acute effects of acrolein. Mortality was high (56%) in rats exposed to 4.0 ppm (9.2 mg/m^3). The observed mortality was due to acute bronchopneumonia in these cases. The animals from this group that survived had reduced body weight. No histological changes were observed in extrarespiratory tissues in any group. There was a concentration-dependent increase in histological changes to the nasal turbinates and rhinitis, beginning at 0.4 ppm. Concentration-dependent damage to the peribronchiolar and bronchiolar regions was also observed. No lung lesions were observed in the 0.4 ppm group. The NOAEL for nasal lesions (squamous epithelial metaplasia and neutrophil infiltration) in this study was 0.4 ppm.

Feron *et al.* (1978) exposed groups of 20 Syrian golden hamsters, 12 SPF Wistar rats and 4 Dutch rabbits (of both sexes) to acrolein vapor at 0, 0.4, 1.4 and 4.9 ppm (0, 0.92, 3.2, and 11.3 mg/m^3) 6 h/day, 5 days/week for 13 weeks. The most important effects at the highest level included mortality in rats (3 of each sex), and ocular and nasal irritation, growth depression, and histopathological changes of the respiratory tract in each species. The changes in the airways induced by acrolein consisted both of destruction and of hyperplasia and metaplasia of the lining epithelium accompanied by inflammatory alterations. Rats were the most susceptible species examined and showed treatment-related histopathological abnormalities in the nasal cavity down to 0.4 ppm (LOAEL), whereas this level was a NOAEL in hamsters and rabbits. The results for individual rats at 0.4 ppm were not given.

The concentration required for depression of the respiratory rate of mice by 50% (RD_{50}) during 15 minutes of acrolein exposure was estimated as 1.7 ppm (Kane *et al.*, 1979). These authors

proposed that the highest concentration suitable for a human air quality standard was 0.001 x RD_{50}, or 0.002 ppm (0.005 mg/m^3). Buckley et al. (1984) investigated whether lesions occur in the respiratory tract of Swiss-Webster mice after exposure to the RD_{50} concentrations of ten sensory irritants including acrolein. After exposure of mice for 6 hr/day for 5 days to 1.7 ppm acrolein, the respiratory tract was examined for histopathologic changes. Acrolein (and all other irritants) produced lesions in the nasal cavity with a distinct anterior-posterior severity gradient. Acrolein specifically caused severe exfoliation and squamous metaplasia of the respiratory epithelium and moderate ulceration of the olfactory epithelium. Acrolein did not induce lesions in the lower respiratory tract.

Bouley *et al.* (1975,1976) exposed male SPF OFA rats continuously to 0.55 ppm (1.3 mg/m^3) of acrolein for up to 63 days. This level of acrolein led to a greater susceptibility to airborne *Salmonella enteritidis* infection during the first three weeks compared to control rats but it disappeared spontaneously when exposure was continued beyond three weeks. The general toxic effect of diminished weight gain (due to reduced feeding) compared to the control group lasted as long as exposure and disappeared only after acrolein was discontinued. Sneezing, a sign of nasal irritation, was consistently observed in the exposed animals on days 7 through 21 but ceased thereafter. No histopathology of the nasal cavity of or any other tissue was reported.

The pulmonary immunological defense against a bacterial challenge using *Staphylococcus aureus* in mice was impaired in a dose-dependent manner following exposure to acrolein at concentrations of 3 and 6 ppm (6.9 and 13.8 mg/m^3) for 8 hours (Astry and Jakab, 1983). In this study, the control exposure was not described.

Leach and associates (1987) found histological changes in pulmonary epithelium and mucosa in a group of 40 male Sprague-Dawley rats exposed to 3 ppm acrolein 6 hours/day, 5 days/week, for 3 weeks. Tests for pulmonary and systemic immune function revealed no significant differences between treated and control animals. Similarly, no difference was observed in survival from a bacterial challenge with *Listeria monocytogenes*, although this challenge was intravenous and not intratracheal, and may not have revealed the pulmonary macrophage impairment indicated by Astry and Jakab (1983).

Lyon and associates (1970) investigated the effects of repeated or continuous exposures of acrolein on Sprague-Dawley rats (n = 15/exposure group), guinea pigs (n = 15), Beagle dogs (n = 2), and male squirrel monkeys (n = 9). Animals were exposed intermittently to 0.7 or 3.7 ppm (1.6 or 8.5 mg/m^3) acrolein for 8 hours/day, 5 days/week, for 6 weeks, or continuously to 0.22, 1.0, or 1.8 ppm (0.5, 2.3, or 4.1 mg/m^3) for 90 days. Two monkeys in the 3.7 ppm intermittent exposure group died within 9 days. Monkeys and dogs salivated excessively during the first week. Squamous metaplasia and basal cell hyperplasia of the trachea were observed in monkeys and dogs; 7 of the 9 monkeys also exhibited bronchiolitis obliterans with squamous metaplasia in the lungs. Bronchopneumonia was noted in the dogs. Inflammation in the lung interstitiae was more prominent in the dogs than in the monkeys. Rats and guinea pigs did not exhibit signs of toxicity when exposed intermittently to 3.7 ppm. Continuous exposure to 1.0 and 1.8 ppm, but not 0.22 ppm acrolein, resulted in salivation and ocular discharge in the monkeys and dogs. Rats and guinea pigs appeared normal at all concentrations. Rats exhibited significant weight loss in the 1.0 and 1.8 ppm continuous exposure groups. Nonspecific

inflammatory changes were observed in sections of brain, heart, lung, liver and kidney from all species exposed to 1.8 ppm. The lungs from the dogs showed confluent bronchiopneumonia. Focal histological changes in the bronchiolar region and the spleen were detected at 0.22 ppm in dogs. Nonspecific inflammatory changes at the 0.22 ppm level were apparent in liver, lung, kidney and heart from monkeys, guinea pigs and dogs. Unfortunately the nasal cavity was not examined in this study. In addition there were no unexposed control animals for any species.

In one of the few chronic studies reported Feron and Kruysse (1977) exposed hamsters (18/gender) to 4 ppm (9.2 mg/m^3) acrolein for 7 hours/day, 5 days/week, for 52 weeks. Mild to moderate histological changes were observed in the upper and lower respiratory tract. No evidence of toxicity to other organs was apparent at necropsy, although body weight was decreased. Hematology, urinalysis, and serum enzymes were not affected by exposure. Thus 4 ppm is a chronic LOAEL for hamsters.

There are no reports of reproductive or developmental toxicity following exposure to acrolein. Kutzman (1981) found no significant changes in embryo viability in rats exposed to 4.0 ppm acrolein throughout pregnancy. Similarly, sperm morphology was reportedly not affected at this level. Bouley *et al.* (1975; 1976) exposed three male and 21 female SPF-OFA rats continuously to 0.55 ppm (1.26 mg/m^3) acrolein vapor for 25 days. The rats were allowed to mate on day 4 of the exposure. The number of acrolein-exposed pregnant rats and the number and mean body weight of their fetuses were similar to controls.

VI. Derivation of Chronic Reference Exposure Level

Study	Kutzman, 1981; Kutzman *et al.*, 1985
Study population	Fischer-344 rats (24 males per group)
Exposure method	Discontinuous whole-body inhalation exposure of 0, 0.4, 1.4, and 4.0 ppm (0, 0.92, 3.2, and 9.2 mg/m^3)
Critical effects	Histological lesions in the upper airways
LOAEL	0.4 ppm (0.92 mg/m^3)
NOAEL	Not observed (see below)
Exposure continuity	6 hours per day, 5 days/week
Exposure duration	62 days
Average experimental exposure	0.071 ppm (0.16 mg/m^3) (0.4 x 6/24 x 5/7)
Human equivalent concentration	0.0087 ppm (gas with extrathoracic respiratory effects, RGDR = 0.14 based on MV = 0.18 m^3/day, SA(ET) = 11.6 cm^2)
LOAEL uncertainty factor	3 (see below)
Subchronic uncertainty factor	3 [62 days/(2x365) = 8.5% of lifetime]
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Reference exposure level	0.03 ppb (0.06 μg/m^3)

The U.S. EPA (1995) based its RfC of 0.02 $\mu g/m^3$ on the same study but used a UF of 10 to "account for the lack of chronic studies." Based on OEHHA's methodology for chronic RELs (OEHHA, 2000), 62 days is 8.5% of 2 years and is just above the minimum length for a subchronic UF of 3. The LOAEL for nasal histological changes in rats was considered by U.S. EPA to be 0.4 ppm (0.92 mg/m^3). Only one rat showed slight metaplastic and inflammatory changes (see Figure 6 of Kutzman *et al.* (1985)), which would be insufficient to demonstrate a statistically significant increase. The potentially slight effect, however, was accounted for by use of only an intermediate LOAEL uncertainty factor of 3. OEHHA accepted U.S. EPA's interpretation.

For comparison with the proposed REL, a REL was estimated from the data of Feron *et al.* (1978) in rats, which found a LOAEL of 0.4 ppm after a 13 week exposure. Using time extrapolation and an RGDR of 0.18, U.S. EPA estimated a LOAEL (HEC) of 0.03 mg/m^3. Using UFs of 3 each for LOAEL to NOAEL, subchronic, and interspecies and of 10 for intraspecies variability (OEHHA, 2000) results in an estimated REL of 0.1 $\mu g/m^3$, slightly higher than the REL calculated from the data of Kutzman *et al.* (1985).

As another comparison, the data of Lyon *et al.* (1970) indicate that 0.22 ppm acrolein was a NOAEL and 1.0 ppm was a LOAEL for salivation and ocular discharge in squirrel monkeys exposed continuously for 90 days. Use of a subchronic UF of 10 (since squirrel monkeys have a lifespan of 15 to 25 years), an interspecies UF of 3 (since monkeys are primates), and an intraspecies UF of 10 (cumulative UF = 300) results in a REL estimate of 0.7 ppb (1.7 $\mu g/m^3$) for ocular discharge. Unfortunately no unexposed monkeys were studied which makes it difficult to evaluate the statements in the paper that "nonspecific inflammatory changes" (p. 730) and possibly "specific inflammatory changes" (p. 731) were present in sections of liver, lung, kidney and heart from the monkeys exposed to 0.22 ppm. In addition the study lasted less than 2% of a squirrel monkey's life span. The value of 0.7 ppb (1.7 $\mu g/m^3$) is also higher than OEHHA's acute REL of 0.19 $\mu g/m^3$ (OEHHA, 1999), which is based on an acute human study (Darley *et al.*, 1960). In any case, the proposed chronic REL of 0.03 ppb (0.06 $\mu g/m^3$) should be protective of primates including man.

VII. Data Strengths and Limitations for Development of the REL

Significant strengths in the REL for acrolein include (1) the use of a well-conducted study with histopathological analysis and (2) the demonstration of consistent adverse effects among multiple studies of several species conducted by independent investigators.

Major areas of uncertainty are (1) the lack of adequate human exposure data, (2) limited reproductive toxicity data, (3) the absence of a definite NOAEL in the major study, and (4) the paucity of chronic inhalation exposure studies in both animals and humans.

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Benzene

Acute Toxicity Summary in Air Toxics "Hot Spots" Risk Assessment Guidelines Part I: Technical Support Document. The Determination of Acute Reference Exposure Levelss for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA. April 1999.

Chronic Toxicity Summary in Air Toxics "Hot Spots" Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA. February 2000.

BENZENE

(benzol; benzole; cyclohexatriene)

CAS Registry Number: 71-43-2

I. Acute Toxicity Summary (for a 6-hour exposure)

Inhalation reference exposure level	**1,300 µg/m³**
Critical effect(s)	Reproductive/developmental toxicity
Hazard Index target(s)	Reproductive/developmental; Immune System; Hematologic System;

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	C_6H_6
Molecular weight	78.1
Density	0.879 g/cm^3 @ 25°C
Boiling point	80.1°C
Melting point	5.5°C
Vapor pressure	100 mm Hg @ 26.1°C
Flashpoint	-11°C
Explosive limits	upper = 8.0% by volume in air lower = 1.4% by volume in air
Solubility	soluble in ethanol, chloroform, ether, carbon disulfide, acetone, oils, and glacial acetic acid; slightly soluble in water
Odor threshold	0.875 ppm (2.8 mg/m³) (Haley, 1977)
Odor description	sweet
Metabolites	hydroquinone, quinone, catechol, phenol
Conversion factor	1 ppm = 3.24 mg/m³

III. Major Uses or Sources

Benzene has been widely used as a multipurpose organic solvent. This use is now discouraged due to its high toxicity. Present uses include benzene as a raw material in the synthesis of styrene, phenol, cyclohexane, aniline, and alkyl benzenes and in the manufacture of various plastics, resins, and detergents. Synthesis of many pesticides and pharmaceuticals also involves benzene as a chemical intermediate (HSDB, 1994). Benzene is emitted in large quantities from refineries and petroleum storage facilities. The tire industry and shoe factories use benzene extensively. Annual demand in the U.S. was estimated to be 6 million tons in 1990 (HSDB, 1994).

IV. Acute Toxicity to Humans

Deaths from acute exposure to benzene are often related to physical exertion and release of epinephrine with subsequent cardiac failure. Frequently, the person trying to rescue a collapsed victim will die during the effort of lifting the unconscious person (HSDB, 1994). Anesthesia may develop at concentrations above 3,000 ppm (9,600 mg/m^3) (Reprotext, 1993). At exposures of greater than 1,000 ppm (3,200 mg/m^3) (duration unspecified), CNS symptoms include giddiness, euphoria, nausea, and headaches; heightened cardiac sensitivity to epinephrine-induced arrhythmias may develop (Snyder, 1987). These effects may be accompanied by symptoms of mild irritation to the eyes and mucous membranes. Acute hemorrhagic pneumonitis is highly likely if benzene is aspirated into the lung (HSDB, 1994). Respiratory tract inflammation, pulmonary hemorrhages, renal congestion, and cerebral edema have been observed at autopsy in cases of acute benzene poisoning (IARC, 1987). In these cases, blood levels of 2 mg/ml benzene were not associated with hematological changes (Winek and Collom, 1971).

Systemic poisoning by benzene can occasionally result in neuroretinal edema and in retinal and conjunctival hemorrhage (Grant, 1986). Additionally, petechial hemorrhages of the brain, pleura, pericardium, urinary tract, mucous membranes, and skin may occur in cases of fatal, acute benzene poisoning (Haley, 1977).

Major concerns of systemic benzene toxicity include aplastic anemia and acute myelogenous leukemia (IARC, 1987; Reprotext, 1993). Both of these conditions are typically seen in the chronic and subchronic exposures, but may be of concern following acute exposures as well. Myeloid and erythroid components of the bone-marrow are specific targets of benzene toxicity, which leads to aplastic anemia (IARC, 1982).

In men and women exposed to benzene for 4 hours, 46.9% of the inhaled dose was absorbed. Of this absorbed fraction, 30.1% was retained and 16.8% was excreted unchanged in the expired air (Nomiyama and Nomiyama, 1974). Most of the catechol and phenol metabolites are excreted within 24 hours in the urine, while hydroquinone requires 48 hours (Teisinger *et al.*, 1952).

Exposure at the odor threshold (0.875 ppm or 2.8 mg/m^3) for a brief duration is reported to enhance the electropotential of the brain (Haley, 1977).

Predisposing Conditions for Benzene Toxicity

Medical: People with existing hematologic disorders and cellular anemias may be more sensitive to the acute toxicity of benzene to the bone-marrow (Reprotext 1993, 1999). People with heart conditions may also be at increased risk for cardiac arrhythmias induced by exposure to high levels of benzene. Administration of epinephrine is known to potentiate the cardiac toxicity of benzene (Reprotext, 1993).

Females may be more sensitive to benzene toxicity than males due to higher average body fat content, which serves as a storage reservoir for the chemical

(Reprotext, 1993). Similarly, obese individuals of either sex may be more sensitive to benzene toxicity.

Chemical: Previous acute exposure to toluene inhibits benzene metabolism to toxic metabolites, and may reduce toxicity (Reprotext, 1993). Consumption of ethanol potentiates the bone-marrow toxicity of inhaled benzene in mice (Baarson *et al.*, 1982).

V. Acute Toxicity to Laboratory Animals

The oral LD_{50} in rats is reported to be 3.4 g/kg in young rats and 4.9 g/kg in older rats (Kimura *et al.*, 1971). Mortality was observed in 2 out of 10 rats exposed to 33,000 mg/m^3 (10,300 ppm) for 12.5-30 minutes daily for either 1 or 12 days (IARC, 1982). A 4-hour LC_{50} of 13,700 ppm (43,800 mg/m^3) was reported in female rats (IARC, 1982). An LC_{Lo} of 45,000 ppm (144,000 mg/m^3) is reported in rabbits (RTECS, 1994). In mice, an LC_{50} of 9,800 ppm (31,400 mg/m^3) is reported (RTECS, 1994). Leukopenia has been demonstrated to occur in rabbits exposed to 240 ppm (767 mg/m^3) for 10 hours/day for 2 weeks (IARC, 1982).

Brief inhalation of air saturated with benzene vapor (concentration unknown) resulted in ventricular extrasystole in cats and primates, with periods of ventricular tachycardia that occasionally terminated in ventricular fibrillation (Clayton and Clayton, 1981).

An attempt by Nielsen and Alarie (1982) to determine the inhalation RD_{50} for benzene was not successful. These investigators showed that inhalation of 5,800 ppm (18,800 mg/m^3) benzene in mice caused an increase in respiratory rate beginning at 5 minutes following onset of exposure. They speculated that the stimulation of respiratory rate resulted from the action of benzene on the central nervous system. In this study, benzene was not irritating to the upper airways of the animals.

The pharmacokinetics of benzene in the rat reportedly follows a 2-compartment model. The rapid phase has an elimination half-life ($t_{1/2}$) of 0.7 hours, and the $t_{1/2}$ for the longer phase is 13.1 hours (Rickert *et al.*, 1979). The long elimination half-life for benzene is due to the formation of catechol, quinone, and hydroquinone in the bone marrow. These reactive metabolites are not readily excreted, and are cytotoxic to the germinal cells in the bone marrow (Greenlee *et al.*, 1981). A 3-compartment model was fitted to human data on benzene disposition and bone-marrow metabolism (Watanabe *et al.*, 1994). The general relationship between cumulative quantity of metabolites produced and inhalation concentration was not linear, but was S-shaped, inflecting upward at low concentrations, and saturating at high concentrations.

Mice, particularly the DBA/2 strain, are more sensitive to myelotoxicity from benzene than are rats or rabbits (IARC, 1982). Colony-forming unit cells (CFUs; leukocyte precursors) were depleted in bone-marrow cultures taken from mice exposed to 4,610 ppm (14,950 mg/m^3) benzene for 8 hours. Recovery of CFUs was noted 7 days after exposure (IARC, 1982).

In addition to myelotoxicity, acute exposure to benzene may disrupt erythropoiesis and result in genotoxicity. Erythropoiesis, as measured by uptake of radiolabeled iron in the bone-marrow,

has been shown to be inhibited by subcutaneous injection of 10 mmol/kg benzene in mice (Bolcsak and Nerland, 1983).

Results from subacute exposures further illustrate the hematotoxic effects of benzene and the potential for immunotoxicity. Inhalation of 103 ppm (334 mg/m^3) benzene for 6 hours/day for 7 days by mice caused decreased spleen and marrow cellularities and decreased spleen weights (Green *et al.*, 1981). Benzene inhalation at concentrations of 0, 10, 30, 100, and 300 ppm (0, 32.4, 97.3, 324, and 973 mg/m^3) for 6 hours/day for 5 days resulted in a decreased host-resistance to bacterial infection by Lysteria monocytogenes (Rosenthal and Snyder, 1985). The numbers of L. monocytogenes bacteria isolated from the spleen were increased in a dose-dependent manner on day 4 of infection. The total numbers of T- and B-lymphocytes in the spleen and the proliferative ability of the splenic lymphocytes were decreased in a dose-dependent manner by benzene exposures of 30 ppm (97.3 mg/m^3) or greater. In this study, no decrement in host resistance or immune response was observed at 10 ppm (32 mg/m^3) benzene. Later studies in mice have also shown that exposure to 10 ppm for a subacute duration does not significantly alter hematological parameters in blood, spleen, thymus, or bone marrow (Farris *et al.*, 1996; 1997).

Farris *et al.* (1997) reported the hematological consequences of benzene inhalation in B6C3F1 mice exposed to 1, 5, 10, 100, and 200 ppm benzene for 6 hr/day, 5 days/week for 1, 2, 4, or 8 weeks and a recovery group. There were no significant effects on hematopoietic parameters from exposure to 10 ppm benzene or less. Thus 10 ppm was a NOAEL for 1 week of exposure (and longer). Exposure to 100 and 200 ppm benzene reduced the number of total bone marrow cells, progenitor cells, differentiating hematopoietic cells, and most blood parameters. Replication of primitive progenitor cells in the bone marrow was increased during the exposure period as a compensation for the cytotoxicity. At 200 ppm, the primitive progenitor cells maintained an increased percentage of cells in S-phase through 25 days of recovery compared with controls.

Inhalation of 3 ppm (9.6 mg/m^3) benzene for 6 hours by rats resulted in a significant increase over controls in the frequency of sister chromatid exchanges in peripheral blood lymphocytes (Erexson *et al.*, 1986).

Evans *et al.* (1981) observed an increase in active behavior in the form of eating and grooming in mice following exposure to 300 ppm (960 mg/m^3) benzene for 6 hours.

VI. Reproductive or Developmental Toxicity

Coate *et al.* (1984) exposed groups of 40 female rats to 0, 1, 10, 40, and 100 ppm (0, 3.24, 32.4, 129.6, or 324 mg/m^3) benzene for 6 hours/day during days 6-15 of gestation. In this study, teratologic evaluations and fetotoxic measurements were done on the fetuses. A significant decrease was noted in the body weights of fetuses from dams exposed to 100 ppm (324 mg/m^3). No effects were observed at a concentration of 40 ppm (129.6 mg/m^3).

Keller and Snyder (1986) reported that exposure of pregnant mice to concentrations as low as 5 ppm (16 mg/m^3) benzene on days 6-15 of gestation (6 hr/day) resulted in bone-marrow

hematopoietic changes in the offspring that persisted into adulthood. However, the hematopoietic effects (e.g., bimodal changes in erythroid colony-forming cells) in the above study were of uncertain clinical significance. In a similar, later study, Keller and Snyder (1988) found that exposure of mice in utero to 20 ppm (64 mg/m^3) benzene on days 6-15 of gestation resulted in neonatal suppression of erythropoietic precursor cells and persistent, enhanced granulopoiesis. This effect was considered significant bone-marrow toxicity by the authors. No hematotoxicity was seen in this study at 10 ppm (32 mg/m^3).

An exposure of 500 ppm (1,600 mg/m^3) benzene through days 6-15 of gestation was teratogenic in rats while 50 ppm (160 mg/m^3) resulted in reduced fetal weights on day 20 of gestation. No fetal effects were noted at an exposure of 10 ppm (Kuna and Kapp, 1981). An earlier study by Murray *et al.* (1979) showed that inhalation of 500 ppm benzene for 7 hours/day on days 6-15 and days 6-18 of gestation in mice and rabbits, respectively, induced minor skeletal variations.

Tatrai *et al.* (1980) demonstrated decreased fetal body weights and elevated liver weights in rats exposed throughout gestation to 150 mg/m^3 (47 ppm).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Level protective against mild adverse effects: While benzene exposure results in decreased immune response and hematopoietic effects in laboratory animals following 5 day exposures, it was problematic to extrapolate from these repeated dose studies for these endpoints. Thus, no level protective against mild adverse effects for one-hour is being recommended. The REL is based on developmental toxicity, a severe adverse effect.

Reference Exposure Level for a 6-hour exposure (Level Protective Against Severe Adverse Effects): 1,300 μg/m^3

Because of the uncertainty of extrapolating from repeated exposures to a one-hour concentration, we have chosen to use a single day exposure in the reproductive studies with no time extrapolation as an REL. In the case of benzene, the REL is for a 6-hour exposure.

Study	Coate *et al.*, 1984; (supported by Kuna and Kapp, 1981; Keller and Snyder, 1988)
Study population	pregnant female rats
Exposure method	inhalation of 0, 1, 10, 40, or 100 ppm
Critical effects	decreased fetal body weights
LOAEL	100 ppm
NOAEL	40 ppm
Exposure duration	6 hours per day (for 5 days)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10

Cumulative uncertainty factor	100
Reference Exposure Level	0.4 ppm (1.3 mg/m³; 1,300 µg/m³)

Pregnant female rats (40 per group) were exposed for 6 hours/day on days 6-15 of gestation to benzene concentrations of 0, 1, 10, 40, and 100 ppm (0, 3.24, 32.4, 129.6, and 324 mg/m³) (Coate *et al.*, 1984). The mean fetal weights from the females treated with 100 ppm benzene were significantly decreased ($p < 0.05$) compared to controls. No teratogenic, fetotoxic, or maternally toxic effects were observed in rats exposed to 40 ppm (129.6 mg/m³) benzene or less. The 40 ppm (129.6 mg/m³) concentration is considered a NOAEL for reduced fetal weight. The value of 40 ppm for a 6-hour exposure was extrapolated to a 1-hour exposure using the equation $C^n * T = k$, where $n = 2$. The resulting 100 ppm extrapolated value was used to determine the level protective against severe adverse effects using uncertainty factors of 10 for intraspecies and 10 for interspecies variation. The level protective against severe adverse effects for benzene is therefore 1.0 ppm or 3.24 mg/m³.

Kuna and Kapp (1981) found direct teratogenic effects measured as decreased crown-rump length, exencephaly, and angulated ribs in rats when pregnant females were exposed 6 hours/day during days 6-15 of gestation to a concentration of 500 ppm. In this study, a concentration of 50 ppm during gestation resulted in lower fetal weights measured on day 20 of gestation. No fetal effects were noted at an exposure of 10 ppm (32 mg/m³). Keller and Snyder (1988) reported a NOAEL of 10 ppm for developmental hematopoietic effects in mice. The highest reported NOAEL (i.e., 40 ppm) consistent with reported LOAEL values was chosen for the derivation of the Reference Exposure Level (severe adverse effect level, in this case) for benzene.

Level Protective Against Life-threatening Effects

Svirbely *et al.* (1943) exposed mice for 7 hours to various benzene concentrations. They determined a NOAEL (0/18 animals) for lethality of 4,980 ppm and a LOAEL (3/18 animals) of 7,490 ppm. A benchmark concentration derived (BC_{05}) using a log-normal model with these data is 5,650 ppm (MLE = 6,550 ppm). A life-threatening level was calculated using these data with an uncertainty factor of 30 (10 for individual variability, and 3 for interspecies uncertainty using the BC_{05} as the starting point for the calculation). The level protective against life-threatening effects is therefore 5,650 ppm ÷ 30 = 190 ppm (620 mg/m³).

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CHRONIC TOXICITY SUMMARY

BENZENE

(Benzol; Benzole; Cyclohexatriene)

CAS Registry Number: 71-43-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**60 μg/m^3 (20 ppb)**
Critical effect(s)	Lowered red and white blood cell counts in occupationally exposed humans
Hazard index target(s)	Hematopoietic system; development; nervous system

II. Physical and Chemical Properties (HSDB, 1994; 1999)

Description	Colorless liquid
Molecular formula	C_6H_6
Molecular weight	78.1 g/mol
Density	0.879 g/cm^3 @ 25° C
Boiling point	80.1°C
Vapor pressure	100 torr @ 26.1°C
Solubility	Soluble in ethanol, chloroform, ether, carbon disulfide, acetone, oils, and glacial acetic acid; slightly soluble in water
Conversion factor	1 ppm = 3.2 mg/m^3 @ 25° C

III. Major Uses or Sources

Benzene has been widely used as a multipurpose organic solvent. This use is now discouraged due to its high toxicity, including carcinogenicity. Present uses include use as a raw material in the synthesis of styrene, phenol, cyclohexane, aniline, and alkyl benzenes in the manufacture of various plastics, resins, and detergents. Syntheses of many pesticides and pharmaceuticals also involve benzene as a chemical intermediate (HSDB, 1994). The tire industry and shoe factories use benzene extensively in their manufacturing processes. Annual demand in the U.S. was estimated to be 6 million tons in 1990 (HSDB, 1994). Benzene exposure also occurs as a result of gasoline and diesel fuel use and combustion (Holmberg and Lundberg, 1985). In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of benzene was approximately 0.7 ppb (CARB, 1999a). Annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 750,364 pounds of benzene (CARB, 1999b). (This does not include the large amount of benzene emitted by mobile sources.)

IV. Effects of Human Exposure

The primary toxicological effects of chronic benzene exposure are on the hematopoeitic system. Neurological and reproductive/developmental toxic effects are also of concern at slightly higher concentrations. Impairment of immune function and/or various anemias may result from the hematotoxicity. The hematologic lesions in the bone marrow can lead to peripheral lymphocytopenia and/or pancytopenia following chronic exposure. Severe benzene exposures can also lead to life-threatening aplastic anemia. These lesions may lead to the development of leukemia years after apparent recovery from the hematologic damage (DeGowin, 1963).

Kipen *et al.* (1988) performed a retrospective longitudinal study on a cohort of 459 rubber workers, examining the correlation of average benzene exposure with total white blood cell counts taken from the workers. These researchers found a significant ($p < 0.016$) negative correlation between average benzene concentrations in the workplace and white blood cell counts in workers from the years 1940-1948. A reanalysis of these data by Cody *et al.* (1993) showed significant decreases in RBC and WBC counts among a group of 161 workers during the 1946-1949 period compared with their pre-exposure blood cell counts. The decline in blood counts was measured over the course of 12 months following start of exposure. During the course of employment, workers who had low monthly blood cell counts were transferred to other areas with lower benzene exposures, thus potentially creating a bias towards non-significance or removing sensitive subjects from the study population. Since there was a reported 75% rate of job change within the first year of employment, this bias could be highly significant. In addition, there was some indication of blood transfusions used to treat some "anemic" workers, which would cause serious problems in interpreting the RBC data, since RBCs have a long lifespan in the bloodstream. The exposure analysis in this study was performed by Crump and Allen (1984). The range of monthly median exposures was 30-54 ppm throughout the 12-month segment examined. Despite the above-mentioned potential biases, workers exposed above the median concentrations displayed significantly decreased WBC and RBC counts compared with workers exposed to the lower concentrations using a repeated measures analysis of variance.

Tsai *et al.* (1983) examined the mortality from all cancers and leukemia, in addition to hematologic parameters in male workers exposed to benzene for 1-21 years in a refinery from 1952-1978. The cohort of 454 included maintenance workers and utility men and laborers assigned to benzene units on a "regular basis". Exposures to benzene were determined using personal monitors; the median air concentration was 0.53 ppm in the work areas of greatest exposure to benzene. The average length of employment in the cohort was 7.4 years. The analysis of overall mortality in this population revealed no significant excesses. Mortality from all causes and from diseases of the circulatory system was significantly below expected values based on comparable groups of U.S. males. The authors concluded the presence of a healthy worker effect. An internal comparison group of 823 people, including 10% of the workers who were employed in the same plant in operations not related to benzene, showed relative risks for 0.90 and 1.31 for all causes and cancer at all sites, respectively ($p < 0.28$ and 0.23). A subset of 303 workers was followed for medical surveillance. Up to four hematological tests per year were conducted on these workers. Total and differential white blood cell counts, hemoglobin,

hematocrit, red blood cells, platelets and clotting times were found to be within normal (between 5% and 95% percentile) limits in this group.

Collins *et al.* (1997) used routine data from Monsanto's medical/industrial hygiene system to study 387 workers with daily 8-hour time-weighted exposures (TWA) averaging 0.55 ppm benzene (range = 0.01 – 87.69 ppm; based on 4213 personal monitoring samples, less than 5% of which exceeded 2 ppm). Controls were 553 unexposed workers. There was no increase in the prevalence of lymphopenia, an early, sensitive indicator of benzene toxicity, among exposed workers (odds ratio = 0.6; 95% confidence interval = 0.2 to 1.8), taking into account smoking, age, and sex. There also was no increase in risk among workers exposed 5 or more years (odds ratio = 0.6; 95% confidence interval = 0.2 to 1.9). There were no differences between exposed and unexposed workers for other measures of hematotoxicity, including mean corpuscular volume and counts of total white blood cells, red blood cells, hemoglobin, and platelets.

Rothman *et al.* (1996) compared hematologic outcomes in a cross-sectional study of 44 male and female workers heavily exposed to benzene (median = 31 ppm as an 8-hr TWA) and 44 age and gender-matched unexposed controls from China. Hematologic parameters (total WBC, absolute lymphocyte count, platelets, red blood cells, and hematocrit) were decreased among exposed workers compared to controls; an exception was the red blood cell mean corpuscular volume (MCV), which was higher among exposed subjects. In a subgroup of 11 workers with a median 8 hr TWA of 7.6 ppm (range = 1-20 ppm) and not exposed to more than 31 ppm on any of 5 sampling days, only the absolute lymphocyte count was significantly different between exposed workers and controls ($p = 0.03$). Among exposed subjects, a dose response relationship with various measures of current benzene exposure (i.e., personal air monitoring, benzene metabolites in urine) was present only for the total WBC count, the absolute lymphocyte count, and the MCV. Their results support the use of the absolute lymphocyte count as the most sensitive indicator of benzene-induced hematotoxicity.

An examination of 32 patients, who were chronically exposed to benzene vapors ranging from 150 to 650 ppm for 4 months to 15 years, showed that pancytopenia occurred in 28 cases. Bone marrow punctures revealed variable hematopoeitic lesions, ranging from acellularity to hypercellularity (Aksoy *et al.*, 1972).

Central nervous system disorders have been reported in individuals with pancytopenia following chronic occupational benzene exposure to unknown concentrations for an average length of time of 6 years (Baslo and Aksoy, 1982).

Runion and Scott (1985) estimated a composite geometric mean benzene concentration in various workplaces containing benzene to be 0.1 ppm (0.32 mg/m^3) (geometric standard deviation = 7.2 ppm, 23.3 mg/m^3). This estimate was based on samples collected by industrial hygienists between the years 1978 and 1983.

V. Effects of Animal Exposure

A number of animal studies have demonstrated that benzene exposure can induce bone marrow damage, changes in circulating blood cells, developmental and reproductive effects, alterations of the immune response, and cancer. With respect to chronic toxicity, hematological changes appear to be the most sensitive indicator.

Wolf *et al.* (1956) studied the effects of repeated exposure to benzene in rabbits (80 ppm, 175 total exposures), rats (88 ppm, 136 total exposures) and guinea pigs (88 ppm, 193 total exposures). The observed effects included leukopenia, increased spleen weight, and histological changes to the bone marrow. Hematologic effects, including leukopenia, were observed in rats exposed to mean concentrations of 44 ppm (143 mg/m^3) or greater for 5-8 weeks (Deichmann *et al.*, 1963). Exposure to 31 ppm (100 mg/m^3) benzene or less did not result in leukopenia after 3-4 months of exposure. Snyder *et al.* (1978) exposed Sprague-Dawley rats and AKR/J mice to 300 ppm benzene, 6 hours/day, 5 days/week for life. Lymphocytopenia, anemia and decreased survival time were observed in both species. Cronkite *et al.* (1982) exposed male mice to 400 ppm benzene, 6 hours/day, 5 days/week for 9.5 weeks and observed depressed bone marrow cellularity, decreased stem cell count, and altered morphology in spleen colony-forming cells.

Mice have been shown to be more sensitive than rats or rabbits to the hematologic and leukemic effects of benzene (Sabourin *et al.*, 1989; IARC, 1982). Sabourin *et al.* (1988) showed that metabolism of benzene to the toxic hydroquinone, muconic acid, and hydroquinone glucuronide was much more prevalent in the mouse than in rats, whereas the detoxification pathways were approximately equivalent between the two species.

A study on the chronic hematological effects of benzene exposure in C57 Bl/6 male mice (5-6 per group) showed that peripheral lymphocytes, red blood cells and colony-forming units (CFUs) in the bone marrow and spleen were significantly decreased in number after treatment with 10 ppm (32.4 mg/m^3) benzene for 6 hours/day, 5 days/week for 178 days (Baarson *et al.*, 1984).

Inhalation of 0, 10, 31, 100, or 301 ppm (0, 32.4, 100.4, 324, or 975 mg/m^3) benzene for 6 hours/day for 6 days resulted in a dose-dependent reduction in peripheral lymphocytes, and a reduced proliferative response of B- and T-lymphocytes to mitogenic agents in mice (Rozen *et al.*, 1984). In this study, total peripheral lymphocyte numbers and B-lymphocyte proliferation to lipopolysaccharide were significantly reduced at a concentration of 10 ppm (32.4 mg/m^3). The proliferation of T-lymphocytes was significantly reduced at a concentration of 31 ppm (100.4 mg/m^3).

Male and female mice (9-10 per group) exposed to 100 ppm (324 mg/m^3) benzene or greater for 6 hours/day, 5 days/week for 2 weeks showed decreased bone marrow cellularity and a reduction of pluripotent stem cells in the bone marrow (Cronkite *et al.*, 1985). The decrease in marrow cellularity continued for up to 25 weeks following a 16-week exposure to 300 ppm (972 mg/m^3) benzene. Peripheral blood lymphocytes were dose-dependently decreased with benzene exposures of greater than 25 ppm (81 mg/m^3) for 16 weeks, but recovered to normal levels following a 16-week recovery period.

Ward *et al.* (1985) exposed 50 Sprague-Dawley rats and 150 CD-1 mice of both sexes to 0, 1, 10, 30, or 300 ppm benzene, 6 hours/day, 5 days/week for 13 weeks. Serial sacrifices were conducted at 7, 14, 28, 56, and 91 days. No hematological changes were found for mice and rats at 1, 10, or 30 ppm in this study. Significant increases in mean cell volume and mean cell hemoglobin values and decreases in hematocrit, hemoglobin, lymphocyte percentages, and decreases in red cell, leukocyte and platelet counts were observed in male and female mice at 300 ppm. The changes were first observed after 14 days of exposure. Histological changes in mice included myeloid hypoplasia of the bone marrow, lymphoid depletion in the mesenteric lymph node, increased extramedullary hematopoiesis in the spleen, and periarteriolar lymphoid sheath depletion. Effects were less severe in the rats.

Aoyama (1986) showed that a 14-day exposure of mice to 50 ppm (162 mg/m^3) benzene resulted in a significantly reduced blood leukocyte count.

The NTP (1986) conducted a bioassay in F344 rats and B6C3F1 mice of benzene by corn oil gavage. Doses were 0, 25, 50, and 100 mg/kg-day for females and 0, 50, 100, and 200 mg/kg-day for males. Dose-related lymphocytopenia and leukocytopenia were observed in both species in all dosed groups but not controls. Mice exhibited lymphoid depletion of the thymus and spleen and hyperplasia of the bone marrow.

Cronkite *et al.* (1989) exposed CBA/Ca mice to 10, 25, 100, 300, 400 and 3000 ppm benzene 6 hours/day, 5 days/week for up to 16 weeks. No effects were observed at the 10 ppm level. Lymphopenia was observed in the 25 ppm exposure group. Higher concentrations of benzene produced dose-dependent decreases in blood lymphocytes, bone marrow cellularity, spleen colony-forming units, and an increased percentage of CFU-S in S-phase synthesis.

Farris *et al.* (1997) exposed $B6C3F_1$ mice to 1, 5, 10, 100, and 200 ppm benzene for 6 hr/day, 5 days/week, for 1, 2, 4, or 8 weeks. In addition some animals were allowed to recover from the exposure. There were no significant effects on hematopoietic parameters from exposure to 10 ppm benzene or less. Exposure to higher levels reduced the number of total bone marrow cells, progenitor cells, differentiating hematopoietic cells, and most blood parameters. The replication of primitive progenitor cells was increased. The authors suggested that this last effect, in concert with the genotoxicity of benzene, could account for the carcinogenicity of benzene at high concentrations.

Reproductive and developmental effects have been reported following benzene exposure. Coate *et al.* (1984) exposed groups of 40 female rats to 0, 1, 10, 40, and 100 ppm (0, 3.24, 32.4, 129.6, or 324 mg/m^3) benzene for 6 hours/day during days 6-15 of gestation. In this study, teratologic evaluations and fetotoxic measurements were done on the fetuses. A significant decrease was noted in the body weights of fetuses from dams exposed to 100 ppm (324 mg/m^3). No effects were observed at a concentration of 40 ppm (129.6 mg/m^3).

Keller and Snyder (1986) reported that exposure of pregnant mice to concentrations as low as 5 ppm (16 mg/m^3) benzene on days 6-15 of gestation (6 hr/day) resulted in bone-marrow hematopoietic changes in the offspring that persisted into adulthood. However, the hematopoietic effects (e.g. bimodal changes in erythroid colony-forming cells) in the above study were of uncertain biological significance. In a similar later study, Keller and Snyder (1988) found that exposure of mice *in utero* to 20 ppm (64 mg/m^3) benzene on days 6-15 of

gestation resulted in neonatal suppression of erythropoietic precursor cells and persistent, enhanced granulopoiesis. This effect was considered significant bone-marrow toxicity by the authors. No hematotoxicity was seen in this study at 10 ppm (32 mg/m^3).

An exposure of 500 ppm (1,600 mg/m^3) benzene through days 6-15 gestation was teratogenic in rats while 50 ppm (160 mg/m^3) resulted in reduced fetal weights on day 20 of gestation. No fetal effects were noted at an exposure of 10 ppm (Kuna and Kapp, 1981). An earlier study by Murray *et al.* (1979) showed that inhalation of 500 ppm benzene for 7 hours/day on days 6-15 and days 6-18 of gestation in mice and rabbits, respectively, induced minor skeletal variations in the absence of maternal toxicity. Red and white blood cell counts in the adults of either species were measured by Murray *et al.* (1979) but were not significantly different from control animals. However, fetal mouse hematological effects were not measured.

Tatrai *et al.* (1980) demonstrated decreased fetal body weights and elevated liver weights in rats exposed throughout gestation to 150 mg/m^3 (47 ppm).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Tsai *et al.* (1983)
Study population	303 Male refinery workers
Exposure method	Occupational exposures for 1-21 years
Critical effects	Hematological effects
LOAEL	Not observed
NOAEL	0.53 ppm
Exposure continuity	8 hr/day (10 m^3 per 20 m^3 day), 5 days/week
Exposure duration	7.4 years average (for the full cohort of 454); 32% of the workers were exposed for more than 10 years
Average occupational exposure	0.19 ppm
Human equivalent concentration	0.19 ppm
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level	0.02 ppm (20 ppb; 0.06 mg/m^3; 60 $\mu g/m^3$)

Staff identified Tsai *et al.* (1983) as the most appropriate study for a chronic REL derivation. The authors examined hematologic parameters in 303 male workers exposed to benzene for 1-21 years in a refinery from 1952-1978. Follow-up success was 99.3% in the entire cohort of 359. A total of approximately 1400 samples for hematological tests and 900 for blood chemistry tests were taken between 1959 and 1979. Exposures to benzene were determined using personal monitors. Data consisting of 1394 personal samples indicated that 84% of all benzene samples were less than 1 ppm; the median air concentration of benzene was 0.53 ppm in the work areas

of greatest exposure to benzene ("benzene related areas", for example, production of benzene and cyclohexane and also of cumene). The average length of employment in the cohort was 7.4 years. Mortality from all causes and from diseases of the circulatory system was significantly below expected values based on comparable groups of U.S. males. The authors concluded the presence of a healthy worker effect. An analysis using an internal comparison group of 823 people, including 10% of the workers who were employed in the same plant in operations not related to benzene, showed relative risks for 0.90 and 1.31 for all causes and cancer at all sites, respectively ($p < 0.28$ and 0.23). Total and differential white blood cell counts, hemoglobin, hematocrit, red blood cells, platelets and clotting times were found to be within normal (between 5% and 95% percentile) limits in this group. Although the exposure duration averaged only 7.4 years, the study was considered to be chronic since 32% of the workers had been exposed for more than 10 years.

VII. Data Strengths and Limitations for Development of the REL

Both the animal and human databases for benzene are excellent. Although the study by Tsai *et al.* (1983) is a free-standing NOAEL, the endpoint examined is a known sensitive measure of benzene toxicity in humans. In addition, the LOAEL for the same endpoint in workers reported by Cody *et al.* (1993) help form a dose-response relationship and also yield an REL which is consistent with that derived from Tsai *et al.* (1983). The study by Cody *et al.* (1993), since it failed to identify a NOAEL and was only for a period of 1 year, contained a greater degree of uncertainty in extrapolation to a chronic community Reference Exposure Level. The recent results of Collins *et al.* (1997) that included a NOAEL of 0.55 ppm and of Rothman *et al.* (1996) that included a LOAEL of 7.6 ppm are consistent with those of Tsai *et al.* Therefore the study by Tsai *et al.* (1983) was used as the basis for the chronic REL for benzene.

In the Cody *et al.* (1993) study, significant hematological effects, including reduced RBC and WBC counts, were observed in 161 male rubber workers exposed to median peak concentrations (i.e., only the peak concentrations for any given exposure time were reported) of 30-54 ppm or more for a 12-month period during 1948. The 30 ppm value was considered a 1-year LOAEL for hematological effects. In this rubber plant, workers who had blood dyscrasias were excluded from working in the high benzene units. Furthermore, individual workers having more than a 25% decrease in WBC counts from their pre-employment background count were removed from the high benzene units and placed in other units with lower benzene concentrations. Sensitive individuals therefore could have been excluded from the analysis. The 30 ppm value is the low end of the range of median values (30-54 ppm) reported by Crump and used in the Kipen *et al.* (1988) and Cody *et al.* (1993) studies. An equivalent continuous exposure of 10.7 ppm can be calculated by assuming that workers inhaled 10 m^3 of their total 20 m^3 of air per day during their work-shift, and by adjusting for a normal 5 day work week. Application of uncertainty factors for subchronic exposures, estimation of a NOAEL, and for protection of sensitive subpopulations (10 for each) results in an REL of 0.01 ppm (10 ppb; 30 $\mu g/m^3$). This is comparable to the REL based on Tsai *et al.* (1983).

Ward *et al.* (1996) determined a relationship between occupational exposures to benzene and decreased red and white cell counts. A modeled dose-response relationship indicated a possibility for hematologic effects at concentrations below 5 ppm. However, no specific

measures of the actual effects at concentrations below 2 ppm were taken, and the Tsai *et al.* (1983) data were not considered in their analysis. The purpose of this study was to characterize the trend for effects at low concentrations of benzene. A NOAEL or LOAEL was not identified in the study. The selection of a NOAEL of 0.53 ppm is therefore not inconsistent with the results of the Ward *et al.* (1996) study.

The human data presented by Tsai and associates were selected over animal studies because the collective human data were considered adequate in terms of sample size, exposure duration, and health effects evaluation.

For comparison with the REL of 20 ppb based on human data, we estimated a REL based on the chronic inhalation study in mice by Baarson *et al.* (1984), which showed that bone-marrow progenitor cells were markedly suppressed after intermittent exposures (6 hr/day, 5 days/week) to 10 ppm benzene for 6 months. An extrapolation of this value to an equivalent continuous exposure resulted in a concentration of 1.8 ppm. Application of an RGDR of 1 for a systemic effect and uncertainty factors of 3 and 10 for inter- and intraspecies variability, and 10 for estimation of a NOAEL from the LOAEL would result in an REL of 6 ppb (20 $\mu g/m^3$). The Farris *et al.* (1997) 8 week study indicated a LOAEL of 100 ppm and a NOAEL of 10 ppm for hematological effects. Application of an RGDR of 1 and UFs of 10 for subchronic, 3 for interspecies and 10 for intraspecies extrapolation (total UF = 300) also resulted in an estimated REL of 6 ppb, in reasonable agreement with the proposed REL of 20 ppb. One could also crudely approximate an inhalation REL from the oral NTP bioassay where a dose of 25 mg/kg-day was associated with hematological effects. The concentration approximately equivalent to a 25 mg/kg dose for a 70 kg human breathing 20 cubic meters per day is 27 ppm. Assuming this is a LOAEL and applying an RGDR of 1 for systemic effects, a 3 fold UF for extrapolation to humans, a 10-fold UF for LOAEL to NOAEL extrapolation and a 10-fold UF for intraspecies extrapolation yields a REL of 90 ppb. There are a number of uncertainties to this approach, yet it comes within a factor of 5 of the proposed REL based on human studies.

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Carbon Monoxide

Acute Toxicity Summary in Air Toxics "Hot Spots" Risk Assessment Guidelines Part I: Technical Support Document. The Determination of Acute Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA. March 1999.

ACUTE TOXICITY SUMMARY

CARBON MONOXIDE

(carbon monoxide)

CAS Registry Number: 630-08-0

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**23 mg/m³**
Critical effect(s)	angina in persons with known cardiovascular diseases who are exercising heavily
Hazard Index target(s)	Cardiovascular System

II. Physical and Chemical Properties (HSDB, 1994)

Description	colorless gas
Molecular formula	CO
Molecular weight	28.01
Density	1.25 g/L @ 0°C
Boiling point	-191.5°C
Melting point	-205°C
Vapor pressure	>760 mm Hg @ 20°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in benzene, ethyl acetate, chloroform, acetic acid
Odor threshold	not applicable
Odor description	odorless
Metabolites	unknown
Conversion factor	1 ppm = 1.15 mg/m³ @ 25°C

III. Major Uses or Sources

Carbon monoxide (CO) is formed during the incomplete combustion of organic substances including gasoline, diesel, natural gas, wood, coal, tobacco, and other vegetation. The California Air Resources Board (CARB) Staff Report (1989) estimated that approximately 70% of the CO present in California urban atmospheres was due to emissions from mobile sources. Solid waste combustion, agricultural burning, and various industrial processes accounted for most of the remaining urban CO.

IV. Acute Toxicity to Humans

The severity of symptoms due to CO exposure increases with the blood carboxyhemoglobin (COHb) level. The first signs of CO exposure include mild headache and breathlessness with moderate exercise (HSDB, 1994). Continued exposure may lead to more severe headache, irritability, impaired judgment and memory, and rapid onset of fatigue (Winter and Miller, 1976). Persons with existing cardiovascular conditions, such as angina pectoris, are likely to be more sensitive to the effects of CO exposure. Earlier onset of angina was reported in exercising subjects with coronary heart disease exposed to 100 ppm (120 mg/m^3) carbon monoxide (resulting in 2.9% blood COHb level) (Kleinman *et al.*, 1989).

In another study, men with confirmed coronary artery disease and stable exertional angina were exposed to air with or without one of two levels of CO for 1 hour while at rest. They then exercised until the onset of angina (Allred *et al.*, 1989). A 4.2% decrease in time to angina compared to control exercise periods ($p = 0.03$; 95% CI = 0.4-8.74) was observed following a 1-hour exposure to a mean concentration of 117 ppm (135 mg/m^3) CO (resulting in 2% blood COHb level). Similarly, a 1-hour exposure to a mean concentration of 253 ppm (291 mg/m^3) CO resulted in 4% blood COHb level and a 7.1% decrease in time to onset of angina compared to control exercise periods ($p = 0.002$; 95% CI = 5.18-14.46).

The California Ambient Air Quality Standard (CAAQS) for CO is based on the conclusion of the California Air Resources Board (CARB) (1982, 1989) that "exposure to carbon monoxide has been clearly demonstrated to cause aggravation of angina and other cardiovascular diseases. Carbon monoxide exerts its effect primarily by binding to hemoglobin and forming carboxyhemoglobin (COHb), thereby reducing the oxygen-carrying capacity of the blood. These effects are considered to be adverse and have been shown to occur at COHb levels in the range of 2.0 to 3.0 percent COHb." Aronow (1981) reported that the lowest demonstrated effect level for aggravation of angina was as low as 2% COHb.

In double blinded exposures (Benignus *et al.*, 1987), 18 nonsmoking, young men at rest were exposed to high levels of CO in order to elevate COHb to levels of 15-20% in 3-5 minutes, followed by continued exposure to 232 ppm CO in order to maintain a constant COHb level for a total of 130 minutes, which resulted in COHb values of 16-23% (average = 19%). These values did not produce significantly more symptoms such as headache, dizziness, and nausea (as reported in open-ended questioning of the subjects) than in the control group ($n = 23$) exposed to air. The authors theorized that neurological symptoms reported for similar levels of COHb in the discussion of CO poisoning in medical standard references (cited in Benignus *et al.*, 1987) may have resulted (1) from CO exposure in combination with exposure to other substance(s), (2) from stress, or (3) from higher COHb levels before the initial blood sample to measure COHb was taken.

Predisposing Conditions for Carbon Monoxide Toxicity

Medical: Persons with cardiovascular disease, including those with angina, persons with chronic obstructive pulmonary disease, persons with anemia, and fetuses may be more sensitive to the adverse effects of carbon monoxide exposure (CARB, 1982). The fetuses of pregnant women, especially those mothers exercising vigorously, may be especially vulnerable due to the much higher affinity of fetal hemoglobin for CO compared to adult hemoglobin.

Chemical: Persons exposed to methylene chloride are more sensitive to the effects of CO exposure because CO is a metabolite of methylene chloride. Smokers will experience an additional burden of COHb since their carboxyhemoglobin levels are already elevated by smoking.

V. Acute Toxicity to Laboratory Animals

Four-hour LC_{50}s for rats, mice, and guinea pigs are 1,807, 2,444, and 5,718 ppm (2,078, 2,811, and 6,576 mg/m^3) CO, respectively (Rose *et al.*, 1970). The lowest reported lethal concentration in dogs (the level at which one dog in the group died) was 4,000 ppm (4,600 mg/m^3) CO for a 46-minute exposure (RTECS, 1994).

Anesthetized, open-chested dogs were exposed for 2 hours to air or to 100 ppm (120 mg/m^3) CO (Aronow *et al.*, 1979). Postexposure blood COHb levels were 6.5%. Electrical shocks of varying amplitude were applied to the myocardium to induce ventricular fibrillation. A decrease in the ventricular fibrillation threshold was observed in CO-exposed dogs compared to controls.

A dose-dependent decrement in performance was observed in maze running in rats following a 30-minute exposure to 2,000, 3,000, 3,500, or 4,000 ppm (2,300, 3,500, 4,030, or 4,600 mg/m^3) CO (Annau, 1987). As exposure concentration increased, a greater proportion of rats failed to reach the goal and there was a decrease in goal directed behavior. The authors compare these results to lethargy and confusion observed in human victims following smoke inhalation.

VI. Reproductive or Developmental Toxicity

Carbon monoxide is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a chemical known to the State to cause developmental toxicity.

A prospective study of pregnancy outcomes reported an increased risk of fetal neurologic disorders following maternal CO poisoning. This resulted in blood COHb levels of 21% or greater with symptoms including, but not limited to, disorientation, depressed sensorium, limited and inappropriate response to simple commands, and coma (Koren *et al.*, 1991).

Pregnant rats were exposed to 150 ppm (170 mg/m^3) CO continuously for the duration of gestation (Fechter and Annau, 1980). The offspring of the CO exposed rats exhibited decreased

birth weights and decreased growth rates prior to weaning. Behavioral testing revealed decreased performance on negative geotaxis (performing a 180° turn to face the top of an incline plane) and homing (orientation by the rat pup towards its home cage) tests in offspring of CO-exposed rats compared to controls.

Pregnant mice were exposed to 65, 125, 250, or 500 ppm (75, 144, 290, or 580 mg/m^3) CO continuously on days 7-18 of gestation (Singh and Scott, 1984). A significant increase in fetal mortality was observed following maternal exposure to 500 ppm CO. A significant decrease in fetal body weight was observed following maternal exposure to CO at concentrations of 125 ppm or greater. Delayed ossification was observed in all dose groups but was not statistically significant or dose-dependent. No significant developmental effects were observed following maternal exposure to 65 ppm CO.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Level Protective Against mild adverse effects)

Because angina is a severe effect, there is no level protective against mild adverse effects.

Reference Exposure Level **(level protective against severe adverse effects) :**20 ppm (23 mg/m^3)

Study	Aronow, 1981
Study population	humans
Exposure method	inhalation
Critical effects	aggravation of angina and other cardiovascular diseases
LOAEL	2% carboxyhemoglobin in blood
NOAEL	1.1%-1.3% carboxyhemoglobin in blood (corresponds to 20 ppm CO, calculated toxicokinetically)
Exposure duration	1 hour
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	20 ppm (23 mg/m^3, 23,000 µg/m^3)

Level Protective Against Life-threatening Effects

The NRC (1984) selected an EEGL of 400 ppm (460 mg/m^3). The NRC document states that 400 ppm (460 mg/m^3) was determined as the concentration of CO to which a 1-hour exposure would result in a carboxyhemoglobin (COHb) level of less than 10% in resting individuals. The committee cautions that sensitive individuals, such as persons with angina or heart disease, should not be exposed to concentrations approaching the EEGL as they may incur serious adverse health effects. The Coburn model (Coburn *et al.*, 1965) estimates that only at a low ventilation rate (e.g., 5 liters/ min) would a 1-hour exposure to 400 ppm CO result in a COHb of less than 10%. At a ventilation rate of 15 liters/min, the same exposure would be expected to result in 16% COHb (Shusterman, 1994). The NRC (1984) acknowledged that at the EEGL of 400 ppm physical activity might increase the COHb to 20% or higher by 1 hour. The exposure level of 400 ppm may not protect sensitive subpopulations, since persons with cardiovascular disease would experience serious health effects such as angina pectoris (Aronow, 1981; Allred *et al.*, 1989). According to NRC (1984), "It must also be stressed that, in people with atherosclerosis, the danger of myocardial infarction, angina pectoris, or even sudden death might be increased by exposure to CO." The EEGL of 400 ppm is recommended as the level protective against life-threatening effects with a cautionary note that people with heart disease, as noted by NRC, may not be protected. In addition, the NRC notes that the EEGL is derived for resting individuals. Individuals engaged in activities other than resting will achieve a higher COHb level and will beat increased risk.

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Executive Summary in Health Effects of Exposure to Environmental Tobacco Smoke. Final Report, OEHHA, September 1997.

Executive Summary

Exposure to environmental tobacco smoke (ETS) has been linked to a variety of adverse health outcomes. Many Californians are exposed at home, at work and in public places. In the comprehensive reviews published as *Reports of the Surgeon General* and by the U.S. Environmental Protection Agency (U.S. EPA) and the National Research Council (NRC), ETS exposure has been found to be causally associated with respiratory illnesses, including lung cancer, childhood asthma and lower respiratory tract infections. Scientific knowledge about ETS-related effects has expanded considerably since the release of these reviews. The State of California has therefore undertaken a broad review of ETS, covering the major health endpoints potentially associated with ETS exposure: perinatal and postnatal manifestations of developmental toxicity, adverse impacts on male and female reproduction, respiratory disease, cancer, and cardiovascular disease. A "weight of evidence" approach has been used to describe the body of evidence to conclude whether or not ETS exposure is causally associated with a particular effect. Because the epidemiological data are extensive, they serve as the primary basis for assessment of ETS-related effects in humans. The report also presents an overview on measurements of ETS exposure, particularly as they relate to characterizations of exposure in epidemiological investigations, and on the prevalence of ETS exposure in California and nationally.

ETS, or "secondhand smoke", is the complex mixture formed from the escaping smoke of a tobacco product, and smoke exhaled by the smoker. The characteristics of ETS change as it ages and combines with other constituents in the ambient air. Exposure to ETS is also frequently referred to as "passive smoking", or "involuntary tobacco smoke" exposure. Although all exposures of the fetus are "passive" and "involuntary", for the purposes of this review *in utero* exposure resulting from maternal smoking during pregnancy is not considered to be ETS exposure.

General Findings

ETS is an important source of exposure to toxic air contaminants indoors. There is also some exposure outdoors, in the vicinity of smokers. Despite an increasing number of restrictions on smoking and increased awareness of health impacts, exposures in the home, especially of infants and children, continue to be a public health concern. ETS exposure is causally associated with a number of health effects. Listed in Table ES.1 are the developmental, respiratory, carcinogenic and cardiovascular effects for which there is sufficient evidence of a causal relationship, including fatal outcomes such as sudden infant death syndrome and heart disease mortality, as well as serious chronic diseases such as childhood asthma. There are in addition effects for which evidence is suggestive of an association but further research is needed for confirmation. These include spontaneous abortion, cervical cancer, and exacerbation of asthma in adults (Table ES.1). Finally, it is not possible to judge on the basis of the current evidence the impact of ETS on a number of endpoints, including congenital malformations, changes in female fertility and fecundability, male reproductive effects, rare childhood cancers and cancers of the bladder, breast, stomach, brain, hematopoietic system, and lymphatic system.

TABLE ES.1
HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

Effects Causally Associated with ETS Exposure

Developmental Effects
Fetal Growth: Low birthweight or small for gestational age
Sudden Infant Death Syndrome (SIDS)

Respiratory Effects
Acute lower respiratory tract infections in children
(*e.g.*, bronchitis and pneumonia)
Asthma induction and exacerbation in children
Chronic respiratory symptoms in children
Eye and nasal irritation in adults
Middle ear infections in children

Carcinogenic Effects
Lung Cancer
Nasal Sinus Cancer

Cardiovascular Effects
Heart disease mortality
Acute and chronic coronary heart disease morbidity

Effects with Suggestive Evidence of a Causal Association with ETS Exposure

Developmental Effects
Spontaneous abortion
Adverse impact on cognition and behavior

Respiratory Effects

Exacerbation of cystic fibrosis
Decreased pulmonary function

Carcinogenic Effects
Cervical cancer

Many Californians are exposed to ETS, and the number of people adversely affected may be correspondingly large. Table ES.2 presents morbidity and mortality estimates for health effects causally associated with ETS exposure. For cancer, cardiovascular and some respiratory endpoints, estimates are derived from figures published for the U.S. population, assuming that the number affected in California would be 12% of the total. The estimates for middle ear infection, sudden infant death syndrome and low birthweight were derived using information on prevalence of ETS exposure in California and the U.S.

Relative risk estimates associated with some of these endpoints are small, but because the diseases are common the overall impact can be quite large. A relative risk estimate of 1.3 for heart disease mortality in nonsmokers is supported by the collective evidence; this corresponds to a lifetime risk of death of roughly 1 to 3% for exposed nonsmokers and approximately 4,000 deaths annually in California. The relative risk estimate of 1.2 to 1.4 associated with low birthweight implies that ETS may impact fetal growth of 1,200 to 2,200 newborns in California, roughly 1 to 2% of newborns of nonsmokers exposed at home or work. ETS may exacerbate asthma ($RR \approx 1.6$ to 2) in 48,000 to 120,000 children in California. Large impacts are associated with relative risks for respiratory effects in children such as middle ear infection ($RR \approx 1.62$), and lower respiratory disease in young children ($RR \approx 1.5$ to 2). Asthma induction ($RR \approx 1.75$ to 2.25) may occur in as many as 0.5 to 2% of ETS-exposed children. ETS exposure may be implicated in 120 SIDS deaths per year in California ($RR \approx 3.5$), with a risk of death to 0.1% of infants exposed to ETS in their homes. Lifetime risk of lung cancer death related to ETS-exposed nonsmokers may be about 0.7% ($RR \approx 1.2$). For nasal sinus cancers, observed relative risks have ranged from 1.7 to 3.0, but future studies are needed to confirm the magnitude of ETS-related risks.

Specific Findings and Conclusions

Exposure Measurement and Prevalence

ETS is a complex mixture of chemicals generated during the burning and smoking of tobacco products. Chemicals present in ETS include irritants and systemic toxicants such as hydrogen cyanide and sulfur dioxide, mutagens and carcinogens such as benzo(a)pyrene, formaldehyde and 4-aminobiphenyl, and the reproductive toxicants nicotine, cadmium and carbon monoxide. Many ETS constituents have been identified as hazardous by state, federal and international agencies. To date, over 50 compounds in tobacco smoke have been identified as carcinogens and six as developmental or reproductive toxicants under California's Proposition 65 (California Health and Safety Code 25249.5 *et seq.*).

Exposure assessment is critical in epidemiological investigations of the health impacts of ETS, and in evaluating the effectiveness of strategies to reduce exposure. Exposure can be assessed through the measurement of indoor air concentrations of ETS constituents, through surveys and questionnaires, or more directly through the use of personal monitors and the measurement of biomarkers in saliva, urine and blood. There are

TABLE ES.2

ESTIMATED ANNUAL MORBIDITY AND MORTALITY IN NONSMOKERS ASSOCIATED WITH ETS EXPOSURE

Condition	Number of People or Cases[a]	
	in the U.S.	in California
Developmental Effects		
Low birthweight	□ 9,700 - 18,600 cases[b]	□ 1,200 - 2,200 cases[b]
Sudden Infant Death Syndrome (SIDS)	□ 1,900 - 2,700 deaths[b]	□ 120 deaths[b]
Respiratory Effects in Children		
Middle ear infection	0.7 to 1.6 million physician office visits[b]	78,600 to 188,700 physician office visits[b]
Asthma induction	8,000 to 26,000 new cases[c]	960 to 3120 new cases[c]
Asthma exacerbation	400,000 to 1,000,000 children[c]	48,000 to 120,000 children[c]
Bronchitis or pneumonia in infants and toddlers (18 months and under)	150,000 to 300,000 cases[c] 7,500 to 15,000 hospitalizations[c] 136 - 212 deaths[c]	18,000 to 36,000 cases[c] 900 to 1800 hospitalizations[c] 16 - 25 deaths[c]
Cancer		
Lung	3000 deaths[c]	360 deaths[c]
Nasal sinus	N/A[d]	N/A[d]
Cardiovascular Effects		
Ischemic heart disease	35,000 - 62,000 deaths[c]	4,200 - 7,440 deaths[c]

[a] The numbers in the table are based on maximum likelihood estimates of the relative risk. As discussed in the body of the report, there are uncertainties in these estimates, so actual impacts could be somewhat higher or lower than indicated in the table. The endpoints listed are those for which there is a causal association with ETS exposure based on observations of effects in exposed human populations.

[b] California estimates for low birthweight, SIDS, and middle ear infection (otitis media) are provided in Chapters 3, 4, and 6, respectively. U.S. estimates are obtained by dividing by 12%, the fraction of the U.S. population residing in California.

[c] Estimates of mortality in the U.S. for lung cancer and respiratory effects, with the exception of middle ear infection (otitis media), come from U.S. EPA (1992). U.S. range for heart disease mortality reflects estimates reported in Wells (1988 and 1994), Glantz and Parmley (1991), Steenland (1992). California predictions are made by multiplying the U.S. estimate by 12%, the fraction of the U.S. population residing in the State. Because of decreases in smoking prevalence in California in recent years, the number of cases for some endpoints may be somewhat overestimated, depending on the relative impacts of current versus past ETS exposures on the health endpoint.

[d] Estimates of the impact of ETS exposure on the occurrence of nasal sinus cancers are not available at this time.

advantages and disadvantages associated with the various techniques, which must be weighed in interpreting study results. One important consideration in epidemiologic studies is misclassification of exposure. Studies on the reliability of questionnaire responses indicate qualitative information obtained is generally reliable, but that quantitative information may not be. Also, individuals are often unaware of their ETS exposure, particularly outside the home. In studies using both self-reporting and biological markers, the exposure prevalence was higher when determined using biological markers.

Available data suggest that the prevalence of ETS exposure in California is lower than elsewhere in the U.S. Among adults in California, the workplace, home and other indoor locations all contribute significantly to ETS exposure. For children the most important single location is the home. Over the past decade ETS exposures in California have decreased significantly in the home, workplace and in public places. Over the same period, restrictions on smoking in enclosed worksites and public places have increased (*e.g.*, Gov. Code, Section 19994.30 and California Labor Code, Section 6404.5) and the percentage of the adults who smoke has declined. Decreases in tobacco smoke exposure may not be experienced for some population subgroups, as patterns of smoking shift with age, race, sex and socioeconomic status. For example, from 1975 to 1988, the overall smoking prevalence among 16 to 18 year olds declined, but after 1988 the trend reversed.

Perinatal Manifestations of Developmental Toxicity

ETS exposure adversely affects fetal growth, with elevated risks of low birth weight or "small for gestational age" observed in numerous epidemiological studies. The primary effect observed, reduction in mean birthweight, is small in magnitude. But if the distribution of birthweight is shifted lower with ETS exposure, as it appears to be with active smoking, infants who are already compromised may be pushed into even higher risk categories. Low birthweight is associated with many well-recognized problems for infants, and is strongly associated with perinatal mortality.

The impact of ETS on perinatal manifestations of development other than fetal growth is less clear. The few studies examining the association between ETS and perinatal death are relatively non-informative, with only two early studies showing increased risk associated with parental smoking, and with the sparse data on stillbirth not indicative of an effect. Studies on spontaneous abortion are suggestive of a role for ETS, but further work is needed, particularly as a recent report did not confirm the findings of four earlier studies. Although epidemiological studies suggest a moderate association of severe congenital malformations with paternal smoking, the findings are complicated by the use of paternal smoking status as a surrogate for ETS exposure, since a direct effect of active smoking on sperm cannot be ruled out. In general, the defects implicated differed across the studies, with the most consistent association seen for neural tube defects. At this time, it is not possible to determine whether there is a causal association between ETS exposure and this or other birth defects.

Postnatal Manifestations of Developmental Toxicity

Numerous studies have demonstrated an increased risk of sudden infant death syndrome, or "SIDS," in infants of mothers who smoke. Until recently it has not been possible to separate the effects of postnatal ETS exposure from those of prenatal exposure to maternal active smoking. Recent epidemiological studies now have demonstrated that postnatal ETS exposure is an independent risk factor for SIDS.

Although definitive conclusions regarding causality cannot yet be made on the basis of available epidemiological studies of cognition and behavior, there is suggestive evidence that ETS exposure may pose a hazard for neuropsychological development. With respect to physical development, while small but consistent effects of active maternal smoking during pregnancy have been observed on height growth, there is no evidence that postnatal ETS exposure has a significant impact in otherwise healthy children. As discussed in greater detail below, developmental effects of ETS exposure on the respiratory system include lung growth and development, childhood asthma exacerbation, and, in children, acute low respiratory tract illness, middle ear infection and chronic respiratory symptoms.

Female and Male Reproductive Toxicity

Though active smoking by women has been found to be associated with decreased fertility in a number of studies, and tobacco smoke appears to be anti-estrogenic, the epidemiological data on ETS exposure and fertility are not extensive and show mixed results, and it is not possible to determine whether ETS affects fecundability or fertility. Regarding other female reproductive effects, while studies indicate a possible association of ETS exposure with early menopause, the analytic methods of these studies could not be thoroughly evaluated, and therefore at present, there is not firm evidence that ETS exposure affects age at menopause. Although associations have been seen epidemiologically between active smoking and sperm parameters, conclusions can not be made regarding ETS exposure and male reproduction, as there is very limited information available on this topic.

Respiratory Effects

ETS exposure produces a variety of acute effects involving the upper and lower respiratory tract. In children, ETS exposure can exacerbate asthma, and increases the risk of lower respiratory tract illness, and acute and chronic middle ear infection. Eye and nasal irritation are the most commonly reported symptoms among adult nonsmokers exposed to ETS. Odor annoyance has been demonstrated in several studies.

Regarding chronic health effects, there is compelling evidence that ETS is a risk factor for induction of new cases of asthma as well as for increasing the severity of disease among children with established asthma. In addition, chronic respiratory symptoms in children, such as cough, phlegm, and wheezing, are associated with parental smoking. While the results from all studies are not wholly consistent, there is evidence that childhood exposure to ETS affects lung growth and development, as measured by small, but statistically significant decrements in pulmonary function tests; associated reductions may persist into adulthood. The effect of chronic ETS

exposure on pulmonary function in otherwise healthy adults is likely to be small, and unlikely by itself to result in clinically significant chronic disease. However, in combination with other insults (*e.g.*, prior smoking history, exposure to occupational irritants or ambient air pollutants), ETS exposure could contribute to chronic respiratory impairment in adults. In addition, regular ETS exposure in adults has been reported to increase the risk of occurrence of a variety of lower respiratory symptoms.

Children are especially sensitive to the respiratory effects of ETS exposure. Children with cystic fibrosis are likely to be more sensitive than healthy individuals. Several studies of patients with cystic fibrosis, a disease characterized by recurrent and chronic pulmonary infections, suggest that ETS can exacerbate the condition. Several studies have shown an increased risk of atopy (a predisposition to develop IgE antibodies against common allergens, which can then be manifested as a variety of allergic conditions) in children of smoking mothers, though the evidence regarding this issue is mixed.

Carcinogenic Effects

The role of ETS in the etiology of cancers in nonsmokers was explored, as smoking is an established cause of a number of cancers (lung, larynx, oral cavity, esophagus and bladder), and a probable cause of several others (cervical, kidney, pancreas, and stomach). Also, ETS contains a number of constituents which have been identified as carcinogens.

Reviews published in the 1986 *Report of the Surgeon General,* by the National Research Council in 1986, and by the U.S. EPA in 1992 concluded that ETS exposure causes lung cancer. Three large U.S. population-based studies and a smaller hospital-based case control study have been published since the completion of the U.S. EPA review. The population-based studies were designed to and have successfully addressed many of the weaknesses for which the previous studies on ETS and lung cancer have been criticized. Results from these studies are compatible with the causal association between ETS exposure and lung cancer already reported by the U.S. EPA, Surgeon General, and National Research Council. Of the studies examining the effect of ETS exposure on nasal sinus cancers, all three show consistent associations, presenting strong evidence that ETS exposure increases the risk of nasal sinus cancers in nonsmoking adults. Further study is needed to characterize the magnitude of the risk of nasal sinus cancer from ETS exposure.

The epidemiological and biochemical evidence suggest that exposure to ETS may increase the risk of cervical cancer. Positive associations were observed in two of three case-control studies and a statistically nonsignificant positive association was observed in the only cohort study conducted. Findings of DNA adducts in the cervical epithelium as well as nicotine and cotinine in the cervical mucus of ETS-exposed nonsmokers provides biological plausibility.

For other cancer sites in adults, there has been limited ETS-related epidemiological research in general: there is currently insufficient evidence to draw any conclusion regarding the relationship between ETS exposure and the risk of occurrence. A review of the available literature clearly indicates the need for more research. For example, although compounds established as important in the etiology of stomach cancer are present in tobacco smoke, only a

single cohort study has been performed for this site. Precursors of endogenously formed N-nitroso compounds suspected of causing brain tumors are present in high concentrations in ETS, and the one cohort and two case-control studies available suggest a positive association, but the results are based on small numbers and may be confounded by active smoking. In biochemical studies of nonsmokers, higher levels of hemoglobin adducts of the established bladder carcinogen, 4-aminobiphenyl, have been found in those exposed to ETS. However, no significant increases in bladder cancer were seen in the two epidemiological studies (case-control) conducted to date, although both studies were limited in their ability to detect an effect. Several compounds in tobacco smoke are associated with increased risk of leukemia, but only one small case-control study in adults, reporting an increased risk with ETS exposure during childhood, has been performed. Finally, all four studies on ETS exposure and breast cancer suggest an association, but in two of the studies the associations were present only in select groups, and in three studies there is either no association between active smoking and the risk of breast cancer or the association for active smoking is weaker than for passive smoking. Moreover, there is no indication of increasing risk with increasing intensity of ETS exposure. Still, results from a recent study suggest that tobacco smoke may influence the risk of breast cancer in certain susceptible groups of women, and this requires further investigation.

Regarding childhood cancers, it is unclear whether parental smoking increases risk overall, or for specific cancers such as acute lymphoblastic leukemia and brain tumors, the two most common cancers in children. The lack of clarity is due to the conflicting results reported and the limitations of studies finding no association. The epidemiological data on ETS exposure and rare childhood cancers also provide an inadequate foundation for making conclusions regarding causality. Some studies found small increased risks in children in relation to parental smoking for neuroblastoma, Wilm's tumor, bone and soft-tissue sarcomas, but not for germ cell tumors. Studies to date on these rare cancers have been limited in their power to detect effects. The impact of ETS exposure on childhood cancer would benefit from far greater attention than it has received to date.

Cardiovascular Effects

The epidemiological data, from prospective and case-control studies conducted in diverse populations, in males and females and in western and eastern countries, are supportive of a causal association between ETS exposure from spousal smoking and coronary heart disease (CHD) mortality in nonsmokers. To the extent possible, estimates of risk were determined with adjustment for demographic factors, and often for other factors related to heart disease, such as blood pressure, serum cholesterol level and obesity index. Risks associated with ETS exposure were almost always strengthened by adjustment for other cofactors. For nonsmokers exposed to spousal ETS compared to nonsmokers not exposed, the risk of CHD mortality is increased by a factor of 1.3. The association between CHD and risk is stronger for mortality than for non-fatal outcomes, including angina.

Data from clinical studies suggest various mechanisms by which ETS causes heart disease. In a number of studies in which nonsmokers were exposed to ETS, carotid wall thickening and compromise of endothelial function were similar to, but less extensive than those experienced by active smokers. Other effects observed include impaired exercise performance, altered

lipoprotein profiles, enhanced platelet aggregation, and increased endothelial cell counts. These findings may account for both the short- and long-term effects of ETS exposure on the heart.

Attachment I

Review of the OEHHA Assessment of Environmental Tobacco Smoke by the Scientific Review Panel (SRP)

Interest in the health effects of second hand tobacco smoke on the part of members of the Scientific Review Panel (SRP) on Toxic Air Contaminants led to a request by the SRP for a health assessment of environmental tobacco smoke, and a collaborative agreement between the Office of Environmental Health Hazard Assessment (OEHHA) and the Air Resources Board (ARB) to initiate such an assessment. SRP members reviewed the drafts as they were developed and participated in each of the workshops held as the document underwent public review (see Preface for details). The Final Draft reflected the input of SRP members, as well as that of other reviewers.

Specific changes made at the request of the SRP following its review of the Final Draft include the addition of new studies (e.g., the results of Kawachi *et al.*'s analysis of cardiovascular disease risk in the Nurse's Health study, published after the release of the Final Draft, in which it was reported as an abstract), a discussion of issues related to misclassification of smoking status and cancer risk, and clarifying language in the presentation of attributable risk estimates; minor editorial changes were also requested and made. The SRP discussed the assessment and made findings on the health effects of exposure to environmental tobacco smoke as a result of its review; these findings are included in this Attachment.

Formaldehyde

Acute Toxicity Summary in Air Toxics "Hot Spots" Risk Assessment Guidelines Part I: Technical Support Document. The Determination of Acute Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA. March 1999.

Chronic Toxicity Summary in Air Toxics "Hot Spots" Risk Assessment Guidelines Part III: Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA. February 2000.

ACUTE TOXICITY SUMMARY

FORMALDEHYDE

(methanal, oxomethane, oxymethylene, methylene oxide, formic aldehyde, methyl aldehyde)

CAS Registry Number: 50-00-0

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**94 µg/m³**
Critical effect(s)	eye irritation
Hazard Index target(s)	Eyes; Respiratory System; Immune System

II. Physical and Chemical Properties (HSDB, 1993)

Description	colorless gas
Molecular formula	CH_2O
Molecular weight	30.03
Density	0.815 g/L @ -20°C
Boiling point	-19.5°C
Melting point	-92°C
Vapor pressure	3883 mm Hg @ 25°C (Howard, 1989)
Flashpoint	300° C or 573°F
Explosive limits	upper = 73% lower = 7%
Solubility	soluble in water, alcohol, ether, other polar solvents
Odor threshold	0.05-0.5 ppm
Odor description	very pungent odor; straw-like
Metabolites	formic acid
Conversion factor	1 ppm = 1.24 mg/m³ @ 25°C

III. Major Uses or Sources

Formaldehyde is used in the manufacture of melamine, polyacetal, and phenolic resins. It is also used as a preservative, a hardening and reducing agent, a corrosion inhibitor, a sterilizing agent, and in embalming fluids. Mobile home interiors and pressed wood furniture are two other common sources of formaldehyde exposure.

IV. Acute Toxicity to Humans

Exposure to moderate levels of formaldehyde (1-3 ppm) can result in eye and upper respiratory tract irritation (Weber-Tschoppe *et al.*, 1977; Kulle *et al.*, 1987). Feinman (1988) states that

most people cannot tolerate exposures to more than 5 ppm formaldehyde in air; above 10-20 ppm symptoms become severe and shortness of breath occurs. High concentrations of formaldehyde may result in nasal obstruction, pulmonary edema, choking, dyspnea, and chest tightness (Porter, 1975; Solomons and Cochrane, 1984).

A few human case studies report severe pulmonary symptoms. A medical intern with known atopy and exposure to formaldehyde over a period of 1 week developed dyspnea, chest tightness, and edema, following a final 2 hour exposure to high concentrations of formaldehyde (Porter, 1975). Five workers exposed to high concentrations of formaldehyde from urea-formaldehyde foam insulation experienced intolerable eye and upper respiratory tract irritation, choking, marked dyspnea, and nasal obstruction (Solomons and Cochrane, 1984). However, the concentration of formaldehyde and the contribution of other airborne chemicals were unknown in both of the reports.

Numerous acute controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritative and pulmonary effects (Harving *et al.*, 1990; Kulle *et al.*, 1987; Sheppard *et al.*, 1984; Witek *et al.*, 1986; Witek *et al.*, 1987; Schachter *et al.*, 1986; Schachter *et al.*, 1987; Sauder *et al.*, 1986; Sauder *et al.*, 1987; Frigas *et al.*, 1984; Uba *et al.*, 1989; Akbar-Khanzadeh *et al.*, 1994). Short exercise sessions during exposure on a bicycle ergometer were included in some of the studies. Concentrations of formaldehyde in the human exposure studies ranged as high as 3 ppm for up to 3 hours. The major findings in these studies were mild to moderate eye and upper respiratory tract irritation, typical of mild discomfort from formaldehyde exposure.

In a human irritation study by Weber-Tschoppe *et al.* (1977), 33 subjects were exposed to formaldehyde at concentrations ranging from 0.03-3.2 ppm (0.04-4.0 mg/m^3) for 35 minutes. Thresholds were 1.2 ppm (1.5 mg/m^3) for eye and nose irritation, 1.7 ppm (2.1 mg/m^3) for eye blinking, and 2.1 ppm (2.6 mg/m^3) for throat irritation.

Kulle *et al.* (1987) exposed nonasthmatic humans to up to 3.0 ppm (3.7 mg/m^3) formaldehyde in a controlled environmental chamber for 3 hours. Significant dose-response relationships were seen with odor and eye irritation. At 0.5 ppm for 3 hours, none of 9 subjects had eye irritation. At 1.0 ppm, 3 of 19 subjects reported mild eye irritation and one experienced moderate irritation. At 2.0 ppm, 6 subjects reported mild and 4 reported moderate eye irritation. Nasal flow resistance was increased at 3.0 ppm but not at 2.0 ppm (2.5 mg/m^3). There were no significant decrements in pulmonary function nor increases in methacholine induced bronchial reactivity as a result of 3-hour exposures to 0.5-3.0 ppm (0.6-3.7 mg/m^3) formaldehyde at rest or at exercise, including 24 hours post exposure.

Eleven healthy subjects and nine patients with formalin skin sensitization were exposed to 0.5 mg/m^3 formaldehyde for 2 hours (Pazdrak *et al.*, 1993). Nasal lavage was performed prior to and 5 to 10 minutes, 4 hours, and 18 hours after exposure. Rhinitis was reported and increases in the number and proportion of eosinophils, elevated albumin and increased protein levels were noted in nasal lavage fluid 4 and 18 hours after exposure. No differences were found between patients with skin sensitization and healthy subjects.

In a study by Green *et al.* (1987), volunteer asthmatic and normal subjects exposed to formaldehyde developed clinically significant decrements in pulmonary function. Exposure to 3 ppm formaldehyde for 1 hour resulted in clinically significant reductions of FEV_1 (defined as > 20% or more) and FEV_1/FVC (ratio 70% or less) in 5 individuals in the study (2 of 16 asthmatics, 2 of 22 normal subjects, and one clinically normal subject with hyperactive airways). Of these individuals, 3 had reductions of FEV_1 of 20% or more during exposure. One of 22 asthmatics had a greater than 20% reduction in FEV_1 (-25.8%) at 17 minutes into exposure following a 15 minute moderate exercise session (minute ventilation [V_E] = 30-40 l/min), which, according to the authors, was low enough to prevent exercise-induced bronchospasm. One of 22 normal subjects also exhibited a greater than 20% clinically significant reduction in FEV_1 (-24.4%) and in FEV_1/FVC, which occurred at 47 minutes into exposure to 3 ppm formaldehyde. These reductions occurred following a second 15 minute heavy exercise session (V_E = 60-70 l/min) near the end of the 1 hour exposure period. A third asymptomatic "normal" subject with hyperactive airways had a clinically significant reduction of FEV_1 (-20.5%) at 17 minutes, following the first heavy exercise session. This subject exhibited occult airway hyperactivity and was excluded from analysis with the other exposure groups due to his respiratory condition. Subjects exhibiting reductions in FEV_1 of greater than 20% following exposure also exhibited FEV_1/FVC ratios of less than 70%. However, none of the subjects in the study exhibited a clinically significant reduction of 50% or greater in airway conductance (SG_{aw}) during exposure to 3 ppm formaldehyde. Other than mild nose and throat irritation, no severe respiratory signs and symptoms were apparently reported.

Sim and Pattle (1957) exposed twelve men to 17.3 mg/m^3 (13.9 ppm) formaldehyde for 30 minutes. This concentration caused "considerable nasal and eye irritation when they first entered the chamber; but despite the continued mild lacrimation for some period of time, there was no marked response (pulmonary or cardiovascular) to the exposure." The eye irritation was not severe, according to the authors, and resolved after 10 minutes in the chamber.

Kriebel and associates (1993) studied 24 physical therapy students dissecting cadavers for 3 h per week for 10 weeks. Measured formaldehyde exposures in the breathing zone ranged from 0.49 to 0.93 ppm (geometric mean ± SD = 0.73 ± 1.22). There was a pronounced increase in irritant symptoms over the duration of the each laboratory period, but this effect was stronger at the beginning of the study period. Peak expiratory flow (PEF) declined over the 10 week study by an average of 10 L/min (statistically significant trend in random-effects regression models). Fourteen weeks after ceasing exposures, the group mean baseline PEF had returned to the pre-exposure level. Mean PEF decreased over each laboratory period, although this effect was less noticeable over the course of the semester.

Rhinitis and a wide range of asthma-like conditions can result from exposure to formaldehyde. Some studies have reported that workers exposed to low concentrations may develop severe prolonged asthma attacks after prior exposure; this suggests that they may have become sensitized (Feinman, 1988). However, there is little evidence to suggest that formaldehyde exposure can result in sensitization through IgE- and IgG-mediated mechanisms (Chang and Gershwin, 1992; Heck *et al.*, 1990; Bardana and Montanaro, 1987).

Formaldehyde provocation of human subjects, occupationally exposed to formaldehyde and suffering from asthma-like symptoms such as wheezing, shortness of breath, or rhinitis, occasionally resulted in pulmonary function decrements (2 to 33% response rate) consistent with immediate, delayed, or both immediate and delayed bronchoconstriction (Nordman *et al.*, 1985; Burge *et al.*, 1985; Henrick and Lane, 1977; Wallenstein *et al.*, 1978). While some of the concentrations of formaldehyde that elicited a positive response following provocation tests (6 to 20.7 ppm) were quite high, the authors suggested that formaldehyde-induced bronchial hyperreactivity is due to specific sensitization to the gas. However, no study was able to detect antibodies to formaldehyde which would prove that sensitization to formaldehyde occurs through an immunologic pathway.

In controlled studies with asthmatics from urea-formaldehyde insulated homes, formaldehyde concentrations equal to or greater than those found in indoor environments have not resulted in hematologic or immunologic abnormalities. These tests include: blood count and differential, erythrocyte sedimentation rate; lymphocyte subpopulations (E-rosetting, T3, T4, T8, B73.1, Fc receptor positive lymphocytes and large granular lymphocytes); lymphocyte response to phytohemagglutinin and formalin-treated red blood cells; serum antibody against the Thomsen-Friedenrich RBC antigen and against formalin-RBC; and natural killer, interferon-boosted natural killer, and antibody-dependent cell-mediated cytotoxicity (Pross *et al.*, 1987). In addition, nearly all exposure studies on patients with asthma have failed to demonstrate that exposure to formaldehyde results in onset or aggravation of the patients' asthmatic symptoms (Harving *et al.*, 1990; Sheppard *et al.*, 1984).

The binding of formaldehyde to endogenous proteins creates haptens which can elicit an immune response. Chronic exposure to formaldehyde has been associated with immunological hypersensitivity as measured by elevated circulating IgG and IgE autoantibodies to human serum albumin (Thrasher *et al.*, 1987). In addition, a decrease in the proportion of T-cells was observed, indicating altered immunity. Thrasher *et al.* (1990) later found that long-term exposure to formaldehyde was associated with autoantibodies, immune activation, and formaldehyde-albumin adducts in patients occupationally exposed, or residents of mobile homes or of homes containing particleboard sub-flooring. The authors suggest that the hypersensitivity induced by formaldehyde may account for a mechanism for asthma and other health complaints associated with formaldehyde exposure.

The effects of formaldehyde on asthmatics appear to be dependent on previous, repeated exposure to formaldehyde. Burge *et al.* (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors at concentrations from 1.5 ppm to 20.6 ppm for brief durations exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and FEV_1) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m^3) formaldehyde (Nordman *et al.*, 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not occupationally exposed to formaldehyde, Sheppard *et al.* (1984) found that a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume.

Dermal contact with formaldehyde may result in an erythematous or eczematous dermatitis reaction on exposed areas (Feinman, 1988). Dermal sensitization can result.

Gorski et al (1992) evaluated the production of active oxygen species by neutrophils in 18 persons exposed to 0.5 mg/m^3 formaldehyde for 2 hours. All 13 subjects who had allergic contact dermatitis (tested positive to formaldehyde in skin patch) exhibited significantly higher chemiluminescence of granulocytes isolated from whole blood 30 minutes and 24 hours post-exposure than the individuals who were not formaldehyde sensitive. Thus, the immune cellular response of skin-sensitized individuals to an inhalation exposure to formaldehyde indicates increased production of active oxygen species. The significance of this result is unclear but may have repercussions for toxicological effects mediated by active oxygen species.

Predisposing Conditions for Formaldehyde Toxicity

Medical: Persons with eye, skin, respiratory, or allergic conditions (especially asthma) may be more sensitive to the effects of formaldehyde (Reprotext, 1999). Asthmatics sensitized to formaldehyde may be more sensitive to formaldehyde at low concentrations than non-sensitized individuals.

Chemical: Formaldehyde reacts with hydrochloric acid to form bis-chloroacetyl ether, a carcinogen (Reprotext, 1993).

V. Acute Toxicity to Laboratory Animals

In 72 rats exposed to approximately 600-1,700 mg/m^3 (500-1,400 ppm) formaldehyde vapor for 30 minutes the LC_{50} was found to be 1,000 mg/m^3 (800 ppm) (Skog, 1950). The first deaths did not occur until 6 hours after cessation of exposure. Respiratory difficulty lasted several days after exposure and the last of 49 rats died after 15 days of purulent bronchitis and diffuse bronchopneumonia. Three weeks following exposure, histological examinations of the 23 surviving animals revealed bronchitis, pulmonary microhemorrhages, and edema. No changes were seen in other organs.

A multispecies study by Salem and Cullumbine (1960) showed that a 10-hr exposure to 15.4 ppm (19 mg/m^3) formaldehyde vapor killed 3/5 rabbits, 8/20 guinea pigs, and 17/50 mice. The report stated that formaldehyde exposure resulted in delayed lethality.

Alarie (1981) determined the 10 minute LC_{50} for formaldehyde in mice to be 2,162 ppm (95% confidence interval, 1,687-2,770 ppm). The post-exposure observation period was 3 hours. From the concentration mortality graph provided in the report, an MLE_{05} and BC_{05} of 1,440 ppm and 778 ppm, respectively, could be estimated for a 10 minute formaldehyde exposure. However, as indicated in the previous reports, delayed deaths occur with formaldehyde which suggests that the 3-hour post-exposure observation period used in this study may not have been long enough.

In other lethality studies, Nagornyi *et al.* (1979) determined a 4 hour formaldehyde LC_{50} in rats and mice to be 588 mg/m^3 (474 ppm) and 505 mg/m^3 (407 ppm), respectively. However, the raw data for this study were not included in the report. Horton *et al.* (1963) observed that 2 hour exposure of mice to 0.9 mg/l (900 mg/m^3) formaldehyde resulted in deaths from massive pulmonary hemorrhage and edema, but 2 hour exposure to 0.14 mg/l (140 mg/m^3) did not produce signs of "substantial distress." In a lethality study by Carpenter *et al.* (1946), 250 ppm formaldehyde for 4 hours resulted in deaths of 2-4 out of 6 albino rats (actual number of deaths not specified) and exposure to 125 ppm formaldehyde for 4 hours resulted in deaths of 0-1 out of 6 albino rats.

Swiecechowski *et al.* (1993) exposed groups of five to seven guinea pigs to 0.86, 3.4, 9.4, or 31.1 ppm (1.1, 4.2, 11.6, or 38.6 mg/m^3) formaldehyde for 2 hr, or to 0.11, 0.31, 0.59, or 1.05 ppm (0.14, 0.38, 0.73, 1.30 mg/m^3) formaldehyde for 8 hours. An 8-hour exposure to $\geq$ 0.3 ppm ($\geq$ 0.4 mg/m^3) formaldehyde was sufficient to produce a significant increase in airway reactivity. Similar effects occurred after > 9 ppm (> 11 mg/m^3) formaldehyde for the 2-hour exposure group. Formaldehyde exposure also heightened airway smooth muscle responsiveness to acetylcholine (or carbachol) *ex vivo*. No inflammation or epithelial damage was seen up to 4 days post exposure. The researchers suggest that duration of exposure is important to the induction of airway hyperreactivity and that prolonged (8-hour), low-level exposures may generate abnormal physiologic responses in the airways not detectable after acute (2-hour) exposures.

Male F-344 rats, 7-9 weeks old, were exposed to 0.5, 2, 6 or 15 ppm formaldehyde for 6 hours per day for 1 to 4 days (Monteiro-Riviere and Popp, 1986). Effects noted in the rat nasal respiratory epithelium with 0.5 or 2 ppm were limited to altered cilia with occasional wing-like projections on the ends of the ciliary shafts. Effects noted at 6 ppm for 1 day were autophagic vacuoles in some basal cells, neutrophils in the basal and suprabasal layers, and hypertrophy of goblet and ciliated cells. Loss of microvilli in ciliated cells was noted at all exposure concentrations.

Rats were exposed to 0, 5, 10 or 20 ppm formaldehyde for 3 hours per day on 2 consecutive days (Boja *et al.*, 1985). Decreased motor activity and neurochemical changes in dopamine and 5-hydroxytryptamine neurons were reported.

VI. Reproductive or Developmental Toxicity

There are no studies that conclusively show adverse reproductive or developmental effects in animals exposed to formaldehyde (Shepard's Catalog of Teratogenic Agents, 1993; Feinman, 1988). In humans there are few data on the association of teratogenicity or adverse reproductive effects with formaldehyde exposure. Existing data do not suggest that formaldehyde, by any route, produces significant teratogenic or reproductive effects (Reprotext, Shepard's Catalog of Teratogenic Agents, 1993; Feinman, 1988).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 94 μg/m³

Study	Kulle *et al.* (1987)
Study population	19 nonasthmatic, nonsmoking human subjects
Exposure method	0.5-3.0 ppm
Critical effects	mild and moderate eye irritation
LOAEL	1 ppm
NOAEL	0.5 ppm
Benchmark concentration	0.44 ppm (BC_{05})
Exposure duration	3 hours
Extrapolated 1 hour concentration	0.76 ppm (0.44^2 ppm* 3 h = C^2 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	not required in BC approach
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.076 ppm (0.094 mg/m³; 94 μg/m³)

The recommended REL was estimated by a benchmark concentration (BC_{05}) approach, using log-probit analysis (Crump, 1984; Crump and Howe, 1983). The BC_{05} is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting BC_{05} from this analysis was 0.44 ppm (0.53 mg/m³) formaldehyde. This value was adjusted to a 1-hour duration using the formula $C^n * T = K$, where n = 2 (AICE, 1989), resulting in a value of 0.74 ppm. An uncertainty factor (UF) of 10 was used to account for individual variation. Generally an uncertainty factor of 3 would be used with the BC_{05} for intraindividual variability, since the BC_{05} accounts for some degree of individual variation. However, information from the literature indicates a wide variability in response to formaldehyde irritancy including reports of irritation (NIOSH HHE reports 1981-1996; Liu et al. 1991; Horvath et al, 1985) or cellular changes associated with irritation and an immune response at levels below the one-hour extrapolated BC_{05} (Pazdrak et al, 1993; Gorski et al, 1992). For these reasons, we used an uncertainty factor of 10 to account for intraindividual variability in the human population.

$$REL = BC_{05}/(UF)$$

The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for response rates of 1% and 5% are compared below. For a graphical representation of the derivation of the REL, refer to section IX.

The study reported by Pazdrak and associates (1993) was not selected as the key study because lack of information on the method used to estimate exposure concentrations and additional limitations in reporting data reduce the level of confidence in this study. The study adds weight, however, to the REL and to the conclusion that low-level exposures may cause adverse health effects.

Table 1. Comparison of benchmark concentration calculations (1% vs 5%)

Response rate	MLE (ppm)	95% LCL (ppm)
1%	0.50	0.25
5%	0.72	0.44

Level Protective Against Severe Adverse Effects

Based on the results of Green *et al.* (1987), an acute LOAEL of 3 ppm formaldehyde in asthmatics for a duration of 17 minutes (immediately following moderate exercise for 15 minutes) was determined. The researchers felt that, when examined along with the other 3 studies in the series (Kulle *et al.*, 1987; Sauder *et al.*, 1987; Sauder *et al.*, 1986), this study represented a threshold where protective mechanisms of the respiratory tract were beginning to be overwhelmed. Only Green *et al.* (1987) identified 5 out of 39 asthmatic and healthy subjects as having clinically significant decrements in FEV_1 (defined as > 10%). However, 3 of these 5 subjects (out of 39 asthmatic and healthy subjects) responded with a 20% or greater decrease in FEV_1, which is considered a severe adverse effect for acute toxicity exposure. The dose of formaldehyde necessary to produce pulmonary deficits in the Green *et al.* study is consistent with the dose necessary to produce pulmonary deficits in asthmatics or workers in other, less reliable reports (Hendrick *et al.*, 1982; Burge *et al.*, 1985; Nordman *et al.*, 1985).

Because the LOAEL actually represents a threshold for pulmonary effects in asthmatics due to formaldehyde inhalation, and because exercise during exposure was required to observe pulmonary deficits, the LOAEL was considered to be a NOAEL and no uncertainty factor was applied. Note that in Sauder *et al.* (1987) no asthmatic subjects experienced significant bronchoconstriction (> 10% decrease in FEV_1) when exposed to 3 ppm formaldehyde at rest for 3 hours. The 3 ppm value was adjusted to a 1-hour exposure, using a modification of Haber's equation, $C^n \times T = K$, where $n = 2$ for extrapolation from a shorter duration to 1 hour. The exponent $n = 2$ was based on findings in the AICE Guidelines (AICE, 1989). The resulting level protective against severe adverse effects is 1.6 ppm for 1-hour exposure to formaldehyde.

Level Protective Against Life-threatening Effects

Alarie (1981) estimated a 10 minute LC_{50} for formaldehyde in mice of 2,162 ppm (95% confidence interval = 1,687-2,770 ppm). The post-exposure observation period was 3 hours. Formaldehyde exposure to 250 ppm (310 mg/m^3) for 4 hours killed 4/6 rats within a 14 day observation period (Carpenter *et al.*, 1946). Among 72 rats exposed to 600-1,700 mg/m^3 formaldehyde vapor for 30 minutes the LC_{50} was found to be 1,000 mg/m^3 (800 ppm) (Skog, 1950).

Of the lethality studies summarized above, the study by Alarie (1981) best presents mortality data for the determination of a BC_{05} with an adequate post-exposure period. The major

limitation of this study was the short post-exposure observation period of 3 hours. Given the paucity of exposure data resulting in potentially lethal effects, this study currently represents the best estimate for the development of a life-threatening level for formaldehyde. A BED_{05} (which represents an experimental threshold for lethality) of 778 ppm (965 mg/m^3) for a 130 minute exposure was estimated from the data (Crump, 1984; Crump and Howe, 1983), but a BC_{05} could not be determined due to lack of data. The BED_{05} was adjusted for a 1-hour exposure using a modification of Haber's equation $C^n \times T = K$, where $n = 2$ for extrapolation from a shorter duration to a 1 -hour level, resulting in a value of 318 ppm (400 mg/m^3). The exponent $n = 2$ was based on findings in the AICE Guidelines (AICE, 1989). Uncertainty factors applied to the 1-hour BC_{05} were 3-fold to account for interspecies differences and 10-fold for increased susceptibility of sensitive human individuals. The cumulative uncertainty factor was thus 30, which results in an estimated level protective against life-threatening effects of 11 ppm (13 mg/m^3) for a 1-hour exposure to formaldehyde.

NIOSH (1995) lists a (revised) IDLH for formaldehyde of 20 ppm based on several reports of acute inhalation toxicity data, mainly in workers. Thus there is no consideration of sensitive subpopulations.

VIII. References

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CHRONIC TOXICITY SUMMARY

FORMALDEHYDE

(methanal; oxoymethane; oxomethylene; methylene oxide; formic aldehyde; methyl aldehyde)

CAS Registry Number: 50-00-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**3 μg/m^3 (2 ppb)**
Critical effect(s)	Upper and lower airway irritation and eye irritation in humans; degenerative, inflammatory and hyperplastic changes of the nasal mucosa in humans and animals
Hazard index target(s)	Respiratory system; eyes

II. Physical and Chemical Properties (HSDB, 1994; CRC, 1994)

Description	Colorless gas
Molecular formula	CH_2O
Molecular weight	30.03 g/mol
Density	0.815 g/L @ -20°C
Boiling point	-19.1°C
Melting point	-92°C
Vapor pressure	220 kPa @ 0°C
Solubility	Soluble in water, ethanol, ether, acetone
Conversion factor	1 ppm = 1.23-1.25 mg/m^3 @ 25° C

III. Major Uses or Sources (CARB, 1992; HSDB, 1995)

Formaldehyde is used in the manufacture of melamine, polyacetal, and phenolic resins. Phenol-formaldehyde resins are used in the production of plywood, particleboard, foam insulation, and a wide variety of molded or extruded plastic items. Formaldehyde is also used as a preservative, a hardening and reducing agent, a corrosion inhibitor, a sterilizing agent, and in embalming fluids. Indoor sources include upholstery, permanent press fabrics, carpets, pesticide formulations, and cardboard and paper products. Outdoor sources include emissions from fuel combustion (motor vehicles), industrial fuel combustion (power generators), oil refining processes, and other uses (copper plating, incinerators, etc.). In 1997, the population-weighted annual average exposure in the South Coast Air Basin was estimated (using a model calibrated against actual atmospheric measurements) to be 4.7 ppb formaldehye (CARB, 1999a). The annual statewide industrial

emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1,589,810 pounds of formaldehyde (CARB, 1999b).

IV. Effects of Human Exposure

Formaldehyde primarily affects the mucous membranes of the upper airways and eyes. Exposed populations that have been studied include embalmers, residents in houses insulated with urea-formaldehyde foam, anatomy class students, histology technicians, wood and pulpmill workers, and asthmatics. The voluminous body of data describing these effects has been briefly summarized below. For the sake of brevity, only the studies that best represent the given effects are presented.

Kerfoot and Mooney (1975) reported that estimated formaldehyde exposures of 0.25-1.39 ppm evoked numerous complaints of upper respiratory tract and eye irritation among 7 embalmers at 6 different funeral homes. Three of the 7 embalmers in this study reportedly had asthma. Levine *et al.* (1984) examined the death certificates of 1477 Ontario undertakers. Exposure measurements taken from a group of West Virginia embalmers were used as exposure estimates for the embalming process, ranging from 0.3-0.9 ppm (average 1-hour exposure) and 0.4-2.1 ppm (peak 30-minute exposure). Mortality due to non-malignant diseases was significantly elevated due to a two-fold excess of deaths related to the digestive system. The authors suggest increased alcoholism could have contributed to this increase.

Ritchie and Lehnen (1987) reported a dose-dependent increase in health complaints (eye and throat irritation, and headaches) in 2000 residents living in 397 mobile and 494 conventional homes, that was demonstrated by logistic regression. Complaints of symptoms of irritation were noted at concentrations of 0.1 ppm formaldehyde or above. Similarly, Liu *et al.* (1991) found that exposure to 0.09 ppm (0.135 mg/m^3) formaldehyde exacerbated chronic respiratory and allergy problems in residents living in mobile homes.

Employees of mobile day-care centers (66 subjects) reported increased incidence of eye, nose and throat irritation, unnatural thirst, headaches, abnormal tiredness, menstrual disorders, and increased use of analgesics as compared to control workers (Olsen and Dossing, 1982). The mean formaldehyde concentration in these mobile units was 0.29 ppm (0.43 mg/m^3) (range = 0.24 - 0.55 mg/m^3). The exposed workers were exposed in these units a minimum of 3 months. A control group of 26 subjects in different institutions was exposed to a mean concentration of 0.05 ppm (0.08 mg/m^3) formaldehyde.

Occupants of houses insulated with urea-formaldehyde foam insulation (UFFI) (1726 subjects) were compared with control subjects (720 subjects) for subjective measures of irritation, pulmonary function (FVC, FEV_1, FEF_{25-75}, FEF_{50}), nasal airway resistance, odor threshold for pyridine, nasal cytology, and hypersensitivity skin-patch testing (Broder *et al.*, 1988). The mean length of time of exposure to UFFI was 4.6 years. The mean concentration of formaldehyde in the UFFI-exposed group was 0.043 ppm, compared with 0.035 ppm for the controls. A significant increase in symptoms of eye, nose and throat irritation was observed in subjects from UFFI homes, compared with controls. No other differences from control measurements were observed.

An increase in severity of nasal epithelial histological lesions, including loss of cilia and goblet cell hyperplasia (11%), squamous metaplasia (78%), and mild dysplasia (8%), was observed in 75 wood products workers exposed to between 0.1 and 1.1 mg/m^3 formaldehyde for a mean duration of 10.5 years (range = 1 - 39 years), compared to an equal number of control subjects (Edling *et al.*, 1988). Only three exposed men had normal mucosa. A high frequency of symptoms relating to the eyes and upper airways was reported in exposed workers. Nasal symptoms included mostly a runny nose and crusting. The histological grading showed a significantly higher score for nasal lesions when compared with the referents (2.9 versus 1.8). Exposed smokers had a higher, but non-significant, score than ex-smokers and non-smokers. When relating the histological score to duration of exposure, the mean histological score was about the same regardless of years of employment. In addition, no difference in the histological scores was found between workers exposed only to formaldehyde and those exposed to formaldehyde and wood dust.

Alexandersson and Hedenstierna (1989) evaluated symptoms of irritation, spirometry, and immunoglobulin levels in 34 wood workers exposed to formaldehyde over a 4-year period. Exposure to 0.4 - 0.5 ppm formaldehyde resulted in significant decreases in FVC, FEV_1, and FEF_{25-75}. Removal from exposure for 4 weeks allowed for normalization of lung function in the non-smokers.

Kriebel *et al.* (1993) conducted a subchronic epidemiological study of 24 anatomy class students exposed to a range of formaldehyde of 0.49 to 0.93 ppm (geometric mean = 0.73 $\pm$ 1.22 ppm) for 3 hours per week for 10 weeks. One subject was a smoker, 2 reported current asthma, and 3 reported childhood asthma without current symptoms. Eye and throat irritation was significantly elevated in the students after classes compared with pre-laboratory session exposures. In addition, peak expiratory flow measurements declined by an average of 10 L/minute (2% of baseline), but returned to normal after 14 weeks of non-exposure.

Histology technicians (280 subjects) were shown to have reduced pulmonary function, as measured by FVC, FEV_1, FEF_{25-75}, and FEF_{75-85}, compared with 486 controls (Kilburn *et al.*, 1989). The range of formaldehyde concentrations was 0.2 - 1.9 ppm, volatilized from formalin preservative solution.

Malaka and Kodama (1990) investigated the effects of formaldehyde exposure in plywood workers (93 exposed, 93 controls) exposed for 26.6 years, on average, to 1.13 ppm (range = 0.28 - 3.48 ppm). Fifty-three smokers were present in both study groups. Exposure assessment was divided into 3 categories: high (> 5 ppm), low (< 5 ppm), and none (reference group). Subjective irritation and pulmonary function tests were performed on each subject, and chest x-rays were taken of 10 randomly selected volunteers from each group. Respiratory symptoms of irritation were found to be significantly increased in exposed individuals, compared with controls. In addition, exposed individuals exhibited significantly reduced FEV_1, FEV_1/FVC, and FEF_{25-75}, compared with controls. Forced vital capacity was not significantly reduced. Pulmonary function was not found to be different after a work shift, compared to the same measurement taken before the shift. No differences in chest x-rays were observed between exposed and control workers.

Occupational exposure to formaldehyde concentrations estimated to be 0.025 ppm (0.038 mg/m^3) for greater than 6 years resulted in complaints by 22 exposed workers of respiratory, gastrointestinal, musculoskeletal, and cardiovascular problems, and in elevated formic acid excretion in the urine (Srivastava *et al.*, 1992). A control group of 27 workers unexposed to formaldehyde was used for comparison. A significantly higher incidence of abnormal chest x-rays was also observed in formaldehyde-exposed workers compared with controls.

Chemical plant workers (70 subjects) were exposed to a mean of 0.17 ppm (0.26 mg/m^3) formaldehyde for an unspecified duration (Holmstrom and Wilhelmsson, 1988). Compared with 36 control workers not exposed to formaldehyde, the exposed subjects exhibited a higher frequency of eye, nose, and deep airway discomfort. In addition, the exposed subjects had diminished olfactory ability, delayed mucociliary clearance, and decreased FVC.

Alexandersson *et al.* (1982) compared the irritant symptoms and pulmonary function of 47 carpentry workers exposed to a mean concentration of formaldehyde of 0.36 ppm (range = 0.04 - 1.25 ppm) with 20 unexposed controls. The average length of employment for the exposed workers was 5.9 years. Symptoms of eye and throat irritation as well as airway obstruction were more common in exposed workers. In addition, a significant reduction in FEV_1, FEV_1/FVC, and MMF was observed in exposed workers, as compared with controls.

Horvath *et al.* (1988) compared subjective irritation and pulmonary function in 109 workers exposed to formaldehyde with similar measures in a control group of 254 subjects. The formaldehyde concentrations for the exposed and control groups were 0.69 ppm (1.04 mg/m^3) and 0.05 ppm (0.08 mg/m^3), respectively. Mean formaldehyde concentration in the pre-shift testing facility and the state (Wisconsin) ambient outdoor - formaldehyde level were both 0.04 ppm (0.06 mg/m^3). Duration of formaldehyde exposure was not stated. Subjects were evaluated pre- and post work-shift and compared with control subjects. Significant differences in symptoms of irritation, FEV_1, FEV_1/FVC ratio, FEF_{50}, FEF_{25}, and FEF_{75} were found when comparing exposed subjects' pre- and post work-shift values. However, the pre-workshift values were not different from controls.

The binding of formaldehyde to endogenous proteins creates haptens that can elicit an immune response. Chronic exposure to formaldehyde has been associated with immunological hypersensitivity as measured by elevated circulating IgG and IgE autoantibodies to human serum albumin (Thrasher *et al.*, 1987). In addition, a decrease in the proportion of T-cells was observed, indicating altered immunity. Thrasher *et al.* (1990) later found that long-term exposure to formaldehyde was associated with autoantibodies, immune activation, and formaldehyde-albumin adducts in patients occupationally exposed, or residents of mobile homes or of homes containing particleboard sub-flooring. The authors suggest that the hypersensitivity induced by formaldehyde may account for a mechanism for asthma and other health complaints associated with formaldehyde exposure.

Symptoms of irritation were reported by 66 workers exposed for 1 - 36 years (mean = 10 years) to a mean concentration of 0.17 ppm (0.26 mg/m^3) formaldehyde (Wilhelmsson and Holmstrom,

1992). Controls (36 subjects) consisted of office workers in a government office and were exposed to a mean concentration of 0.06 ppm (0.09 mg/m^3) formaldehyde. The significant increase in symptoms of irritation in exposed workers did not correlate with total serum IgE antibody levels. However, 2 exposed workers, who complained of nasal discomfort, had elevated IgE levels. In another occupational health study, 37 workers, who were exposed for an unspecified duration to formaldehyde concentrations in the range of 0.003 to 0.073 ppm, reported ocular irritation; however, no significant serum levels of IgE or IgG antibodies to formaldehyde-human serum albumin were detected (Grammer *et al.*, 1990).

An epidemiological study of the effects of formaldehyde on 367 textile and shoe manufacturing workers employed for a mean duration of 12 years showed no significant association between formaldehyde exposure, pulmonary function (FVC, FEV_1, and PEF) in normal or asthmatic workers, and occurrence of specific IgE antibodies to formaldehyde (Gorski and Krakowiak, 1991). The concentrations of formaldehyde did not exceed 0.5 ppm (0.75 mg/m^3).

Workers (38 total) exposed for a mean duration of 7.8 years to 0.11 - 2.12 ppm (mean = 0.33 ppm) formaldehyde were studied for their symptomatology, lung function, and total IgG and IgE levels in the serum (Alexandersson and Hedenstierna, 1988). The control group consisted of 18 unexposed individuals. Significant decrements in pulmonary function (FVC and FEV_1) were observed, compared with the controls. Eye, nose, and throat irritation was also reported more frequently by the exposed group, compared with the control group. No correlation was found between duration of exposure, or formaldehyde concentration, and the presence of IgE and IgG antibodies.

The effects of formaldehyde on asthmatics appears to be dependent on previous, repeated exposure to formaldehyde. Burge *et al.* (1985) found that 3 out of 15 occupationally exposed workers challenged with formaldehyde vapors at concentrations from 1.5 ppm to 20.6 ppm for brief duration exhibited late asthmatic reactions. Six other subjects had immediate asthmatic reactions likely due to irritant effects. Asthmatic responses (decreased PEF, FVC, and FEV_1) were observed in 12 occupationally-exposed workers challenged with 1.67 ppm (2.5 mg/m^3) formaldehyde (Nordman *et al.*, 1985). Similarly, asthmatic responses were observed in 5 of 28 hemodialysis workers occupationally exposed to formalin and challenged with formaldehyde vapors (concentration not measured) (Hendrick and Lane, 1977). In asthmatics not occupationally exposed to formaldehyde, Sheppard *et al.* (1984) found that a 10-minute challenge with 3 ppm formaldehyde coupled with moderate exercise did not induce significant changes in airway resistance or thoracic gas volume.

V. Effects of Animal Exposure

Fischer-344 rats and B6C3F1 mice (120 animals/sex) were exposed to concentrations of 0, 2.0, 5.6, or 14.3 ppm formaldehyde vapor for 6 hours/day, 5 days/week for 24 months (Kerns *et al.*, 1983). The exposure period was followed by up to 6 months of non-exposure. Interim sacrifices were conducted at 6, 12, 18, 24, 27, and 30 months. Both male and female rats in the 5.6 and 14.3 ppm groups demonstrated decreased body weights over the 2-year period. At the 6 month sacrifice, the rats exposed to 14.3 ppm formaldehyde had non-neoplastic lesions of epithelial

dysplasia in the nasal septum and turbinates. As the study progressed, epithelial dysplasia, squamous dysplasia, and mucopurulent rhinitis increased in severity and distribution in all exposure groups. In mice, cumulative survival decreased in males from 6 months to the end of the study. Serous rhinitis was detected at 6 months in the 14.3 ppm group of mice. Metaplastic and dysplastic changes were noted at 18 months in most rats in the 14.3 ppm group and in a few mice in the 5.6 ppm exposure group. By 24-months, the majority of mice in the 14.3 ppm group had metaplastic and dysplastic changes associated with serous rhinitis, in contrast to a few mice in the 5.6 ppm group and a few in the 2 ppm group (exact number not given).

Woutersen *et al.* (1989) exposed male Wistar rats (60 animals/group) 6 hr/day for 5 days/week to 0, 0.1, 1.0 and 10 ppm formaldehyde vapor for 28 months. Compound-related nasal lesions of the respiratory and olfactory epithelium were observed only in the 10 ppm group. In the respiratory epiethlium, the lesions consisted of rhinitis, squamous metaplasia and basal cell/pseudoepithelial hyperplasia. In the olfactory region, the lesions included epithelial degeneration and rhinitis. No differences in behavior or mortality were noted among the various groups. However, growth retardation was observed in the 10 ppm group from day 14 onwards. In a parallel study, male Wistar rats were exposed to 0, 0.1, 1.0 and 10 ppm formaldehyde for 3 months followed by a 25-month observation period. Compound-related histopathological changes were found only in the noses of the 10 ppm group and comprised of increased incidences of squamous metaplasia of the respiratory epithelium and rhinitis.

In a chronic exposure study that primarily investigated aspects of nasal tumor development, Monticello *et al.* (1996) examined nasal cavities of male F-344 rats (0 - 10 ppm, 90 animals/group; 15 ppm, 147 animals) following exposure to 0, 0.7, 2, 6, 10, and 15 ppm formaldehyde for 6 hours/day, 5 days/week for 24 months. Treatment-related decreases in survival were apparent only in the 15 ppm group. Nasal lesions at the two highest doses included epithelial hypertrophy and hyperplasia, squamous metaplasia, and a mixed inflammatory cell infiltrate. Lesions in the 6 ppm group were minimal to absent and limited to focal squamous metaplasia in the anterior regions of the nasal cavity. No formaldehyde-induced lesions were observed in the 0.7 or 2 ppm groups.

Kamata *et al.* (1997) exposed 32 male F-344 rats/group to gaseous formaldehyde at 0, 0.3, 2, and 15 ppm 6 hr/day, 5 days/week for up to 28 weeks. A room control, non-exposed group was also included in the study. Five animals per group were randomly selected at the end of the 12th, 18th, and 24th months, and surviving animals at 28 months were sacrificed for full pathological evaulation. Behavioural effects related to sensory irritation were evident in the 15 ppm group. Significant decreases in food consumption, body weight and survival were also evident in this group. No exposure-related hematological findings were observed. Biochemical and organ weight examination revealed decreased triglyceride levels and absolute liver weights at the highest exposure, but was likely related to reduced food consumption. Abnormal histopathological findings were confined to the nasal cavity. Inflammatory cell infiltration, erosion or edema of the nasal cavity was evident in all groups, including controls. Significantly increased incidence of non-proliferative (squamous cell metaplasia without epithelial cell hyperplasia) and proliferative lesions (epithelial cell hyperplasia with squamous cell metaplasia) were observed in the nasal cavities beginning at 2 ppm. In the 0.3 ppm group, a non-significant

increase in proliferative nasal lesions (4/20 animals) were observed in rats that were either sacrificed or died following the 18th month of exposure.

Rusch *et al.* (1983) exposed groups of 6 male cynomolgus monkeys, 20 male or female rats, and 10 male or female hamsters to 0, 0.2, 1.0, or 3.0 ppm (0, 0.24, 1.2, or 3.7 mg/m^3) formaldehyde vapor for 22 hours/day, 7 days/week for 26 weeks. There was no treatment-related mortality during the study. In monkeys, the most significant findings were hoarseness, congestion and squamous metaplasia of the nasal turbinates in 6/6 monkeys exposed to 2.95 ppm. There were no signs of toxicity in the lower exposure groups. In the rat, squamous metaplasia and basal cell hyperplasia of the nasal epithelia were significantly increased in rats exposed to 2.95 ppm. The same group exhibited decreased body weights and decreased liver weights. In contrast to monkeys and rats, hamsters did not show any signs of response to exposure, even at 2.95 ppm.

Kimbell et al. (1997) exposed male F-344 rats ($\leq$ 6/group) to 0, 0.7, 2, 6, 10, and 15 ppm 6 hr/day, 5 days/week for 6 months. Squamous metaplasia was not observed in any regions of the nasal cavity in any of the control, 0.7, or 2 ppm groups. However, the extent and incidence of squamous metaplasia in the nasal cavity increased with increasing dose beginning at 6 ppm.

In subchronic studies, Wilmer *et al.* (1989) found that intermittent (8 hours/day, 5 days/week) exposures of rats to 4 ppm formaldehyde for 13 weeks resulted in significant histological changes in the nasal septum and turbinates. In contrast, continuous exposure of rats for 13 weeks to 2 ppm formaldehyde did not produce significant lesions. This study revealed the concentration dependent nature of the nasal lesions caused by formaldehyde exposure. Zwart *et al.*, (1988) exposed male and female Wistar rats (50 animals/group/sex) to 0, 0.3, 1, and 3 ppm formaldehyde vapor for 6 hr/day, 5 days/week for 13 weeks. Compound related histopathological nasal changes varying from epithelial disarrangement to epithelial hyperplasia and squamous metaplasia were found in the 3 ppm group, and were restricted to a small area of the anterior respiratory epithelium. These changes were confirmed by electron microscopy and were not observed in other groups. Wouterson *et al.* (1987) exposed rats (20 per group) to 0, 1, 10, or 20 ppm formaldehyde 6 hours/day, 5 days/week for 13 weeks. Rats exposed to 20 ppm displayed retarded growth, yellowing of the fur, and significant histological lesions in the respiratory epithelium. Exposure to 10 ppm did not affect growth, but resulted in significant histological lesions in the respiratory tract. No effects on specific organ weights, blood chemistries, liver glutathione levels, or urinalysis were detected at any level. No significant adverse effects were seen at the 1.0 ppm exposure level.

Appelman *et al.* (1988) found significant nasal lesions in rats (20 per group; 0, 0.1, 1.0, or 10.0 ppm) exposed to 10 ppm formaldehyde 6 hours/day, 5 days/week for 52 weeks, but exposure to 1.0 ppm or less for this period did not result in nasal histological lesions. However, the rats exposed to formaldehyde displayed decreased body weight in all groups compared with controls.

Apfelbach and Weiler (1991) determined that rats (5 exposed, 10 controls) exposed to 0.25 ppm (0.38 mg/m^3) formaldehyde for 130 days lost the olfactory ability to detect ethyl acetate odor.

Maronpot *et al.* (1986) exposed groups of 20 mice to 0, 2, 4, 10, 20, or 40 ppm formaldehyde 6 hours/day, 5 days/week, for 13 weeks. Histological lesions in the upper respiratory epithelium were seen in animals exposed to 10 ppm or greater. Exposure to 40 ppm was lethal to the mice.

A six-month exposure of rats to 0, 0.5, 3, and 15 ppm formaldehyde (3 rats per group) resulted in significantly elevated total lung cytochrome P450 in all formaldehyde-exposed groups (Dallas *et al.*, 1989). The degree of P450 induction was highest after 4 days exposure and decreased slightly over the course of the experiment.

A developmental toxicity study on formaldehyde was conducted by Martin (1990). Pregnant rats (25 per group) were exposed to 0, 2, 5, or 10 ppm formaldehyde for 6 hours/day, during days 6-15 of gestation. Although exposure to 10 ppm formaldehyde resulted in reduced food consumption and body weight gain in the maternal rats, no effects on the number, viability or normal development of the fetuses were seen. In addition, Saillenfait *et al.* (1989) exposed pregnant rats (25 per group) to 0, 5, 10, 20, or 40 ppm formaldehyde from days 6 - 20 of gestation. Maternal weight gain and fetal weight were significantly reduced in the 40 ppm exposure group. No significant fetotoxicity or teratogenic defects were observed.

VI. Derivation of Chronic Reference Exposure Level (REL)

Studies	Wilhelmsson and Holmstrom, 1992; supported by Edling *et al.*, 1988
Study population	Human chemical plant workers (66 subjects)
Exposure method	Discontinuous occupational exposure
Critical effects	Nasal and eye irritation, nasal obstruction, and lower airway discomfort; histopathological nasal lesions including rhinitis, squamous metaplasia, and dysplasia
LOAEL	Mean of 0.26 mg/m^3 (range = 0.05 to 0.6 mg/m^3) (described as exposed group)
NOAEL	Mean of 0.09 mg/m^3 (described for control group of office workers)
Exposure continuity	8 hours/day, 5 days/week (assumed)
Exposure duration	10 years (average); range = 1-36 years
Average occupational concentration	0.032 mg/m^3 for NOAEL group (0.09 x 10/20 x 5/7)
Human equivalent concentration	0.032 mg/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference level	0.003 mg/m^3 (3 $\mu g/m^3$; 0.002 ppm; 2 ppb)

The Wilhelmsson and Holmstrom (1992) study was selected because it was a human occupational study that contained a LOAEL and a NOAEL, was recent, and contained a

reasonable number of subjects. The supporting occupational study by Edling *et al.* (1988) noted similar sensory irritation results due to long-term formaldehyde exposure. In addition, nasal biopsies from exposed workers in the Edling *et al.* (1988) study exhibited nasal epithelial lesions similar to those found in subchronic and chronic animal studies.

For comparison with the proposed REL of 3 $\mu g/m^3$, we estimated a REL from Edling *et al.* (1988). A median concentration of 0.6 mg/m^3 was determined for the LOAEL from the TWA range of 0.1-1.1 mg/m^3. A NOAEL was not reported. The average continuous occupational concentration was 0.2 mg/m^3 (0.6 x 10/20 x 5/7) and the exposure duration was 10.5 years (range = 1 – 39 years). Application of a UF of 10 for intraspecies variability and a UF of 10 for estimation of a NOAEL from the LOAEL would result in a REL of 2 $\mu g/m^3$ (2 ppb).

Table 1 presents a summary of potential RELs based on chronic and subchronic animal studies. The toxicological endpoint was nasal lesions, consisting principally of rhinitis, squamous metaplasia, and dyplasia of the respiratory epithelium.

Table 1. Summary of Chronic and Subchronic Formaldehyde Studies in Experimental Animals

Study	*Animal*	Exposure Duration	LOAEL/ NOAEL (mg/m^3)	HEC adj. (mg/m^3)	Cumulative UF	REL ($\mu g/m^3$)
Woutersen *et al.*, 1989	rat	28 mo	9.8 / 1.0	0.06	30	2
Kerns *et al.*, 1983	rat	24 mo	2.0 / NA	0.1	300	0.3
Monticello *et al.*, 1996	rat	24 mo	6.01 / 2.05	0.1	30	4
Kamata *et al.*, 1997	rat	24-28 mo	0.30 / NA	0.02	100	0.2
Appelman *et al.*, 1988	rat	52 wk	9.4 / 1.0	0.06	30	2
Rusch *et al.*, 1983	rat	26 wk	2.95 / 0.98	0.2	30	7
Kimbell *et al.*, 1997	rat	26 wk	6 / 2	0.1	30	3
Wilmer *et al.*, 1989	rat	13 wk	4 / 2	0.2	300	0.7
Woutersen *et al.*, 1987	rat	13 wk	9.7 / 1.0	0.03	100	0.3
Zwart *et al.*, 1988	rat	13 wk	2.98 / 1.01	0.2	300	0.7
Kerns *et al.*, 1983	mouse	24 mo	2.0 / NA	0.05	100	0.5
Maronpot *et al.*, 1986	mouse	13 wk	10.1 / 4.08	0.09	100	0.9
Rusch *et al.*, 1983	monkey	26 wk	2.95 / 0.98	none	300	4

The most striking observation is the similarity of potential RELs among the rat chronic studies (exposures $\geq$ 26 weeks) that contain a NOAEL. The range of RELs from these animal studies, 2 – 7 $\mu g/m^3$, is comparable to the proposed REL based on a human study. Another related observation is that the NOAEL and LOAEL are similar among all the studies, regardless of exposure duration. The NOAEL and LOAEL are generally in the range of 1-2 mg/m^3 and 2-10 mg/m^3, respectively, with the exception of the study by Kamata *et al.* (1997). These results indicate that the formation of formaldehyde-related nasal lesions are more concentration dependent than time, or dose, dependent.

A limitation of a majority of the occupational studies is their high reliance on surveys and other methods that focus on sensory irritation. Such sensory irritant results, as exhibited in the Wilhelmsson and Holmstrom (1992) study, may be more related to recurrent acute injury rather than a true chronic injury. The concentration dependent nature of the nasal lesions in the supporting animal studies, and suggested in the supporting human nasal biopsy study, would also imply that the nasal cavity endpoint may be a recurrent acute effect. However, Kerns *et al.* (1983) and Kamata *et al.* (1997) clearly demonstrated that near the LOAEL, increasing exposure durations would result in nasal lesions at lower formaldehyde concentrations. Also, the rat study by Woutersen *et al.* (1989) demonstrated that subchronic exposure to formaldehyde concentrations that produce nasal lesions could result in lifelong changes of the nasal epithelium. These findings substantiate the chronic nature of the nasal/upper airway injury that results from long-term formaldehyde exposure.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL include the use of human exposure data from workers exposed over a period of years and the observation of a NOAEL. In addition, a number of well-conducted animal studies supported the derivation of the REL. The major areas of uncertainty are the uncertainty in estimating exposure in the occupational studies and the potential variability in exposure concentration.

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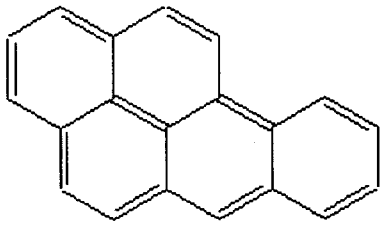
Polycylic Organic Matter in Prioritization of Toxic Air Contminants Under the Children's Environmental Health Protection Act, October 2001.

Benzo(A)Pyrene in Air Toxics "Hot Spots" Risk Assessment Guidelines Part II: Technical Support Document for Describing Available Cancer Potency Factors. Office of Environmental Health Hazard Assessment, Cal/EPA. April 1999.

Polycyclic Organic Matter

(including, but not limited to: benzo[*a*]pyrene, benzo[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, dibenz[*a,j*]acridine, dibenz[*a,h*]acridine, 7H-dibenzo[*c,g*]carbazole, dibenzo[*a,e*]pyrene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, dibenzo[*a,l*]pyrene, fluoranthene, 2-methyl fluoranthene, 3-methyl fluoranthene, indeno[1,2,3-*cd*]pyrene, 5-methylchrysene, naphthalene, 1-nitropyrene, 4-nitropyrene, 1,6-dinitropyrene, 1,8-dinitropyrene, 6-nitrochrysene, 2-nitrofluorene, chrysene, dibenz[*a*,h]anthracene, 7,12-dimethylbenzanthracene, 3-methylcholanthrene, 5-nitroacenaphthene)



Benzo[*a*]pyrene: 50-32-8

Physical and Chemical Properties - Benzo[*a*]pyrene

Description	Yellow crystalline solid: volatile at elevated temperatures.
Molecular formula	$C_{20}H_{12}$
Molecular weight	252.3
Air concentration conversion	1 ppm = 10.3 mg/m^3

The compound benzo[*a*]pyrene is one of the most extensively studied members of the class of Polycyclic Aromatic Hydrocarbons (PAHs). This class, along with various PAH derivatives important as environmental pollutants, is also described as Polycyclic Organic Matter (POM). POM has been identified as a Toxic Air Contaminant by the Air Resources Board. POM consists of over 100 identified compounds, and is defined by the Federal Clean Air Act as organic compounds with more than one benzene ring that have a boiling point greater than or equal to 100°C. The usual definition of a PAH specifies that the compounds are hydrocarbons with no hetero-atom substitutents or ring members, and that the compound include at least two (or, according to some authors, three) concatenated aromatic (usually benzene-like) rings. Although benzo[*a*]pyrene is one of the more abundant members of the class, it comprises no more than 5 percent of the total PAHs present in the atmosphere (Ronia *et al.*, 1983). PAHs, and derivatives such as nitro-PAHs and PAH quinones, are included under the TAC category of POM. Additionally, although naphthalene is included within the Federal Clean Air act definition of POM, it is also separately listed as a Federal hazardous air pollutant and thus as a California TAC. In this summary, the toxicity of PAHs and nitro-PAHs is reviewed for potential impacts on the health of children and infants, with specific reference to those PAHs identified or evaluated as carcinogens by U.S. EPA, IARC, and the California TAC program (see Section V.C.) Additional specific compounds, and mixtures containing PAHs, were considered where data indicate carcinogenic or other biological activities similar to those seen for the identified carcinogenic PAHs, especially where these data include evidence of differential impacts on infants and children.

Most of the POM occurring as air pollution is attached to particulate matter. Compounds with two rings (e.g., naphthalene), although solid at room temperature in bulk, are sufficiently volatile that as air pollutants they occur in the vapor phase. Compounds with three to four rings (e.g., pyrene) occur either in the vapor phase or bound to particles, depending on the temperature and pressure. Compounds with five rings (e.g., dibenzo[*a,h*]anthracene, benzo[*a*]pyrene) exist as particles in the atmosphere (Atkinson, 1995). PAHs may also exist as solids in soil or sediment (ATSDR, 1993). PAH-derivatives include nitro-PAHs, amino-PAHs, oxygenated PAHs (phenols, quinones), and heterocyclic aromatic compounds containing nitrogen, sulfur and oxygen (Finlayson-Pitts and Pitts, 1986).

Overview

There are a number of toxicological endpoints associated with PAHs to which infants and children may be especially susceptible.

- There is a general concern, based on mechanistic arguments and experimental and epidemiological data for a number of carcinogens, that exposure to a carcinogen early in life may have a greater overall impact than

a similar exposure to an adult. Numerous investigators have used neonatal exposures in rodents, which have generally been found to show greater sensitivity to carcinogenesis (i.e. the number of compounds showing a statistically significant effect, the incidence and latency of tumors, and the sites affected), relative to adults (Vesselinovitch *et al.*, 1979). In addition, specific data are available showing increased sensitivity to PAHs and derivatives in young animals. A number of PAHs, PAH derivatives and mixtures containing PAHs have been identified as carcinogens in animals or humans.

- Comparative studies of the relative susceptibility to carcinogenesis at different ages have been reported. Intraperitoneal injections of benzo[*a*]pyrene to infant (day 1 or day 15) or young adult (day 42) mice produced greater lifetime incidence of lung and liver tumors in the mice treated at younger ages (Vesselinovitch *et al.*, 1975). When 3 doses of fluoranthene, 2- or 3-methylfluoranthene were injected into newborn CD-1 mice, there were high incidences of liver and lung tumors following a short latency period (Lavoie *et al.*, 1994). When 8 doses of 1-nitropyrene, 1,3-dinitropyrene, 1,6-dinitropyrene or 1,8-dinitropyrene were injected into newborn CD rats, there were increases in various tumors, some of which occurred after a very short latency period (Imaida *et al.* 1995). In addition, 1,6-dinitropyrene or 1,8-dinitropyrene produced an early increase in leukemia. These experiments are described in detail in a later section of this summary.
- Several studies in animals and humans indicate that prenatal exposure to PAHs results in serious or irreversible effects in the fetus, including cancer, teratogenesis and low birthweight. As discussed in the introductory section of this report, fetal damage sustained as a result of exposure to environmental toxicants is a source of adverse postnatal health impacts, and therefore falls within the scope of this report.
- Transplacental carcinogenesis by PAHs is a well-known phenomenon (Sram *et al.*, 1998; Anderson *et al.*, 1995). In one experiment, this was associated with induction of a specific mutation in the Ha-*ras* proto-oncogene in the fetus, which can be expressed post-natally with appropriate promotion (Yamasaki *et al.*, 1987). Thus, it appears that the mechanisms underlying transplacental carcinogenesis are similar to those for carcinogenesis after postnatal exposure, but the sites of tumor appearance are frequently more diverse, and the sensitivity is greater (Nikonova, 1977).
- Several non-carcinogenic effects have been observed following exposure *in utero* to PAHs or to mixtures containing them. These included teratogenesis (Shum *et al.*, 1979; Feuston and Mackerer, 1996), low birth weight in humans (Perera *et al.*, 1998; Dejmek *et al.*, 2000) and rodents (McKee *et al.*, 1987b), immunotoxicity (Urso *et al.*, 1992), loss of fertility in rodents exposed to benzo[a] pyrene *in utero* (Mackenzie and Angevine, 1981), human transplacental exposure resulting in hemolytic anemia (Zinkharn and Childs, 1958; Anziulewicz *et al.*, 1959) and disruption of lymphocyte maturation and hematopoiesis (Holladay and Smith, 1994). These occurred at doses at which maternal toxicity (other than long-term effects such as carcinogenesis) is minimal or absent. In several cases the effects observed after exposure *in utero* parallel toxic effects in the adult (e.g. immunotoxicity, reproductive toxicity, myelotoxicity), but whereas the effects are reversible after exposure of the adult, exposure of the fetus results in an irreversible effect.
- In addition to differential sensitivity to toxic effects in young animals and humans, there is greater exposure of children to environmental PAHs (Chuang et al., 1999). Children's daily doses of PAHs (per kg of body weight) were generally higher from all routes of exposure than those of adults in the same household (Chuang et al., 1999) or city (Ptashekas et al., 1996). PAH-DNA adducts have been detected in the human placenta (Everson et al., 1986, Weston et al., 1989), the umbilical cord blood of newborns (Whyatt et al., 1989), and the fetuses of experimental animals (Withey et al., 1992; 1993).
- Based on these observations, studies in humans and animals suggest that children may be more sensitive to the toxic effects of PAHs and PAH derivatives (including, but not limited to, benzo[*a*]pyrene, benzo[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, dibenz[*a,j*]acridine, dibenz[*a,h*]acridine, 7H-dibenzo[*c,g*]carbazole, dibenzo[*a,e*]pyrene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, dibenzo[*a,l*]pyrene, fluoranthene, 2-methyl fluoranthene, 3-methyl fluoranthene, indeno[1,2,3-*cd*]pyrene, 5-methylchrysene, naphthalene, 1-nitropyrene, 4-nitropyrene, 1,6-dinitropyrene, 1,8-dinitropyrene, 6-nitrochrysene, 2-nitrofluorene, chrysene, dibenz[*a*,h]anthracene, 7,12-dimethylbenzanthracene, 3-methylcholanthrene, 5-nitroacenaphthene), and mixtures containing PAHs.

Principal Sources of Exposure

PAHs and other POM components are produced by the incomplete combustion of any carbon-containing materials, including fossil fuels and vegetable matter. PAHs have been detected in exhaust from both gasoline and diesel powered motor vehicles, smoke from residential wood combustion, and fly ash from coal-fired electric generating

plants (Finlayson-Pitts and Pitts, 1986). Burning of vegetable materials and other waste is responsible for 50 percent of the total statewide emissions of benzo[*a*]pyrene. Other sources of benzo[*a*]pyrene, such as residential wood combustion, coal combustion, and residual oil combustion, are responsible for about 15 percent of the total statewide emissions. Some sources of PAHs and other POM components are non-anthropogenic; these can be formed during any naturally occurring combustion, such as forest fires (U.S. EPA, 1994). Benzo[*a*]pyrene and other PAHs occur in crude oils, shale oils, and coal tars, and are emitted with gases and fly ash from active volcanoes (HSDB, 1995). In spite of these natural sources, the most important contributors to air pollution by PAHs are usually anthropogenic.

Mobile sources

In California, mobile sources contribute more than 35 percent of the total benzo[*a*]pyrene emissions. (Benzo[*a*]pyrene in air is quantifiable by standardized methods and is frequently used as a marker for emissions of a range of PAHs and other POM components.) Within the mobile source category, light duty vehicles are responsible for 30 percent of benzo[*a*]pyrene emissions, while heavy duty vehicles contribute approximately 10 percent (OEHHA, 1993). Before the introduction of catalytic converters (around 1974), mobile sources were the major contributor of benzo[*a*]pyrene emissions. The decreasing number of older, more polluting vehicles, and the introduction of low and even zero emission vehicles and clean fuels as part of California's Motor Vehicle Program has led to a significant and continuing reduction of POM emissions (including benzo[*a*]pyrene and other PAHs) from light-duty vehicles. Emissions from on-road mobile source diesel exhaust PM_{10} in California are expected to decline by approximately 50 percent from 1990 until about 2010 as a result of mobile source standards and regulations adopted by the ARB through 1996 (ARB, 1998). However, the proportional reductions in emissions per mile from heavy-duty (primarily diesel powered) vehicles have so far been less dramatic than those from gasoline-powered vehicles. This has focused attention on the role of diesel exhaust as an important source of air pollutants, including both volatile and particulate POM, especially in metropolitan areas (SCAQMD, 2000). Stationary sources using diesel engines are also significant sources in some areas. Additional efforts to address this issue include the replacement of diesel powered heavy and medium-duty vehicles with clean-fuel alternatives (such as those using methanol or compressed natural gas), and the use of particle traps and other pollution reduction technologies on new and existing diesel engines. However, the impact of these changes has so far been limited.

Stationary Sources

The primary stationary sources that have reported emissions of benzo[*a*]pyrene or other PAHs in California are paper mills, manufacturers of miscellaneous wood products, industrial machinery manufacturers, petroleum refining and the wholesale trade in petroleum and petroleum products (ARB, 1997). Estimated total emissions of PAHs from stationary sources in California are about 370,000 pounds per year, based on data reported under the Air Toxics "Hot Spots" Program (AB 2588). Table 1 lists the emissions of some individual PAHs. In addition there are approximately 2,600 pounds of unspecified POM and 250,000 pounds of unspecified PAHs reported as emissions from Hot Spots facilities. (ARB, 1997).

Table 1: California Emissions for Individual PAHs

Compound	Emissions (pounds/year)
Acenaphthene	6
Acenaphthylene	27
Anthracene	285
Benzo[*a*]pyrene*	304
Benz[*a*]anthracene*	175
Benzo[*b*]fluoranthene*	175
Benzo[*k*]fluoranthene*	181
Benzo[*g,h,i*]perylene	10
Chrysene*	275
Dibenz[*a,h*]anthracene*	211
Dibenz[*a,e*]pyrene*	3
Fluoranthene	23
Fluorene	32
Indeno[1,2,3-*cd*]pyrene*	204
Naphthalene	360,000
Phenanthrene	63
Pyrene	42

(Data from ARB, 1997)

* Chemicals for which PEFs are available (OEHHA, 1993)

OEHHA reviews risk assessments submitted under the Air Toxics "Hot Spots" Program (AB 2588). Of the risk assessments reviewed as of April 1996, PAHs were a major contributor to the overall cancer risk in 43 of the approximately 550 risk assessments reporting a total cancer risk equal to or greater than 1 in 1 million, and contributed to the total cancer risk in 166 of these risk assessments. PAHs also were the major contributor to overall cancer risk in 8 of the approximately 130 risk assessments reporting a total cancer risk equal to or greater than 10 in 1 million, and contributed to the total cancer risk in 54 of these risk assessments (OEHHA, 1996).

Ambient Concentrations

California Air Resources Board's air toxics network monitors several PAHs routinely. Table 2 gives the network's mean concentration of various PAHs from January 1996 through December 1996 (ARB, 1998). The population-weighted annual ambient concentration of benzo[*a*]pyrene in California was estimated as 0.53 ng/m^3 based on 1988 to 1989 monitoring data (ARB, 1997). There are no Air Resources Board ambient measurements of naphthalene. However, Atkinson (1995) measured 12 hour average ambient concentrations of naphthalene in Redlands, California in October 1994. The levels observed ranged from 348 to 715 ng/m^3. The overall mean concentration for POM from several study areas throughout the United States during 1984-91 was 8.4 ng/m^3 (U.S. EPA, 1993).

Table 2: California Ambient Concentrations of PAHs

PAH Compound	Mean Concentration (ng/m^3)
Benzo[*a*]pyrene	0.194
Benzo[*b*]fluoranthene	0.245
Benzo[*g,h,i*]perylene	0.619
Benzo[*k*]fluoranthene	0.100
Dibenz[*a,h*]anthracene	0.031
Indeno[1,2,3-*cd*]pyrene	0.327

(Data from ARB, 1997)

Indoor Air

Benzo[*a*]pyrene and other POM components are significant as indoor air pollutants. According to two large field studies conducted in California, the major sources of indoor PAHs are tobacco smoking, wood burning in fireplaces and wood stoves, and infiltration of polluted outdoor air (ARB, 1992; Sheldon *et al.*, 1993). The largest field study was conducted in northern California, in which 13 PAHs were measured inside 280 homes during the winter. Concurrent outdoor samples were collected at each home for 24 hours. The homes were selected based upon the occupants' use of tobacco, fireplaces, wood stoves, and gas heat. Table 3 lists the average indoor concentrations for some PAHs for each type of combustion source.

Average indoor PAH levels ranged from about one-fourth to 6 times the average of outdoor levels. When compared to concentrations inside homes with no obvious combustion sources ("no source"), substantially higher concentrations of all 13 PAHs were measured inside homes where smoking occurred. In addition, wood burning in fireplaces and wood stoves appeared to cause slight to moderate increases in indoor concentrations of benzo[*a*]anthracene, chrysene, benzofluoranthenes, and benzo[*a*]pyrene. Investigators estimated that infiltration of polluted outdoor air was also a major contributor to indoor concentrations of PAHs, particularly outdoor air polluted by wood smoke (Sheldon *et al.*, 1993).

Table 3: Average PAH Concentrations in Northern California Homes (ng/m^3)

PAH Compound(s)	Smoking	Fireplace	Woodstove	Gas Heat	No Source
Benzo[*a*]pyrene	2.2	1.0	1.2	0.41	0.83
Benzo[*e*]pyrene	1.1	0.49	0.55	0.25	0.42
Indeno[1,2,3-*cd*]pyrene	2.8	1.7	1.9	0.92	1.4
Benzo[*ghi*]perylene	2.0	1.4	1.5	0.78	1.3
Pyrene	4.1	2.0	2.5	1.6	1.8
Chrysene	2.0	0.56	0.61	0.24	0.4
Fluoranthene	4.5	1.9	2.3	1.4	1.6
Benzo[*a*]anthracene	1.3	0.43	0.55	0.17	0.32
Benzofluoranthenes	3.7	1.6	2.0	0.81	1.5

(Data from Sheldon et al., 1993)

Another field study measured 12 PAH compounds inside 125 southern California homes during a relatively warm fall season. At each home, two consecutive 12-hour samples were collected. Concurrent samples were also collected outside 65 of those homes. Average indoor PAH concentrations ranged from about one-half to two times the corresponding outdoor levels. Table 4 shows average concentrations (combined daytime/nighttime) for some PAHs. Levels of most PAHs were significantly higher in homes where smoking occurred than in nonsmokers' homes. As in the northern California study, investigators estimated that infiltration of polluted outdoor air was a major source of PAHs indoors (ARB, 1992).

Table 4: Average PAH Concentrations in Southern California Homes (ng/m^3)

PAH Compound(s)	Indoor Average	Outdoor Average
Benzo[*a*]pyrene	0.70	0.30
Benzo[*e*]pyrene	0.39	0.28
Indeno[ghi]perylene	1.1	0.51
Benzo[ghi]perylene	2.4	1.0
Pyrene	2.8	2.2
Chrysene	0.30	0.39
Fluoranthene	2.2	2.5
Benzo[*a*]anthracene	0.16	0.18

(Data from ARB, 1992)

Exposures to Children

There is evidence that children are more heavily exposed to PAHs than adults (on a body-weight adjusted basis), and thus may suffer disproportionately from their impact, whether or not they are more susceptible to PAH toxicity. This is a result of the body size and activity patterns of children, higher breathing rates (on a body weight adjusted basis, especially for infants), and their propensity for greater dust and soil contact than adults. In particular, children in low-income families may have high exposures to PAHs. Such exposures could result from household proximity to heavy traffic or industrial sources, environmental tobacco smoke, contaminated house dust or soil, among others. A series of studies (Chuang *et al.*, 1999) in Durham, NC and adjacent rural areas were conducted to estimate total PAH exposure of children in low-income families, and the relative importance of the environmental pathways for PAH exposure (Table 5).

Table 5: Potential daily dose of carcinogenic (US EPA B2) PAHs (ng/kg b.w./day)

Pathway	Average	S.D.	Minimum	Maximum
Adults				
Inhalation	1.77	3.29	0.12	15.3
Non-diet ingestion	1.28	0.91	0.38	4.24
Diet	16.3	16.7	1.61	60.9
Total	19.4	16.8	4.12	62.0
Children				
Inhalation	3.93	4.88	0.37	19.6
Non-diet ingestion	8.88	6.21	2.62	29.2
Diet	24.8	23.7	1.35	97.0
Total	37.6	23.7	12.2	107

(Data from Chuang et al., 1999)

Higher indoor PAH levels were observed in the smokers' homes compared to nonsmokers' homes. Higher outdoor PAH levels were found in the inner city versus rural areas. Airborne PAHs deposit on soil and household surfaces, thus contributing to PAH exposures from dust (via ingestion, and inhalation of re-suspended dust) and food. The relative concentration trend for PAH in dust and soil was: house dust > entryway dust > pathway soil. The PAH concentrations were generally higher in adults' than in children's food samples. Children's potential daily doses of PAH were higher than those of adults in the same household, when intakes were normalized to body weights. Inhalation is an important pathway for children's exposure to total PAH because of the high levels of naphthalene present in both indoor and outdoor air. Ingestion pathways became more important for children's exposure to the subset of PAHs ranked as B2 (probable human carcinogens) by the U.S. EPA (see Section V.C.), most of which are of low volatility. These PAHs are included in our proposed listing. The analysis of variance results showed that inner city participants had higher total exposure to B2 PAHs than did rural participants.

Such differences between children and adults may be even more noticeable in highly contaminated environments. A monitoring program (Ptashekas *et al.*, 1996) which included benzo[*a*]pyrene was carried out in two Lithuanian cities, Vilnius, the capital of the country, and Siauliai during 1991 to 1995. Higher amounts of benzo[*a*]pyrene were found in the urine of children compared to adults, in both the control and high-risk zones. Both this and the previous study indicate that environmental PAH exposures of children result in higher body burdens than for adults in the same environments.

Crawford *et al.* (1994) examined biomarkers of environmental tobacco smoke in preschool children and their mothers. There were increases in the biologically effective dose of the carcinogenic (PAH) components of ETS in children exposed to ETS, as assessed by levels of PAH-albumin adducts. Tang *et al.* (1999) confirmed these findings in further studies of molecular and genetic damage from environmental tobacco smoke in young children, and found not only increases in protein adducts with PAHs and 4-aminobiphenyl, but also of sister-chromatid exchanges in peripheral lymphocytes of Hispanic and African-American children with home exposure to environmental tobacco smoke. Thus children exposed to ETS show increases not only in general tobacco-related biomarkers such as cotinine, but in biomarkers specific for PAHs and in genetic damage.

Airborne PAHs may contribute to exposure of children by non-inhalation routes. For example, breast milk is a route of exposure in infancy. Few studies of PAH occurrence in breast milk have been carried out, but Somogyi and Beck (1993) described a study conducted in the Federal Republic of Germany that found a number of single PAH compounds at concentrations of 5-15 ng/kg milk and, among these, benzo[*a*]pyrene, was detected at a concentration of 6.5 ng/kg. This is consistent with the findings of West and Horton (1976), who observed transfer of polycyclic hydrocarbons from the diet to milk in rats, rabbits, and sheep. Interestingly, this was more extensive in the rat (an omnivore like humans) than in the herbivorous rabbit and sheep. Lavoie *et al.* (1987) also observed transfer of benzo[*a*]pyrene and two tobacco-specific carcinogens into the milk of lactating rats.

Exposures in utero

Exposure of the fetus to airborne PAHs can occur via transplacental transfer from the mother. This contributes to the body burden of PAH and PAH-DNA adducts in the child. A study (Klopov, 1998) of pregnant women in the

Russian Arctic region found substantial maternal exposure to PAHs, and detected PAHs in most samples of cord blood and placenta analyzed. The results support the barrier role of the placenta, because levels of many PAH compounds in cord blood were lower than in maternal blood. Nevertheless, these compounds were passing through the placental barrier, at least partially, with the concentrations of some PAHs (anthracene and benzo[e]pyrene) higher in cord blood than in maternal blood. Autrup *et al.* (1995) and Autrup and Vestergaard (1996) measured the polycyclic aromatic hydrocarbon-albumin adduct level in serum isolated from the mother and the umbilical cord. The median maternal/fetal adduct ratio was approximately 1.3 (maternal blood/umbilical cord blood) and a positive association between the adduct levels in the mother and umbilical cord blood was observed.

These observations are consistent with the observation of PAH compounds and their metabolites in the fetus after maternal exposure in experimental animal studies (Withey *et al.*, 1993, Withey *et al.*, 1992; Kelman and Springer, 1982; Kihlstrom, 1986). Howard *et al.* (1995) showed that 1-nitropyrene was transported both across the placenta and into milk in mice following oral or intraperitoneal dosing. 0.7% of the administered dose crossed the placenta as 1-nitropyrene and/or its metabolites, and accumulated in the fetuses and amniotic fluid, with both C-oxidized and nitro-reduced metabolites being detected.

Everson *et al.* (1986) reported detection of smoking-related covalent DNA adducts in human placenta. Weston *et al.* (1989) isolated PAH-DNA adducts specifically identified as r-7,t-8,t-9,c-10-tetrahydroxy-7,8,9,10-tetrahydroBaP residues from human placenta. Arnould *et al.* (1997) also reported detection of benzo[*a*]pyrene-DNA adducts in human placenta and umbilical cord blood. Determination of tobacco consumption by urinary cotinine established that among smokers, adducts were found in 13 placenta specimens (from 10 to 60 fmol/50 μg DNA) and 12 umbilical cord blood samples (from 10 to 22.15 fmol/50 μg DNA). Thus a mother's tobacco consumption is linked to the accumulation of benzo[*a*]pyrene-DNA adducts in the placenta and cord blood. These adducts are seen in smaller quantities in the umbilical cord blood, probably because of the metabolic capacity of the placenta which impacts transfer of benzo[*a*]pyrene from the mother to the fetus.

Zenzes *et al.* (1999) investigated whether benzo[*a*]pyrene diol epoxide-DNA adducts are detectable in pre-implantation embryos, and studied their relationship to parental smoking. Seventeen couples were classified by their smoking habits: (i) both smokers; (ii) wife non-smoker, husband smoker; and (iii) both non-smokers. Their 27 embryos were exposed to a monoclonal antibody that recognizes benzo[*a*]pyrene diol epoxide-DNA adducts. The proportion of stained blastomeres was higher for embryos of smokers than for non-smokers (0.723 versus 0.310). The mean intensity score was also higher for embryos of smokers (1.40±0.28) than for non-smokers (0.38±0.14; $P = 0.015$), but was similar for both types of smoking couples. The mean intensity score was positively correlated with the number of cigarettes smoked by fathers ($P = 0.02$). Increased mean immunostaining in embryos from smokers, relative to non-smokers, indicated a relationship with parental smoking. The similar levels of immunostaining in embryos from both types of smoking couples suggest that transmission of modified DNA is mainly through spermatozoa. Paternal transmission of modified DNA was confirmed by detection of benzo[*a*]pyrene diol epoxide-DNA adducts in spermatozoa of a smoker father and his embryo.

The results of Whyatt *et al.* (1998) indicate that PAH-induced DNA damage in mothers and newborns is increased by ambient air pollution. These investigators measured PAH-DNA adducts in maternal and umbilical white blood cells of 70 mothers and newborns from Krakow, Poland. The modulation of DNA adduct levels by genotypes previously linked to risk of lung cancer was also investigated. There was a dose-related increase in maternal and newborn adduct levels with ambient air pollution at the women's place of residence among subjects who were not employed away from home ($p \leq 0.05$). Maternal smoking (active and passive) significantly increased maternal ($p<0.01$), but not newborn adduct levels. Neither the CYPIAI MspI nor the GSTM1 polymorphism was associated with maternal adducts. However, adducts were significantly higher in newborns heterozygous or homozygous for the CYP1A1 MspI RFLP compared to newborns without the RFLP ($p=0.04$). In the fetus, DNA damage appears to be enhanced by the CYP1A1 MspI polymorphism. A novel feature of this study was the measurement of PAH-DNA adduct levels in white blood cells of mother-newborn pairs. Transplacental exposures to PAHs are generally an order of magnitude lower than maternal exposure. The finding that levels of adducts in newborns were similar to those in mothers (in spite of the protective effects of metabolism by maternal and placental enzymes) suggests an enhanced susceptibility to DNA damage in a fetus compared to the mother.

In a separate analysis, Whyatt *et al.* (1998) determined PAH-DNA adduct levels in mother-new born pairs from Limanowa, a rural area outside Krakow where ambient pollution levels are lower but where home use of coal for heating is significantly greater. Among the 67 pairs analyzed, mean adduct levels in the newborns significantly exceeded those in the mothers. This suggests that adduct formation and the resulting DNA damage caused by maternal exposure to PAHs could be amplified in the fetus.

Summary of Key Human Studies

Carcinogenicity

Systematic studies addressing the relative sensitivity of infants and children to carcinogenesis by PAHs were not identified in the scientific literature. However, there is an enormous literature on the carcinogenicity of polycyclic hydrocarbons, and various mixtures containing them that may be encountered in the workplace or the general environment. Indeed, the observations of Pott (1775) on scrotal cancer in chimney sweeps (who were mostly children, and were exposed to soot from coal fires, a rich source of PAHs and other POM) are generally regarded as the first objective account of chemical carcinogenesis in humans.

Developmental Toxicity

Developmental toxicity has been identified as a process having impacts on children's health, as noted in the introductory chapter of this report. PAH effects reported in animals have included obvious anatomical abnormalities (see Section IV.B.b.1), but perhaps because of the less extreme exposures of humans in polluted environments compared to the animal toxicity experiments, these have not been clearly associated with human PAH exposures. However, more subtle changes such as morphometric abnormalities indicative of developmental delay, and intrauterine growth retardation (IUGR) leading to low birth weight infants have been reported both for populations living in polluted environments, and for mothers who smoke or are exposed to secondhand tobacco smoke. Recent studies of these effects are described below. While these exposures involve complex mixtures with many toxic components, the detailed associations shown, the finding of chemical-specific DNA adducts in affected offspring (see Section V.A) and the concordance with animal effects implicate PAHs as important causative toxicants for these effects. Low birth weight and developmental delay are associated with adverse experience of morbidity and mortality in childhood (and also with adverse health impacts later in life), so it is of particular concern that well-documented reports of IUGR in humans exposed to PAH-polluted air have appeared.

Perera *et al.* (1998) studied developmental effects of fetal exposure to PAHs via ambient pollution. The study was carried out in an industrialized area of Poland with relatively high levels of PAH pollution from coal burning. PAH-DNA adducts in leukocytes and plasma cotinine were measured in umbilical cord blood, as dosimeters of transplacental PAH and cigarette smoke, respectively. The study subjects were 70 newborns from the industrialized city of Krakow and 90 newborns from Limanowa, a rural town with far greater use of coal for home heating. Newborns whose levels of PAH-DNA adducts were above the median ($3.85/10^8$ nucleotides) had a significantly decreased birth weight, birth length, and head circumference (Table 6). Cotinine was also significantly inversely associated with birth weight and length.

Table 6: Birth outcomes in Polish Newborns.

	Birth Weight (g)		Birth Length (cm)		Head Circumference (cm)	
Group	**Difference**	**P value**	**Difference**	**P value**	**Difference**	**P value**
Krakow	- 205	0.11	-1.8	0.02 *	-0.9	0.05 *
Limanowa	-129	0.16	-0.8	0.17	-1.2	0.0004 *
All	-147	0.05 *	-1.1	0.02 *	-0.9	0.0005 *

(Data from Perera et al., 1998)

Difference between those with high (above median) and low (below median) leukocyte levels of PAH-DNA adducts.

Dejmek *et al.* (2000) found that exposure to carcinogenic PAHs in air pollution during early pregnancy was associated with an increased adjusted odds ratio for low birth weight ("intrauterine growth retardation" - IUGR). Birth outcomes were studied over a four-year period in two towns in Bohemia (Czech Republic): Teplice (1100 births/yr) and Prachatice (450 births/year). Teplice is located in an industrialized area with surface mining of brown coal, chemical industry and large coal-fired power plants; in this area the level of general air pollution, including both particulate material (PM) and PAHs, is high. Prachatice on the other hand is located in a more rural and mountainous area without major industrial activity, and the general level of pollution (including PM) is much lower in this area. However, there is a single large point source of PAH emissions in the town. At both locations, levels of air pollution by PM and PAHs varied seasonally and over the duration of the study. Air pollution levels were

measured continuously at both locations. Seven specific PAHs identified by IARC as potentially carcinogenic to humans (c-PAHs: chrysene, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, dibenz[*a,h*]anthracene, indeno[1,2,3-*c,d*]pyrene) were measured. These PAHs are identified as carcinogenic in our TAC identification document (OEHHA, 1993).

IUGR was defined as birth weight below the 10th percentile, by sex and gestational week, in the general Czech population. Of 3,349 pregnancies at Teplice, 322 (9.6%) exhibited IUGR. At Prachatice, 124 (8.2%) of 1505 pregnancies were affected. (The study cohorts were limited to full-term pregnancies of mothers of European origin). When births were categorized according to the exposures to PM_{10}, $PM_{2.5}$ and PAH, there was a significant association with exposure to air pollution, specifically to the carcinogenic PAHs. In Teplice the PAH and PM levels are highly correlated so the effects of these two pollutants could not be distinguished at this site alone. However, at Prachatice there is much less particulate pollution relative to the amount of PAH, and by comparing results at both sites it was concluded that the effect was associated with the PAH content of the pollution, not the $PM_{(10 \text{ or } 2.5)}$.

Results relating incidence of IUGR to pollution experienced in the first gestational month are presented in Table 7 as adjusted odds ratios (AOR) for the medium and high exposure categories, relative to the low exposure category. These adjusted odds ratios were calculated using a logistic regression model in which adjustments were applied for the identified confounding variables: parity, maternal age and height, pre-pregnancy weight, education, marital status, month-specific maternal smoking, season, seasonal and long-term conception rate effects, and year of study. The association between exposure to PAH and incidence of IUGR was only significant when exposure during the first month of gestation was considered (AOR for medium exposure = 1.63, 95% CI 0.87 - 3.06, $p < 0.13$; AOR for high exposure = 2.39, 95% CI 1.01 – 5.65, $p < 0.045$). Exposure at other times had no consistent effect, although a possible weak association with exposure during the eighth month was noted in Teplice only. This was interpreted as indicating that the induction of IUGR by PAH exposure resulted from an early developmental effect: this is consistent with other data suggesting that IUGR results from specific impairments of placental development soon after implantation (Zhang et al., 1995). Trends of IUGR vs. PAH exposure during the first month of exposure were highly significant in Teplice; each 10 ng increase in PAH exposure level resulted in an increase in AOR of 1.22 (95% CI 1.07 – 1.39, $p < 0.004$). A similar trend was observed in Prachatice, although it did not achieve statistical significance by this analysis.

The presence of other materials besides POM in air pollution and cigarette smoke makes it difficult to definitively state the impact of PAHs on birth weight and development. However, there was specific correlation of these outcomes with PAH-DNA adducts. There is extensive evidence from other studies showing PAH-DNA adducts in humans exposed to air pollution or cigarette smoke; and there are animal studies where developmental delay and low birth weight are seen after exposure to pure PAHs. This evidence makes a causal relationship between low birth weight and developmental changes and exposure to PAHs highly plausible.

Acute Toxicity in Children

Hemolysis has been reported in infants exposed to very high doses of naphthalene (Siegel and Wason, 1986). The effect appears to be caused by the metabolites (1- and 2- naphthol and naphthoquinones), which produce methemoglobinemia. This mode of action implies a potential for differential sensitivity of infants, due to their reduced capacity for methemoglobin reduction compared to adults. However, even in infants the doses required to produce this effect are much greater than could plausibly result from airborne levels of naphthalene; the case reports generally involved absorption by the dermal or oral routes. Zinkharn and Childs (1958) reported examining an infant exhibiting acute hemolytic anemia that was only exposed during gestation. His mother had inhaled and ingested mothballs containing naphthalene during pregnancy (especially during the last trimester). However, it was not possible to provide an estimated infant exposure.

Table 7: Adjusted Odds Ratios of Intrauterine Growth Retardation by c-PAHs and PM_{10} in the first gestational month in Teplice and Prachatice.

Pollutant	Specification	District	Medium [a]		High [a]	
			AOR[b]	95% CI	AOR[b]	95% CI
PM_{10}	—	Teplice	1.44	(1.03–2.02)	2.14	(1.42–3.23)
	—	Prachatice	2.11	(1.03–4.33)	1.09	(0.49–2.46)
c-PAHs	—	Teplice	1.59	(1.06–2.39)	2.15	(1.27–3.63)
	—	Prachatice	1.49	(0.81–2.73)	1.26	(0.60–2.63)
	<7.5 km (n=551) [c]	Prachatice	1.89	(0.56–6.29)	2.44	(0.60–9.83)
	Lower cut-offs [d]	Prachatice	1.63	(0.87–3.06)	2.39	(1.01–5.65)

Data from Dejmek et al. (2000)

a. Cutoffs for PM_{10}: Low= < 40 $\mu g/m^3$, Medium = 40 to < 50 $\mu g/m^3$, and High = ≥50 $\mu g/m^3$.
Cutoffs for Carcinogenic PAHs (c-PAHs): Low = < 15 ng/m^3, Medium = 15 to < 30 ng/m^3, and High = ≥30 ng/m^3.
b. Medium to Low and High to Low, adjusted for parity, maternal age and height, pre-pregnancy weight, education, marital status, month-specific maternal smoking, season, seasonal and long-term conception rate effects, and year of the study.
c. Only mothers living up to 7 km from the monitor station in Prachatice region.
d. c-PAHs: Low = < 2 ng/m^3 ; Medium = 2 to < 20 ng/m^3 ; High = ≥20 ng/m^3 .

B. Summary of Key Animal Studies

Carcinogenicity

The carcinogenicity of PAHs and other POM constituents in animals is well known; the literature, which is very extensive, has been evaluated by IARC (1987, 1989). It is generally considered both on theoretical grounds and as a result of experimental evidence that exposures to carcinogens early in life may result in higher tumor yields. Shorter average times to tumor, and a wider range of sensitive sites, have also been reported following early in life exposures in some experiments. As discussed in the introduction to this report, there is concern that children may suffer adverse health consequences including enhanced rates of cancer from exposure to any carcinogen, due to the increased sensitivity *in utero* and early in life. There is particular concern where specific evidence of enhanced sensitivity at younger ages exists for the specific compound or class of compounds considered.

Although in the standard rodent bioassay protocol exposure begins at the young adult stage, neonatal or young rodents have often been used in carcinogenesis bioassays, including the early carcinogenesis studies by Innes *et al.* (1969). It has generally been supposed that starting exposure at an early age would maximize the sensitivity of the assay, and this has been observed in practice (Vesselinovitch *et al.*, 1979). In some cases, such as the widely used neonatal Strain A mouse lung adenoma assay (Stoner *et al.*, 1984), the combination of neonatal exposure, a highly sensitive strain and selective endpoint definition has been used to produce a result in a matter of weeks. This contrasts with the two years usually required for a bioassay using the standard NTP protocol.

Vesselinovitch *et al.* (1975) studied the carcinogenicity of benzo[*a*]pyrene in two hybrid strains of mice exposed by a single intraperitoneal injection at 1, 15 or 42 days old. Tumors were observed at several sites, and the relationship between tumor incidence and age at exposure varied from site to site. In the case of liver and lung tumors, young mice were more sensitive than older mice, showing both higher tumor incidence and shorter time before appearance of tumors. Incidence of tumors was generally higher for liver and lung tumors than for other sites.

The strains used were C57BL/6J x C3HeB/FeJ F_1 ("$B6C3F_1$") and C3HeB/FeJ x A/J F_1 ("$C3AF_1$"); treated group sizes varied from 30 to 62 animals whereas control groups contained 98 to 100 animals. Doses of 75 or 150 µg benzo[*a*]pyrene were dissolved in trioctanoin. Control animals had low mortality; controls included two groups, in one of which survivors were necropsied at age 90 weeks and in the other survivors were necropsied at age 142 weeks. Incidences of all tumors in controls were low, except for lung tumors in the $C3AF_1$ mice (Males: 49/97 at

Table 8. For liver tumors in both strains, the incidence was greater, and the average age of tumor appearance was lower, in animals treated at 1 day than at 15 days. This trend continued when comparing those treated at 42 days. The authors judged these differences to be significant ($P < 0.01$) using the χ^2 test for incidence comparisons and Student's t-test for comparing averages at which tumors were detected at autopsy. Similar trends were observed for lung tumors, although the high background incidence of this tumor in the $C3AF_1$ mice reduced the extent and statistical significance of the differences.

Lavoie *et al.* (1994) examined the tumorigenic activity of fluoranthene, 2-methylfluoranthene and 3-methylfluoranthene in newborn CD-1 mice. All three compounds were assayed at intraperitoneal doses of 3.46 and 17.3 μmol, given during the course of three injections on days 1, 8 and 15 after birth. Effective group sizes were between 16 and 34 (alive at 1 year: survival was about 50%). The bioassay was terminated when mice were 1 year old. Fluoranthene, a compound of interest as an air pollutant, is inactive as an initiator in the skin-painting assay (with phorbol ester promotion) in the adult mouse, which is often regarded as a particularly sensitive assay for the carcinogenic activity of PAHs. Among the five isomers of methylfluoranthene, only 2-methylfluoranthene (2-MeFA) and 3-methylfluoranthene (3-MeFA) are active as tumor initiators on adult mouse skin. But fluoranthene and 2-MeFA induced lung tumors in both male and female neonatal mice (Table 9).

Table 8: Incidence of lung and liver tumors in mice treated with benzo[*a*]pyrene at various ages

		Liver tumors				Lung tumors					
	Dose:	75mg/kg		150 mg/kg		75mg/kg			150 mg/kg		
Strain/ Sex	Age when dosed [a] (days)	% tumors [b]	Time to tumor [c] (weeks)	% tumors [b]	Time to tumor [c] (weeks)	% tumors [b]	Time to tumor [c] (weeks)	Multi-plicity [d]	% tumors [b]	Time to tumor [c] (weeks)	Multi-plicity [d]
B6C3F$_1$											
Males	1	55	86	81	81	43	103	3	59	84	4
	15	60	93	58	81	25	103	2	36	82	2
	42	13	108	9	87	36	119	2	38	95	2
Females	1	7	129	18	121	49	126	3	62	112	4
	15	7	116	7	90	33	122	2	40	101	3
	42	0		0		26	131	2	17	118	3
C3AF$_1$											
Males	1	34	80	46	69	93	78	6	92	70	8
	15	27	90	23	77	93	87	5	94	75	6
	42	0		3	79	93	91	5	87	85	6
Females	1	2	91	2	70	93	82	7	93	73	7
	15	2	102	2	62	94	98	5	91	79	6
	42	0		0		87	93	5	90	83	6

(Data from Vesselinovitch et al., 1975)

a. Age (in days) at which animals received i.p. injections of BP at the stated dose level, dissolved in trioctanoin.
b. Number of mice bearing liver or lung tumors / effective number exposed, expressed as a percentage.
c. Average age (in weeks) at which tumors were observed.
d. Average number of grossly visible lung tumors per whole lung.

Table 9: Carcinogenicity of fluoranthenes in neonatal mice.

Compound	Dose	Newborn Mouse			Adult mouse results (skin bioassays)
		Sex	Lung Tumors %	Liver Tumors %	
Fluoranthene	17.3 µmol	F	86***	7	-ve
		M	65**	100***	
	3.46 µmol	F	35*	0	
		M	43*	64***	
2-Methyl Fluoranthene	17.3 µmol	F	69***	31***	+ve
		M	96***	92***	
	3.46 µmol	F	18	3	
		M	16	45*	
3- Methyl Fluoranthene	17.3 µmol	F	21	11*	+ve
		M	19	69***	
	3.46 µmol	F	15	0	
		M	25	33	
DMSO Control	17.3 µmol	F	12	6	
		M	17	17	

(Data from LaVoie et al., 1994)
P: *** < 0.001, ** < 0.005, *< 0.05

Fluoranthene, 2-MeFA and 3-MeFA when administered to newborn mice also induced a significant incidence of liver tumors among male mice, although only 2-MeFA was tumorigenic in the liver of female mice.

The findings in this study are typical of those obtained in neonatal rodent experiments, in that tumors appeared after a relatively short latency, at multiple sites. As in the case of other similar bioassays using the neonatal mouse model, it is notable that a high yield (up to 100% for some compound, site and sex combinations in the high-dose groups of this experiment) is obtained after only three injections early in life, with a very small total dose. While the testing of these compounds in adults is inadequate, the limited data available suggest that the carcinogenic response in adults is not so strong. In adult bioassays, dosing even with potent carcinogens must usually be continuous or repeated for several months, or else continued doses of promoters applied (as in the case of the skin studies reported for these fluoranthenes), before a statistically significant incidence of tumors is observed. LaVoie et al. (1994) also commented, in comparing the results of this study with those of earlier similar experiments, that although a substantial tumor yield was obtained with studies which were terminated earlier, this experiment showed increased appearance of tumors due to the continuation of the study into mid-life (1 year old). They also noted an apparent increase in the grade of the lesions (carcinomas vs. adenomas) in the longer experiment, which supports the concept that the lesions observed in the adult mice after neonatal exposure are the result of progression of lesions created, but not necessarily evident, in infancy, soon after the exposure.

Another bioassay, reported by Imaida et al. (1995), illustrates a typical experimental design where the bioassay is started with neonatal rodents to maximize the sensitivity and shorten the duration of the experiment. This was performed with 1-nitropyrene, and 1,3-, 1,6- and 1,8-dinitropyrene; except for 1,3-dinitropyrene, these PAH derivatives have established cancer potency equivalency factors (OEHHA 1993; OEHHA, 1999). (In other experiments reported in the same paper, the effects of 4-nitropyrene, and phenolic metabolites of 1-nitropyrene were also described.) Newborn female CD rats received subcutaneous injections of 1-nitropyrene or dinitropyrenes at 8 weekly intervals starting on the day of birth (total dose = 6.3 µmol). Controls received injections of the solvent, dimethyl sulfoxide, only. The rats were killed at 67 weeks. As shown in Table 10, the dinitropyrenes induced malignant fibrous histiocytoma (MFH) at the site of injection. 1,6- and 1,8-dinitropyrene produced 100% incidences of this tumor, and also induced leukemia with incidences of around 20%. 1-nitropyrene induced a 33% incidence of mammary tumors.

Table 10: Induction by 1-NP and dinitropyrenes of MFH, mammary tumors and leukemia in newborn female CD rats by s.c. injection

Compound[a]	Effective no. of rats	No. of rats with MFH (%)	Average MFH induction period (d)	No. of rats with mammary tumors (%)	Average mammary tumor induction period (d)	No. of rats with leukemia (%)	Average survival period (d)
1-NP	49	0	-	16 (33)[b]	441	0	481
1,3-DNP	43	5 (12)[b]	247	9 (21)	472	0	468
1,6-DNP	46	46 (100)[d]	115	5 (11)	150	9 (20)[c]	149
1,8-DNP	37	37 (100)[d]	122	5 (14)	143	8 (22)[c]	164
DMSO	40	0	-	8 (20)	450	0	495[e]

(Data from Imaida et al., 1995)

a The animals received eight s.c. injections with nitropyrenes, at weekly intervals starting on the day of birth (total dose = 6.3 μmol). The rats were killed at 67 weeks.

b $p < 0.05$ as compared to the solvent control.

c $p < 0.005$.

d $p < 0.0001$.

e One animal had a carcinoma of the Zymbal gland.

MFH = malignant fibrous histiocytoma NP = nitropyrenes DNP = dinitropyrene DMSO = dimethyl sulfoxide.

In all cases the average time to tumor was short compared to a standard two-year bioassay, in which tumors are usually observed mostly towards the end of the experiment. This was particularly notable for 1,6- and 1,8-dinitropyrene, where the average time to tumor for both the MFH and the leukemia was between 100 and 150 days. (The leukemias were either fatal or, if incidental, observed at necropsy, so the average survival time is taken as time to tumor in this case.) Wislocki et al. (1986) obtained similar results with regard to induction of lung tumors in neonatal mice for a number of nitroaromatics, including nitropyrenes. The total doses used were somewhat lower, but smaller incidences of tumors were observed. Also, the neonatal mouse lung adenoma bioassay is generally considered to be an even more sensitive test system than the neonatal rats used by Imaida et al. (1995). The experiments by Wislocki et al. (1986) were used by OEHHA (1993) in calculating potency equivalence factors for some nitropyrenes.

Since these PAH derivatives induce leukemia, a cancer to which children are known to be particularly susceptible, there may be further cause for anticipating a differential impact of these pollutants on children, although it is not known how, or if, these agents may interact with other causes of childhood leukemia. The possible differential impact of leukemogenic agents on infants and children is discussed in the introductory section of this report.

Developmental Toxicity

Teratogenesis

As noted in the discussion of developmental toxicity in the introduction to this report, the induction of either anatomical or functional terata is considered an effect having an adverse effect on the health of infants and children. Similarly, where such effects are noted in animal experiments, this is supporting evidence of the potential for impacts on the health of infants and children. Postnatal mortality is clearly an effect within these terms of reference, but fetal mortality (usually identified as resorptions in animal experiments) is not. However, the occurrence of pre-natal mortality should be noted as an indicator of fetotoxicity, since many fetotoxins (including PAHs, as described below) produce a spectrum of effects. These include anatomical and functional teratogenesis, prenatal mortality, perinatal mortality (stillbirth), postnatal mortality, growth retardation and developmental delay. The combination of these outcomes observed in a particular experiment may depend on dose level and timing, test species used, and other experimental conditions.

Intraperitoneal benzo[*a*]pyrene, at doses between 50 and 300 mg 1 mg/kg body weight given at day 7 or 10 of gestation, causes *in utero* toxicity and teratogenicity in mice (Shum *et al.*, 1979). A reduction in the number of

surviving offspring (resulting both from resorptions and stillbirths) was observed in all cases. The severity of the effect was correlated with the ability of the fetus and maternal systems to metabolize benzo[*a*]pyrene, which is influenced by induction of aryl hydrocarbon hydroxylase (AHH). Mice (and other mammals) are described as genetically "responsive" when AHH activity is induced by exposure to PAHs and other activators of the *Ah* receptor. A greater impact on pre-and post-natal mortality was observed in C57BL/6 mice which are responsive to AHH induction than in non-responsive AKR inbred mice. Malformations were noted in the responsive mice only; these included club foot, hemangioendothelioma, cleft palate and various other anomalies of the skeleton and soft tissues. Representative results from this study are shown in Table 11.

Table 11: Impact of benzo[*a*]pyrene treatment on fetal and newborn survival and malformations in responsive and non-responsive mice.

Dosed on Gestation Day	Strain	# Litters	# Implant-ations	# Stillborn	# Resorptions	# Malformed	% all effects
7	B6	7	48	2	19	17	79
	AK	6	43	0	9	0	21
10	B6	10	62	0	11	18	47
	AK	11	78	1	8	0	12
12	B6	7	47	1	20	3	51
	AK	5	45	0	6	0	13
Control	B6	31	187	2	33	0	19
	AK	12	107	0	6	0	6.5

(Data from Shum et al., 1979)
B6 = C57BL/6 mice, responsive to AHH induction.
AK = AKR mice, non-responsive to AHH induction.
Dose given was 200 mg/kg benzo[*a*]pyrene i.p

With the use of AKR x (C57BL/6) (AKR)F_1 and (C57BL/6) (AKR)F_1 x AKR backcrosses, it was shown that allelic differences at the *Ah locus* in the fetus could be correlated with dysmorphogenesis. If the mother is non-responsive *(Ah^d/Ah^d)*, the Ah^b/Ah^d genotype in the fetus is associated with more stillborns, and resorptions, decreased fetal weight, increased congenital anomalies, and enhanced P_1-450-mediated covalent binding of BP metabolites to fetal protein and DNA, when compared with the Ah^d/Ah^d genotype in the fetus from the same uterus. If the mother is responsive *(Ah^b/Ah^d)*, however, none of these parameters can be distinguished between Ah^b/Ah^d and Ah^d/Ah^d individuals in the same uterus, presumably because enhanced BP metabolism in maternal tissues and placenta cancels out these differences between individual fetuses.

Other investigators have also shown teratogenesis as a result of exposure *in utero* to PAHs, including mixed materials such as are often encountered as environmental contaminants. Feuston and Mackerer (1996) administered clarified slurry oil (CSO), a refinery stream produced by processing crude oil, to pregnant Sprague-Dawley rats on gestation days [GD] 9-12, via dermal application, at doses of 0, 10, 100, and 1000 mg/kg. Maternal toxicity was evident in the dams exposed to CSO, but clear evidence of developmental toxicity was observed at 1000 mg/kg. The effects seen included increased embryolethality, decreased body weight, and anomalous development (cleft palate, brachydactyly, edema). A low incidence of abnormal fetal development was observed at 100 mg/kg. Three to seven-ring polycyclic aromatic compounds are present in CSO, and the authors considered that these PAHs were responsible for the developmental toxicity.

McKee *et al.* (1987a;b) reported reproductive and subchronic toxicity studies of liquids derived from liquefaction of coal. These materials were of interest as a potential novel route to liquid fuels, but the products contain a number of polycyclic aromatic hydrocarbons, which are concentrated in the high-boiling fractions of the coal-derived liquids. Following treatment of pregnant Sprague-Dawley rats with 0.02, 0.1, 0.5 or 1 g/kg of coal-derived fuel oil or recycle solvent, significant fetal growth retardation was observed, as well as the induction of a small number of diverse skeletal and visceral terata. Results of an experiment with "EDS recycle solvent", a PAH-containing fraction from the coal liquefaction process, are shown in Table 12; significant reductions in number, crown-rump length and weight of fetuses were observed at 0.5 and 1.0 g/kg.

Table 12: Fetal measurements following exposure *in utero* to EDS recycle solvent

Measurement[a]	Dosage group			
	Control	Low (0.1 g/kg)	Mid (0.5 g/kg)	High (1.0 g/kg)
Number of male fetuses / litter	5.96 ± 2.05 (49)	5.79 ± 1.69 (24)	3.96* ± 2.37 (25)	0.13** ± 0.46 (23)
Number of female fetuses / litter	5.61 ± 2.06 (49)	5.67 ± 1.52 (24)	3.64* ± 2.23 (25)	0.35** ± 0.57 (23)
Crown-rump length: male fetuses (mm)	3.60 ± 0.16 (292)	3.58 ±0.15 (139)	3.37*** ± 0.17 (99)	3.06*** ± 0.28 (3)
Crown-rump length: female fetuses (mm)	3.52 ± 0.18 (275)	3.48 ± 0.19 (136)	3.27*** ± 0.20 (91)	3.07*** ± 0.19 (8)
Weight of male fetuses (g)	4.23 ± 0.32 (288)[b]	4.22 ± 0.30 (139)	3.82*** ± 0.41 (99)	2.79*** ± 0.45 (3)
Weight of female fetuses (g)	4.07 ± 0.33 (273)	3.96 ± 0.38 (136)	3.47*** ± 0.38 (91)	3.07*** ± 0.35 (8)

(Data from McKee et al., 1987)

a Results expressed as the group mean ± S.D. (n)

b There were 6 fetuses in 1 litter which were measured, but not weighed.

* $p < 0.05$ by ANOVA.

** $p < 0.01$ by ANOVA.

*** Significantly different from controls ($P < 0.05$) by standard nested analysis of variance.

Developmental reproductive toxicity

Infertility was observed in CD-1 mice after exposure *in utero* to benzo[*a*]pyrene (Mackenzie and Angevine, 1981). Groups of 30 or 60 pregnant female mice were given doses of 10, 40 or 160 mg/kg/day benzo[*a*]pyrene in 0.2 ml corn oil on days 7 through 16 of gestation; controls received corn oil only. There was no maternal toxicity or embryolethality at any dose level, although pregnancy maintenance was impaired at 160 mg/kg/day. Mean pup weight was reduced in the litters of all treated dams, with the effect becoming more noticeable with age. As adults, offspring which were exposed to benzo[*a*]pyrene *in utero* showed loss of fertility in controlled breeding studies with untreated partners: at the higher doses this included complete infertility, and histological abnormalities of the gonads. Treated pup weights, and results of the breeding studies with the F_1 mice are shown in Table 13.

Table 13: Pup weight and reproductive performance of male and female F1 mice exposed prenatally to benzo[*a*]pyrene

	Benzo[*a*]pyrene (mg/kg/day)[a]			
	0	**10**	**40**	**160**
Treated Pup Weight				
Mean pup weight at 4 days (g)	2.7 ± 0.02	2.8 ± 0.04	2.5 ± 0.02	2.2 ± 0.04
Mean pup weight at 20 days (g)	11.2 ± 0.1	11.6 ± 0.1	10.4 ± 0.1**	9.7 ± 0.2**
Mean pup weight at 42 days (g)	29.9 ± 0.2	28.2 ± 0.3**	28.0 ± 0.2**	26.8 ± 0.4**
F_1 Male breeding study				
Number of F_1 males tested[b]	45	25	45	20
Fertility index[c]	80.4	52.0*	4.7**	0.0**
Mean litter size	11.0 ± 0.1[d]	10.7 ± 0.2	10.8 ± 0.6	-
F_1 Female breeding study				
Number of F_1 females tested[e]	35	35	55	20
Fertility index	100.0	65.7**	0.0**	0.0**
Mean litter size	12.9 ± 0.2	10.4 ± 0.4**	-	-

(Data from MacKenzie and Angevine, 1981)

a Mice were exposed prenatally to benzo[a]pyrene on days 7 through 16 of gestation.

b Beginning at 7 weeks of age, each F_1 male was exposed to 10 untreated females over a period of 25 days.

c Fertility index: Females pregnant/females exposed to males x 100.

d Mean ± SEM.

e Beginning at 6 weeks of age, each F_1 female was cohabitated continuously with an untreated male for 6 months.

* Significantly different from controls ($P<0.05$).

** Significantly different from controls ($P<0.01$).

Thus, *in utero* exposure to benzo[*a*]pyrene interfered with the development of the reproductive organs. The severity of the effects seen in this experiment are notable: males exposed to 40 mg/kg benzo[*a*]pyrene showed severely atrophied and essentially aspermic seminiferous tubules. Exposed females showed hypoplastic ovaries with very few follicles or corpora lutea; most of the animals exposed to the higher doses had no identifiable ovaries or only remnants of ovarian tissue. The endocrine effects of such changes are likely to be substantial throughout postnatal growth and development as well as in the adult. The observation in this experiment of low pup weight as a trend of marginal significance immediately after birth, but becoming more noticeable and statically significant in older (20 or 42 day old) pups may be indicative of endocrine effects.

Similar reductions in fertility of female NMRI mice were observed by Kristensen *et al.* (1995) after exposure *in utero* to 10 mg/kg/day oral benzo[*a*]pyrene on days 7-16 of pregnancy.

Developmental Immunotoxicity

As discussed in the introductory section of this report, the immune system is an important potential target for impacts on children's health. This is not only because of the prevalence of infections in children (e.g. otitis media, respiratory infections etc.) but because the immune system is far from mature in the neonate, and undergoes important structural and functional changes during infancy and childhood. In view of this continuing postnatal development phase it is very likely that there would be enhanced sensitivity to exposures to toxicants during infancy, and greater severity of the response, similar to the effects reported in this section.

Urso and Gengozian (1982), Urso and Johnson (1988) and Urso *et al.* (1992) reported a series of experiments in mice which demonstrated that a single exposure to benzo[*a*]pyrene during pregnancy results in immunosuppression in the offspring which is noticeable not only in the neonates but also later in life, and also changes in the maternal

immune system which may impact the maintenance of pregnancy and the subsequent immunological status of the offspring. (They suggested that the effects in the offspring might be related to the later development of tumors at a large number of sites in these mice.) The immune responses were measured as the degree of anti-sheep erythrocyte plaque-forming response, mixed lymphocyte response of cultured lymphocytes, and measures of T-cell function. A typical experiment reported by Urso *et al.* (1992), in which mice were treated at mid-pregnancy with a single intraperitoneal injection of 150 mg/kg benzo[*a*]pyrene, is shown in Table 14.

Table 14: Progeny and maternal mixed lymphocyte response

	MLR expressed as % controls*			
	Progeny		Maternal	
Time after treatment	**Spleen**	**Thymus**	**Spleen**	**Thymus**
17 days gestation (G)		95	50	47
19 days G		105	51	15
1 day postnatal (P)		61		
3 days P		60		14
7 days P	55	26	40	8
4 weeks P	13			
20 weeks P	44			
53 weeks P	60			
104 weeks P	43			

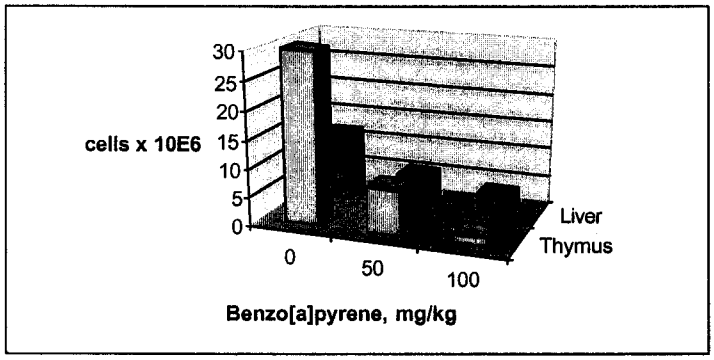
Data from Urso et al. (1992)

* MLR, mixed lymphocyte response by responder cells cultured for 4 days with allogeneic stimulator cells (mitomycin C inactivated) after a [^{3}H]-thymidine pulse. Each value represents 6-10 determinations; fetal thymus value is a pool of tissue from fetuses (3-6) of one mother. Values above 95%, not significant; all others significant at $P < 0.05$ to $P < 0.0001$ (Student's t-test).

The maturation of the immune system involves a process of growth, differentiation and selection of various classes of lymphocyte, and also movement from initial locations in the fetal liver and thymus to the bone marrow and peripheral lymphoid tissues. The differentiation and selection processes result in different functional classes of T cells whose interactions are essential in establishing the characteristics of the adult immune system such as self-tolerance, recognition of foreign antigens and appropriate balance of humoral and cell-mediated responses. Disruption of these developmental processes can have diverse and deleterious effects, including autoimmune disease, atopy and immunosuppression.

Holladay and Smith (1994) demonstrated severe depletion of both thymus and liver cell of B6C3F$_1$ mice exposed to benzo[*a*]pyrene (maternal dose 50, 100 or 150 mg/kg/day) on days 13-17 of gestation. Numbers of thymocytes and fetal liver cells (obtained by mechanical disruption, resuspension and washing in lysing solution to remove erythrocytes) determined by Coulter counter are shown in Figure 1.

Figure 1: Fetal thymus and liver cellularity in B6C3F$_1$ mice exposed to benzo[*a*]pyrene *in utero*



(Data from Holladay and Smith, 1994.)

Differences in the proportions of various classes of surface antigens (CD4, CD8 and HSA) were also noted in perinatally isolated thymocytes. The authors concluded that the changes were suggestive of impaired maturation in the surviving thymocytes, and that these and other changes observed were consistent with the long-term immunosuppression seen in mice exposed to benzo[*a*]pyrene *in utero*. Similar effects of benzo[*a*]pyrene on development of T-cells, with long-term consequences for development of the immune system, have been reported by others, including Rodriguez *et al.* (1999).

Pulmonary Toxicity (naphthalene)

Naphthalene is a quantitatively important member of the PAH class, and shares a number of toxic effects (including carcinogenicity, as recently reported by NTP [2000]) with PAHs of greater molecular size and complexity. Naphthalene causes damage to both ciliated and Clara cells of the bronchiolar epithelium in mice (Van Winkle et al., 1995; Plopper, 1992a,b). Neonatal mice were more sensitive to this damage than adult mice (Fanucchi et al, 1997). Swiss Webster Mice at post-natal day (PND) 7 or 14, or adults, received 25, 50 or 100 mg/kg naphthalene by intraperitoneal injection, and the lungs were prepared for histological examination. Both observational and morphometric evaluation showed dose-dependent damage to the bronchiolar epithelium. There was loss of both ciliated and non-ciliated (Clara) cells, as indicated by changes in total epithelial thickness and in volume fractions of the various cell types, and appearance of vacuolated (injured) cells. Effects were similar in adults and young mice, but whereas the adult mice showed a LOAEL of 100 mg/kg for most effects, the 7 and 14-day old mice showed LOAELs of 25-50 mg/kg. Although the doses in this experiment were given intraperitoneally, the effects appear to depend on metabolism of naphthalene in the target tissues and are therefore anticipated to occur regardless of the dose route. Mice, which have high cytochrome P-450 activity in the bronchiolar epithelium, are more sensitive to naphthalene than rats or hamsters where this activity is lower (Plopper et al 1992b). These data indicate that infants and children may be more susceptible to the effects of naphthalene than adults.

Additional Information

Metabolism of PAHs and formation of PAH adducts

We assume that the majority of the toxic end points described in this summary, in both animals and humans, are the result of the generation of reactive intermediates by metabolism, followed by reactions of these intermediates with sensitive sites in the cell, particularly DNA, as has been observed for benzo[*a*]pyrene and other PAHs in both adult and fetal tissues (Kleihues *et al.*, 1980; Shugart and Matsunami, 1985; Bolognesi *et al.*, 1985). Unless repaired, the adducts give rise to mutations, followed by cytotoxicity and/or cancer. Teratogenicity also apparently involves reactive intermediate toxicity (Wells and Winn, 1996). Some PAH metabolites, such as quinones, are highly reactive in redox reactions, and thus some additional mechanisms may include the action of reactive oxygen species with cellular components rather than direct reactions with PAH metabolites.

In the metabolism, and ultimately carcinogenicity, of PAHs, both Phase I (activation) enzymes and Phase II (detoxification and conjugation) enzymes are important. Enzymes of both phases are inducible by PAHs and by other related compounds. Both the structural genes determining the stability and activity of the enzymes, and the regulatory genes controlling the induction of the enzymes, are subject to important polymorphisms in both humans and animals. Thus determination of the metabolic capabilities present in the fetus and young animal helps to identify situations where these life stages might be more susceptible to the toxicity of PAHs.

Phase I metabolism of low-molecular-weight chemicals appears only near term in the rodent, and is poorly inducible transplacentally (Anderson *et al.*, 1989); such agents are relatively ineffective as fetal carcinogens. Phase I metabolism of aromatic carcinogens (including PAHs) appears early in gestation and is highly inducible transplacentally in rodents by PAHs, resulting in dramatic proportional increases in enzyme activity. Phase II enzymes convert the Phase I metabolites of PAHs or other aromatic compounds to water-soluble forms, and, compared with Phase I enzymes, generally have higher constitutive activity, but a lower degree of inducibility in the fetus. In the mouse a single dominant gene, Ah, confers responsiveness to induction of PAH metabolism by cytochrome P-4501A1; the recessive allele is associated with non-responsiveness. Transplacental exposure to 3-methylcholanthrene also had a permanent imprinting effect, increasing the capacity of the livers to metabolize PAHs as adults 13 months after exposure.

The potential for differential effects is clearly presented by the existence of a highly inducible cytochrome P-4501A1 capable of PAH metabolism in the fetus and at subsequent developmental stages, coupled with a less inducible Phase II system following a different developmental timetable. Cresteil *et al.* (1986) examined cytochrome P-450 isoenzyme content in fetal and postnatal rat liver. In the untreated rat fetus, cytochrome P-450 was easily quantified spectrally, but no isoenzyme could be detected immunochemically. After birth, each isoenzyme develops independently in untreated animals. β-naphthoflavone and benzo[*a*]pyrene hydroxylase activities were significantly increased by 3-methylcholanthrene at any age, whereas the induction of the isosafrole isoenzyme was effective only after 2 weeks of age. Similarly, pretreatment with phenobarbital resulted in the induction of the phenobarbital-B and pregnenolone-16α-carbonitrile isoenzymes and their associated mono-oxygenase activities in fetal and neonatal rat liver, but at different times. Thus P-450 isoenzymes develop independently and different mechanisms regulate the temporal expression of P-450 genes. P-450s present in fetal and early neonatal rats are replaced in older animals by immunologically different isoenzymes. Pretreatment with 3-methylcholanthrene or phenobarbital induces identical isoenzymes in fetal, neonatal and adult rat livers *in vivo*. In addition, 3-methylcholanthrene and phenobarbital are potent inducers of the TCDD-binding protein in the fetal rat liver, where this is a rate-limiting step in induction of cytochrome P-450 (Marie *et al.*, 1988). These reports present a complex picture for the Phase I activities of interest for PAH metabolism.

Neubert and Tapken (1988) found that three oral doses of 17.5 mg benzo[*a*]pyrene /kg body wt just significantly induce benzo[*a*]pyrene hydroxylase in maternal liver. In contrast, induction of benzo[*a*]pyrene hydroxylase was demonstrable in 9-12 day old embryos at tissue levels about one tenth those required for induction in maternal liver (0.3 – 1.1 μmol/kg wet weight in whole embryo vs. 5.9 – 1.1 μmol/kg in maternal liver). The benzo[*a*]pyrene tissue concentrations required to induce benzo[*a*]pyrene hydroxylase in fetal liver on day 18 of gestation were about one half of those necessary for induction in maternal liver (1.3 – 3.4 μmol/kg in whole embryo vs. 1.4 – 7 μmol/kg in maternal liver).

The preceding reports (complemented by other related findings, *e.g.* Sunouchi *et al.*, 1984; Lum *et al.*, 1985) show developmental changes in metabolism in the liver. Similar considerations apply to metabolism in other tissues. Benzo[*a*]pyrene induces Phase II enzymes in the developing rodent. Administration of benzo[*a*]pyrene (50 mg/kg/d) to pregnant rats significantly increased glutathione-S-transferase (GST) activity in placental tissue-extract and total fetal tissue-extract (Cervello *et al.*, 1992).

Rouet *et al.* (1984) studied developmental patterns of drug-metabolizing enzymes in the C57Bl/6 mouse brain, lung and liver. These could be divided into three stages: (I) at the end of intrauterine life, where an increase in activity was observed; (II) during the first days after birth, where a decrease was seen; and (III) from the 6th day until weaning, where there was a gradual increase, reaching adult values. Pulmonary benzo[*a*]pyrene hydroxylase activity showed an abrupt burst starting on day 6 of postnatal life, then decreased slowly to become steady, and finally increased again. The major metabolic pathways catalyzed by glutathione-S-transferase and epoxide hydrolase were operative in mouse fetal brain and lung, just as in liver. In addition, enzymatic systems were found to be inducible during fetal life by exogenous compounds such as β-naphthoflavone.

Sindhu *et al.* (1996) found that repeated exposure of both male and female juvenile ferrets to ETS results in an increased production, by lung tissue *in vitro,* of (+)-*anti*-benzo[*a*]pyrene diol epoxide (the ultimate carcinogen) from benzo[*a*]pyrene diol. They also observed increases in DNA binding in the assay.

Dvorchik and Hartman (1982) demonstrated that liver obtained from the fetal stump-tailed monkey (*Macaca arctoides*) is capable of catalyzing the hydroxylation of benzo[*a*]pyrene as early as midterm, and that the apparent K_m is similar to that obtained with human fetal microsomes. The rate of benzo[*a*]pyrene hydroxylation increased almost 100-fold between midterm and 2 weeks after birth.

Metabolism of PAHs in human fetus and placenta.

The liver of the human fetus is an active site for drug metabolism, and multiple P450s are present in fetal liver that can catalyze, albeit with lower activity, the same reactions as in adult human liver. Cresteil *et al.* (1982) measured P450 concentration, related mono-oxygenase activities, epoxide hydrolase, and glutathione-S-transferase activities

in the liver of human fetuses aged from 15 to 38 wk and in adults. Aniline hydroxylase, benzphetamine demethylase, epoxide hydrolase, and glutathione-S-transferase activities reach about half of adult values as early as 15-25 wk of gestation. The metabolism of benzo[*a*]pyrene, ethoxycoumarin, and testosterone in position 6 beta is very low in the non-induced fetus.

The human placenta has metabolizing capabilities for various xenobiotics, including PAH. Blanck *et al.* (1983) demonstrated biotransformation of benzo[*a*]pyrene and 7-ethoxyresorufin in microsomes from human fetal liver and placenta. Pelkonen (1984) reviewed maternal, placental, and fetal xenobiotic metabolism and found evidence for extensive xenobiotic metabolism in both fetus and placenta. There was a very large inter-individual variation in enzyme activities. Manchester *et al.* (1984) found indications of first pass protection of the fetus by placental xenobiotic metabolism. Placental metabolism is generally considered to be protective of the fetus, by converting benzo[*a*]pyrene or other PAHs to deactivated metabolites before they can impact the fetus.

Barnea and Avigdor (1991) found that benzo[*a*]pyrene at 50 μM caused a significant increase in the AHH enzyme activity of first-trimester human placenta explants after an incubation of 6 h. In contrast, 50 μM 3-methylcholanthrene had no effect. Pasanen and Pelkonen (1994) reported that P450 enzymes in human placenta metabolize several xenobiotics, although compared with the liver the spectrum of substrates and metabolic activities is somewhat restricted. Maternal cigarette smoking increases the expression of CYP1A1. This induced activity results in greater activation of benzo[*a*]pyrene and formation of DNA adducts. Marker activities for CYP3A enzymes, the most abundant P450s in adult human liver and active in fetal liver, were not detectable in human placental microsomes.

Maternal smoking is known to induce AHH in the placenta. As one example, Huel *et al.* (1989) examined AHH in human placenta of both active and passive smokers and confirmed that smoking during pregnancy is associated with a marked increase in placental AHH. Placental AHH was related to the number of cigarettes smoked per day. Moreover, AHH was significantly higher in pregnant women passively exposed to tobacco smoke, relative to controls.

Regulatory Background

Polycyclic Organic Matter (POM) is a federal hazardous air pollutant, and this was identified as a toxic air contaminant in April 1993 under AB 2728. OEHHA prepared health risk assessment documents (OEHHA, 1993; 1999) for the California Toxic Air Contaminants program in which benzo[*a*]pyrene and various other PAHs were considered.

The U.S. EPA and IARC have classified benzo[*a*]pyrene as a probable human carcinogen (U.S. EPA, 1994; IARC, 1987). IARC (1987; 1989; 1996) has also identified a number of other specific PAHs as probable or possible human carcinogens (Table 15). The State of California has determined under Proposition 65 that several POM compounds (including benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, chrysene, indeno[1,2,3-*cd*]pyrene, 3,7-dinitrofluoranthene, and 3,9-dinitrofluoranthene) are carcinogens (California Code of Regulations (CCR), 1997).

An inhalation potency for benzo[*a*]pyrene was developed for the California Toxic Air Contaminants program (OEHHA, 1993) using a linearized multistage model applied to respiratory tract tumor incidence data from an inhalation bioassay in male hamsters (Thyssen *et al.*, 1981). The cancer potency factor calculated was 3.9 $(mg/kg\text{-}day)^{-1}$, corresponding to a unit risk of 1.1×10^{-3} $(\mu g/m^3)^{-1}$. An oral potency factor of 12 $(mg/kg\ day)^{-1}$ for benzo[*a*]pyrene was also developed, based on the incidence of gastric tumors (papillomas and squamous cell carcinomas) in male and female mice (Neal and Rigdon, 1967; OEHHA, 1993). A number of PAHs were identified by IARC as carcinogens (Class 2B or above), but data were inadequate to permit calculation of specific inhalation cancer potency factors for these compounds. OEHHA (1993) assessed these, along with chrysene and some nitro-PAHs using a relative potency scheme (Collins *et al.*, 1998) with benzo[*a*]pyrene as a reference compound (Table 16).

In addition to the listing of benzo[*a*]pyrene and other PAHs as a toxic air contaminant, it should be noted that diesel exhaust particulate matter has been listed as a toxic air contaminant, and diesel exhaust is listed as a carcinogen under Proposition 65. Both the volatile and particulate fractions of diesel exhaust contain PAHs and nitro-PAHs, which are considered important, but not exclusive, contributors to the carcinogenicity and other adverse health effects of diesel exhaust.

Table 15: IARC groupings of PAHs, mixtures with PAHs, and derivatives.

Group 1	Group 2A	Group 2B
Coal-tar pitches	Benz[*a*]anthracene	Benzo[*b*]fluoranthene
Coal-tar	Benzo[*a*]pyrene	Benzo[*j*]fluoranthene
Coal gasification	Creosotes	Benzo[*k*]fluoranthene
Coke production	Dibenzo[*a,h*]anthracene	Carbon black extracts
Mineral oils	Diesel engine exhaust	Carbon black
Shale-oils		Dibenz[*a,h*]acridine
Soots		Dibenz[*a,j*]acridine
Tobacco smoke		7H-Dibenzo[*c,g*]carbazole
Smokeless tobacco products		Dibenzo[*a,e*]pyrene
Aluminum production		Dibenzo[*a,h*]pyrene
		Dibenzo[*a,i*]pyrene
		Dibenzo[*a,l*]pyrene
		Indeno[1,2,3-*cd*]pyrene
		5-Methylchrysene
		5-Nitroacenaphthene
		1-Nitropyrene
		4-Nitropyrene
		1,6-Dinitropyrene
		1,8-Dinitropyrene
		6-Nitrochrysene
		2-Nitrofluorene
		3,7-Dinitrofluoranthene
		3,9-Dinitrofluoranthene
		Gasoline engine exhaust

(Data from IARC Supplement 7, 1987, and IARC Volumes 46, 1989 and 65, 1996.)

Group1: carcinogenic to humans.

Group 2A: probably carcinogenic to humans.

Group 2B: possibly carcinogenic to humans.

Table 16: OEHHA Potency Equivalency Factors (PEF)

PAH or Derivative	CAS Number	Suggested PEF
benzo[*a*]pyrene	50-32-8	1.0 (Index compound)
benz[*a*]anthracene	56-55-3	0.1
benzo[*b*]fluoranthene	205-99-2	0.1
benzo[*j*]fluoranthene	205-82-3	0.1
benzo[*k*]fluoranthene	207-08-9	0.1
dibenz[*a,j*]acridine	224-42-0	0.1
dibenz[*a,h*]acridine	226-36-8	0.1
7H-dibenzo[*c,g*]carbazole	194-59-2	1.0
dibenzo[*a,e*]pyrene	192-65-4	1.0
dibenzo[*a,h*]pyrene	189-64-0	10
dibenzo[*a,i*]pyrene	189-55-9	10
dibenzo[*a,l*]pyrene	191-30-0	10
indeno[1,2,3-*cd*]pyrene	193-39-5	0.1
5-methylchrysene	3697-24-3	1.0
1-nitropyrene	5522-43-0	0.1
4-nitropyrene	57835-92-4	0.1
1,6-dinitropyrene	42397-64-8	10
1,8-dinitropyrene	42397-65-9	1.0
6-nitrochrysene	7496-02-8	10
2-nitrofluorene	607-57-8	0.01
Chrysene	218-01-9	0.01
dibenz[*a*,h]anthracene*	53-70-3	1.1
7,12-dimethylbenzanthracene*	57-97-6	65
3-methylcholanthrene*	56-49-5	5.7
5-nitroacenaphthene*	602-87-9	0.034

The nitro-PAHs are those listed as IARC class 2B. Although chrysene is an IARC class 3 carcinogen, the U.S. EPA classifies it as Group B2.

* Inhalation unit risks were calculated independently for these compounds by OEHHA; the PEF shown is the ratio of the calculated unit risks for these compounds to that for benzo[a]pyrene.

Conclusions

This evaluation of POM as a toxic air contaminant causing health effects in infants and children was primarily based on the known health effects of PAHs (which are the major components of POM), and of related specific chemicals that occur as components of POM. Also considered were exposures to air pollutant mixtures from defined sources, of which POM is a known component and where health effects can be at least partly ascribed to this POM component or to specific PAHs identified in the mixture. These mixtures include diesel exhaust, environmental tobacco smoke, and air pollutants emitted by domestic or industrial combustion of solid fuels (coal etc.).

Many PAHs, PAH derivatives and pollutant mixtures containing them have been shown to be carcinogenic in animals and/or humans. There is a general concern that exposure to a carcinogen early in life may have a greater overall impact than a similar exposure to an adult. Additionally, there are experimental data showing that young animals are more sensitive to the carcinogenicity of certain PAHs and PAH derivatives.

Prenatal exposure to PAHs results in serious or irreversible effects in the fetus. Fetal damage sustained as a result of exposure to environmental toxicants is a source of adverse postnatal health impacts. For instance, PAHs are transplacental carcinogens. The mechanisms underlying transplacental carcinogenesis are apparently similar to those for carcinogenesis after postnatal exposure, but the sensitivity and diversity of tumor sites are often greater.

Fetotoxicity and teratogenesis have been observed following animal exposure *in utero* to PAHs or to mixtures containing them. Such exposures to PAHs, or to mixtures containing them, have also been found to result in related adverse effects, such as low birth weight in both humans and rodents. PAH exposures *in utero* have also been found to cause structural and functional disturbances of the immune and hematopoietic systems, and loss of fertility, in the offspring. These occurred at doses causing little or no concurrent maternal toxicity. Some of these effects observed after exposure *in utero* parallel toxic effects in the adult (e.g. immunotoxicity, reproductive toxicity, myelotoxicity), but whereas these effects are reversible in the adult, the effect of fetal exposure is irreversible.

There is greater exposure of children to environmental PAHs compared to adults. Children's daily doses of PAHs (per kg of body weight) were generally higher from all routes of exposure than those of adults in the same household. Biomarkers for direct impacts associated with adverse health outcomes, such as DNA adducts, are increased in children exposed to environmental pollution by PAHs and related POM components.

In view of this range of evidence for differential sensitivity of the fetus, infants and children to health effects induced by POM components such as PAHs, and for greater exposure of children to POM, OEHHA has placed POM in Tier 1 of the priority list.

VII. References

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BENZO[*A*]PYRENE

CAS No: 50-32-8

I. PHYSICAL AND CHEMICAL PROPERTIES (From HSDB, 1998)

Molecular weight	252.3
Boiling point	360° C
Melting point	179° C
Vapor pressure	1 mm Hg at 20° C
Air concentration conversion	1 ppm = 10.3 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor:		1.1 E-3 $(ug/m^3)^{-1}$
Slope Factor:	(inhalation)	3.9 E+0 $(mg/kg\text{-}day)^{-1}$
	(oral)	1.2 E+1 $(mg/kg\text{-}day)^{-1}$

[Inhalation: male hamster respiratory tract tumor incidence (Thyssen *et al.*, 1981), unit risk calculated using a linearized multistage procedure (OEHHA, 1993).
Oral: male and female gastric tumor (papillomas and squamous cell carcinomas) incidence (Neal and Rigdon, 1967), cancer potency factor calculated using a linearized multistage procedure (OEHHA, 1993).]

III. CARCINOGENIC EFFECTS

Human Studies

The predominant sources of airborne benzo[*a*]pyrene (BaP) are combustion processes. Thus, this compound rarely enters the environment alone but rather is associated with additional PAHs and other components frequently present in both vapor phase and particulate form. Available epidemiological information, therefore, is from persons exposed to mixtures such as tobacco smoke, diesel exhaust, air pollutants, synthetic fuels, or other similar materials. Several IARC publications have been dedicated to the analysis of cancer in processes which involve exposure to polynuclear aromatic compounds (PAHs) (IARC, 1983; 1984a; 1984b; 1985; 1987). The types of cancer reported are often consistent with the exposure pathway: scrotal cancer and lung cancer in chimney sweeps exposed to soot; skin cancer (including scrotal cancer) where shale oils are used; and lung cancer where airborne exposure of PAHs occurs, such as in iron and steel foundries.

Shamsuddin and Gan (1988) examined several human tissues collected at surgery or autopsy using rabbit high-specificity antibody to benzo[*a*]pyrene diol epoxide (BPDE)-DNA adducts and light immunocytochemistry. Antigenicity was detected in the lung, ovary, placenta, uterine cervix, and white blood cells. Their results indicated that the tissue concentration of adducts varies substantially in the human population and that BPDE-DNA adducts can be detected in human tissues by immunochemical techniques.

Five of twelve human lung samples obtained at surgery, from smokers or former smokers, showed positive antigenicity for BPDE-DNA adducts (Garner *et al.*, 1988). Higher DNA-adduct levels were detected in the white blood cells of Finnish iron workers with jobs in high PAH exposure areas than in the white blood cells of workers with jobs in low PAH exposure areas (Perera *et al.*, 1988; Hemminki *et al.*, 1990). Workers were classified as high, medium, or low BaP exposure and there was a highly significant correlation between BaP exposure and DNA-adduct levels (Reddy *et al.*, 1991). A similar observation was noted by Ovrebo *et al.* (1992) in a study of workers exposed around coke ovens. Perera *et al.* (1993) extended the technique and found that PAH adducts were higher in an industrialized area in winter than both in a more rural area in winter and in the same urban area in summer (when less burning of fuel would occur).

In studies looking at PAH-derived adducts bound to serum protein, higher levels of PAH-albumin adducts were found in foundry workers and in roofers than in their respective reference groups (Lee *et al.*, 1991). Smokers had higher levels of BaP-derived adducts bound to serum protein than non-smokers, and workers in high BaP exposure areas (foundry) had two to three times the levels of workers in low exposure areas (Sherson *et al.*, 1990).

Studies with human placental tissues have shown that aryl hydrocarbon hydroxylase (AHH) activity is several times higher in smokers than non-smokers and that this activity increases in a sigmoidal manner with increased numbers of cigarettes smoked (Gurtoo *et al.*, 1983). Genetic factors probably contribute to this variability and, ultimately, to susceptibility of individuals to tumor development (Manchester and Jacoby, 1984).

Animal Studies

BaP is carcinogenic by intratracheal, inhalation, and dermal exposure, by intraperitoneal injection, and when given in the diet.

(a) Inhalation and Intratracheal Exposures

Early experiments by Saffiotti *et al.* (1968) indicated that PAHs are at least weakly carcinogenic to the respiratory tract. A mixture of BaP (3 mg) and Fe_2O_3 (hematite, 0.25 μm) (3 mg) in a saline suspension was administered to Syrian golden hamsters by intratracheal instillation, once per week for 15 weeks. Most surviving animals receiving BaP plus Fe_2O_3 developed tumors of the respiratory tract (mostly bronchogenic carcinoma) whereas control animals receiving Fe_2O_3 only or those receiving no treatment did not develop tumors.

Subsequently, Saffiotti *et al.* (1972) determined the carcinogenic dose-response relationship after intratracheal instillation of a suspension of BaP and Fe_2O_3 in male and female Syrian golden hamsters. Test materials were administered once weekly for 30 weeks at 2.0, 1.0, 0.5, and 0.25 mg BaP/animal and an equivalent weight of Fe_2O_3 (hematite) as particulate carrier. Tumors were not present in animals receiving ferric oxide or in untreated controls. Respiratory tract tumors (including squamous cell carcinomas of the larynx, of the trachea, and of the bronchi, adenocarcinomas of the bronchi, and adenomas of the bronchi and of the bronchioles and alveoli) developed in all groups of BaP/Fe_2O_3 treated animals. The response was dose related.

In another experiment, Feron *et al.* (1973) gave male Syrian golden hamsters intratracheal doses of 0, 0.0625, 0.125, 0.5, or 1 mg BaP weekly for 52 weeks. A variety of tumors were produced throughout the respiratory tract, including bronchoalveolar adenomas and carcinomas.

Thyssen *et al.* (1980) conducted an inhalation study in which male Syrian golden hamsters were exposed to BaP condensation aerosol (in 0.1% saline; particle size ranging from 0.2 to 1.5 μm) for 10 to 16 weeks at a concentration of 9.8 to 44.8 mg BaP/m^3. Neoplastic changes in the respiratory tract were not seen.

In a subsequent experiment, Thyssen *et al.* (1981) exposed male Syrian golden hamsters to BaP condensed onto sodium chloride particles at BaP concentrations of 2.2, 9.5, and 46.5 mg BaP/m^3. Tumors were not observed in the respiratory tract of the unexposed control group or the group that received 2.2 mg/m^3. The incidence of tumors in this organ system increased in a dose dependent manner for the 9.5 and 46.5 mg/m^3 exposure groups. Papillomas, papillary polyps, and squamous cell carcinomas were seen in the nasal cavity, larynx, trachea, pharynx, esophagus, and forestomach. Lung tumors were absent.

(b) Feeding Studies

Feeding of pelletized chow containing BaP (50 to 250 ppm BaP for 4 to 6 months) to male and female CFW mice caused gastric tumors (papillomas and squamous cell carcinomas), pulmonary adenomas, and leukemia (Rigdon and Neal, 1966; 1969; Neal and Rigdon, 1967). The pulmonary adenomas, gastric tumors, and leukemia occurred independently of each other (Rigdon and Neal, 1969). The overall data strongly suggest a positive carcinogenic effect since there were no gastric tumors in 289 control mice while 178 out of 454 mice fed various levels of BaP had gastric tumors (Neal and Rigdon, 1967).

(c) Dermal Application

BaP has been shown to be carcinogenic by dermal application (ATSDR, 1990). Wynder and associates demonstrated a positive dose-response relationship for BaP-induction of skin tumors in Swiss and in C57BL mice and showed a tumor response at doses as low as 0.001% BaP applied topically in acetone every 2 weeks for up to 2 years (Wynder and Hoffmann, 1959; Wynder *et al.*, 1957; 1960). In addition, incidences of 95% for papillomas and carcinomas of the skin were obtained by chronic administration (3 times weekly for 1 year) of 0.001% BaP to the skin of Swiss mice (Wynder and Hoffman, 1959). Extensive experiments conducted by Conney and associates demonstrated the tumor initiating activity of BaP and several of its epoxide and hydroxy derivatives (summarized by US EPA, 1979 and by Conney, 1982).

IV. DERIVATION OF CANCER POTENCY

Basis for Cancer Potency

A very large number of experiments have demonstrated that BaP causes tumors at several sites, by several routes of administration, in both sexes, and in several animal species. Many studies, however, are very limited in scope or in data reported and are not suitable for risk assessment (Zeise and Crouch, 1984).

OEHHA guidelines prescribe that risk assessment use the most sensitive sex, site, and species where a significant increase in cancer incidence is observed (CDHS, 1985). Since there is no

adequate information regarding the carcinogenicity of BaP to humans from epidemiological studies, data from animal bioassays were extrapolated to estimate human cancer risk. Potency estimates were derived by OEHHA (1993) from gastric tumors (papillomas and squamous cell carcinomas) observed in male and female mice due to feeding of BaP (Neal and Rigdon, 1967), respiratory tract tumors in hamsters from the inhalation bioassay of Thyssen *et al.* (1981), and from data obtained after intratracheal administration of BaP (Saffiotti *et al.*, 1972; Feron *et al.*, 1973). The dose-response data from these studies are presented in Tables 1-4 below.

Table 1: Gastric tumors in mice from feeding benzo[*a*]pyrene[a].

Exposure (ppm)	Calculated daily dose (mg/kg-day) (animal)	Incidence of gastric tumors
0	0	0/289
1	0.078	0/25
10	0.781	0/24
20	1.563	1/23
30	2.344	0/37
40	3.126	1/40
45	3.516	4/40
50	3.908	24/34
100	7.815	19/23
250	19.538	66/73

[a]Source: OEHHA (1993). Adapted from Neal and Rigdon (1967) and US EPA (1984).

Table 2: Respiratory tract tumors in hamsters from benzo[*a*]pyrene inhalation[a]

Exposure (mg/m^3)	Hamster dose (mg/kg-day)		Tumor incidence
	based on U.S EPA (1994)	based on US EPA (1988)	
0	0	0	0/27
2.2	0.089	0.152	0/27
9.5	0.385	0.655	9/26
46.5			13/25[b]

[a]Source: OEHHA (1993). Adapted from Thyssen *et al.* (1981) and US EPA (1984)
[b]These data were not used due to shortened lifespan of the hamsters in the exposure group. The carcinogenic response, however, is apparent.

Table 3: Respiratory tract tumors from intratracheal instillation of benzo[*a*]pyrene in hamsters – 30 week exposure[a].

Weekly Dose (mg)	Average Daily Dose (mg)	Lifetime Adjusted Daily Dose (mg/kg-day)	Human Equivalent Dose (mg/kg-day)	Tumor Incidence (Males)	Tumor Incidence (Females)
0	0	0	0	0/47	0/45
0.25	0.036	0.119	0.013	6/47	4/41
0.5	0.071	0.239	0.027	10/33	9/30
1.0	0.143	0.477	0.054	22/33	20/34
2.0	0.286	0.953	0.107	17/28	17/29[b]

[a]Source: OEHHA (1993). Adapted from Saffiotti *et al.*, 1972.
[b]Data group was not used since exposure started 7 weeks after other groups.

Table 4: Bronchoalveolar tumors from intratracheal instillation of benzo[*a*]pyrene in hamsters – 52 week exposure[a].

Weekly dose (mg)	Average daily dose (mg)	Lifetime adjusted daily dose (mg/kg-day)	Human equivalent dose (mg/kg-day)	Tumor incidence
0	0	0	0	0/29
0.0625	0.009	0.0495	0.0059	1/30
0.125	0.018	0.0989	0.0118	4/30
0.25	0.036	0.198	0.0237	6/30
0.5	0.071	0.395	0.0473	17/30
1.0	0.143	0.791	0.0947	19/30

[a]Source: OEHHA (1993). Adapted from Feron *et al.*, 1973.

Methodology

Cancer risk associated with exposure to ambient levels of BaP was estimated by extrapolating from the experimental data to ambient levels by means of the best fitting linearized multistage procedure GLOBAL86 (Howe *et al.*, 1986). In addition, other models were fit to the data for comparison. In its risk assessment, the US EPA used the data for stomach tumors from oral exposure to BaP in mice and the data for respiratory tract tumors from inhalation exposure in hamsters to estimate cancer potency and unit risks associated with exposure to BaP (US EPA, 1984).

For BaP there is compelling evidence that it is genotoxic and an initiator of tumorigenesis. Therefore, OEHHA staff treated BaP-induced carcinogenesis as a nonthreshold phenomenon and, as such, applied a nonthreshold, linear extrapolation model for cancer potency estimation.

The linearized multistage model was fit to the respiratory tract tumor data resulting from inhalation exposure of hamsters to BaP (OEHHA, 1993; Thyssen *et al.*, 1981). The data from the highest dose group were not used since these animals had an appreciably shortened lifespan (59 weeks versus 96 weeks in other groups) (Thyssen *et al.*, 1981; US EPA, 1984). By considering the conditions of exposure given in the report and using an inhalation rate of 0.063 m^3/day and a "standard" body weight of 0.12 kg for hamsters (US EPA, 1988), a dose of BaP in mg/kg-day was estimated. A q_1^* (animal) equal to 0.43 $(mg/kg\text{-}day)^{-1}$ is obtained. Multiplying by the interspecies surface area correction factor of $(70/0.1)^{1/3}$ yields a human equivalent $q_1^* = 1.1 \times 10^{-3}$ $(\mu g/m^3)^{-1}$ for inhalation.

Because of the limited amount of data currently available for risk assessment of BaP, the inhalation unit risk of 1.1×10^{-3} $(\mu g/m^3)^{-1}$ based on respiratory tract tumors in hamsters is used as a best value for inhalation exposures. For exposures to BaP by other routes, the potency of 11.5 $(mg/kg\text{-}day)^{-1}$ based on gastric tract tumors in mice can be used (Neal and Rigdon, 1967).

Cancer Potency for Other PAHs

IARC (1987; 1989) has classified a number of PAHs, their mixtures and derivatives, as carcinogens (Group 1, Groups 2A and Group 2B) and a large number of PAHs into Group 3, a class of chemicals for which there are no human data but limited or inadequate data in animals (Tables 5 and 6). The US EPA has classified several PAHs in Group B2, possibly carcinogenic to humans and Group D, unclassifiable as to carcinogenicity (Table 7).

In their risk assessment, OEHHA staff concluded that while the studies available for carcinogenic risk assessment of BaP are not ideal for risk assessment, those for practically all other individual PAHs are less complete for risk assessment (OEHHA, 1993). However, there are extensive data establishing the genotoxicity, and in some cases the carcinogenicity, of many PAHs or their genotoxic metabolites. In other cases, some PAHs are not considered carcinogens. Several authors have used mutagenicity and various tests of carcinogenicity to rank several PAHs for their relative carcinogenicity (e.g., Deutsch-Wenzel *et al.*, 1983; Bingham and Falk, 1969; Habs *et al.*, 1980; Wynder and Hoffman, 1959; Wislocki *et al.*, 1986) and their relative genotoxicity (Brown, 1989). Many of these comparisons were summarized by Clement Associates (1988) and Krewski *et al.* (1989). In these analyses dibenz(*a,h*)anthracene was shown to be more potent than BaP, while other PAHs tested were less or much less potent. These comparisons indicated that considering all PAHs to be equivalent in potency to BaP would overestimate the cancer potency of a PAH mixture, but such an assumption would be health protective and is likely to be helpful in a screening estimate of PAH risks (OEHHA, 1993).

If one assumes that PAHs are as carcinogenic as they are genotoxic, then their hazard relative to BaP would be dependent on their concentration in the environment. In light of the limited information available on other PAHs, BaP remains an important representative or surrogate for this important group of chemically diverse air pollutants.

Selection of Risk Values for Other PAHs

BaP was chosen as the primary representative of the class because of the large amount of toxicological data available on BaP (versus the relatively incomplete database for other PAHs), the availability of monitoring techniques for BaP, and the significant exposure expected (and found). Nisbet and LaGoy (1992) presented a Toxic Equivalency Factor (TEF) scheme for 17 PAHs. The paper was an extension of earlier work by other investigators (Clement Associates, 1987; 1988; Krewski *et al.*, 1989). Along similar lines, OEHHA has developed a Potency Equivalency Factor (PEF) procedure to assess the relative potencies of PAHs and PAH derivatives as a group. This would address the impact of carcinogenic PAHs in ambient air since they are usually present together.

Table 5: IARC groupings of PAHs, mixtures with PAHs, and derivatives.

Group 1	Group 2A	Group 2B
Coal-tar pitches	Benz[*a*]anthracene	Benzo[*b*]fluoranthene
Coal-tar	Benz[*a*]pyrene	Benzo[*j*]fluoranthene
Coke production	Creosotes	Benzo[*k*]fluoranthene
Mineral oils	Dibenzo[*a,h*]anthracene	Carbon black extracts
Shale-oils		Dibenz[*a,h*]acridine
Soots		Dibenz[*a,j*]acridine
Tobacco smoke		7H-Dibenzo[*c,g*]carbazole
		Dibenzo[*a,e*]pyrene
		Dibenzo[*a,h*]pyrene
		Dibenzo[*a,i*]pyrene
		Dibenzo[*a,l*]pyrene
		Indeno[1,2,3-*cd*]pyrene
		5-Methylchrysene
		5-Nitroacenaphthene
		1-Nitropyrene
		4-Nitropyrene
		1,6-Dinitropyrene
		1,8-Dinitropyrene
		6-Nitrochrysene
		2-Nitrofluorene

Source: OEHHA (1993)
Abstracted from IARC Supplement 7 (1987) and IARC Volume 46 (1989).
Group1: carcinogenic to humans.
Group 2A: probably carcinogenic to humans.
Group 2B: possibly carcinogenic to humans.

Table 6: IARC Group 3 PAHs and PAH derivatives[1]

Chemical	Animal Evidence
Acridine orange	inadequate
5-Aminoacenaphthene	inadequate
2-Aminoanthraquinone	limited
Anthanthrene	limited
Anthracene	inadequate
Benz[*a*]acridine	inadequate
Benz[*c*]acridine	limited
Benzo[*g*,*h*,*i*]fluoranthene	inadequate
Benzo[*g*,*h*,*i*]perylene	inadequate
Benzo[*c*]phenanthrene	inadequate
Benzo[*e*]pyrene	inadequate
Carbazole	limited
Chrysene	limited
Cyclopenta[*c*,*d*]pyrene	limited
Dibenz[*a*,*c*]anthracene	limited
Dibenz[*a*,*j*]anthracene	limited
Dibenz[*a*,*e*]fluoranthene	limited
Dibenzo[*h*,*rst*]pentaphene	limited
3,7-Dinitrofluoroanthene	limited
3,9-Dinitrofluoroanthene	limited
1,3-Dinitropyrene	limited
Fluoranthene	inadequate
Fluorene	inadequate
1-Methylchrysene	inadequate
2-Methylchrysene	limited
3-Methylchrysene	limited
4-Methylchrysene	limited
6-Methylchrysene	limited
2-Methylfluoranthene	limited
1-Methylphenanthrene	inadequate
1,5-Naphthalenediamine	limited
9-Nitroacenaphthene	limited
9-Nitroanthracene	no adequate data
7-Nitrobenz[*a*]anthracene	limited
6-Nitrobenzo[*a*]pyrene	limited
3-Nitrofluoranthene	inadequate
1-Nitronaphthalene	inadequate
2-Nitronaphthalene	inadequate
3-Nitroperylene	inadequate
2-Nitropyrene	inadequate
Perylene	inadequate
Phenanthrene	inadequate
N-Phenyl-2-naphthylamine	limited
Pyrene	inadequate
Triphenylene	inadequate

[1]Source: OEHHA (1993). Abstracted from IARC Supplement 7 (1987) and IARC Volume 46 (1989). Group 3 have either limited or inadequate evidence in animals and are not classifiable as to their carcinogenicity in humans due to no adequate data.

Table 7: US EPA groupings of PAHs[1]

Group B2	Group D
Benz[*a*]anthracene	Acenaphthylene
Benzo[*a*]pyrene	Anthracene
Benzo[*b*]fluoranthene	Benzo[*e*]pyrene
Benzo[*j*]fluoranthene	Benzo[*g,h,i*]perylene
Benzo[*k*]fluoranthene	Fluorene
Chrysene	Naphthalene
Dibenz[*a,h*]anthracene	Phenanthrene
Indeno[1,2,3-*cd*]pyrene	

[1]Source: OEHHA (1993). Abstracted from US EPA (1993a). Group B2: possibly carcinogenic to humans. Group D is unclassifiable as to carcinogenicity.

Due to the variety of data available on the carcinogenicity and mutagenicity of PAHs, an order of preference for the use of available data in assessing relative potency was developed. If a health effects evaluation and quantitative risk assessment leading to a cancer potency value had been conducted on a specific PAH, then those values were given the highest preference.

If potency values have not been developed for specific compounds, a carcinogenic activity relative to BaP, rather than a true potency, can be developed. These relative activity values are referred to by OEHHA as PEFs. For air contaminants, relative potency to BaP based on data from inhalation studies would be optimal. Otherwise, intrapulmonary or intratracheal administration, such as those published by Deutsch-Wenzel *et al.* (1983), would be most relevant, since such studies are in the target organ of interest. Next in order of preference is information on activity by the oral route and skin painting. Intraperitoneal and subcutaneous administration rank at the bottom of the *in vivo* tests considered useful for PEF development because of their lack of relevance to environmental exposures. Next in decreasing order of preference are genotoxicity data which exist for a large number of compounds. In many cases genotoxicity information is restricted to mutagenicity data. Finally, there are data on structure-activity relationships among PAH compounds. Structure-activity considerations may help identify a PAH as carcinogenic, but at this time have not been established as predictors of carcinogenic potency.

Using this order of preference, PEFs were derived for 21 PAHs and are presented in Table 8. The cancer potencies of four other PAH compounds are given in Table 9. Explanation of the derivation of each PEF, type of data used in the derivation, and the relevant references are given below.

Table 8: OEHHA PEF weighting scheme for PAHs[1]

PAH or derivative	PEF
benzo[*a*]pyrene	1.0 (index compound)
benz[*a*]anthracene	0.1
benzo[b]fluoranthene	0.1
benzo[*j*]fluoranthene	0.1
benzo[k]fluoranthene	0.1
dibenz[*a,j*]acridine	0.1
dibenz[*a,h*]acridine	0.1
7H-dibenzo[c,*g*]carbazole	1.0
dibenzo[*a,e*]pyrene	1.0
dibenzo[*a,h*]pyrene	10
dibenzo[*a,i*]pyrene	10
dibenzo[*a,l*]pyrene	10
indeno[1,2,3-*cd*]pyrene	0.1
5-methylchrysene	1.0
1-nitropyrene	0.1
4-nitropyrene	0.1
1,6-dinitropyrene	10
1,8-dinitropyrene	1.0
6-nitrochrysene	10
2-nitrofluorene	0.01
Chrysene	0.01

[1]Source: OEHHA (1993)

Table 9: Potencies of PAHs and derivatives[1]

Chemicals	Cancer potency factors $(mg/kg\text{-}day)^{-1}$	Unit risks $(\mu g/m^3)^{-1}$
benzo[*a*]pyrene	11.5	1.1×10^{-3}
dibenz[*a,h*]anthracene	4.1	1.2×10^{-3}
7,12-dimethylbenzanthracene	250	7.1×10^{-2}
3-methylcholanthrene	22	6.3×10^{-3}
5-nitroacenaphthene	0.13	3.7×10^{-5}

[1]Source: OEHHA (1993). It is assumed that unit risks for inhalation have the same relative activities as cancer potencies for oral intake.

Potency and Potency Equivalency Factors (PEFs) for Selected PAHs

1. Benzo[*a*]pyrene. Benzo[*a*]pyrene (BaP) was the index compound for relative potency and for Potency Equivalency Factors (PEF) for PAHs and derivatives. It has a cancer potency of 11.5 $(mg/kg\text{-}day)^{-1}$ and inhalation unit risk of 1.1×10^3 $(\mu g/m^3)^{-1}$. For the potency equivalency scheme, it was assigned a PEF of 1.

2. Dibenz[*a,h,*]anthracene. An expedited potency of 4.1 $(mg/kg\text{-}day)^{-1}$ was derived using the linearized multistage model with the only dose-response data set available - a drinking water study (Snell and Stewart, 1962) which reported alveolar carcinomas of the lung in male DBA/2 mice due to dibenz[*a,h*]anthracene (incidence = 14/21 at 28.3 mg/kg-day versus 0/25 in controls). An inhalation unit risk can be obtained from a potency under the assumption that the chemicals are equally absorbed and are equally potent by oral and inhalation routes and that a 70 kg person inhales 20 cubic meters of air per day. When the potency in units of $(mg/kg\text{-}day)^{-1}$ is divided by 3500 (70 kg * 1000 μg/mg/20 m^3), an inhalation unit risk is obtained in units of $(\mu g/m^3)^{-1}$.

3. 7,12-Dimethylbenzanthracene. An expedited potency of 250 $(mg/kg\text{-}day)^{-1}$ was derived. The only study listed in the Gold *et al.* cancer potency (TD50) database (Gold *et al.*, 1984; 1986; 1987; 1989; 1990) is the feeding study by Chourolinkov *et al.* (1967) in female albino mice. Significant increases in malignant angioendotheliomas of the mesenteric intestine and papillomas of the forestomach were observed in animals treated with 0.39 mg/kg-day of 7,12-dimethylbenzanthracene. Cancer potency is based on mesenteric intestine angioendothelioma incidence (incidence = 49/75 versus 0/40 in controls).

4. 3-Methylcholanthrene. An expedited potency of 22 $(mg/kg\text{-}day)^{-1}$ was derived. Results of 3 studies in male Long Evans rats, one study in an unspecified strain of female rats, and 10 studies in female Wistar rats were included in the Gold *et al.* database. All studies in female rats found highly significant increases in tumors of the mammary gland. The cancer potency for 3-methylcholanthrene was taken as the geometric mean of cancer potencies estimated from 9 of the 10 studies in female rats (Shay *et al.*, 1962; Gruenstein *et al.*, 1964; Shay *et al.*, 1961). The upper bound on potency could not be estimated from one of the studies by Shay *et al.* (1961), because 100% of the treated animals developed mammary gland tumors.

5. 5-Nitroacenaphthene. An expedited potency of 0.13 $(mg/kg\text{-}day)^{-1}$ was derived based on the combined incidence of benign and malignant tumors of the ear canal in female rats. Usable studies were feeding studies by Takemura *et al.* (1974) in female Syrian golden hamsters and by the National Cancer Institute (1978) in male and female $B6C3F_1$ mice and F344 rats. The compound 5-nitroacenaphthene induced increases in tumor incidences at multiple sites in rats and female mice. Rats were the most sensitive species; the sensitivity of males were similar to that of females.

6. Benzo[*b*]fluoranthene. Benzo[*b*]fluoranthene was assigned a PEF of 0.1. Clement Associates (1988) applied both a two stage model and the multistage model to various data sets for several PAHs. The two models generally gave similar results for relative potency. In order to verify the results, OEHHA staff (OEHHA, 1993) used GLOBAL86 to fit the multistage model to the tumor data used by Clement Associates and obtained relative cancer potencies similar to those obtained by Clement Associates. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Habs *et al.* (1980) and the intrapulmonary administration to rats by Deutsch-Wenzel *et al.* (1983) to estimate a cancer potency for benzo[*b*]fluoranthene relative to BaP. As an example of the type of data used, Deutsch-Wenzel *et al.* obtained pulmonary tumor incidences of 0, 2.9, and 25.7% after intrapulmonary administration of 0.1, 0.3, and 1 mg benzo[*b*]fluoranthene, respectively, whereas they obtained 11.8, 60.0, and 94.3% tumor incidences after the same doses of benzo[*a*]pyrene. Clement Associates estimated a relative cancer potency for benzo[*b*]fluoranthene of 0.140 after fitting the two stage model to the data

and 0.105 after fitting the multistage model. Using the data of Habs *et al.* a relative cancer potency of 0.167 was obtained with the two stage model and 0.201 with the multistage model. The results from the multistage model were averaged, then rounded (down) to 0.1 to obtain the PEF. OEHHA obtained a relative potency of 0.208 for benzo[*b*]fluoranthene fitting the multistage model to the data from Habs *et al.* OEHHA staff were also able to reproduce the calculations for the two stage model in the accepted model for cancer risk assessment in California; results from the multistage model have been used to obtain PEFs although the two models usually gave the same PEF.

7. Benzo[*j*]fluoranthene. Benzo[*j*]fluoranthene was assigned a PEF of 0.1. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Habs *et al.* (1980) to estimate a cancer potency relative to BaP of 0.0648. OEHHA staff estimated 0.065 using the same data. This was rounded to 0.1 to obtain the PEF. Clement Associates did not use the data of Deutsch-Wenzel *et al.* (1983) on benzo[*j*]fluoranthene to calculate a relative potency but Deutsch-Wenzel *et al.* found that it was very similar in tumorigenic activity to benzo[*k*]fluoranthene.

8. Benzo[*k*]fluoranthene. Benzo[*k*]fluoranthene was assigned a PEF of 0.1. Clement Associates (1988) used mouse skin carcinogenesis data obtained by Habs *et al.* (1980) to obtain a cancer potency relative to BaP of 0.0235 and the intrapulmonary administration to rats by Deutsch-Wenzel *et al.* (1983) to estimate a PEF of 0.085. Because the latter was obtained by the pulmonary route it was chosen to be the basis of the PEF. The value was rounded to 0.1 to obtain the PEF.

9. Benz[*a*]anthracene. Benz[*a*]anthracene was assigned a PEF of 0.1. In the case of benz[*a*]anthracene, mouse skin carcinogenesis data obtained by Bingham and Falk (1969) were used by Clement Associates (1988) to calculate potencies for benz[*a*]anthracene. For this chemical the multistage model gave a relative potency of 0.0137. Using the two stage model a higher cancer potency of 0.145 relative to BaP was obtained. In the Wislocki *et al.* (1986) report, in which lung adenomas were induced in newborn mice, benz[*a*]anthracene (2.8 micromoles) was less carcinogenic (12/71 or 17% versus 7/138 or 5% in controls) relative to 0.56 micromoles BaP (24/64 or 38% versus 7/138 in controls). The relative potency was 0.08, which rounds to 0.1. Since the US EPA was using a PEF of 0.1 for this PAH (US EPA, 1993b) and the data from the Wislocki study were consistent with a PEF of 0.1, a value of 0.1 was selected by OEHHA.

10. Dibenz[*a,j*]acridine. Dibenz[*a,j*]acridine was assigned a PEF of 0.1. Warshawsky *et al.* (1992) compared the tumor-initiating ability of dibenz[*a,j*]acridine to BaP in mouse skin. Two hundred nanomoles of each compound were applied to groups of 30 mice, then the skin lesion was promoted with a phorbol ester for 24 weeks. Twenty-seven out of 30 BaP mice (90%) had skin papillomas, while 17 of 30 (57%) of the dibenz[*a,j*]acridine mice had skin papillomas. The multistage model was fit to both sets of data and the ratio of upper 95% confidence limits on the linear coefficient was 0.36. This was rounded to a PEF of 0.1.

11. Dibenz[*a,h*]acridine. Dibenz[*a,h*]acridine was also assigned a PEF of 0.1. Its carcinogenic classification by IARC was based on studies published in 1940 and earlier and the studies did not appear appropriate for estimation of a PEF. Since its structure is similar to dibenz[*a,j*]acridine, it was assigned the same PEF as dibenz[*a,j*]acridine until usable compound-specific bioassay data becomes available.

12. 7H-Dibenzo[*c,g*]carbazole. 7H-dibenzo[*c,g*]carbazole was assigned a PEF of 1.0. Warshawsky *et al.* (1992) compared the tumor-initiating ability of 7H-dibenzo[*c,g*]carbazole to BaP in mouse skin. Two hundred nanomoles of each compound were applied to 30 mice, then promoted with a phorbol ester for 24 weeks. Twenty-seven out of 30 BaP-treated mice (90%) had skin papillomas, while 26 of 30 (87%) of the dibenzo[*a,j*]acridine-treated mice had skin papillomas for a relative tumorigenic activity of 0.97. This was rounded to a PEF of 1.

13. Dibenzo[*a,l*]pyrene. Dibenzo[*a,l*]pyrene was assigned a PEF of 10. Cavalieri *et al.* (1989; 1991) studied the tumor-initiating and dose-response tumorigenicity of dibenzo[*a,l*]pyrene in mouse skin and rat mammary gland. BaP was used as a reference compound in some experiments. Dibenzo[*a,l*]pyrene was the most potent member of the group. Several levels of PAHs were tested. When results from 33.3 nanomoles of dibenzo[*a,l*]pyrene as a skin tumor initiator (with promotion by a phorbol ester) were compared to results using the same amount of BaP, dibenzo[*a,l*]pyrene induced skin tumors in 23/24 (96%) of the animals while BaP induced tumors in 10/23 (43%) which resulted in a relative potency of 5.8. Dibenzo[*a,l*]pyrene induced approximately 5 times as many tumors per tumor-bearing animal. In a second experiment 4 nanomoles of each chemical were compared. Ninety-two percent (22/24) of the dibenzo[*a,l*]pyrene-treated mice had tumors but only 4% (1/24) of the BaP animals, which yielded a relative potency of 25.1. In a third experiment 100 nM were compared without promotion. Twenty-nine percent (7/24) of the dibenzo[*a,l*]pyrene-treated mice had tumors but only 4% (1/24) of the BaP animals, for a relative potency of 4. Finally, with direct application to the mammary gland, 0.25 and 1.0 nanomoles dibenzo[*a,l*]pyrene led to tumors in all the rats treated (19 and 20 per group, respectively) whereas only one animal in the 0.25 micromoles BaP group showed a tumor for a relative potency greater than 100. Based on its much greater tumorigenic activity than BaP in the above tests, dibenzo[*a,l*]pyrene was assigned a PEF of 10.

14. Dibenzo[*a,h*]pyrene. Dibenzo[*a,h*]pyrene was assigned a PEF of 10 since, in the experiments by Cavalieri *et al.* (1989) in which all four dibenzo[a]pyrenes were studied, its tumor causing activity was similar to dibenzo[*a,l*]pyrene. For example, when used to initiate tumors in mouse skin, 18 of 24 (75%) of mice treated with dibenzo[*a,h*]pyrene had tumors compared to 22 of 24 (92%) with dibenzo [*a,l*]pyrene. Controls showed skin tumors in 2 of 23 mice (9%).

15. Dibenzo[*a,i*]pyrene. Dibenzo[*a,i*] pyrene was assigned a PEF of 10 since, in the experiments by Cavalieri *et al.* (1989) in which all four dibenzo[*a*]pyrenes were studied, its tumor-causing activity was similar to dibenzo[a,l]pyrene. For example, when used to initiate tumors in mouse skin, 15 of 24 (63%) of mice treated with dibenzo[a,i]pyrene had tumors compared to 22 of 24 (92%) with dibenzo [*a,l*]pyrene. Controls showed skin tumors in 2 of 23 mice (9%).

16. Dibenzo[*a,e*]pyrene. Dibenzo[*a,e*]pyrene was assigned a PEF of 1.0. Dibenzo[*a,e*]pyrene was the least potent of the four dibenzo[*a*]pyrenes studied by Cavalieri *et al.* (1989; 1991). In the experiments in which all four dibenzo[*a*]pyrenes were compared (Cavalieri *et al.*, 1989), its tumor-causing activity was approximately one-tenth to one-twentieth that of dibenzo[*a,l*]pyrene.

17. Indeno[1,2,3-*cd*]pyrene. Indeno[1,2,3-*cd*]pyrene was assigned a PEF of 0.1. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Habs *et al.* (1980) and by

Hoffman and Wynder (1966) and the lung tumor data obtained by Deutsch-Wenzel *et al.* (1983) after intrapulmonary administration to estimate cancer potencies relative to BaP of 0.0302, 0.0292, and 0.246, respectively. These were averaged and rounded to obtain a PEF of 0.1.

18. 5-Methylchrysene. 5-Methylchrysene was assigned a PEF of 1.0. The activity of 5-methylchrysene relative to BaP has been studied by Hecht *et al.* (1976) using skin tumor initiation with phorbol ester (tetradecanoyl phorbol acetate) promotion as well as skin tumor induction in mice. In the skin tumor induction test the tumorigenic activities of 5-methylchrysene and BaP were comparable enough so that a PEF of 1.0 was selected for 5 methylchrysene. Weekly application of 0.01% 5-methylchrysene led to skin carcinomas in 10 of 15 mice treated for up to 62 weeks, while 0.01% BaP led to skin carcinomas in 14 of 18 mice. The results for 0.005% of the 2 chemicals were 6 of 9 and 7 of 10, respectively.

19. 1-Nitropyrene. 1 Nitropyrene has been assigned a PEF of 0.1. In the Wislocki *et al.* (1986) report, in which lung tumors were induced in newborn mice, 1-nitropyrene (0.7 micromoles) was weakly carcinogenic in males (6/34 or 18% versus 4/45 or 9% in controls) and not carcinogenic in females (3/50 or 6% versus 2/34 or 6% in controls) relative to 0.56 micromoles BaP (13/37 or 35% in males versus 1/28 or 4% in control males and 13/27 or 48% in females versus 0/31 in control females). The relative potency was 0.348 in males and 0.076 in females. A PEF of 0.1 was assigned based on the experiment.

20. 4-Nitropyrene. 4-Nitropyrene was assigned a PEF of 0.1. Wislocki *et al.* (1986) compared the lung tumorigenicity of nitrated derivatives of pyrene to BaP in a newborn mouse assay. The background incidences were 4% in males and 0% in females. The administration of 2.8 micromoles of 4-nitropyrene gave a net incidence of 34% tumors in males and 31% in females, while 0.56 micromoles BaP gave 31% tumors in males and 48% in females. The potency of 4-nitropyrene relative to BaP was 0.23 in males and 0.12 in females. These were averaged and rounded to a PEF of 0.1.

21. 1,6-Dinitropyrene. 1,6-Dinitropyrene was assigned a PEF of 10. In the Wislocki *et al.* (1986) report, 1,6-dinitropyrene (0.2 micromoles) was weakly carcinogenic in inducing lung tumors in females (2/29 versus 0/31 in controls) and essentially not carcinogenic in males (1/25 versus 1/28 in controls) relative to 0.56 micromoles BaP (see 1-nitropyrene above for BaP data). The weak response combined with the low dose of 1,6-dinitropyrene (0.2 micromoles) relative to BaP (0.56 micromoles) resulted in a relative potency of 0.52 in females and 0.54 in males. In an intratracheal injection experiment (Takayama *et al.*, 1985) hamsters were given 26 weekly instillations of 0.5 mg BaP. All 10 males and 9 of 10 females developed respiratory tract tumors. A unit risk of 2.9×10^{-2} $(\mu g/m^3)^{-1}$ obtained from the female data which is 6.4 times the unit risks obtained from intratracheal studies using BaP and 26 times that using inhalation data. In a study by Iwagawa *et al.* (1989) using several doses of 1,6-dinitropyrene or BaP implanted directly into the lungs, a relative potency of 5.1 was obtained from the resulting lung cancer data. In light of the two experiments showing high relative potency and of 1,6-dinitropyrene's strong mutagenicity, a PEF of 10 appeared to be more appropriate than 1.0.

22. 1,8-Dinitropyrene. 1,8-Dinitropyrene was assigned a PEF of 1.0. In the Wislocki *et al.* (1986) report, 1,8-dinitropyrene (0.2 micromoles) was weakly carcinogenic in females (2/29 versus 0/31 in controls) and not carcinogenic in males (1/31 versus 1/28 in controls) relative to 0.56 micromoles BaP. However, due again to the low dose of 1,8-dinitropyrene chosen, the

relative potency was 0.46 in females and 0.41 in males. In view of the high PEF of 1,6-dinitropyrene derived above and the very high mutagenicity of 1,8-dinitropyrene, the default PEF of 1.0 was assigned to 1,8-dinitropyrene until better *in vivo* data becomes available to derive a PEF.

23. 6-Nitrochrysene. 6-Nitrochrysene was assigned a PEF of 10. In the Wislocki *et al.* (1986) report, 0.7 micromoles of 6-nitrochrysene gave a net incidence of 76% lung tumors in males (28/33 versus 4/45 in controls) and 84% in females (36/40 versus 2/34 in controls). The potency of 6-nitrochrysene relative to BaP was 3.27 in males and 2.50 in females. In the newborn mouse assay of Busby *et al.* (1988), "(t)he ED50 for total lung tumors was 0.02 μmol for 6-NC and 0.2 μmol for BaP, thus showing a 10-fold higher potency for 6-NC compared with the 25-fold difference noted with tumor multiplicity." In a subsequent report (Busby *et al.*, 1989), 0.03 micromoles of 6-nitrochrysene caused lung adenomas and adenocarcinomas in 19/26 males and 13/22 females (versus controls of 13/91 in males and 7/101 in females) while 0.24 micromoles BaP caused lung adenomas and adenocarcinomas in 13/28 males and 19/27 females (against the same controls). The relative potencies were 17.51 for males and 6.17 for females. Based on the several experiments a PEF of 10 was selected.

24. 2-Nitrofluorene. 2-Nitrofluorene was assigned a PEF of 0.01. Miller *et al.* (1955) fed 2-nitrofluorene at a level of 1.62 mmol(215 mg)/kg diet to rats. This is estimated to give an animal dose of 33.1 mg/kg-day and a human equivalent dose of 4.7 mg/kg-day. In one experiment 17 of 20 male rats (85%) developed forestomach tumors by 12 months. In another experiment 4 of 9 female rats (44%) developed mammary tumors by 10 months. These experiments yielded cancer potencies of 0.25 and 0.62 $(mg/kg\text{-}day)^{-1}$, approximately 0.02 and 0.05 that of BaP obtained in this risk assessment. The values of 0.02 and 0.05 were averaged and rounded down to obtain a PEF of 0.01.

25. Chrysene. Chrysene was assigned a PEF of 0.01. Clement Associates (1988) used the mouse skin carcinogenesis data obtained by Wynder and Hoffman (1959) to estimate a cancer potency relative to BaP of 0.0132. This was rounded to obtain a PEF of 0.01.

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PARTICULATE MATTER AND SULFATE: EVALUATION OF CURRENT CALIFORNIA AIR QUALITY STANDARDS WITH RESPECT TO PROTECTION OF CHILDREN

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Prepared for
California Air Resources Board
California Office of Environmental Health Hazard Assessment

September 1, 2000

Abstract

Epidemiological evidence indicates that present-day ambient particulate matter (PM) and/or sulfate air pollution exposures are associated with adverse health effects in children, including that:

Short-term PM and/or sulfate exposures to children are associated with:

- reduced pulmonary function;
- increased respiratory symptoms in asthmatics (e.g., asthma attacks) and non-asthmatics;
- increased incidence of respiratory doctor's visits;
- increased incidence of emergency department (ED) visits and hospital admissions (HA's);
- increased mortality, and;
- especially increased infant morbidity and mortality;

Long-term chronic PM and/or sulfate exposures to children are associated with:

- reduced lung function;
- increased respiratory symptoms; and,
- increased infant mortality, intrauterine growth reduction, or pre-term delivery.

Especially apparent in the many studies examined, and of notable concern, are results indicating much higher risks for children in the neonatal (< 1 month) and post-neonatal (1-12 months) age groups. Furthermore, an examination of key medical visits and hospital admissions studies indicates that the existing Federal and California PM_{10} and $PM_{2.5}$ mass and sulfate ambient air quality standards are not presently sufficiently protective of public health, as significant adverse health impacts have been documented in published studies at mean ambient levels below these standards.

Both biological and physical exposure-related factors enhance the risk to children from PM and sulfate exposures. These risk-enhancing factors include:

- higher PM concentration exposures resulting from children's greater activity levels;
- larger PM doses in children from increased ventilation rates;
- greater doses of ultrafines among children 14-18 years of age;
- enhanced PM doses in children, especially infants, per body weight and lung surface area;
- diminished and developing defense systems in infants;
- higher prevalence of children with asthma than in other age groups;
- larger percentage of children made susceptible by poverty than other age groups; and,
- gas-particle interactions and particle-allergen interactions, potentially making the individual pollutant standards not fully protective to susceptible populations, such as children.

Based on the above insights, it is recommended that future PM research should focus on:

- improved identification of the specific characteristics of PM (e.g., ultrafines, acidity, elemental composition, etc.) that are contributing most to noted PM effects, and quantification of their relative roles in PM toxicity;
- further investigation as to whether acute exposures less than one day in length (e.g., 1-hr. daily maximum), or longer multi-day exposures (e.g., 2 or more day average PM), also have health importance, over and above that captured by the 24-hr. PM peak PM concentration measurement;
- further investigations into particle-gas and particle-allergen interactions;
- using both experimental and epidemiological methods, conduct further investigations of apparently larger acute and long-term effects of PM on children, and especially infants.

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I. Background

This section briefly summarizes the existing California state and federal ambient standards for particulate matter (PM) and sulfate ($SO_4^=$), and the rationale for these standards.

According to California State Code of Regulations Section 39606 (b), the state board shall adopt standards of ambient air quality for each air basin in consideration of the public health, safety, and welfare, including, but not limited to, health, illness, irritation to the senses, aesthetic value, interference with visibility, and effects on the economy. These standards may vary from one air basin to another. Standards relating to health effects are to be based upon the recommendations of the State Department of Health Services. The term "Ambient air quality standards" means specified concentrations and exposure durations of air pollutants that reflect the relationship between the intensity and composition of air pollution to undesirable effects established by the state board or, where applicable, by the federal government. "Air contaminant" or "air pollutant" means any discharge, release, or other propagation into the atmosphere and includes, but is not limited to, smoke, charred paper, dust, soot, grime, carbon, fumes, gases, odors, particulate matter, acids, or any combination thereof.

The present particulate matter (PM) mass-based ambient air quality standard in California is indexed to PM_{10}, which refers to atmospheric particles, solid and liquid, except uncombined water, as measured by a PM_{10} sampler that collects 50 percent of all particles of 10 micrometers (um) aerodynamic diameter, and that collects a declining fraction of particles as their diameter increases and an increasing fraction of particles as their diameter decreases, reflecting the characteristic of lung deposition. Suspended particulate matter (PM_{10}) is to be measured by the size selective inlet high volume (SSI) PM_{10} sampler method in accordance with ARB Method P, as adopted on August 22, 1985, or by an equivalent PM_{10} sampler method, for purposes of monitoring for compliance with the PM_{10} standards.

As noted in Table 1, the State of California, unlike the Federal government, also has an air quality standard that was promulgated in the 1970s for the sulfate portion of PM_{10}. Sulfates are the water soluble fraction of suspended particulate matter containing the sulfate radical ($SO_4^=$) including, but not limited to, strong acids and sulfate salts, as measured by AIHL Method No. 61 (Turbidimetric Barium Sulfate) (December 1974, as revised April 1975 and February 1976) or equivalent method. The present sulfate standard is a 24-hour average concentration not to be exceeded more than once per year. In recognition of an inability to discern a threshold at and below which no effects can occur from exposure to this pollutant, this standard is set at a "Critical Harm" level.

Currently, most of the state is in non-attainment with the PM10 standard. The PM_{10} air quality levels dropped from a statewide average of approximately 80 ug/m^3 in 1988 to about 50 ug/m^3 in 1995 and 1996, but rose again to almost 60 ug/m^3 in 1997 (CARB, 1999). State average annual maximum sulfate concentrations dropped by about half between 1980 and 1990 (from about 60 ug/m^3 to about 30 ug/m^3), and have remained fairly stable since

that time. Peak summer sulfate in the LA Basin in 1996 was about 17 ug/m^3, and for the last 10 years the mean summer 24-hour concentrations were less than 8 ug/m^3. Thus, typical concentrations are now below the existing sulfate standard, but this is not the case for PM_{10}.

The United States Environmental Protection Agency ("EPA") also recognized the adverse health effects of small particulate pollution as early as 1987 when, pursuant to its authority under the Clean Air Act, it promulgated a National Ambient Air Quality Standard ("NAAQS") for particulate matter that is 10 micrometers in diameter or smaller (PM_{10}). The NAAQS promulgated by EPA are required for certain air pollutants "that may reasonably be anticipated to endanger public health and welfare." The NAAQS' air criteria must be "requisite to protect the public health" with an "adequate margin of safety." Under the particulate matter NAAQS, states must reduce PM_{10} concentrations in their ambient atmosphere to no more than 50 micrograms per cubic meter on an annual average basis, and to no more than 150 micrograms per cubic meter on an average 24-hour period. Prior to 1987, EPA's particulate NAAQS had only regulated total suspended particulate matter. Its focus in 1987 on smaller particles -- that is, 10 micrometers or less -- resulted from increasing scientific evidence that human inhalation of smaller particles had more serious respiratory effects than larger particles.

Table 1. Present California Ambient Air Quality Standards for Particulate Matter and Sulfates (Source: California State Code of Regulations)				
Substance	Concentration and Methods	Duration of Averaging Periods	Most Relevant Effects	Comments
Suspended Particulate Matter (PM_{10})	50 ug/m^3 PM_{10} 30 ug/m^3 PM_{10}	24 hour sample Annual Geometric Mean of 24 hr. Samples	Prevention of excess deaths from short-term exposures and of exacerbation of symptoms in sensitive patients with respiratory disease. Prevention of excess seasonal declines in pulmonary function, especially in children	The standard applies to suspended particulate matter as collected by a PM_{10} sampler, which collects 50% of all particles of 10 um aerodynamic diameter and collects a decreasing fraction of particles as diameter increases, and an increasing fraction as their diameter decreases, reflecting the characteristics of lung deposition.
Sulfates	25 ug/m^3 Total Sulfates AIHL #61 (Turbidimetric Barium Sulfates)	24 hour sample	a. Decreases in ventilatory function b. aggravation of asthmatic symptoms c. Aggravation of cardio-pulmonary diseases d. Vegetative Damage e. Degradation of visibility f. Property damage.	This standard is based as a Critical Harm Level, not a threshold value.

In 1994, the EPA began the process of re-reviewing its particulate matter standards. In 1996, the EPA proposed a new NAAQS for even smaller particles -- those that are 2.5 micrometers in diameter or smaller ($PM_{2.5}$). This new proposed standard was based on an increasing scientific consensus that the current NAAQS for PM_{10} was not sufficiently protective of human health. EPA's scientific review concluded that fine particles, in the 2.5 micrometer and smaller range, penetrate more deeply into the lungs, and may be more likely than coarse particles to contribute to the health effects (e.g., premature mortality and hospital admissions) found in a number of recently published community epidemiological studies at concentrations that extend well below those allowed by the current U.S. PM_{10} standards. As EPA stated in its proposed regulation, a greatly expanded body of community epidemiological studies provide "evidence that serious health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM, even in concentrations below current U.S. PM standard" (*Federal Register*, July 18, 1997, Vol. 62, No. 138, pg. 38655).

The recently promulgated NAAQS for $PM_{2.5}$ is 15 micrograms per meter cubed (ug/m^3) based upon the 3-year average of annual arithmetic mean $PM_{2.5}$ concentrations at multiple sites, and 65 ug/m^3 based upon the 3-year average of the 98th percentile of the 24-hour PM_{10} concentration at individual sites. These standards are presently being contested in Federal courts (See: American Trucking Associations, Inc. v. USEPA, 175 F.3d 1027 (D.C. Cir. 1999), modified, 190 F.3d 4 (D.C. Cir. 1999), cert. granted in Browner v. American Trucking Associations, 120 S. Ct. 2003 (2000) (No. 99-1257), and in American Trucking Associations v. Browner, 120 S. Ct. 2193 (2000) (No. 99-1426)).

II. Factors in Particulate Matter (PM) and Sulfate Exposure and Dose Assessment

This section includes, to the extent that information is available, a description of exposure patterns among infants and children that are likely to result in disproportionately high exposures to ambient air pollutants in comparison to the general population.

II.A. PM Concentration Exposures from Children's Activities

Personal activities, such as exercise, cigarette smoking, hobbies, and occupational tasks generate a plume of particles that surround the person generating the particles. Such personal activity sources can exist either indoors or outdoors. These are microscale PM generating activities that primarily influence the exposure of the person performing the activity. Thus, personal activity PM exposure is only measured by a personal monitor carried by the subject, because a stationary monitor located nearby will not measure the high PM concentration generated by that activity. The difference between a personal monitor measurement and an area-representative measurement several meters away is sometimes called a "personal cloud" (Wallace, 1999).

However, personal PM exposure monitoring studies have indicated that personal activities, along with PM generated by personal and indoor sources (e.g., cigarette smoking), can lead to PM indoors and personal exposures to total PM that exceed the concentration of the PM found in the immediate outdoor air or in the local ambient air (Binder et al., 1976; Repace and Lowrey, 1980; Spengler et al., 1980). Fine particles have been found to readily penetrate buildings, but indoor activity adds incrementally to outdoor levels and, frequently, somewhat higher levels of fine particles are observed indoors. Indeed, human activity, such as smoking and cooking, does generate fine particles (<2.5 um); cooking, dusting, vacuuming and general activity can generate coarser particles (>2.5 um), or can resuspend coarse particles that previously had settled out (Litzistorf et al., 1985; Thatcher and Layton, 1995; Abt et al., 1999, 2000).

Children are well documented to have greater activity levels than adults, and therefore are likely to have increased personal exposures, relative to adults, because of an enhanced personal cloud of particles. In recent surveys of the activity patterns of California children and adults (Wiley et al, 1991a,b), it was found that children 11 years of age and under spend an average of 124 minutes/day doing active sports, walking/hiking, or outdoor recreation, vs. only 21 minutes for adults. In personal exposure studies in the Netherlands, it has been found that, given roughly the same outdoor concentrations, children have a much higher personal PM_{10} exposure than adults (Janssen, et al. 1997, 1998). While children's homes in these studies had a mean outdoor concentration similar to that of adults (41.5 ug/m^3 vs. 38.5 ug/m^3 for adults), children's personal exposures averaged 66.8 ug/m^3 above ambient vs. 26.9 ug/m^3 above ambient for adults. This indicates a much higher "personal cloud" for children than adults. In regressions, personal activity was one of the more important contributors to the children's extra personal exposure concentration, contributing approximately 12 ug/m^3. The children's personal exposure was also some 43 ug/m^3 higher than their time-weighted average of indoor and outdoor concentrations, indicating most of the personal vs. outdoor PM_{10} difference to be due to their personal cloud, rather than generally higher PM_{10} concentrations indoors. Most of these particles are likely to be of indoor origins, however. Thus, PM exposure of a child can be substantially higher than that for adults because of the extra PM that is generated by their own increased activity levels, but the importance of this effect to outdoor air pollution standard setting is limited by the fact that most of these activity generated particles are of indoor origins.

For sulfates, the "personal cloud" phenomenon apparently does not apply as it does for PM mass in general, as sulfate is derived almost exclusively from the outdoors. Indeed, in the PTEAM study (Ozkaynak et al, 1996) conducted in Riverside, CA in 1990, it was found that sulfate concentrations indoors and outdoors were the same,

and the researchers concluded that there appeared to be no indoor or personal sources of exposure to sulfate particles. As shown in Figure 1, $SO_4^=$ measured at central monitoring stations in the PTEAM study is closely correlated with $SO_4^=$ as measured by personal exposure monitors. In that figure, the deviations from the line of identity can be largely accounted for by a model that incorporates other known influences. Such close correspondence between personal and outdoor concentrations was not seen for PM_{10} or $PM_{2.5}$ mass concentrations, or for other measured constituents. The close correspondence for $SO_4^=$ can be attributed to it being: a) chemically and physically stable in the air and on sampling filters; b) present primarily as submicrometer-sized particles which penetrate into indoor spaces efficiently with infiltrating air; c) a secondary aerosol that is distributed quite uniformly across large geographic areas; and d) without common indoor sources.

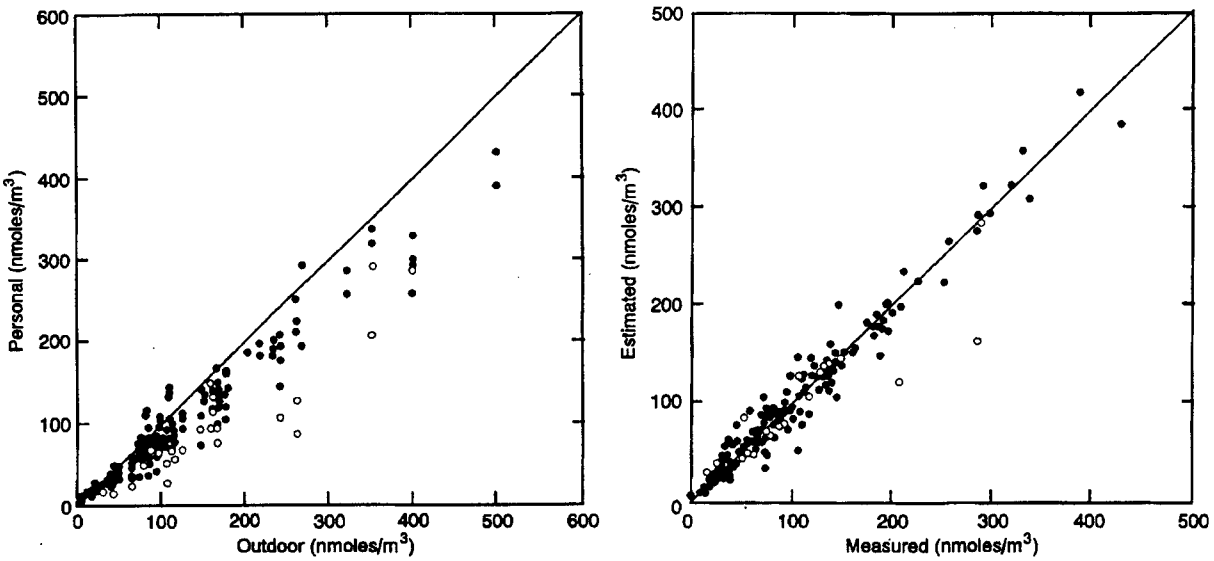

Figure 1. Left Panel: Comparison of personal monitoring data on $SO_4^=$ concentration with temporally coincident central monitoring station $SO_4^=$ in California. (Open circles are air-conditioned residences.)
Right panel: Comparison of measured ambient $SO_4^=$ concentrations with estimated personal $SO_4^=$ exposures based on PTEAM model incorporating known influences on personal exposures.
From: U.S. EPA (1995).

Thus, unlike for PM_{10}, children's personal concentration exposures to sulfates are similar to those of adults, and are well represented by a central site monitors. However, the acidity of sulfates has been found to differ indoors and outdoors, with diminished acidity indoors due to ammonia sources indoors that can convert the acidic sulfates to ammonium sulfate (e.g., see Suh et al, 1994). Thus, while total sulfate exposures are similar for adults and children, the sulfates that children are exposed to are likely more acidic as a result of their greater time spent outdoors, as sulfates are more likely to be in an acidic form outdoors (i.e., as sulfuric acid and/or ammonium bisulfate). Therefore, the greater outdoor time and activity of children outdoors places them at greater risk than adults of exposure to acidic sulfates and acidic gases (e.g., nitric acid).

II.B. Variations in Lung Deposition Fraction in Children vs. Adults

Lung and airway characteristics vary with age, and these variations can change the deposition pattern of inhaled particles. The limited experimental studies available indicate

results ranging from no clear dependence of total deposition on age to slightly higher deposition in children than in adults. Potential deposition differences between children and adults have been assessed to a greater extent using mathematical models, as shown in Figure 2, as derived from the ICRP model (U.S. EPA, 1995). These results indicate that extra-thoracic (ET) deposition (i.e., to the nose, naso-oropharyngeal passages, and larynx) in children is generally higher than in adults, but that tracheo-bronchiolar (TB) and alveolar (A) regional deposition in children may be either higher or lower than the adult, depending upon particle size and age of the child. Overall, available studies do not provide clear evidence for significant differences in deposition fraction between adults and children.

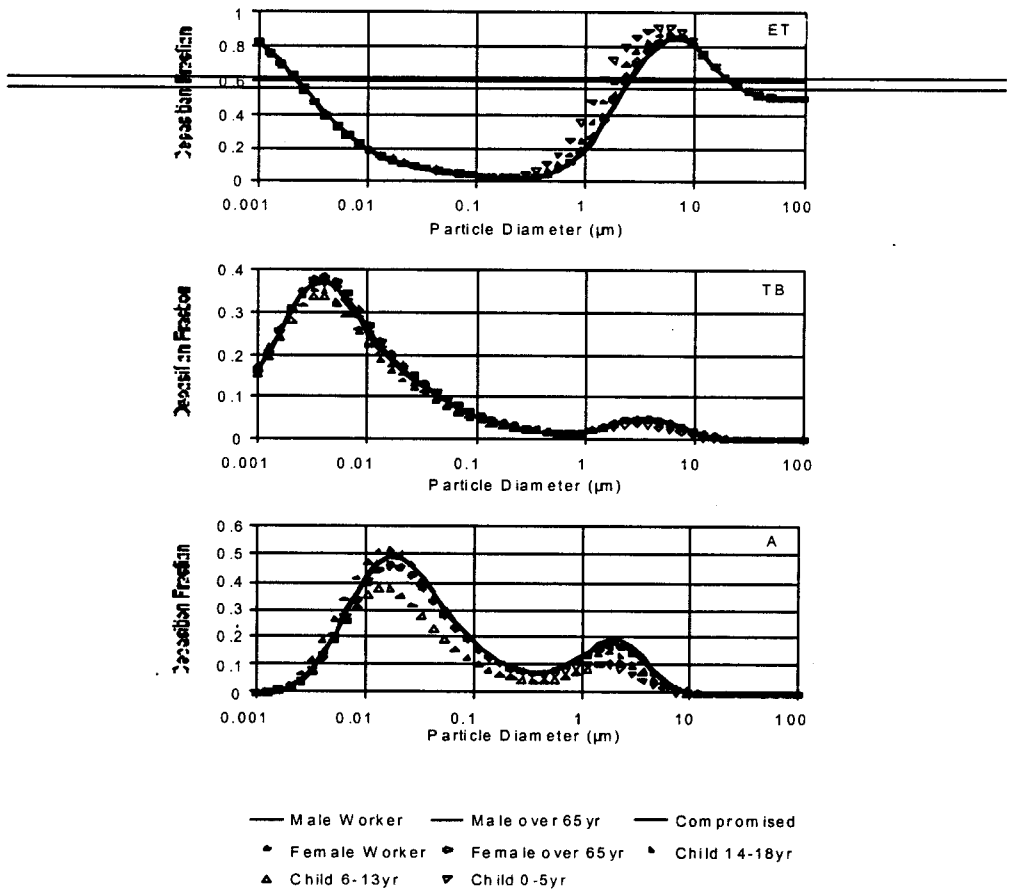

Figure 2. Daily mass particle deposition fraction in each respiratory tract region as predicted by the International Commission on Radiological Protection (ICRP66) (Source: U.S. EPA, 1995).

II.C. PM Doses in Children from Increased Ventilation Rates

While the fraction deposited on a mass basis is not generally very different between adults and children, differences in levels of activity between adults and children play a large role in age-related differences in their respective doses of ambient particles. Children generally have higher activity levels during the day (as noted above), yielding higher daily minute ventilation,

especially when viewed on a per body weight basis. The typical total volume (m^3) breathed in 24 hours for children (0-5 years) is 11.6; children (6-13 years) is 18.2; and for children (14-18 years) is 25.5. The above childhood ventilation rates compare with an average 19.4 m^3 breathed in 24 hours for male worker (18-44 years of age). Thus, even without adjusting for body weight or lung surface area, teenagers breathe a greater volume of air than adults, due to their more active lifestyles, which increases the PM pollution dose they receive. Combining the deposition information in Figure 2 with these ventilation rates, it is seen in Figure 3 that children generally receive a greater inhaled dose of particle mass per given ambient PM mass concentration, especially in children aged 14-18.

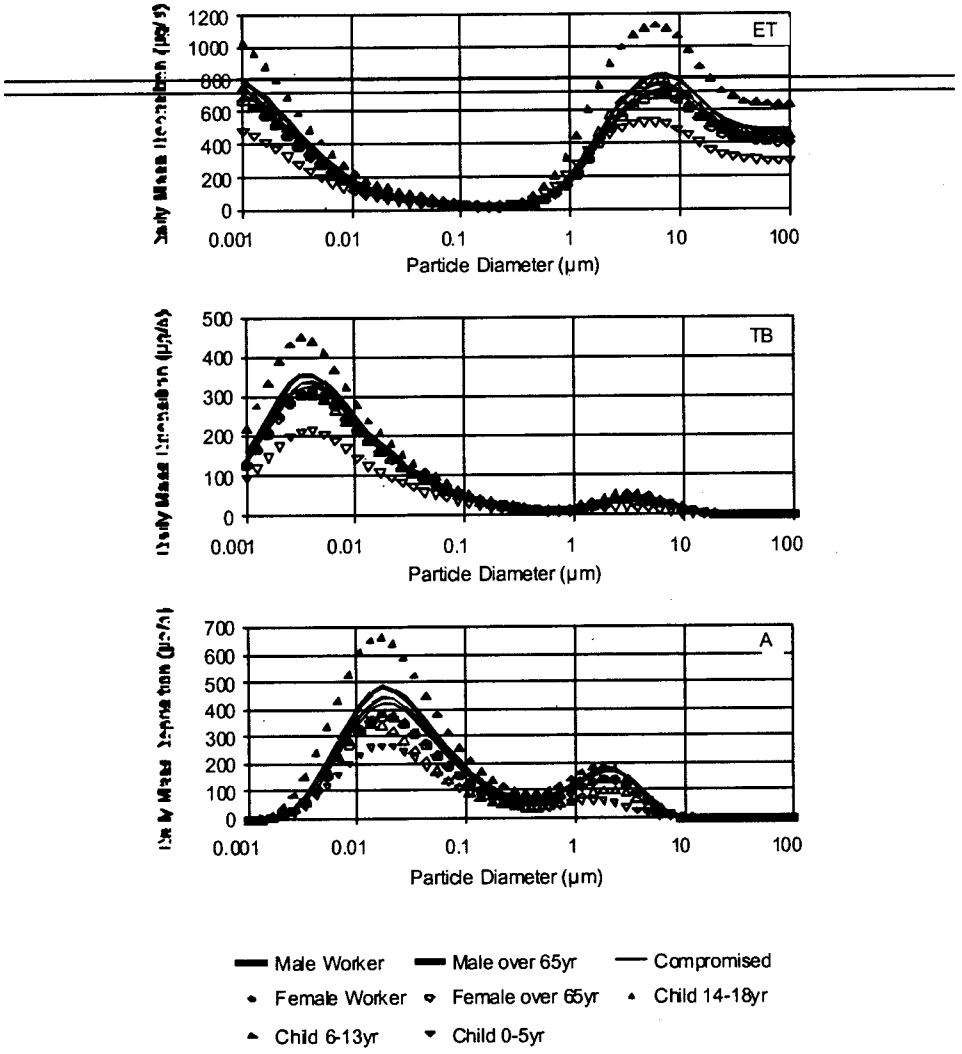

Figure 3. Daily PM deposition rates (ug/day) for 24 hour exposure at 50 ug/m^3 in each respiratory tract region as predicted by the International Commission on Radiological Protection (ICRP66).(U.S. EPA, 1996).

II.D. Doses of Ultrafines among Children 14-18 Years of Age

It is important to note, when evaluating the enhanced mass deposition in the ultrafine fraction for children 14-18 years of age, that the number of particle "hits" may be of paramount importance to health, rather than the PM_{10} mass. Thus, the enhanced alveolar deposition mass shown in Figure 3 in the ultrafine range represents a significant increase in the total number concentration dose experienced by children. The enormous numbers and huge surface area of the ultrafine particles demonstrate the importance of considering the size of the particle in assessing response. Ultrafine particles with a diameter of 20 nm when inhaled at the same mass concentration have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5 um diameter particle, and particle surface area is also greatly increased, as shown in Table 2.

Table 2. Numbers and Surface Areas of Monodisperse Particles of Unit Density of Different Sizes at a Mass Concentration of 10 $\mu g/m^3$

Particle Diameter (μm)	Particle Number (per cm^3 Air)	Particle Surface Area (μm^2 per cm^3 Air)
0.02	2,400,000	3,016
0.1	19,100	600
0.5	153	120
1.0	19	60
2.5	1.2	24
Source: Oberdorster et al. (1995).		

If the number concentration exposure in the alveolar part of the lung is of great health significance, as has been hypothesized by Seaton et al. (1995), then the greater ultrafine exposure in children 14-18 could take on greater importance than the disparities indicated by adult versus childhood mass concentration exposures and doses. Indeed, many studies summarized in the U.S. Environmental Protection Agency's PM Criteria Document (1995) suggest that the surface of particles, or substances that are on or are released from the surface (e.g., acids and/or transition metals), interact with the biological system and that surface-associated free radicals or free radical-generating systems may be responsible for toxicity. Thus, if ultrafine particles were to cause toxicity by a transition metal-mediated mechanism, for example, then the relatively large surface area for a given mass of ultrafine particles would mean higher concentrations of transition metals being available to cause oxidative stress to cells in the lungs of children vs. adults who breathe these aerosols.

II.E. Biological Factors that Increase PM Susceptibility in Children

In addition to differences in the ambient concentrations that children are exposed to relative to adults, the implications of those exposures are different due to biological differences between adults and children. In this section, these differences and their implications are discussed.

1. Enhanced PM Doses in Children per Body Weight and Lung Surface Area

In addition to the fact that children can get higher absolute PM doses due to their greater activities and higher PM personal clouds, children also have smaller lungs and much lower body weights, both of which increase the toxicity of a given PM dose. For example, a newborn typically weighs 3 kg, a young child 10 kg, an older child 33 kg, and an adult 70 kg (Snodgrass, 1992). Thus, PM doses, when viewed on a per kg body weight basis, are much higher for children than adults. This is graphically displayed in Figure 4, which indicates that the amount of air inhaled per kg body weight increases dramatically as age decreases below adult levels, with the inhalation rate (in m^3/kg/day) of a 10-year old being roughly twice that of a 30-year old person, and this estimate does not even consider the higher personal exposure concentrations that a child is usually exposed to as a result of his or her high activity levels. Thus, for a given exposure concentration, young children get roughly 3 times higher air pollution doses than do adults, when viewed on a per unit body weight basis.

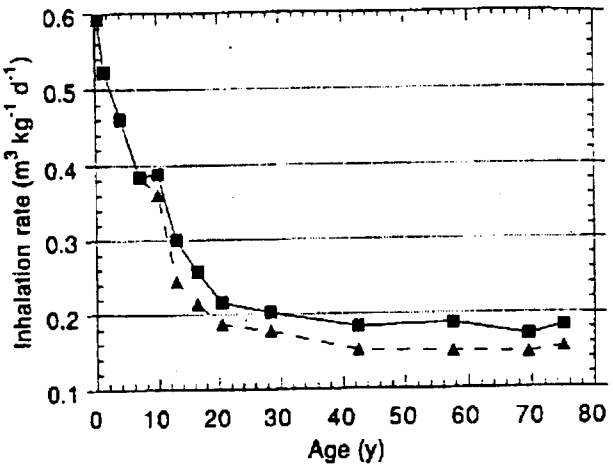

FIGURE 4. Inhalation rates on a per body-weight basis for males (■) and females (▲) by age. (Layton, 1993).

Child-adult dosage disparities are even greater when viewed on a per lung area basis, which may be more important than body weight if the number of particle "hits" per unit lung surface is the important health impact metric, which may well be the case for ultrafine particles. A newborn infant has approximately 10 million alveoli vs. some 300 million as an adult. The alveolar surface area increases from approximately 3 m^2 at birth to about 75 m^2 in adulthood, causing infants' and children's doses per lung surface area to be much higher than in adults, even given the same personal exposures (which is not the case, as they generally have greater PM_{10} personal exposures than adults, as noted above). Thus, PM air pollution doses are significantly higher in children than adults when one considers their higher personal exposures, their greater activity rates, and their smaller body weights and lung surface areas.

2. Diminished and Developing Defense Systems in Infants

As discussed by Plopper and Fanucchi (2000), the limited experimental and epidemiologic studies currently available identify the early post neonatal period of lung development as a time of high susceptibility for lung damage created by exposure to environmental toxicants. For example, due to the relatively diminished defenses of their developing immune systems, infants are disproportionately susceptible to infections and other diseases. Indeed, in 1998 in the U.S., the rate (per 1000) of Meningococcal disease by age group was 11.47 for <1 year versus: 2.75 for 1-4 years; 0.90 for 5-14 years; 1.27 for 15-24 years, 0.41 for 25-39 years; 0.49 for 40-64 years; and, 1.13 for >=65 years (CDC, 1999). Recent research indicates that there is a relationship between respiratory infections and air pollution effects in children (Sarafino et al., 1998). Thus, the higher rate of infectious diseases among infants is an indicator of diminished defenses against health insults, and is likely to cause them to have diminished reserves, and therefore to be more greatly affected by exposures to air pollution.

In addition to their insufficiently developed immune systems, infants are growing rapidly, and limited recent evidence supports the hypothesis that environmental pollution can significantly alter development of the respiratory system at that period of life. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi, 2000; Fanucchi and Plopper, 1997). In addition, acute injury to the lung during early postnatal development causes a failure of normal repair processes, including down-regulation of cellular proliferation at sites of injury in animals. (Smiley-Jewel, et al., 2000, Fanucchi et al., 2000). Thus, it may be that both infants' diminished defenses and pollution-induced impairment of repair mechanisms can therefore coincide during infancy, making the neonatal and post-neonatal period one of especially elevated susceptibility to damage by environmental toxicants like PM.

III. Key Studies of PM and Sulfate Health Effects

As discussed by Bates (1995), air pollution has been documented for many decades to be associated with a wide variety of health impacts in humans, and especially among the elderly and children. Indeed, as shown in the table below, infants less than one year of age (0-1 months Neonatal, 1-12 months Post-neonatal) experienced larger increases in mortality than older children or young adults during the notorious London Fog air pollution episode of 1952, and infants are indicated to be an especially susceptible subgroup of children. Among adults, recent research indicates that those with prior or coincident respiratory infections are among those

especially affected by air pollution (Zanobetti et al, 2000), which may also be a factor placing infants at higher risk of being affected by air pollution, given their high rates of infectious diseases.

Table 3. Deaths Registered in London Administrative County Classified by Age (Bates, 1995)

	< 1 Month of Age	1-12 Mo. Old	1-14 Years of Age	15-44 Years of Age	45-64 Years of Age	65-74 Years of Age	75+ Years of Age
Week Before the Episode	16	12	10	61	237	254	335
Week After the Episode	28	26	13	99	652	717	949
Before/After Episode Ratio	1.75	2.17	1.3	1.62	2.75	2.82	2.83

More recent epidemiological evidence indicates that lower present-day ambient PM air pollution exposure is also associated with adverse health effects in children in general, and, as will be discussed in detail below, these effects can include:

From short-term PM exposures to children:

- reduced pulmonary function;
- increased respiratory symptoms in asthmatics (e.g., asthma attacks) and non-asthmatics;
- increased incidence of respiratory doctor's visits;
- increased incidence of emergency department (ED) visits and hospital admissions (HA's);
- increased mortality, and;
- especially increased infant morbidity and mortality;

From long-term chronic PM exposures to children:

- Reduced lung function;
- increased respiratory symptoms; and,
- Increased infant mortality, intrauterine growth reduction, or pre-term delivery.

The PM indices most commonly evaluated in epidemiological and toxicological studies are those that have been most routinely measured: PM_{10}, total suspended particulate matter (TSP), and Black Smoke (BS, an index of primary carbonaceous particle mass collected primarily in Britain and Europe). However, significant effects are also reported for less often measured $PM_{2.5}$, sulfates (SO_4^-), and acidic aerosols (H^+).

This section seeks to summarize the most pertinent available evidence for acute and chronic health impacts of particulate matter and sulfates (including relevant toxicology, controlled exposures, and epidemiological studies, as available). These discussions emphasize studies involving children and adolescents, but rely on studies among adults when children's studies are not available. This section will also include, to the extent that information is available, a discussion of any special biological reasons for, or scientific evidence of, elevated

susceptibility of infants and children to particulate matter and sulfates, in comparison to the general population.

III.A. Lung Function and/or Respiratory Symptom Effects from Acute PM Exposures

While not as adverse as more severe outcomes, such as medical visits or hospital admissions, symptom and lung function impacts do provide supportive evidence of consistent effects across outcomes, and can become medically important in health impaired individuals (e.g., children with asthma). A variety of PM and or sulfate symptom effects have been found in children, particularly in U.S. studies conducted in California. Cough, phlegm, and lower respiratory infections (LRI) are sometimes found to be associated with air pollution in these studies. Delfino and colleagues' (1998) California study reported stronger symptom effects for 1-h and 8-h PM_{10} exposures, rather than 24-hr average PM_{10}, is noteworthy. This may indicate the need for a PM standard applicable to more acute exposure peaks of only a few hours.

Many asthmatics self-medicate with bronchodilators, which may also be a useful indicator of respiratory distress in these subjects. In the case of the Thurston et al. (1997) study of children with asthma at a summer camp, the medications were prescribed in cases where an asthma exacerbation was verified by a resident physician, indicating this to be a metric of severe air pollution effects associated with acidic sulfates (and ozone) in this case. A number of investigators have found statistically significant peak expiratory flow reduction (PEFR) associated with PM_{10} and other PM indices, and some have reported significant reduction in FEV_1 and FVC. For example, Figure 5 shows the relationship found between sulfates and PEFR, lower respiratory chest symptoms, and medication use in children with asthma in the Thurston et al summer camp study.

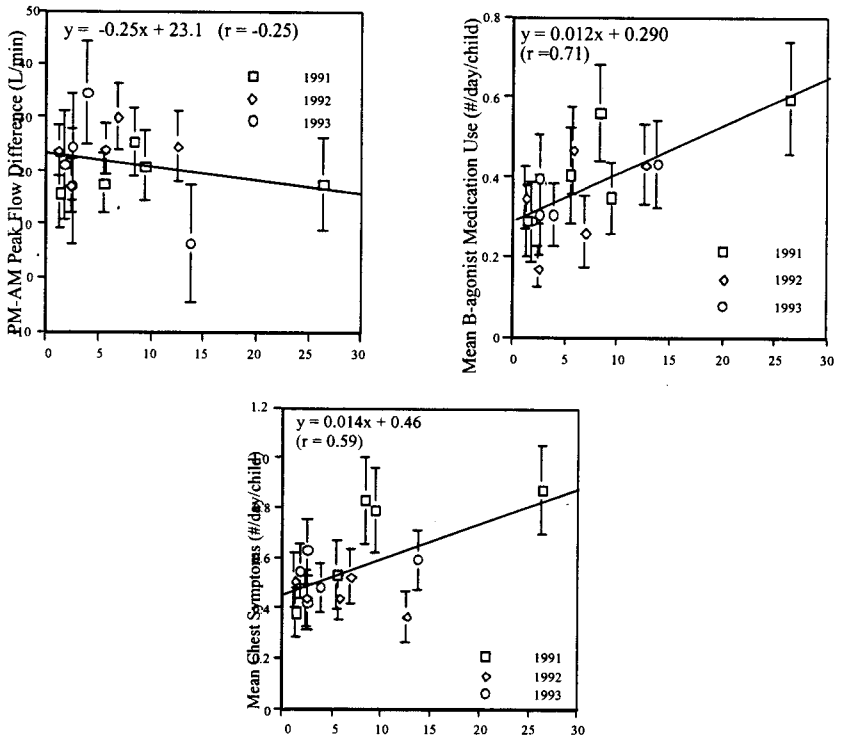

Figure 5. Lung Function, Symptom, and Inhaler Medication Use Association with Sulfate Concentration in children (ages 8-12) with asthma at a summer camp (Thurston et al., 1997)

Thus, as indicated by the studies summarized in Table 4, there is an overall indication that respiratory symptoms in children are exacerbated by exposure to airborne particles and sulfates. These effects have greater health implications in children with asthma, and can and do lead to an increased incidence of asthma attacks. Since the prevalence of asthma is much higher among children than among adults (CDC, 1996a,b), these enhanced acute effects of air pollution on those with asthma put more children at higher risk of PM health effects than adults.

III.B. Lung Function and/or Respiratory Symptoms from Long-Term PM Exposures

For decades, there has been accumulating evidence suggesting that higher long-term ambient particulate matter exposures are associated with higher rates of chronic respiratory disease. Much of this evidence has been based on cross-sectional analyses, comparing disease or symptom prevalence rates in different communities with different average pollution levels (e.g., Ferris et al., 1973; 1976; Hodgkin et al., 1984; Mullahy and Portney, 1990). This type of study is able to indicate associations, but they are often criticized because these analyses cannot be controlled for confounding factors on an individual level, and are more likely to be subject to ecological confounding than prospective cohort studies. Also, chronic symptoms presumably occur as a result of long-term exposures, but cross-sectional analyses are not very informative as to whether, for example, it is the five-year average, the twenty-year average, or the number of times a given level is exceeded that is the relevant health effects exposure measure.

TABLE 4. Recent U.S. Panel Studies Of Pulmonary Function Tests or Acute Respiratory Symptoms Associated with PM Exposure in North American Children

Study	Health Endpoints	Ages (yrs.)	PM Effects	Pollutants Considered	Remarks (N)
Ostro et al. (1995) Los Angeles, CA	Asthma symptoms for at least six weeks	7-12	Shortness of breath risk, 9% per 10 ug/m^3 PM_{10}	PM_{10}, TSP, SO_4, NO_3, O_3, SO_2, NO_2	African-American (N = 83)
Delfino et al. (1998) Alpine, CA	Bothersome asthma symptoms	9-17	Symptoms signif. 1-h, 8-h PM_{10}, 24-h less signif.	PM_{10}, O_3 (others low)	Panel of asthmatics (N = 25)
Delfino et al. (1997) Alpine CA	Symptom score, bronchodilator use		PM_{10} signif. dilator use	PM_{10}, O_3	Asthmatics (N = 13)
Delfino et al. (1996), San Diego, CA	Symptom scores, bronchodilator use		Signif. O_3 personal monitor, N.S. SAM O_3, $PM_{2.5}$	$PM_{2.5}$, O_3	Asthmatics (N = 12)
Hoek et al. (1998) re-analyses of 4 other studies in the U.S. and the Netherlands	PEF, large changes related to symptoms		Signif. PEFR, Cough PEFR N.S. PEFR N.S. PEFR N.S.	PM_{10}	Utah Valley Bennekom Uniontown St. College
Linn et al. (1996) southern CA	Pulmonary function		Morning FVC signif. PM5?, NO_2	PM5?, NO_2	School children (N = 269)
Thurston et al. (1997) Connecticut summer camp	lung function, symptoms, dilator use	8-12	SO_4, O_3 assoc. with symptoms, PEFR, dilator use	PM_{10}, SO_4, H+, O_3,	Asthmatic children (n=55)

Key: PEF = peak expiratory flow; PEFR = reduction in PEF; N.S.= not statistically significant (two-tailed, P > 0.05).

Source: Adapted from US EPA (1998)

More recently published articles have followed cohorts, answering the major criticisms of past studies by allowing confounder controls at the individual level. Abbey and colleagues (1991; 1993; 1995a,b) have reported results of a 10-year cohort study conducted at Loma Linda University in California with a large sample of nonsmoking adults. This follow-up allowed for measures of exposure over the 10-year period and for obtaining information on changes in chronic respiratory disease incidence over time. Abbey et al. (1995a) extends those earlier studies by analyzing associations between these chronic respiratory disease outcomes and both fine particles and sulfates. Logistic models were fitted using the mean concentration of these two pollutants, along with PM_{10}, ozone, and other pollutants. Fine particles were estimated from empirical estimates related to airport visibility. Regarding sulfates, a statistically significant association was observed with airway obstructive disease (AOD). Abbey and colleagues found no association with either SO_2 or NO_x, but sulfate exposure was associated with changes in the severity of AOD and chronic bronchitis over the ten-year study period. Thus, new cases of disease were able to be analyzed in relation to pollution exposure for a matching time period in these studies, providing a more definitive concentration-response function for chronic respiratory disease, while confirming past "ecological" study results.

Children are likely to be at greater risk from long-term exposures because their bodies are growing, and their developmental processes, especially in the lung, may well be interfered with by air pollution exposures. Table 5 shows a number of recent studies involving school-age children indicating adverse respiratory effects from longer-term PM exposures. PM_{10} is not always significantly associated with adverse health effects in these studies, although other PM indicators sometimes are (e.g., $SO_4^=$, H^+). The mechanisms by which elevated PM exposure over

long periods of time may be associated with increased risk of respiratory symptoms or decreased pulmonary function in children are not now understood, but may be analogous to the cumulative effects of smoking or environmental tobacco smoke (ETS) on the human respiratory system.

TABLE 5. Recent PM Studies Of Pulmonary Function Tests Or Respiratory Symptoms Associated With Long-Term PM Exposure In North American School-Age Children

Study	Endpoint	Ages (years)	Significant PM Associations	Pollutants Considered	Remarks (N)
Dockery et al. (1996) 24 U.S. & Can.. Communities	Various	8-12	SO_4 signif. bronchitis; PM_{10} N.S. any endpoint	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Raizenne et al. (1996) 24 U.S., Canadian Communities	Pulmonary function	8-12	Strong signif. H+, Signif. PM_{10}	PM_{10}, PM2.1, SO_4, H+, SO_2, O_3	
Peters et al. (1999a,b) 12 So. CA communities	Asthma, bronchitis, cough, wheeze, lung function	9-12	PM_{10} signif. FVC, FEF25-75% N.S. FEV_1, symptoms, PEFR,		(N =150 each, in grades 4, 7)

Source: Adapted from US EPA (1998)

III.C. Incidence of Medical Visits and Hospital Admissions from Acute PM Exposures

Numerous studies have related acute PM exposure with an increased incidence of hospital admissions (e.g., see Figure 6), but only a limited number have specifically studied the subgroup that are children. Burnett et al (1994) examined the differences in air pollution-hospital admissions associations as a function of age in the province of Ontario. As shown in Table 6, this analysis indicated that the largest percentage increase in admissions was found among infants (neonatal and post-neonatal, one year or less in age), just as was the case for the mortality effects during the London fog of 1952 (see Table 3).

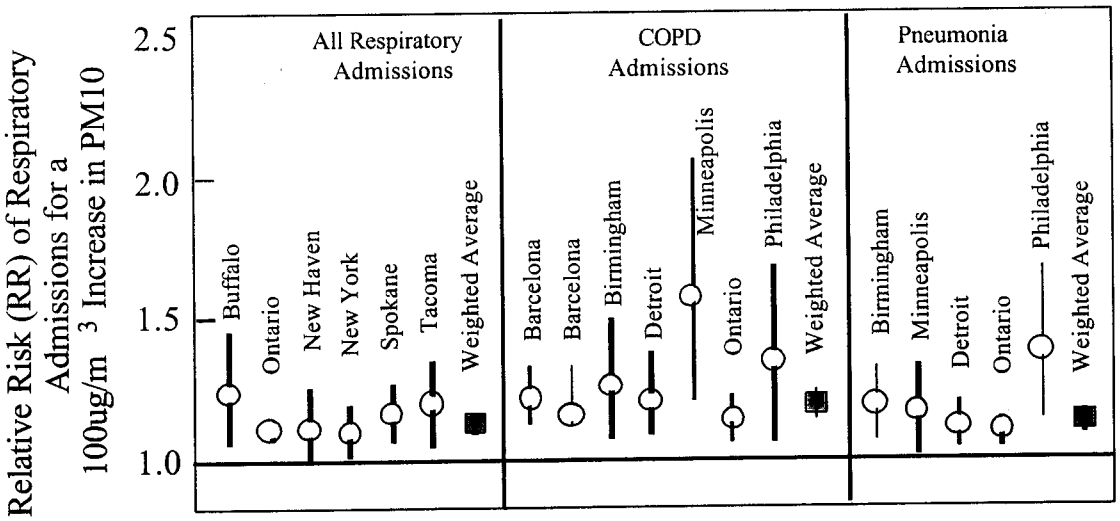

Figure 6. Summary of Respiratory Hospital Admissions-PM_{10} Relative Risk Estimates from Air Pollution Studies Around the World (Schwartz, 1997)

Table 6. Percent Increase in Respiratory Hospital Admissions Associated with Sulfate (5.3 ug/m^3) and Ozone (50 ppb) Air Pollution in Ontario, Canada, by Age (Burnett et al, 1994)

	< 1 Year of Age	2-34 Years of Age	35-64 Years of Age	75+ Years of Age
Asthma Admissions	13.0	5.5	9.8	7.0
Total Respiratory Admissions	14.8	5.5	7.2	4.3

More recent hospital admissions studies listed in Table 7 also indicate positive and often statistically significant associations between PM exposures and medical visits or hospital admissions by children. However, some of these PM-health effect associations listed in Table 7 became statistically non-significant when gaseous co-pollutants were included in the model, including O_3, SO_2, NO_2, CO. This may be due to a statistical artifact of pollutant inter-correlations over time causing enlarged coefficient standard errors, or may suggest that the co-pollutant mixture can collectively play a role in the effects of PM on children (e.g., through gas-particle interactions).

Looking in more detail at the results from each study in Table 7, as provided in Appendix A, reveals that the PM RR's for all children (e.g., 0-14 yrs.) are not usually noticeably larger than those for adults, but such comparisons of RR's must adjust for differences in the baseline risks for each group. For example, if hospital admissions per 100,000 per day for young children are double the rate for adults, then they will have a pollution relative risk (RR) per ug/m^3 that is half that of the adults given the exact same impact in admissions/100,000/ug/m^3/day. Thus, it is important to adjust RR's or Excess Risks (ER's) for each different age groups' baseline, but this information is usually not available (especially the population catchment for each age group in each study). One of the only signals that comes out clearly when comparing children with adults in Appendix A is for the group <1 yr. of age, which (despite higher baseline rates) usually has RR's larger than for other children or adults, as previously found in the Burnett (1994) study.

TABLE 7. Recent Key PM Studies Of Associations Between Medical Visits Or Hospital Admissions and Short-Term PM Exposure In Children

Study	Endpoint	Ages (yrs.)	PM Effects	Pollutants	Remarks (N)
Delfino et al. (1997) Montreal PQ	Emergency Dept. Visits (EDV), 1992-1993	0-1	H+ signif. only 1993	PM_{10}, $PM_{2.5}$, SO_4, H+, O_3	
Medina et al. (1997) Paris, France	Doctor's house calls	0-14	Asthma signif. BS.	PM_{13}, BS, SO_2, NO_2, O_3	Similar RR for PM13, SO_2, NO_2
Sunyer et al. (1997) Barcelona Helsinki London, Paris	emergency hospital admissions (HA's) for asthma	0-14	BS positive, N.S. NO_2 and SO_2 signif.	BS, NO_2, SO_2	
Anderson, et al. (1998) London, UK	HA's for asthma	0-14	BS positive, Signif.	BS, O_3, SO_2, NO_2	O_3, SO_2, NO_2, BS all pos. assoc.
Garty et al. (1998) Israel	EDV for asthma	1-18	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2	N = 1076
Morgan et al, 1998 Sydney, AU	Asthma, COPD, and Cardiac HA's	0-14	PM (nephelometry) NS, NO_2 signif.	PM (nephelometry), O_3, and NO_2	
Rosas et al. (1998) Mexico City	emergency HA's for asthma	0-15	PM_{10} N.S.	PM_{10}, TSP, O_3, SO_2, NO_2	grass, fungal spores signif.
Atkinson et al. (1999) London UK	EDV for respiratory complaints	0-14	PM_{10} signif. total resp., asthma	PM_{10}, BS, O_3, SO_2, NO_2, CO	N.S. in 2-poll. models w. SO_2, NO_2
Atkinson et al. (1999) London UK	Hospital admissions for respiratory complaints	0-14	PM_{10} signif. total resp., asthma	PM_{10}, BS, O_3, SO_2, NO_2, CO	N.S. in 2-poll. models w. SO_2, NO_2
Norris et al. (1999) Seattle WA	EDV for asthma	0-17	PM_{10} signif. all hosp., lt.-scatter each	PM_{10}, light scatter, CO, SO_2, NO_2	PM_1 index from light scattering
Lin et al. (1999) Sao Paulo, Brazil	Respiratory emergency visits	0-12	PM_{10} signif. w. and w/o co-pollutants	PM_{10}, O_3, SO_2, NO_2, CO	LRI, URI, wheezing w. co-pollutants
Braga et al. (1999) Säo Paulo, Brazil	Hospital admissions	0-12	PM_{10} signif., not w. O_3, CO	PM_{10}, SO_2, NO_2, CO	
Ostro et al. (1999) Santiago, Chile	Medical visit for LRI, URI	<2 2-15	LRI 4-12% LRI 3-9%	PM_{10}, O_3	
Hajat et al. (1999) London U.K.	GP visits for asthma, LRI	0-14	PM_{10} N.S., BS signif. LRI	PM_{10}, BS, O_3, SO_2, NO_2, CO	
Wong, et al (1999) Hong Kong, CH	Respiratory HA's	0-4	PM_{10} NO_2, and O_3 signif., SO_2 not signif.	PM_{10}, NO_2, SO_2, O_3	
Gouveia et al (2000) Sao Paulo, BR	Respiratory, Pneumonia, and asthma HA's	<1 <5	Only PM signif., with larger RR than for <5 (pneumonia) All poll RR's>1, but NS. for asthma. Only SO_2 signif for Pneum., and only O_3 signif. for all resp.	PM_{10}, NO_2, SO_2, O_3	

Source: Adapted from US EPA (1998)

Two recent studies have found that air pollution-admissions associations are also stronger for the poor, which has special implications for children. Nauenberg et al. (1999) analyzed the effect of insurance status on the association between asthma-related hospital admissions and exposure to atmospheric particulate matter (PM_{10}) and ozone (O_3) using hospital discharge and air quality data for 1991-1994 for central Los Angeles. They used regression techniques with weighted moving averages (simulating distributed lag structures) to measure the effects of exposure on overall hospital admissions, admissions of uninsured patients, admissions for which MediCal (California Medicaid) was the primary payer, and admissions for which the primary payer was another government or private health insurance program. No associations were found between asthma admissions and O_3 exposure in

LA. An estimated increase from 1991 to 1994 of 50 micrograms per cubic meter in PM_{10} concentrations averaged over eight days was, however, associated with an increase of 21.0% in the number of asthma admissions. An even stronger increase--27.4%--was noted among MediCal asthma admissions. The authors conclude that low family income, as indicated by MediCal coverage, is a useful predictor of strength of asthma associations with air pollution. Similarly, Gwynn and Thurston (2000) have recently found that air pollution effects are worse in the poor and working poor than in other groups, and that these differences account for apparent racial differences in air pollution effects in New York City. These studies' results both indicate that children are especially at risk from air pollution, as they more often live in poverty than any other age group (e.g., in 1989, 27.3% of children in LA lived in poverty, as compared to 18.9% overall, and 10.5% for those 65+ years of age) (U.S. Census, 1994).

III.D. Infant and Child Mortality Associated with Acute PM Exposures

Table 8 shows the results of recent studies in which excess mortality was associated with PM. Significant mortality was reported in three of the four studies, using $PM_{2.5}$ exposure for infants in Mexico City (Loomis et al., 1999), TSP exposure for school- age children (but not younger children) in Delhi (Cropper et al., 1997), and PM_{10} exposure for a composite group of children 0-5 years in Bangkok (Ostro et al., 1998). Pereira et al. (1998) did not find excess stillbirths associated with PM_{10} in Sao Paulo. These studies are highly diverse in terms of age group, location, and environment. As with adult mortality, we do not now know the exact biological mechanisms that specifically account for excess child mortality from short exposures to PM at levels found in these Latin American and Asian countries. However, the available studies suggest that short-term PM exposure in general may cause deaths of some children in urban environments. The mortality findings are consistent with findings noted above of less serious health effects from short-term PM exposure, including lung function decreases, respiratory symptoms, asthma attacks and medical visits that may affect substantial numbers of children.

Table 8. Neonatal, Infant, And Child Mortality Attributable To Short-Term PM Exposure

Study	Mortality	Ages	PM Effects	Pollutants	Remarks (N)
Loomis et al. (1999) Mexico City	Total	0-11 mo.	$PM_{2.5}$ signif. w and w/o co-pollutant	$PM_{2.5}$, O_3, NO_2	
Pereira et al. (1998) São Paulo, Brazil	Intrauterine	0 d	PM_{10} N.S.	PM_{10}, O_3, SO_2, NO_2, CO	
Cropper et al. (1997) Delhi, India	Total, cardiovascular, respiratory	0-4 yr. 5-14 yr.	TSP N.S. for total mort. TSP signif. for total mort	TSP, SO_2, NO_x	Similar RR in both age groups
Ostro et al. (1999) Bangkok, Thailand	Total, cardiovascular, respiratory	0-5 yr.	PM_{10} signif. all	PM_{10}, $PM_{2.5}$	

Source: Adapted from US EPA (1998)

III.E. Increased Infant and Child Mortality Associated with Long-Term PM Exposures

A number of studies suggest that the very young represent an especially susceptible sub-population, although the precise magnitude of the effects of specific levels of air pollution can be expected to vary with other underlying conditions. Lave and Seskin (1977) found mortality among those 0-14 years of age to be significantly associated with TSP. More recently, Bobak and Leon (1992) studied neonatal (ages less than one month) and post-

neonatal mortality (ages 1-12 months) in the Czech Republic, finding significant and robust associations between post-neonatal mortality and PM_{10}, even after considering other pollutants. Post-neonatal respiratory mortality showed highly significant associations for all pollutants considered, but only PM_{10} remained significant in simultaneous regressions. Woodruff et al. (1997) used cross-sectional methods to follow-up on the reported post-neonatal mortality association with outdoor PM_{10} pollution in a U.S. population. This study involved an analysis of a cohort consisting of approximately 4 million infants born between 1989 and 1991 in 86 U.S. metropolitan statistical areas (MSA's). After adjustment for other covariates, the odds ratio (OR) and 95% confidence intervals for total post-neonatal mortality for the high exposure versus the low exposure group was 1.10 (CI=1.04-1.16). In normal birth weight infants, high PM_{10} exposure was associated with mortality for respiratory causes (OR = 1.40, CI=1.05-1.85) and also with sudden infant death syndrome (OR = 1.26, CI=1.14-1.39). Among low birth weight babies, which are lower in counts (and therefore with greater uncertainty and power) high PM_{10} exposure was associated, but not significantly, with mortality from respiratory causes (OR = 1.18, CI=0.86-1.61).

The Woodruff et al. (1997) study was recently corroborated by a more elegant follow-up study by Bobak and Leon (1999), who conducted a matched population-based case-control study covering all births registered in the Czech Republic from 1989 to 1991 that were linked to death records. They used conditional logistic regression to estimate the effects of suspended particles, sulfur dioxide, and nitrogen oxides on risk of death in the neonatal and post-neonatal period, controlling for maternal socioeconomic status and birth weight, birth length, and gestational age. The effects of all pollutants were strongest in the post-neonatal period and were specific for respiratory causes. Only particulate matter showed a consistent association when all pollutants were entered in one model. Thus, it appears that PM is the air pollutant metric most strongly associated with excess post-neonatal deaths.

Collectively, all the recent studies of children less than one year old presented in Table 9 indicate severe adverse consequences to the mother, fetus, and infant from prolonged PM exposure during and shortly after pregnancy. There appears to be a possible relationship between preterm birth (< 37 weeks gestational age) or low birth weight (< 2,500 g) and PM exposure in several locations. A significant relationship with PM_{10} and $PM_{2.5}$ was found in Teplice, Czech Republic (Dejmek et al., 1999), but not with PM_{10} in Los Angeles (Ritz and Yu, 1999). In the case of Ritz and Yu, CO was significant, which might well be serving as an index of traffic-related pollution effects, and therefore possibly related to diesel particulate matter (DPM), but this is not evaluated. Bobak and Leon (1999) did not find a relationship of low birth weight to TSP. There was a significant risk of low birth weight and pre-term delivery in Beijing (Xu et al., 1995; Wang et al., 1997) associated with TSP, but SO_2 was the only co-pollutant considered. However, low birth weight is known to be an important risk factor for infant mortality, so that the findings of excess mortality in U.S. and Czech infants (Woodruff et al., 1997; Bobak and Leon, 1999) are consistent with many of the other findings on intrauterine growth reduction (IUGR), which is supportive of a causal relationship between PM exposure and adverse health effects in this age group.

Several methodological differences across studies make generalized conclusions more difficult to make. Dejmek et al. (1999) characterize IUGR as low-weight-for-gestational-age, whereas others use a fixed weight for full-term infants (37 to 44 weeks) without adjusting for gestational age. Dejmek et al. (1999) also find the average PM during the first month of pregnancy as the index of fetal exposure, whereas Xu et al. (1995), Wang et al. (1997),

and Ritz and Yu (1999) use final trimester averages. Despite these methodological differences, there appears to be an identifiable PM risk to the fetus and infant.

A very recent study of infant mortality in U.S. counties indicates that these effects can occur in the U.S., as well (Chay and Greenstone, 1999). This study uses sharp, differential air quality changes across sites attributable to geographic variation in the effects of the 1981-82 recession to estimate the relationship between infant mortality and particulate matter air pollution. It is shown that, in the narrow period of 1980-82, there was substantial variation across counties in changes in particulate (TSP) pollution, and that these differential pollution reductions appear to be independent of changes in a multitude of other socio-economic and health care factors that may be related to infant mortality. The authors find that a 1 ug/m^3 reduction in TSP resulted in about 4-8 fewer infant deaths per 100,000 live births at the county level of the roughly 1,300 U.S. infant deaths in the first year of life per 100,000 live births (a 0.35-0.45 elasticity). The estimates are remarkably stable across a variety of specifications. The estimated effects are driven almost entirely by fewer deaths occurring within one month and one day of birth (i.e., neonatal), suggesting that fetal exposure to pollution may have adverse health consequences. The estimated effects of the pollution reductions on infant birth weight in this study provide evidence consistent with the infant mortality effects found, suggesting a causal relationship between PM exposure and infant mortality, especially in the first month of life.

Table 9. Adverse Infant Health Effects Associated With Long-Term PM Exposure

Study	Effects	Ages	PM Effects	Pollutants	Remarks (N)
Bobak and Leon (1992) Czech. Repub.	Total infant mortality, respir. mort.	0+ d neonatal post-neonatal post, respir.	TSP-10 N.S. TSP signif. TSP signif.	TSP-10, SO_2, NO_x	Ecologic study; TSP indexed as 90th percentile
Bobak and Leon (1999) Czech. Rep.	Low birth wt. Stillbirth	0 d	TSP N.S.	TSP, SO_2, NO_x	
Chay and Greenstone (1999) California Counties	Infant mortality	0-1 yr.	TSP Signif.	TSP	1 ug/m^3 reduction associated with 4-8 fewer deaths per 100k live births
Dejmek et al. (1999) Teplice, Czech. Rep.	Intrauterine growth reduction	0 d	First month $PM_{2.5}$ > 37, PM_{10} > 40 signif.	PM_{10}, $PM_{2.5}$, SO_2, NO_x, PAH	30-d avg. PM per month of pregnancy
Ritz and Yu (1999) Los Angeles, CA	Low birth weight (adj. Gest age)	0 d	Last trimester PM_{10} N.S.	PM_{10}, O_3, NO_2, CO	CO signif., may be index of traffic air poll., e.g. DPM
Wang et al. (1997) Beijing, PRC	Low birth weight	0 d.	TSP signif. increases risk of LBW	TSP, SO_2 in third trimester	SO_2 also signif. Small reduc. mn.wt.
Woodruff et al. (1997)	Total infant mortality, SIDS, resp.	1-11 mo.	PM_{10} signif. total, SIDS, respir. NBW	PM_{10}	PM_{10} avg. over 2 mos.
Xu et al. (1995) Beijing, PRC	Preterm gestational age	0 d	TSP signif. lag 5-10 days	TSP, SO_2	SO_2 also signif.

Source: Adapted from US EPA (1998)

III.F. Evidence for a Role of Sulfates in PM Health Effects

The characteristics of particles responsible for the adverse health effect associations of PM are not yet known. However, lung injury has been postulated to be mediated by ultrafine

particles, biological agents (e.g., endotoxin), acid aerosols, organic fraction of PM and oxidant generation catalyzed by transition metals associated with particles. Of these, the role of acidic combustion aerosols and their possible mechanisms for effects are among the best documented.

While significant associations are sometimes reported between total suspended particulate (TSP) and health effects in large populations, the degree of association in studies comparing various PM indices (e.g., Ozkaynak and Thurston, 1987; Dockery et al., 1993; Thurston et al., 1994) is as follows:

$$TSP < PM_{10} < PM_{2.5} < SO_4^{=}$$

Each metric is essentially a subset of the one to its left, implying that $SO_4^{=}$, or something in the mixture closely associated with it, is a likely causal factor in the effects reported.

The sulfate ion itself is an unlikely causal factor if it is in a neutralized state. It is already present in body fluids at relatively high concentrations, and controlled inhalation studies in humans and laboratory animals of pH neutral or nearly neutral sulfate salts, such as ammonium sulfate [$(NH_4)_2SO_4$], even at relatively high concentrations, produce none of the effects reported from the epidemiologic studies (Utell et al., 1983; Lippmann et al., 1987; Schlesinger, 1989; Schlesinger et al., 1990). What these controlled exposure studies do show is that sulfate aerosols containing strong acids, such as sulfuric acid (H_2SO_4) and, to a lesser extent, ammonium bisulfate (NH_4HSO_4), do produce functional and structural changes in healthy subjects consistent with those observed in epidemiological studies, and do so at exposures within the upper bounds of current H^+ ambient levels. Furthermore, it is reasonable to speculate that the effects seen in the epidemiological studies are occurring in hyper-susceptible segments of the population, and that controlled exposure studies in susceptible human and animal cohorts, if they could be ethically performed, might well produce comparable effects at low ambient levels of H^+. A working hypothesis, therefore, is that H^+ is a causal factor for human health effects (e.g., see Lippmann and Thurston, 1996) and that, among the commonly measured PM indices, $SO_4^{=}$ is the best surrogate metric for H^+.

Historical and present-day evidence suggest that there can be both acute and chronic effects by acidic sulfates on human health. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations (on the order of 400 ug/m^3 as H_2SO_4, or roughly 8,000 $nmoles/m^3$ H^+) may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and SO_2 (Ministry of Health of Great Britain, 1954). In addition, Thurston et al. (1989) and Ito et al. (1993) both found significant associations between acid aerosols and mortality in London during non-episode pollution levels (30 ug/m^3 as H_2SO_4, or approximately 600 $nmoles/m^3$ H^+), though these associations could not be separated from those for BS or SO_2.

Attempts to date to associate present-day levels of acidic aerosols in the U.S. with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993, Schwartz et al., 1996, and Gwynn, et al., 2000) have had more

mixed results, but there may not have been a sufficiently long series of H^+ measurements to detect H^+ associations in many of these studies. In the Utah Valley studies (Pope et al. 1991, 1992), PM_{10}-health effects association were found, despite limited H^+ sampling indicating low acid aerosol levels. This is not inconsistent with adverse health effects from H^+, however, when it is considered that PM can contain numerous toxic agents other than H^+. The more recent work of Gwynn et al. (2000) reported significant pollutant-health effect associations in Buffalo, NY--most strongly between $SO_4^=$ and respiratory hospital admissions (as indicated by its t-statistic). Additionally, H^+ and $SO_4^=$ demonstrated the most coherent associations with both respiratory hospital admissions and respiratory mortality. The authors concluded that "acidic sulfate aerosols represent a component of PM air pollution that may contribute to the previously noted adverse effects of PM mass on human health."

Pope et al. (1995) linked ambient air pollution data from 151 U.S. metropolitan areas in 1980 with individual risk factor on 552,138 adults who resided in these areas when enrolled in a prospective study in 1982. Deaths were ascertained through December 1989. Exposure to $SO_4^=$ and $PM_{2.5}$ pollution was estimated from national databases. The relationships of air pollution to all-cause, lung cancer, and cardiopulmonary mortality were examined using multivariate analysis that controlled for smoking, education, and other risk factors at the individual level. An association between mortality and particulate air pollution was observed. Figure 7 shows the range of values for the adjusted mortality rates in the various communities versus annual average $SO_4^=$ concentrations. The Pope et al. (1995) results thus indicate that the concerns raised about the credibility of the earlier results, due to their inability to control for potentially confounding factors such as smoking and socioeconomic variables on an individual level, can be eased, and these findings are consistent with the prior findings of Ozkaynak and Thurston (1987) and Lave and Seskin (1970, 1977). Adjusted relative risk ratios (and 95% confidence intervals) of all-cause mortality for the most polluted areas compared with the least polluted were $RR(SO_4^=)$ =1.15 (1.09 to 1.22) and $RR(PM_{2.5})$ = 1.17 (1.09 to 1.26). The findings of Dockery et al. (1993) and Pope et al. (1995) in prospective cohort studies also indicate that mean lifespan shortening of long-term exposures to PM is of the order of two years (Brunekreef, 1997). This implies that some individuals in the population have lives shortened by many years, and that there is excess mortality associated with long-term fine particle exposure that is greater than that indicated by an accumulation of acute effect estimates provided by the time-series studies of daily mortality.

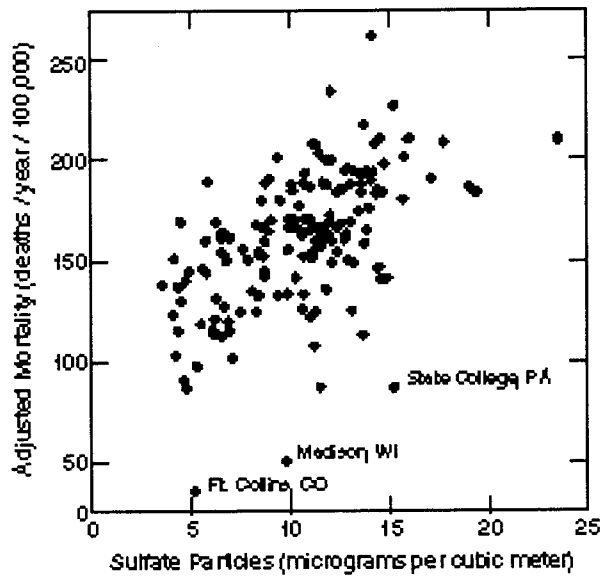

Figure 7. Age-, sex-, and race-adjusted population-based mortality rates for 1980 plotted against mean sulfate air pollution levels for 1980. Data from metropolitan areas that correspond approximately to areas used in prospective cohort analysis. From: Pope, C.A. et al., Am. J. Respir. Crit. Care Med. 151:669-674 (1995).

Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has also been observed under present-day conditions. Thurston et al. (1992) and Thurston et al. (1994) have noted associations between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding temperature effects. In the latter of these studies, significant independent H^+ effects remained even after simultaneously considering the other major co-pollutant, O_3, in the regression model. While the New York State study considered only ozone as a possible confounder, the Toronto study also considered NO_2 and SO_2, but found them to be non-significant. In the Toronto analysis, the increase in respiratory hospital admissions associated with H^+ was indicated to be roughly six times that for non-acidic PM_{10} (per unit mass). In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes ($H^+ > 10$ ug/m^3 as H_2SO_4, or 200 nmoles/m^3 H^+). These studies provide evidence that present-day strongly acidic aerosols can represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Burnett et al. (1994) has related the number of emergency or urgent daily respiratory admissions at 168 acute care hospitals in all of Ontario during 1983 to 1988 to estimates of ozone and sulfates in the vicinity of each hospital. The authors reported that SO_2 and NO_2 were only weakly correlated with SO_4 in these data ($r = 0.3$), so these pollutants were unlikely to be confounders. Long-wave cycles in the admissions data were removed using a 19-day moving average equivalent high pass filter. A random effects model (wherein hospital effects were assumed to be random) was employed, using the generalized estimating equations (GEE). After adjusting admissions data for seasonal patterns, day of week effects, and individual hospital effects, positive and statistically significant associations were found between hospital admissions and both ozone and sulfates lagged 0 to 3 days. Positive associations were found in all age groups (0 to 1, 2 to 34, 35 to 64, 65+). The bivariate relationship found between adjusted admissions and sulfates in these data are shown in Figure 8. Positive and significant air pollution

associations were found for asthma, chronic obstructive pulmonary disease (COPD), and infections, but not for nonrespiratory (control) admissions, nor for respiratory admissions in the winter months (when people are indoors and levels of these pollutants are low). While these analyses employed much more sophisticated statistical methods, the results generally consistent with Bates and Sizto's prior work in this region, though ozone was found to yield a larger effect than sulfates in this study. The authors point out that $PM_{2.5}$ and H^+ are highly intercorrelated with sulfates in the summer months ($r > 0.8$), and that one of these agents may be responsible for the health effects relationships found with sulfates in this work.

Ostro (1988) also conducted a cross-sectional analysis of the U.S. Inhalable Particle Monitoring Network airborne particulate matter dataset, but analyzed the 1979-1981 annual Health Interview Surveys (HIS) to test if there were morbidity associations coherent with those found for mortality by Ozkaynak and Thurston during this period. Ostro reported a stronger association between several measures of morbidity (work loss days, restricted activity days, etc.) and lagged fine particle estimates than found with prior 2-week average TSP levels in 84 U.S. cities. In this analysis, a Poisson model was employed, due to the large number of days with zero cases in the dependent variables, and the analyses focused on adults aged 18 to 65. Smoking was not considered in the model, since not all metropolitan areas had data, but the correlation between smoking and any of the pollutants was less than 0.03 and non-significant in the one-third of the HIS sample for which smoking data were available. This indicates that, while presumably important to morbidity, smoking is not a confounder to pollutants in such cross-sectional analyses. Ostro concluded that his findings were consistent with the results of prior cross-sectional analyses reporting an association between mortality and exposures to fine particles and sulfates.

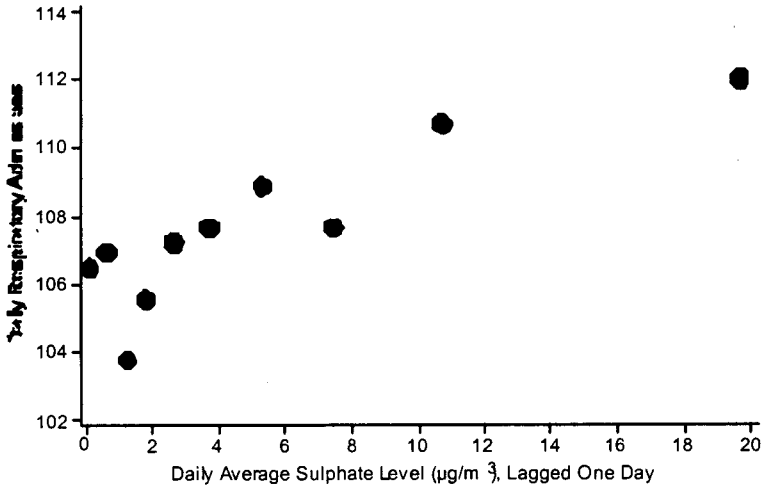

Figure 8. Average number of respiratory admissions among all 168 Ontario hospitals adjusted for other factors, by decile of the daily average sulfate level (ug/m^3), 1 day lag.
Source: Burnett et al., 1994

Taken as a whole, these analyses are suggestive of mortality and morbidity associations with the sulfate fraction of fine particles found in contemporary American urban airsheds. Without nationwide measurements of airborne acidity, however, it is not now possible to evaluate the relative contribution of acid aerosols within these fine particle sulfates to the reported health effects.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic sulfate effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate H^+ associations with lower respiratory symptoms, except at H^+ above 110 moles/m_3 (Schwartz et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of H_2SO_4 (Schwartz, et al., 1991b). Some, but not all, recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3 (Studnicka et al., 1995; Neas et al., 1995).

Studies of the effects of chronic H^+ exposures on children's respiratory health and lung function are generally consistent with effects as a result of long-term H^+ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested associations between summertime average H^+ and chronic bronchitic and related symptoms (Damokosh et al., 1993). The relative odds of bronchitic symptoms with the highest acid concentration (58 nmoles/m^3 H^+) versus the lowest concentration (16 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1996) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly

associated with strongly acidic PM (relative odds = 1.66, 95% CI: 1.11 to 2.48). It was also found that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1996). Thus, epidemiological evidence indicates that chronic exposures to strongly acidic PM can have effects on measures of respiratory health in children.

One plausible mechanism by which acidic sulfates may act to increase the toxicity of PM is by enhancing the effects of soluble metals and reactive oxygen intermediates. PM, and especially combustion-related aerosols, contain transition metals such as iron, copper, nickel, vanadium, and cobalt that are more readily solublized at lower pH. These metals are capable of catalyzing the one-electron reductions of molecular oxygen necessary to generate reactive oxygen species (ROS) (e.g., via the iron-catalyzed Fenton Reactions. Other than Fe, several vanadium compounds have been shown to increase mRNA levels for selected cytokines in BAL cells and also to induce pulmonary inflammation (Pierce et al., 1996). $NaVO_3$ and $VOSO_4$, highly soluble forms of vanadium, tended to induce pulmonary inflammation and inflammatory cytokine mRNA expression more rapidly and more intensely than the less soluble form, V_2O_5, in rats. Neutrophil influx was greatest following exposure to $VOSO_4$ and lowest following exposure to V_2O_5, providing one plausible sulfate PM health effects mechanism.

Many studies investigating the response of animals to particle exposures have used residual oil flyash (ROFA) as a surrogate for ambient particles. ROFA has a high content of water soluble sulfate and metals. As described in the last U.S. PM Criteria Document (U.S. Environmental Protection Agency, 1995), intratracheal instillation of high doses of ROFA suspension generally produced severe inflammation, an indicator of pulmonary injury that included recruitment of neutrophils, eosinophils, and monocytes into the airway. The biological effects of ROFA have been shown to depend on aqueous leachable chemical constituents of the particles. Dreher et al. (1997) have shown that a leachate prepared from ROFA, containing predominantly Fe, Ni, V, Ca, Mg, and sulfate, produced similar lung injury to that induced by the complete ROFA suspension, indicating the potency of this sulfate-metals mixture.

IV. PM and Sulfate Interactions with Other Pollutants

This section addresses any studies examining interactions between PM and sulfates and other pollutants (including noncriteria pollutants or bioaerosols).

IV.A. Interaction of PM with Allergens

There is growing scientific evidence that particulate matter from fossil fuel combustion enhances the immune response to allergens, leading to an increase in allergic inflammation and allergic reactivity. Therefore, particulate air pollutants can be an important contributor to the increased morbidity of acute asthma and allergic rhinitis, as well as being a potential trigger of

asthma in its own right. Furthermore, recent clinical studies and experimental studies have been able to describe the manner in which diesel particles specifically trigger a biochemical reaction which causes the type of allergic inflammation that asthma medications are aimed at preventing (e.g., see: Nel et al., 1998). Nel and colleagues (1998) have suggested that the rise in the U.S. prevalence rate for allergic rhinitis (5% in the 1950s to about 20% in the 1980s) may be related to increased diesel particulate matter (DPM), in addition to other combustion related PM. Combustion particles may also serve as carrier particles for allergens (Knox et al., 1997). These studies provide biological plausibility for the exacerbation of allergic asthma associated with episodic exposure to PM. Although DPM may make up only a fraction of the mass of urban PM, because of their small size, DPM may represent a significant fraction of the ultrafine particle mode in urban air, especially in cities that rely heavily on diesel-powered vehicles. Thus, while not themselves allergens, diesel and other combustion PM may increase an asthma patient's general responsiveness to any and all allergens and pollens to which they are already allergic, thereby increasing the chance that acute asthma problems will be experienced in a given population of persons with asthma.

Alterations in the response to a specific antigenic challenge have also been observed in animal models at high concentrations of acid sulfate aerosols (above 1,000 ug/m^3) (Pinto et al., 1979; Kitabatake et al., 1979; Fujimaki et al., 1992). Several studies have reported an enhanced response to non-specific bronchoprovocation agents, such as acetylcholine and histamine, after exposure to inhaled particles. This non-specific airway hyperresponsiveness, a central feature of asthma, occurs in animals and human subjects exposed to sulfuric acid under controlled conditions (Gearhart and Schlesinger, 1986; Utell et al., 1983). Although its relevance to specific allergic responses in the airways of atopic individuals is unclear, it demonstrates that the airways of asthmatics may become sensitized by acidic sulfates to either specific or non-specific triggers that could result in increases in asthma severity and asthma-related hospital admissions (Peters et al., 1997; Lipsett et al., 1997).

The above noted PM-asthma interactions are of greatest significance to children because the prevalence of asthma children is higher and increasing more rapidly among children than among other age groups. Indeed, the U.S. prevalence rate of asthma in children aged <20 years rose rapidly from approximately 3.5% to 5% during the 1980's, a prevalence that was nearly double adults 20-64 years of age at that time, and higher than all other age groups (U.S. DOH, 1991). Rates for asthma prevalence, hospitalization, and death are especially high among children residing in inner cities, and important risk factors for asthma-related mortality include being poor or black (CDC, 1997a, 1997b). Thus, the above discussed PM-asthma interactions, that suggest that PM air pollution exposure makes people with asthma more reactive to all asthma triggers, mean that children will be at greater risk from PM exposure, as they have the highest prevalence and severity of this worsening disease.

IV.B. Interaction of PM with Gaseous Pollutant Mixtures

Ambient PM usually co-exists in indoor and outdoor air with a number of co-pollutant gases, including ozone, sulfur dioxide, oxides of nitrogen, and carbon monoxide, and this may modify PM toxicity. The presence and nature of any interactions are not well understood at this time, but are likely to depend upon the particle size and the concentration of pollutants in the mixture, exposure duration, and the health endpoint being examined.

One of the primary particle-gas interaction mechanisms documented to-date are chemical interactions between particles and gases that occur on particle surfaces. This forms secondary products on that particle surface that may be more toxicologically active than the primary materials, and that can then be more readily carried to a sensitive sites deeper in the lung. The hypothesis of such chemical interactions has been evaluated in the gas and particle exposure studies of SO_2 and particles by Amdur and colleagues (Amdur and Chen, 1989; Chen et al., 1992). These investigators have demonstrated that synergism occurs as secondary chemical species are produced (e.g., sulfuric acid on the surface of the particles), especially under conditions of elevated relative humidity, such as found in the human lung. Thus, these studies suggest that air quality standards set for individual air pollutants may not be fully protective of human health for exposures to mixed ambient pollutants.

Another hypothesized mechanism of gas-particle interaction may involve pollutant-induced changes in the lung, enhancing the effects of the co-pollutant. For example, Last et al. (1984) indicated that the observed synergism between ozone and acid sulfates in rats was due to a decrease in the local microenvironmental pH of the lung following deposition of acid, enhancing the effects of ozone by producing a change in the reactivity or residence time of reactants, such as radicals, involved in ozone-induced tissue injury. Kleinman et al. (1999) examined the effects of ozone plus fine H_2SO_4 coated carbon particles (MMAD = 0.26 um) for 1 or 5 days. They found the inflammatory response with the ozone-particle mixture was greater after 5 days (4 hours/day) than after day 1. This contrasted with ozone exposure alone (0.4 ppm) which caused marked inflammation on acute exposure, but no inflammation after 5 consecutive days of exposure. Thus, acids and ozone together appear to be of greater impact than either alone.

Two studies have examined interaction between carbon particles and gaseous co-pollutants. Jakab et al. (1996) challenged mice with a single 4-hour exposure to a high concentration of carbon, 10 mg/m^3, in the presence of SO_2 at low and high relative humidity. Macrophage phagocytosis was significantly depressed only in mice exposed to the combined pollutants under high relative humidity conditions. This study demonstrates that fine carbon particles can serve as an effective carrier for acidic sulfates, where chemical conversion of adsorbed SO_2 to acid sulfate species occurred. Interestingly, the depression in macrophage function was present as late as 7 days post-exposure. Bolarin et al. (1997) exposed rats to only 50 or 100 ug/m^3 carbon particles in combination with ammonium bisulfate and ozone. Despite 4 weeks of exposure, they observed no changes in protein concentration in lavage fluid or blood prolyl 4-hydroxylase, an enzyme involved in collagen metabolism. Slight decreases in plasma fibronectin were present in animals exposed to the combined pollutants versus ozone alone. Thus, the potential for

adverse effects in the lungs of animals challenged with a combined exposure to particles and gaseous pollutants is dependent on numerous factors including the gaseous co-pollutant, concentration, and time.

Linn and colleagues (1997) examined the effect of a single exposure to 60 to 140 ug/m^3 H_2SO_4, 0.1 ppm SO_2, and 0.1 ppm ozone in healthy and asthmatic children. The children performed intermittent exercise during the 4-hour exposure to increase the inhaled dose of the pollutants. An overall effect on the combined group of healthy and asthmatic children was not observed. A positive association between acid concentration and symptoms was seen, however, in the subgroup of asthmatic children. The combined pollutant exposure had no effect on spirometry in asthmatic children and no changes in symptoms or spirometry were observed in healthy children. Thus, the effect of combined exposure to PM and gaseous co-pollutants appeared to have less effect on asthmatic children exposed under controlled laboratory conditions in comparison with field studies of children attending summer camp (Thurston et al., 1997). However, prior exposure to H_2SO_4 aerosol may enhance the subsequent response to ozone exposure (Linn et al., 1994; Frampton et al., 1995); the timing and sequence of the exposures may be important. Overall, the evidence suggests that the gaseous-particle interactions of ozone and acidity indicates are more likely to enhance the effects of PM exposures in children than adults, as children playing outdoors would tend to get higher exposures to these air pollution components (as opposed to adults indoors, where acidity and ozone exposure is diminished, relative to the outdoors).

While past acid aerosol research has focused largely on acidity in a particulate form (e.g., as $H_2SO_4^=$), recent research by Peters et al. (1999) as part of the Children's Health Study raises the possibility that the acidity-particle interaction may extend to the interaction of vapor nitric acid (HNO_3) and particles. To study possible chronic respiratory effects of air pollutants, the authors initiated a 10-yr prospective cohort study of Southern California children, with a study design focused on four pollutants: ozone, particulate matter, nitric acid vapor, and nitrogen dioxide (NO_2). Twelve demographically similar communities were selected on the basis of historic monitoring information to represent extremes of exposure to one or more pollutants. In each community, about 150 public school students in grade 4, 75 in grade 7, and 75 in grade 10 were enrolled through their classrooms. Wheeze prevalence was positively associated with levels of both nitric acid (odds ratio [OR] = 1.45; 95% confidence interval [CI], 1.14-1.83) and NO_2 (OR = 1.54; 95% CI, 1.08-2.19) in boys (who usually spend more time outdoors than girls), and only nitric acid vapor was significant overall for boys and girls. The authors conclude, based on this cross-sectional assessment of questionnaire responses, that current levels of ambient air pollution in Southern California may be associated with effects on schoolchildren's respiratory morbidity. However, it seems unlikely that the highly water soluble HNO_3 could reach deep into the lungs without interaction with particles, much the way that SO_2 has been shown to be picked up by particles entering the lung (Amdur and Chen, 1989; Chen et al., 1992). Thus, it may be that there is a nitric acid-particle interaction that is underlying the nitric acid-child health effects associations reported by Peters and colleagues.

V. Implications of Health Effects Findings to the Adequacy of PM and Sulfate Standards

The health effects studies documented in this report provide substantial evidence that PM exposures at present ambient levels are adversely affecting the health of children in places throughout the world, including in California. However, whether a PM-health effects association is present or not at a given ambient level is difficult to determine from such studies because, when an effect is not found to be significant, it may be that there is merely insufficient power (e.g., too small a population, or too short a record period) to find an effect that may really be there. Also, such studies tend to be conducted on large populations, where the power is greatest, but where concentrations are also usually highest (i.e., in cities), so studies of low levels are difficult to find. Thus, it is more challenging to evaluate at exactly what pollution exposure concentrations these documented health effects begin to occur for groups of susceptible individuals such as infants and children with asthma.

Probably the best database available at this time for the evaluation of the levels at which pollutants show significant adverse health effects is the body of medical visits and hospital admissions studies, as: 1) they represent a health effect outcome that is clearly adverse, with only long-term illness or death being worse, and; 2) they are reported in large enough numbers to provide sufficient statistical power, and are statistics that are routinely available for analysis, so there are a large number of studies available to evaluate, as documented in the above sections and Appendix A. Therefore, these studies will be examined here for insights into the adequacy of the present California standards for the protection of children's health.

The hospital admissions study most directly relevant to the question of the U.S. EPA's $PM_{2.5}$ standard's adequacy is that by Norris and colleagues (1999). As noted in Appendix A, the estimated mean $PM_{2.5}$ level (based upon nephelometry data) in that study of asthma hospital visits by Seattle children less than 18 was $PM_{2.5}$ = 12 ug/m^3, and the PM association was still significant at these low levels, even after controlling for co-pollutants. This implies that the $PM_{2.5}$ annual average standard should be below 12 ug/m^3 if it is to protect children with asthma. The maximum $PM_{2.5}$ concentration was approximately 7 times this value, above the 65 ug/m^3 24-hr. maximum standard, but the $PM_{2.5}$ short-term standard is as a 3 year average, so that the standard may well also not have been exceeded at this location where acute effects have been documented. These results therefore indicate that the present Federal $PM_{2.5}$ annual standard is

not sufficiently protective of children with asthma, and further suggest that the 24-hr maximum may also not be sufficiently protective.

However, the Morgan et al (1998) study of asthma hospital admissions in Sydney, Australia experienced a mean $PM_{2.5}$ = 9.6 ug/m^3, but was unable to detect a significant $PM_{2.5}$ association, despite having larger daily counts and a longer record than the Norris et al (1999) study. This Australian study's results, when compared to the Norris and colleagues study results, suggests that the threshold of $PM_{2.5}$ mass effects on asthma admissions in children is approximately 10 ug/m^3 as an annual mean over several years.

Since the mean PM_{10} concentration during the Norris et al (1999) Seattle study was 21.7 ug/m^3, this study further indicates that the present California PM_{10} annual average standard (30 ug/m^3) is also not sufficiently protective. In the case of PM_{10}, this study's results are confirmed by other studies that have demonstrated significant associations at PM_{10} levels below 30 ug/m^3. As shown in Appendix A, Atkinson et al. (1999a,b) found significant associations with both children's respiratory emergency department (ED) visits and hospital admissions in London, England, where the mean PM_{10} = 28.5 ug/m^3. Similarly, Hajet confirms this result for London doctor's visits for asthma and lower respiratory disease in London, with a mean PM_{10} = 28.2 ug/m^3. Medina et al (1997) also finds significant associations between PM_{13} and doctor's house calls at PM_{13} mean = 25 ug/m^3. Since PM_{10} is a sub-component of PM_{13}, and will therefore average less than PM_{13}, this Paris study confirms the Norris et al. result that significant adverse health associations occur even at mean PM_{10} below 25 ug/m^3.

Given the results of Norris et al (1999) and confirming PM studies, it is clear that the sulfate standard of 25 ug/m^3 is far from sufficiently protective. The above sulfate health effects section made clear that sulfate is an especially potent component of $PM_{2.5}$, and it's annual average standard should therefore be even lower than that for $PM_{2.5}$. Available studies of sulfates and hospital admissions confirm this conclusion, including the above discussed Burnett (1994) study summarized in Table 6. The average Southern Ontario sulfate level (after eliminating sulfate artifact) was 5.3 ug/m^3, yet significant associations were found between sulfates and children's respiratory admissions, even after controlling for ozone. Analyses of respiratory admissions in Buffalo and New York City (Thurston et al., 1992) at mean levels of 9.3 and 8.9 ug/m^3, respectively, also find significant sulfate-respiratory associations at mean concentrations well below 25 ug/m^3. In addition, examination of the plot of the Ontario data from the Burnett et al. (1994) study (presented above in Figure 8) suggests that the sulfate

threshold of effects, if it exists, lies below 5 ug/m^3, perhaps at about 2 ug/m^3. Clearly, the existing California $SO_4^=$ standard is not now sufficiently stringent to protect public health.

VI. Conclusions

Based upon the above facts and considerations, it is clear that significant adverse health effects can reasonably be expected to occur at present day ambient levels, especially among infants and children, based on the findings of published studies.

Among the factors that cause children to be especially affected by PM air pollution are:

- higher PM exposure concentrations due to greater PM personal cloud than adults;
- higher PM exposure patterns (e.g., more time spent outdoors and greater activity levels);
- higher doses per body weight and lung surface area;
- diminished pollution defenses in infants vs. older children and adults;
- PM exposures may adversely affect body (e.g., lung) development in children;
- higher prevalence of children with asthma than in other age groups,
- larger percentage of children made susceptible by poverty than other age groups; and,
- gas-particle interactions and particle-allergen interactions apparently make pollutants more toxic than they are alone, potentially making the individual pollutant standards not fully protective to susceptible populations, such as children.

Furthermore, an examination of key medical visits and hospital admissions studies conducted at relatively low ambient concentrations evaluated the adequacy of the existing Federal and California PM_{10} and $PM_{2.5}$ mass and sulfate ambient air quality standards. It was found that these standards are not presently sufficiently protective of public health, since significant adverse health impacts have been documented in published studies to occur at ambient levels averaging well below these standards.

However, to help reduce any remaining uncertainties regarding the impacts of PM and sulfates on the health of infants and children, and to determine how to most optimally control such environmental insults, additional research is needed into many aspects of the PM-health effects association among children, including:

- improved identification of the specific characteristics of PM (e.g., ultrafines, acidity, elemental composition, etc.) that are contributing most to noted PM effects, and quantification of their relative roles in PM toxicity;
- further investigation as to whether acute exposures less than one day in length (e.g., 1-hour daily maximum), or longer multi-day exposures (e.g., 2 or more day average PM), also have health importance, over and above that captured by the 24-hour PM peak PM concentration measurement;
- further investigations into particle-gas and particle-allergen interactions;
- animal studies relating increased infection following particle exposure needed, as well as more epidemiological studies of respiratory infections in infants exposed to ambient particles.
- using both experimental and epidemiological methods, conduct further investigations of apparently larger effects of acute and long-term PM exposures on children, and especially infants.

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Appendix

Recent Studies Evaluating PM Associations with Medical Visits or Hospital Admissions in Infants and Children

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag,, Excess Risk %, (95% CI=LCI-UCL), Co-Pollutants
Anderson, et al. (1998) London ('87-'92) Population = 7.2 MM BS daily mean = 14.6 ug/m^3 BS 25-75th IQR= 24-38	Poisson regression used to estimate the RR of London daily asthma hospital admissions associated with changes in O_3, SO_2, NO_2 and particles (BS) for all ages and for 0-14 (mean=19.5/d), 15-64 (mean=13.1/d) and 65+ years (mean =2.6/d).	O_3, SO_2, NO_2, and particles (BS) were all found to have associations with daily hospital admissions for asthma, but there was a lack of consistency across the age groups in the specific pollutant. The BS association was strongest in the 65+ group, especially in winter.	Asthma Admissions. BS=10 ug/m^3 BS Lag = 0-3 day average concentration All age ER= 2.3%(95%CI: 0.2-4.6%) <15yr. ER= 0.88%(95%CI: 1.8-3.7%) 15-64yr ER=0.47%(95%CI: 2.2-3.2%) 65+ yr. ER=8.6%(95%CI: 2.4-15.2%)
Atkinson et al. (1999a) London ('92-'94) Population = NR PM10 Mean = 28.5 ug/m^3 10th-90th IQR =15.8-46.5 ug/m^3 BS mean =12.7 ug/m^3 10th-90th IQR =5.5-21.6 ug/m^3	All-age Respiratory (mean=90/day), Asthma (25.9/day), and Other Respiratory (64.1/day) ED visits analyzed for associations with air pollutants using Poisson methods. Counts for ages 0-14, 15-64, and >64 also examined.	PM_{10} associated, but BS was not, for all-age/all-respiratory category. This may reflect higher toxicity by secondary particles vs. carbonaceous primary particles. PM_{10} results driven by significant children and young adult associations, while older adult visits had negative (but non-significant) PM_{10}-ED visit relationship.	PM_{10} (30.7 ug/m^3) No co-pollutant: All Respiratory ED visits All age(lag 1d)ER=3.0%(95%CI:0.8-5.2%) <15yrs(lag 2d)ER=3.9%(95%CI: 0.6-7.3%) 15-64yr(lag1d)ER=5.2%(95%CI:2.1-8.4%) Asthma ED visits All age(lag 1d)ER=5.4%(95%CI:1.8-9.0%) <15yrs (lag 2d)ER=7.4%(95%CI:2.1-13%) 15-64yr.(lg 1d)ER=7.8%(95%CI:2.8-13%)
Atkinson et al. (1999b) London ('92-'94) Population = 7.2 MM PM_{10} Mean = 28.5 ug/m^3 10th-90th IQR=15.8-46.5 ug/m^3 BS mean=12.7 ug/m^3 10th-90th IQR=5.5-21.6 ug/m^3	All-age Respiratory (mean=150.6/day), all-age Asthma (38.7/day), COPD plus Asthma in adults >64 (22.9/day), and lower Respiratory (64.1/day) in adults >64 (16.7/day) hospital admissions from London hospitals considered. Counts for ages 0-14, 15-64, and >64 also examined.	Positive associations were found between emergency hospital admissions for respiratory disease and PM_{10} and SO_2, but not for O_3 or BS. When SO_2 and PM_{10} were included simultaneously, the size and significance of each was reduced.	PM_{10} (30.7ug/m^3), no co-pollutant. All Respiratory Admissions: All age(lag 1d)ER=3.0%(95%CI:1.1-4.9%) 0-14 y (lag 1d)ER=4.9%(95%CI:2.1-7.7%) 15-64y(lag 2d)ER=4.2%(95%CI:2.6-7.3%) 65+ y.(lag 3d)ER=3.0%(95%CI:0.47-5.6%) Asthma Admissions: All age(lg 3d)ER=2.1%(95%CI: 1.1-5.4%) 0-14 y (lag 3d)ER=3.3%(95%CI: 0.7-7.5%) 15-64 y(lag 3d)ER=5.7%(95%CI:0.7-11.%) 65+ y.(lag 0d)ER=7.2%(95%CI: 1.25-16%)

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

Reference/Citation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag,, Excess Risk %, (95% CI=LCI-UCL), Co-Pollutants

Braga et al.. (2000?) Author Affiliation: Non-Profit Research Funding: Public Sao Paulo, Brazil ('92-'93) Population = NR PM_{10} mean = 66.3 ug/m^3 PM_{10} Std. Deviation = 26.1 PM_{10} Min./Max. = 26.7/165.4	Pediatric (<13 yrs.) hospital admissions (mean=67.6/day) from public hospitals serving 40% of the population were regressed (using both Poisson and maximum likelihood methods) on pollutants, controlling for month of the year, day-of-week, weather, and the daily number of non-respiratory admissions (mean=120.7/day). Pollutants considered included PM_{10}, O_3, SO_2, CO, and NO_2.	PM_{10} and O_3 were the two pollutants found by the authors to exhibit the most robust associations with respiratory HA's. SO_2 showed no correlation at any lag. Simultaneous regression of respiratory HA's on PM_{10}, O_3, and CO decreased effect estimates and their significance, suggesting that "there may not be a predominance of any one pollutant over the others". No safe threshold was found for PM_{10} or O_3. Associations are ascribed primarily to auto emissions by the authors.	PM_{10} (66.3 ug/m^3), no-co-pollutant Respiratory Hospital Admissions (<13 yr.) (0-5 day lg avg.)ER=12%(95%CI:6.1-18%)
Delfino et al., 1997 Montreal,Canada (6-9/92,6-9/93) Population = 3 million 1993 Means (SD): PM_{10}= 21.7 ug/m^3 (10.2) $PM_{2.5}$= 12.2 ug/m^3 (7.1) $SO_4^=$= 34.8 nmol/m^3 (33.1) H^+= 4 nmol/m^3 (5.2)	Association of daily respiratory ED visits (mean = 98/day from 25 of 31 acute care hospitals) with O_3, PM_{10}, $PM_{2.5}$, $SO_4^=$, and H^+ assessed using linear regression with controls for temporal trends, auto-correlation, and weather. Five age sub-groups considered.	No associations with ED visits in '92, but 33% of the PM data missing then. In '93, only H^+ associated for children <2, despite very low H^+ levels. H^+ effect stable in multiple pollutant models and after excluding highest values. No associations for ED visits in persons 2-64 yrs. of age. For patients >64,O_3, PM_{10}, $PM_{2.5}$, and $SO_4^=$ were all positively associated with visits ($p < 0.02$), but PM effects smaller than for O_3.	Respiratory ED Visits Children <2 yrs: (H^+ lag = 2 day) 4 nmol/m^3 H^+ ER= 5.0% (CI = 0.4-9.6%) Adults >64: (pollutant lags = 1 day) 21.7 ug/m^3 PM_{10} ER= 16% (CI = 4-28%) 12.2 ug/m^3 $PM_{2.5}$ ER= 12% (CI = 2-21%) 34.8 nmol.m^3 $SO_4^=$ ER= 6% (CI = 1-12%)
Gouveia et al (2000) Author Affiliation: Non-profit Research Funding: Public Study Period.:'92-'94 Sao Paulo, Brazil Population = 9.5 MM x 66% PM_{10} mean = 64.9 ug/m^3 PM_{10} IQR = 42.9-75.5 ug/m^3 PM_{10}10/90th%ile=34.5/110ug/m^3 PM_{10} 95th%ile = 131.6 ug/m^3	Daily public hospital admissions for respiratory diseases by children (mean Resp. < 5y = 56.1/d; mean Pneumonia <5y =40.8/d; mean asthma <5 y = 8.5/d; mean Pneum.<1y=24.0) and daily levels of weather and air pollutants (PM_{10}, SO_2, NO_2, O_3, and CO) were analyzed with Poisson regression. PM_{10} measured by Beta-gauge.	Children's HA's for total respiratory and pneumonia gave positive associations with O_3, NO_2, and with PM_{10}. Effects for pneumonia greater than for all respiratory diseases. Effects on infants (<1 yr. old) gave higher estimates. Similar results for asthma, but estimates higher than for other causes. Results noted to agree with prior publications, but smaller RR's. This may be an artifact of higher baseline admission rates in this poor sub-population vs. other studies, but this is not intercompared by the authors.	For PM 10th-90th %ile Δ=75.5 ug/m^3: All Respiratory HA's for children < 5yrs. ER = 4.0% (95% CI = -1.5%, 9.9%) Pneumonia HA's for children <5 yrs. ER = 5.0% (95% CI = -1.6%, 12.1%) Asthma HA's for children <5 yrs. ER = 5.2% (95% CI = -7.7%, 19.8%) Asthma HA's for children <1 yrs. ER = 9.4% (95% CI = 1.3%, 18.0%)

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Hajet et al., 1999 London, England (92'-'94) Population = 282,000 PM_{10} mean = 28.2 ug/m^3 PM_{10} 10^{t}-90th%=16.3-46.4 ug/m^3 BS mean = 10.1 ug/m^3 BS 10^{t}-90th%=4.5-15.9 ug/m^3	Examined associations of PM_{10}, BS, NO_2, O_3, SO_2, and CO, with primary care GP asthma and "other LRD" consultations [asthma means = 35.3 (all ages); = 14.(0-14 yrs,); = 17.7 (15-64 yrs.); = 3.6 (>64 yrs.)] [LRD means = 155. (all ages); = 39.7(0-14 yrs,); = 73.8 (15-64 yrs.); = 41.1 (>64 yrs.)], Time-series analyses of daily numbers of GP consultations were performed, controlling for time trends, season factors, day of week, influenza, weather, pollen levels, and serial correlation.	Positive associations, weakly significant and consistent across lags, were observed between asthma consultations and NO_2 and CO in children, and with PM_{10} in adults, and between other LRD consultations and SO_2 in children.. Across all of the various age, cause, and season categories considered in this research, PM_{10} was the pollutant most coherent in giving positive pollutant RR estimates for both asthma and other LRD (11 of 12 categories positive) in single pollutant models considered.	Asthma Doctor's Visits: 30 ug/m^3 PM_{10} (10-90th %ile Range) -Year-round, Single Pollutant: All ages (lg 2): ER=3.2% (CI=-0.4-6.8%) 0-14 yrs.(lg 1): ER=3.8% (CI=1.0-8.8%) 15-64 yrs.(lg 0): ER=5.4% (CI=1.6-9.2%) >64yrs.(lg 2): ER=7.1% (CI=-1.1-16%) Other Lower Resp. Dis. Doctor's Visits: 30 ug/m^3 PM_{10} (10-90th %ile Range) -Year-round, Single Pollutant: All ages (lg 2): ER=2.1% (CI=-0.4-3.8%) 0-14 yrs.(lg 1): ER=2.5% (CI=-0.7-5.8%) 15-64 yrs.(lg 2): ER=2.2% (CI=0.0-4.5%) >64yrs.(lg 2): ER=3.7% (CI=-0.3-7.2%)
Lin CA, et al, 2000 Author Affiliation: Non-profit Research Funding: NR Sao Paulo, BR ('91-'93) Population = NR PM_{10} mean =65 ug/m^3 PM_{10} SD = 27 ug/m^3 PM_{10} range = 15-193 ug/m^3	Respiratory ED visits by children (0-12 yrs.) to a major pediatric hospital (mean = 56/day) related to PM_{10}, SO_2, NO_2, CO, and O_3 using Gaussian linear regression modeling, Poisson modeling, and a polynomial distributed lag model. Lower Respiratory (mean = 8/day) and Upper Respiratory (mean = 39/day) ED visits, and visits due to Wheezing (mean=9/day), evaluated.	PM_{10} was found to be "the pollutant that exhibited the most robust and stable association with all categories of respiratory disease". O_3 was the only other pollutant that remained associated when other pollutants were all added to the model simultaneously. However, some pollutant coefficients went negative in multiple pollutant regressions, suggesting coefficient intercorrelations in the multiple pollutant models.	For 10 ug/m^3 PM_{10} (0-5 day lag mean) Respiratory ED Visits(<13 yrs.) Single Pollutant Model: PM_{10} ER=4.0% (CI=3.4%-4.6%) All-Pollutant Model: PM_{10} ER=5.2% (CI=4.0%-6.5%) Lower Respiratory ED Visits (<13 yrs.) Single Pollutant Model: PM_{10} ER=4.2% (CI=2.4%-6.0%) All-Pollutant Model: PM_{10} ER=8.0% (CI=5.0%-11%)
Medina et al., 1997 Greater Paris '91-'95 Population = 6.5 MM Mean PM_{13} = 25 ug/m^3 PM_{13} min/max = 6/95 ug/m^3 Mean BS = 21 ug/m^3 BS min/max = 3/130 ug/m^3	Evaluated short-term relationships between PM_{13} BS air pollution and doctors' house calls (mean=8/day; 20% of city total) in Greater Paris using Poisson regression.	A relationship between all age (0-64 yrs.) asthma house calls and PM_{13}, BS, SO_2, NO_2, and O_3 air pollution, especially for children aged 0-14 (mean = 2/day). In two-pollutant models including BS with, successively, SO_2, NO_2, and O_3, only BS and O_3 effects remained stable.	Doctor's Asthma House Visits: 10 to 50 ug/m^3 PM_{13}:5-95th%ile Increment Year-round, Single Pollutant: All ages (lg 2): ER=10% (CI=4-18%) 0-14 yrs.(lg 0-3): ER=32% (CI=16-51%) 15-64 yrs.(lg 2): ER=5% (CI=-5%-13%)

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Moolgavkar, et al (2000b) Author Affiliation: Non-profit Research Funding: Industry Study Period: 1987-1995 Los Angeles (LA County), CA Population = NR PM_{10} median = 44 ug/m^3 PM_{10} IQR= 33-59 ug/m^3 $PM_{2.5}$ median = 22 ug/m^3 $PM_{2.5}$ IQR = 15-31 ug/m^3	Investigated associations between air pollution and COPD HA's in LA, for children 0-19 (med.=17/d), adults 20-64 (med.=24/d), and adults 65+ (med. = 20/d). Used Poisson GAM's controlling for day-of-week, season, and splines of temperature and RH (but not their interaction) adjusted for overdispersion. Co-pollutants were O_3, SO_2, NO_2, and CO. PM data available only every 6th day, vs. every day for gases.	PM was associated with admissions in single pollutant models, but not in two pollutant models. Analysis in 3 age groups in LA yielded similar results. Author concludes that "the gases, other than ozone, were more strongly associated with COPD admissions than PM, and that there was considerable heterogeneity in the effects of individual pollutants in different geographic areas".	Most Significant Positive ER (t-statistic) Single Pollutant Models: LA COPD HA's (25 ug/m^3 PM_{10}, 10 ug/m^3 $PM_{2.5}/PM_{2.5-10}$) (0-19 yrs.): PM_{10} lg2=5.2% (t=3.4) (0-19 yrs.): $PM_{2.5}$ lg0=1.7% (t=1.9) (0-19 yrs.): $PM_{2.5-10}$ lg2=6.5% (t=4.3) (20-64 yrs.): PM_{10} lg2=3.2% (t=2.7) (20-64 yrs.): $PM_{2.5}$ lg2=2.2% (t=3.0) (20-64 yrs.): $PM_{2.5-10}$ lg2=3.5% (t=3.0) (>64 yrs.): $PM_{2.5-10}$ lg3=2.0% (t=1.8)
Morgan et al, 1998 Author Affiliation: Non-profit Research Funding: Public Sydney, AU ('90-'94) Population = NR $PM_{2.5}$ 24h. mean = 9.6 ug/m^3 $PM_{2.5}$ 10th-90th% =3.6-18 ug/m^3 $PM_{2.5}$ max-1h. mean=22.8ug/m^3 $PM_{2.5}$ 10th-90th%=7.5-44.4ug/m^3	A Poisson analysis, controlled for overdispersion and autocorrelation via GEE, of asthma (means: 0-14 yrs.=15.5/day; 15-64=9/day)), COPD (mean 65+yrs. =9.7/day), and heart disease HA's. $PM_{2.5}$ estimated from nephelometry. Season and weather controlled using dummy variables.	Childhood asthma was primarily associated with NO_2, while COPD was associated with both NO_2 and PM. 1-hr. max $PM_{2.5}$ more consistently positively related to respiratory HA's than 24-h avg $PM_{2.5}$. Adding all other pollutants lowered PM effect sizes, although pollutant inter-correlations makes many pollutant model interpretations difficult. No association found between asthma and O_3 or PM.	Asthma HA's Single Pollutant Model: For 24h $PM_{2.5}$ 10th-90th% =3.6-18 ug/m^3 1-14 yrs.(lag1) ER= -0.87%(CI=-4.6 - 3.0) 15-64 yrs.(lag0) ER=1.31%(CI=-2.3 - 5.1) For 1h $PM_{2.5}$ 10th-90th% =7.5-44.4 ug/m^3 1-14 yrs.(lag1) ER= -0.87%(CI=-4.6 - 3.0) 15-64 yrs.(lag0) ER=1.31%(CI=-2.3 - 5.1) Multiple Pollutant Model: For 24h $PM_{2.5}$ 10th-90th% =3.6-18 ug/m^3 1-14 yrs.(lag1) ER= -0.35%(CI=-4.3 - 3.8)

Norris et al (1999) Author Affiliation: Non-profit Research Funding: Public Seattle, WA (9/95-12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.7 ug/m^3 PM_{10} IQR = 11.6 ug/m^3 ϑ_{sp} mean = 0.4 $m^{-1}/10^{-4}$ (≈12.0 ug/m^3 $PM_{2.5}$) ϑ_{sp} IQR = 0.3 $m^{-1}/10^{-4}$ (≈9.5 ug/m^3 $PM_{2.5}$)	The association between air pollution and childhood (<18 yrs.) ED visits for asthma from the inner city area with high asthma hospitalization rates (0.8/day, 23/day/10K persons) compared with lower hospital use areas (1.1/day, 8/day/10K persons). Daily ED counts were regressed against PM_{10}, light scattering (ϑ_{sp}), CO, SO_2, and NO_2 using a semiparametric Poisson regression model evaluated for over-dispersion and auto-correlation.	Associations found between ED visits for asthma in children and fine PM and CO. CO and PM_{10} highly correlated with each other (r=.74) and K, an indicator of woodsmoke pollution. Considering baseline risks/10K population indicates a higher PM attributable risk (AR) in the inner city. These findings were seen even though the mean estimated $PM_{2.5}$ concentration was below the newly adopted annual National Ambient Air Quality Standard of 15 ug/m^3.	<u>Children's (<18 yrs.) Asthma ED Visits</u> Single Pollutant Models: For 24h PM_{10} IQR =11.6 ug/m^3 Lag1 ER= 14% (CI= 8% - 23%) For 24h ϑ_{sp} IQR =0.3 $m^{-1}/10^{-4}$ (≈9.5 ug/m^3 $PM_{2.5}$) Lag1 ER= 15% (CI= 8% - 23%) Multiple Pollutant Models: For 24h PM_{10} IQR =11.6 ug/m^3 Lag1 ER= 14% (CI= 4% - 26%) For 24h ϑ_{sp} IQR=0.3 $m^{-1}/10^{-4}$ (≈9.5 ug/m^3 $PM_{2.5}$) Lag1 ER= 17% (CI= 8% - 26%)

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Norris et al (2000) Author Affiliation: Non-profit Research Funding: Public Spokane, WA (1/95—3/97) Population = 300,000 PM_{10} mean. =27.9 ug/m^3 PM_{10} Min/Max=4.7/186.4 ug/m^3 PM_{10} IQR = 21.4 ug/m^3 Seattle, WA (9/95—12/96) Pop. Of Children <18= 107,816 PM_{10} mean. =21.5 ug/m^3 PM_{10} Min/Max = 8/69.3 ug/m^3 PM_{10} IQR = 11.7 ug/m^3	Associations investigated between an atmospheric stagnation index (# of hours below median wind speed), a "surrogate index of pollution", and asthma ED visits for persons <65 yrs. (mean=3.2) in Spokane and for children <18 (mean=1.8) in Seattle. Poisson GAM modeling, controlled for day of week, long-wave effects, and temperature and dew point (as non-linear smooths). Factor Analysis (FA) applied to identify PM components associated with asthma HA's.	Stagnation persistence index was strongly associated with ED visits for asthma in 2 cities. FA indicated that products of incomplete combustion (especially wood-smoke related K, OC, EC, and CO) are the air pollutants driving this association. Multi-pollutant models run with Stagnation as the "co-pollutant" indicated the importance of general air pollution over any single pollutant index, but provided no indication of the importance of the various pollutants relative to each other.	Asthma ED Visits Single Pollutant Models Persons<65 years (Spokane) For PM_{10} IQR = 21.4 ug/m^3 Lag 3 ER = 1% (95% CI= -5% - 7%) Persons<18 years (Seattle) For PM_{10} IQR = 11.7 ug/m^3 Lag 3 ER = 11% (95% CI= 2% - 20%)
Ostro et al (1999) Author Affiliation: Non-profit Research Funding: World Bank Santiago, CI (7/92—12/93) <2 yrs. Population ≈20,800 3-14 yrs. Population ≈128,000 PM_{10} mean. =108.6 ug/m^3 PM_{10} Min/Max=18.5/380 ug/m^3 PM_{10} IQR = 70.3 – 135.5 ug/m^3	Analysis of daily visits to primary health care clinics for upper or lower respiratory symptoms by children 2-14 years of age (mean LRS=111.1/day) and < age 2 (mean LRS=104.3/day). Daily PM_{10} and O_3 and meteorological variables considered. The multiple regression GAM included controls for seasonality (LOESS smooth), temperature, day of week, and month.	Analyses indicated an association between PM_{10} and medical visits for LRS in children ages 2-14 and in children under age 2. PM_{10} was not related to non-respiratory visits (mean =208/day). Results unchanged by eliminating high PM_{10} (>235 ug/m^3) or coldest days (<8°C). Adding O_3 to the model had little effect on PM_{10}-LRS associations.	Lower Resp. Symptoms Clinic Visits PM_{10} IQR = 50 $^{ug/m3}$, One Poll. Model: -Children<2 years Lag 3 ER = 2.5% (95% CI= 0.2% - 4.8%) -Children 2-14 years Lag 3 ER = 3.7% (95% CI=0.8% - 6.7%) Two Pollutant Models (with O_3): -Children<2 years Lag 3 ER = 2.2% (95% CI= 0% - 4.4%) -Children 2-14 years Lag 3 ER = 3.7% (95% CI=0.9% - 6.5%)

Rosas, et al (1998) Author Affiliation: Non-profit Research Funding: public SW Mexico City ('91) Population = NR PM_{10} mean. =77 ug/m^3 PM_{10} min/max= 25/183 ug/m^3	Log-regression analysis of the relationships between emergency admissions for asthma to a hospital for children <15 years (mean=2.5/day), adults (mean=3.0/day), and older adults >59 years (mean=0.65/day) and lag 0-2 average pollen, fungal spores, air pollutants (O_3, NO_2, SO_2, and PM_{10}) and weather factors. Long wave controlled only by separating the year into two seasons: "dry" and "wet". Day-of-week not included in models.	There were few statistical associations found between asthma admissions and air pollutant. Grass pollen was associated with child and adult admissions, and fungal spores were associated with child admissions. The authors conclude that aeroallergens may be more strongly associated with asthma than air pollutants, and may act as confounding factors in epidemiologic studies. Results are limited by low power and the lack of long-wave auto-correlation controls in the models.	NR

Table A-1. Summaries of Recently Published Acute PM-Medical Visits Studies of Children

ReferenceCitation Location, Duration PM Index/Concentrations	Study Description:	Results and Comments	PM Index, Lag, Excess Risk % (95% LCI/UCL) Co-Pollutants
Sunyer et al (1997) Barcelona ('86-'92) BS Median: 40 ug/m^3 BS Range: 11-258 (B Helsinki ('86-'92) BS Median: - BS Range: - Paris ('86-'92) BS Median: 28 ug/m^3 BS Range: 4-186 ug/m^3 London ('86-'92) BS Median: 13 ug/m^3 BS Range: 3-95 ug/m^3	Daily counts of asthma HA's and ED visits in adults [ages 15-64 years: mean/day = 3.9 (B); 0.7 (H); 13.1 (H); 7.3 (P)] and children [ages < 15 years: mean/day = 0.9 (H); 19.8 (L); 4.6 (P)] related to BS, SO_2, NO_2, and O_3 air pollution. Asthma (ICD9=493) studied in each city, but the outcome examined differed across cities:	In children, daily admissions increased significantly with SO_2 and positively (but non-significantly) with Black Smoke and NO_2, though the latter only in cold seasons. No association was observed in children for O_3. The weakness of PM in these analyses may be result of the use of the BS index, a measure of only the primary carbonaceous particles, which may be less toxic than other (i.e., secondary) aerosols.	ER per 50µg/m^3 BS (24 h Average) Asthma Admissions/Visits: <15 yrs.: London ER = 3.1% (lg 0d) Paris ER = 3.0% (lg 2d) Total ER = 3.0% (95%CI: -2.1%-8.4%) 15-64 yrs: Barcelona ER = 3.6% (lg 3d) London ER = 3.5% (lg 0d) Paris ER = 1.2% (lg 0d) Total ER = 2.1% (95%CI: -1.5%-5.9%)
Wong, et al (1999) Study Period.:'94-'95 Hong Kong Population = NR PM_{10} mean = 50.1 ug/m^3 PM_{10} median = 45.0 ug/m^3 PM_{10} IQR = 30.7, 65.5 ug/m^3	Poisson regression applied to assess association of daily NO_2, SO_2, O_3, and PM_{10} with emergency HA's for all respiratory (median = 131/day) and COPD (median = 101/day) causes. Effects by age groups (0-4, 5-64, and 65+ yrs.) also evaluated.	Positive associations were found for HA's for all respiratory diseases and COPD with all four pollutants. PM_{10} results for lags 0-3 cumulative. Admissions for asthma, pneumonia, and influenza were associated with NO_2, O_3, and PM_{10}. Those aged > or = 65 years were at higher risk, except for PM_{10}.	PM_{10} Δ = 10 ug/m^3 (Lags = 0-3 days) Respiratory HA's All age: ER= 1.6% (95%CI: 1.0, 2.2%) 0-4yrs.: ER= 1.9% (95%CI: 1.1, 2.8%) 5-64yrs.: ER= 1.7% (95%CI: 0.9, 2.6%) 65+ yrs.: ER= 1.8% (95%CI: 1.0, 2.6%)

Polychlorinated Dibenzo-*p*-dioxins (PCDDs) and Dibenzofurans (PCDFs) (Dioxins) (OEHHA, 2001)

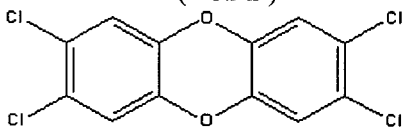
Polychlorinated Dibenzo-*p*-dioxins (PCDDs) and Dibenzofurans (PCDFs)

Including: all 2,3,7,8-chlorinated PCDDs and PCDFs

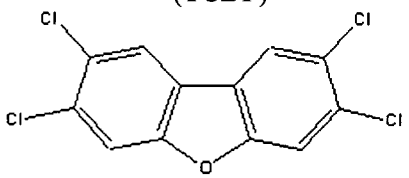
(Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) including 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), which is the principal congener of concern based on toxicity)

Figure 2: Selected structures:

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)



2,3,7,8-Tetrachlorodibenzofuran (TCDF)



Selected Physical and Chemical Properties

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)

Description	White crystalline powder at 25°C
Molecular formula	$C_{12}H_4Cl_4O_2$
Molecular weight	321.97 g
Water solubility	1.93 ng/100 ml at 22°C
Log P (octanol-water)	6.80
Air concentration conversion	Not available

2,3,7,8-Tetrachlorodibenzofuran (TCDF)

Molecular formula	$C_{12}H_4Cl_4O$
Molecular weight	305.975 g
Water solubility	69.2 ng/100 ml at 26°C
Log P (octanol-water)	6.53
Air concentration conversion	Not available

Chronic Toxicity Summary

Inhalation reference exposure level	**0.00004 µg/m^3 (40 pg/m^3)**
Oral reference exposure level	**1 x 10^{-8} mg/kg/day (10 pg/kg/day)**
Critical effect(s)	Increased mortality, decreased weight gain, depression of erythroid parameters, increased urinary excretion of porphyrins and delta-aminolevulinic acid, increased serum activities of alkaline phosphatase, gamma-glutamyl transferase and glutamic-pyruvic transaminase, gross and histopathological changes in the liver, lymphoid tissue, lung and vascular tissues in rats.
Hazard index target(s)	Alimentary system (liver); reproductive system; development; endocrine system; respiratory system; hematopoietic system

(Source: OEHHA, 2000)

Toxicity of PCDDs and PCDFs

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is considered the most potent congener of the polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) families of compounds. Their mechanism of toxicity involves binding to a cytosolic receptor, the Ah receptor, which dimerizes with the Ah receptor nuclear translocator protein (ARNT) in the nucleus. These liganded heterodimeric complexes bind to specific sequences of DNA referred to as dioxin-responsive elements (DREs), resulting in alterations in gene transcription. Potency of PCDD and PCDF congeners thus correlates with the binding affinity to the Ah receptor. Structure activity studies have demonstrated that optimal biological activity and Ah-receptor binding requires congeners with a planar conformation and chlorines at the corners of the molecule at the 2,3,7,8 positions (Poland and Knutson, 1982; Safe, 1986). Chlorines at both ortho positions in these molecules (i.e., positions 1 and 9) sterically hinder a planar conformation that lessens the congeners' biological activity. Thus only 17 of 210 different PCDDs and PCDFs congeners possess significant biological activity based on chlorines in the 2,3,7,8 positions and some degree of planar conformation (Safe, 1986; U.S. EPA 2000). These include two tetrachloro-congeners: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and 2,3,7,8- tetrachlorodibenzofuran; three pentachloro congeners: 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin, 1,2,3,7,8-pentachlorodibenzofuran, and 2,3,4,7,8-pentachlorodibenzofuran; seven hexachloro congeners: 1,2,3,4,7,8 or 1,2,3,6,7,8 or 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxins and hexachlorodibenzofurans and 2,3,4,6,7,8-hexachlorodibenzofuran; three heptachloro congeners: 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin, 1,2,3,4,6,7,8-heptachlorodibenzofuran and 1,2,3,4,7,8,9-heptachlorodibenzofuran; and two octachloro congeners: 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin, and 1,2,3,4,6,7,8,9-octachlorodibenzofuran (U.S. EPA, 2000). The structures of the dibenzo-*p*-dioxins and dibenzofurans along with their numbering schemes are shown in Figure 2. Toxic equivalency factors (TEFs) are estimated relative to the most potent congener, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, and are determined based on structure activity studies examining relative affinity for the Ah receptor as well as on relative in vitro and *in vivo* toxicity of different congeners. Values for the World Health Organization (WHO-97) TEFs are provided in Table 17 (U.S. EPA, 2000).

Table 17: Toxic equivalency factors (TEFs)

Congener	WHO/97 [a]
PCDDs	
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
1,2,3,4,6,7,8,9-OCDD	0.0001
PCDFs	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.05
2,3,4,7,8-PeCDF	0.5
1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
1,2,3,4,6,7,8,9-OCDF	0.0001

[a] van Leeuwen, 1997.

(Source: U.S. EPA, 2000)

Most of the toxicity data available for TCDD are from oral experiments in animals. Very few percutaneous and practically no inhalation exposure toxicity data are available in the scientific literature. Animal data following oral exposure indicate that TCDD is one of the most toxic compounds known and that it produces a wide spectrum of toxic effects (U.S. EPA, 2000). Table 18 illustrates the lowest TCDD dose that was shown to elicit various biological responses in experimental animals. Because of their long half-life in the body, PCDDs acute treatment can be viewed as subchronic exposure. Subchronic/chronic exposures yield toxicity profiles similar to an acute exposure when similar total cumulative doses are administered (U. S. EPA, 2000).

Table 18: Lowest effect levels for biological responses of 2,3,7,8-TCDD in experimental animals

Species	Dose or concentration and duration	Effect	Reference
Guinea pig	0.6 µg/kg[a], single oral dose	Lethality (single dose LD50)	Schwetz *et al.*, 1973
Rhesus monkey	1.0 µg/kg, single oral dose	Acute (systemic) toxicity	McNulty, 1977
Sprague-Dawley rat	2.0 ng/kg, single oral dosea	Induction of AHH (CYP1A1)	Kitchin and Woods, 1979
Marmoset monkey	3.0 ng/kg, single oral dose	Induction of N-demethylation (CYP1A2)	Kruger *et al.*, 1990
Guinea pig	1 ng/kg-day for 8 weeks	Immunosuppression (decreased response to tetanus toxin)	Zinkl *et al.*, 1973
Swiss mouse	1 ng/kg-day for 1 year	Amyloidosis and dermatitis	Toth *et al.*, 1979
Rhesus monkey	500 ppt in diet for 9 months (12 ng/kg-day); 2 ppb in diet for 61 days (50 ng/kg-day)	Chronic lethality	Allen *et al.*, 1977; McNulty, 1977
Rhesus monkey	50 ppt in diet for 20 months (1.5 ng/kg-day)	Chronic toxicity (hair loss)	Schantz *et al.*, 1979
Sprague-Dawley rat	10 ng/kg-day for 2 years in feed	Porphyrin metabolism	Kociba *et al.*, 1978

[a] 0.6 ng/kg = no effect level.
(Source U.S. EPA, 2000)

Effects of animal exposure

Acute toxicity

The lethal toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) varies with species and strain and within a single strain it varies with sex, age and route of administration. Delayed manifestation of lethality is usually seen following TCDD acute toxicity. Lethality generally occurs several weeks after acute exposure, and is preceded by a loss in body weight (wasting syndrome). This body weight loss is a consequence of gluconeogenesis inhibition and suppression of appetite elicited by TCDD. TCDD-induced lethality can vary by more than 8,000 folds. For instance, the lethal dose of TCDD capable of killing 50 % of exposed animals (LD50) vary between 0.6 - 2.1 µg/kg when administered *per os* (p.o.) to male Hartley guinea pigs, the most sensitive species tested (McConnell *et al.*, 1978; Schwetz *et al.*, 1973) and 1,157 – 5,051 µg/kg (p.o.) in male Syrian Golden hamsters (Henck *et al.*, 1981). Further, in rats, Long-Evans (L-E) *Turku* AB strain rats are around 1,000-fold more sensitive to TCDD-induced acute lethality (LD50 about 10 µg/kg) (Tuomisto and Pohjanvirta, 1987) than Han/Wistar (H/W) Kuopio strain rats (LD50 > 3,000 µg/kg) (Pohjanvirta and Tuomisto, 1987; Pohjanvirta *et al.*, 1988). Although also sensitive to enzyme induction, the greater resistance of the H/W rat to acute TCDD toxicity may be due in part to differences in AhR types between rat strains {Pohjanvirta *et al.* 1999; Tuomisto *et al.* 1999}. In rats, wasting, hemorrhage and/or anemia generally precede dioxin-induced lethality. Other signs of acute toxicity

elicited by exposure to TCDD encompass a variety of organ systems in various species. While liver is the primary organ affected by TCDD in rodents and rabbits (McConnell *et al.*, 1978; Moore *et al.*, 1979; Turner and Collins, 1983), thymus and lymphatic tissues are the prominent organs affected by acute exposure of guinea pigs to TCDD. In nonhuman primates dermal effects and changes in cutaneous and internal epithelial tissues are common signs of TCDD toxicity. In these animals, TCDD-induced cutaneous lesions is comparable to chloracne and hyperkeratosis observed in human occupationally exposed to TCDD. Other signs of TCDD toxicity observed in laboratory animal given lethal or near lethal dose include: inhibition of bone marrow hematopoiesis in mice, and thymic atrophy in monkey and guinea pig. Additionally, observations of hepatic porphyria, hemorrhages in various organs, testicular atrophy, reduced prostate weight, reduced uterine weight, increased thyroid weight, lesions of the adrenal glands, decreased serum albumin, and increased serum triglycerides and free fatty acids were also reported in TCDD-acutely exposed animals.

Subchronic toxicity

Based on subchronic studies, the no-observable-adverse-effect levels (NOAELs) for rats (Goldstein *et al.*, 1982), mice (Harris *et al.*, 1973; Vos *et al.*, 1973), and guinea pigs (DeCaprio *et al.* 1986), were estimated to be 1 ng, 100 ng, and 0.6 ng TCDD/kg bw/day, respectively. However, these subchronic data could not be extrapolated toward human for risk assessment since no initial loading dose was used in these experiments. Therefore, it is uncertain whether or not a steady-state for TCDD was achieved except perhaps toward the end of these studies.

Chronic Toxicity

Among the numerous chronic studies reported in the scientific literature, the study of Kociba *et al.* (1978; 1979) is one of the most frequently cited studies. In Kociba *et al.* (1978; 1979) study, groups of 50 female and 50 male Sprague Dawley rats were exposed in their diet to 0.001, 0.01 and 0.1 μg TCDD/kg/day for two years. Female rats appeared to be the most sensitive gender. Increased mortality during the course of the experiment was only observed in female exposed to the highest dose of 0.1 μg TCDD/kg/day. The mean body weight decreased at the highest dose in male and female starting 6 months from the beginning and continuing to the end of the study. Also, increased urinary excretion of coproporphyrin and uroporphyrin were reported in female rats dosed with 0.01 and 0.1 μg TCDD/kg/day. This response was not observed in male given similar TCDD levels. Deleterious hepatic effects constituted the most consistent TCDD-induced alterations. Increased blood serum enzymes activity indicators of impaired hepatic functions were noted in female rats treated with 0.1 μg TCDD/kg/day. Degenerative, inflammatory and necroptic hepatic changes were also more extensive in female. Liver damage was dose-related and no effect was observed at the lowest dose of 0.001 μg TCDD/kg/day. Based on this study Kociba *et al.*, (1978; 1979) estimated a NOAEL of 0.001 μg TCDD/kg/day.

In B6C3F1 male and female mice no adverse effects were observed at the lowest dose tested of 0.01 and 0.04 μg TCDD/kg/week, for males and females respectively (NTP, 1982c).

In rhesus monkeys, signs and symptoms after 9 to 20 months exposure to TCDD were similar to those observed in shorter-term studies. Adverse effects were observed at the lowest dose tested (~ 2-3 ng TCDD/kg bw/day for 20 months) (Schantz *et al.*, 1979).

Signs and Symptoms of TCDD Toxicity

One of the consistent signs of TCDD toxicity in most species is weight loss and thymic atrophy. Other toxic effects include hyperplasia or atrophy of the spleen, testes, or ovaries, bone marrow depletion, and systemic hemorrhage. TCDD at high dose (lethal and near lethal) causes a severe loss of weight (wasting syndrome) a few weeks after starting exposure in several animal species. The wasting syndrome is typically seen as a cessation of weight gain. In the wasting syndrome a progressive hypoglycemia have been suggested as the principal cause of death in several mammalian species (Ebner *et al.*, 1988; Gorski and Rozman, 1987; Gorski *et al.*, 1990). There is a strong correlate between the binding affinity of PCDDs and PCDFs for the Ah receptor and their capacity to induce the wasting syndrome in rats and guinea pigs (Safe, 1990).

The liver is extremely sensitive to TCDD toxicity in all animals. Even at sublethal doses, hepatic lesions are the prominent response to TCDD exposure. TCDD induces hyperplasia and hypertrophy of parenchymal cells in all species tested. The extent and severity of liver lesions vary greatly among the species tested. These liver morphological changes are accompanied by impaired liver function, characterized by:

- Liver enzyme leakage to the serum, such as glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT).
- Increased microsomal monooxygenase activity.
- Porphyrin accumulation.
- Impaired membrane function, indicated by decreased adenosine triphosphatase (ATPase) activity and increased protein kinase C activity.
- Hyperbilirubinemia, hypercholesterolemia, hyperproteinemia, and hyperlipidemia.
- Increased regenerative DNA synthesis.

(U.S. EPA, 1984; 2000; WHO/IPCS, 1989).

Chloracne and other epidermal changes are common responses elicited by high exposure to TCDD in human. This type of response has only been observed in a limited number of animal species (rabbits, monkeys, cows, and hairless mice) (U.S. EPA, 2000). Keratinocytes, the principal cell type in the epidermis, have been utilized to study TCDD-induced hyperkeratosis, both in human- and animal-derived cell cultures (U.S. EPA, 2000).

Enzymes induction, although more of a marker of exposure than one of toxicity, has been extensively used in TCDD studies. For the mixed-function oxidase system (MFO), the aryl hydrocarbon hydroxylase (AHH) and the ethoxyresorufin-O-deethylase (EROD) are the most frequently cited enzymes used to characterize cytochrome P450 1A1 (CYP1A1) induction. This induction of the MFO system might result in an increased biotransformation of foreign compounds leading to either potentiation of toxicity (formation of toxic metabolites) and/or enhanced excretion (formation of more water soluble metabolites) of these compounds. Other enzymes commonly investigated in TCDD studies are enzymes of phase II biotransformation system, such as uridine diphosphate-glucoronosyltransferase (UDPGT) and glutathione-S-transferase (GST) which are involve in the conjugation of a variety of endogenous and exogenous compounds.

Numerous studies have indicated that there is a strong correlation between the AhR-binding affinity of various PCDDs, PCDFs, and co-planar PCBs and their potency to induce AHH, both *in vivo* and in vitro (Safe, 1990). Furthermore, there is a clear correlation between the toxicity and induction potency of PCDDs, PCDFs, and co-planar PCBs (Poland and Glover, 1973; Safe, 1990). A NOEAL value of about 1 ng TCDD/kg body weight was estimated for enzyme (AHH or EROD) induction in rats (Kitchin and Woods, 1979; Abraham *et al.*, 1988) and marmoset monkeys (Kruger *et al.*, 1990; Neubert 1991).

Endocrine effects of TCDD exposure have been suggested from deleterious outcome on reproduction observed in TCDD-exposed experimental animals. This response might occur from TCDD interfering with the estrus cycle and TCDD having some steroid-like activities. Additionally, chronic and subchronic TCDD exposure have been linked to impaired thyroid functions. TCDD was associated with a dose-dependent decrease of plasma thyroxin (T_4) hormone in subchronic studies using rats as a model (van der Kolk *et al.*, 1992; van Birgelen *et al.*, 1995a,b). An intake of 0.047 µg TCDD/kg/day was estimated to be the LOAEL for decreased plasma thyroid hormone levels. Viluksela *et al.* (1998) also observed a decreased plasma T_4 level in rats subchronically exposed to high doses of 1,2,3,7,8-pentaCDD (PeCDD) or 1,2,3,4,7,8-hexaCDD (HxCDD) and low-dose of TCDD/kg.

TCDD interactions with estrogens have been reviewed by Safe *et al.* (1991). The modulation role of estrogens in TCDD promoted liver tumors was demonstrated by Lucier *et al.* (1991) by removing ovaries from female rats before exposure to TCDD. This procedure prevented the tumor-promoting effects of TCDD. Change in testosterone level or activity has also been observed in TCDD-treated animals. TCDD treatment depressed serum testosterone and dihydrotestosterone in a dose-dependent fashion in male Sprague Dawley rats; the ED50 for this effect was approximately 15 µg/kg (Moore *et al.*, 1985). A decrease in 3 ß-, 6 ß-, and 16 ß-hydroxytestosterone and an increase in 7 α-hydroxytestosterone levels have also been observed in young male Wistar rats treated with a single dose of 0.06 µmol TCDD/kg body

weight (Keys *et al.*, 1985). Moreover, a decrease in testicular 16 ß-testosterone hydroxylase, 6 ß-hydroxytestosterone, and 7 ß-hydroxytestosterone activity was observed in young Sprague Dawley rats 90 hours after a single intraperitoneal administration of 0.2, 1, or 5 µg TCDD/kg bw (Mittler *et al.* 1984). Storage of vitamin A in the liver is also reduced in TCDD-treated experimental animals. A single oral dose of 10 µg TCDD/kg administered to adult male Sprague Dawley rats decreased vitamin A liver content to 33 % of that of controls (Thunberg *et al.*, 1979). Brouwer *et al.* (1989) demonstrated that a single dose of TCDD (10 µg/kg) to female Sprague Dawley rats reduced vitamin A in the liver, lungs, intestines, and adrenal glands, while increasing vitamin A concentration in serum, kidneys, and urine. Similarly, Häkansson *et al.* (1989) reported a comparable reduction in liver vitamin A content in male Sprague Dawley rats and Hartley guinea pigs treated (ip) with a single equitoxic dose (a fraction of their respective LD50s) of 40 and 0.5 µg/kg body weight, respectively.

Oxidative stress was observed only at high doses of TCDD following acute exposure. For instance, reactive oxygen species were observed in rats after acute TCDD exposure at high doses (Alsharif *et al.*, 1994a,b). Also, lipid peroxidation (Alsharif *et al.*, 1994b), and decreased membrane fluidity (Alsharif *et al.*, 1990) were reported in rats exposed to high dose of TCDD.

There is some evidence of neurotoxic effects of dioxin-like compounds. Most studies however, are based on dioxin-like PCBs. For instance, a changes in the muscarinic chlorinergic receptor of the hippocampus was observed in mouse exposed to 3,3',4,4'-tetrachlorobiphenyl (PCB #77) (Eriksson *et al.*, 1991). It appears however that such exposure to dioxin-like PCBs is more potent at the fetus/neonate stage as the blood brain barrier is not completely formed. There is extensive evidence of exposure to TCDD and dioxin-like PCBs *in utero* or via lactation leading to behavioral, learning and memory performance changes at adulthood (Eriksson *et al.*, 1991; Eriksson and Fredriksson, 1998; Seo *et al.*, 1999; OEHHA, 2001).

The immune system is a target for the toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and structurally related polyhalogenated aromatic hydrocarbons (PHAHs) (Vos and Luster, 1989; Kerkvliet and Burleson, 1994; Holsapple, 1995), such as the polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and TCDD in particular (Holsapple *et al.*, 1991a, b). Comparison of the immunosuppressive potency of 1,2,3,6,7,8-hexachlorinated dibenzo-*p*-dioxin (HxCDD), 1,2,3,4,6,7,8-heptachlorinated dibenzo-*p*-dioxin (HpCDD), and 1,2,3,4,6,7,8-heptachlorinated dibenzofuran (HpCDF) isomers, which bind the Ah receptor, was reported by Kerkvliet *et al.* (1985). The dose of each isomer producing 50% suppression of the anti-SRBC (anti- sheep red blood cell) response (ID50) was 7.1, 85, and 208 µg/kg for HxCDD, HpCDD, and HpCDF, respectively. The ID50 for TCDD was 0.65 µg/kg (Vecchi *et al.* 1980).

Several studies indicated a reduced resistance to endotoxin (*E. coli* or *S. typhimurium* lipopolysaccharide), after a single or multiple doses of TCDD (Vos *et al.*, 1978; Thomas and Hinsdill, 1979; Rosenthal *et al.*, 1989). Enhanced susceptibility to other diseases such as viral disease was also reported in animal exposed to TCDD (Clark *et al.*, 1983; House *et al.*, 1990; Burleson *et al.*, 1996). Increased mortality to influenza A/Hong Kong/8/68 (H3N2) virus following a single exposure to 0.1, 0.05, or 0.01 µg/kg TCDD was observed by Burleson *et al.* (1996). Thus, 0.01 µg/kg TCDD was the lowest effect level to elicit increased mortality to infectious disease. TCDD exposure has also been shown to enhance susceptibility to infections from parasites (Tucker *et al.*, 1986; Luebke *et al.*, 1994). In mice the immunosuppressive potency of individual PHAHs is related to their structural similarity to TCDD, which corroborate their AhR-mediated mechanism of action.

The primary effects of TCDD exposure on female reproductive system include: decreased fertility, inability to maintain pregnancy for the full gestational period, and in the rat, decreased litter size (U.S. EPA, 2000). In some studies, signs of ovarian dysfunction such as anovulation and suppression of the estrous cycle have been reported (Kociba *et al.*, 1976; Barsotti *et al.*, 1979; Allen *et al.*, 1979; Li *et al.*, 1995a,b). TCDD at dosage as low as 0.01 µg/kg/day in the diet during a three-generation study reduces reproductive capacity in female rats (Murray *et al.*, 1979). However, no effect was observed at 0.001 µg/kg/day (NOAEL). This NOAEL was corroborated by Kociba *et al.*, (1978) in a two-year chronic toxicity and oncogenicity study of TCDD in rats.

In the male reproductive system, TCDD and related compounds decrease testis and accessory sex organ weights, cause abnormal testicular morphology, decrease spermatogenesis, and reduce fertility when given to adult animals in doses sufficient to reduce feed intake and/or body weight. TCDD effect on the spermatogenesis is not a very sensitive endpoint. An exposure to 1 µg/kg/day of postweaning animals over a period of weeks appears to be required to result in suppression of spermatogenesis (U.S. EPA, 2000). Moreover, a single TCDD dose of 0.064 µg/kg given on day 15 of gestation significantly altered the normal

sexual development of male Holtzman rat offspring (Mably *et al.* 1991, 1992a,b,c). However, since 0.064 µg/kg/day was the lowest dose tested, no information on the NOAEL could be obtained from this set of data.
The effect on perinatal viability and male reproductive development are among the most sensitive effects reported. This endpoints occurs at a single prenatal exposure dosage range of as low as 0.05-0.075 µg/kg (U.S. EPA, 2000).

Effects of human exposure

The majority of effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds in human have been reported from studies of occupational exposure or of residents of communities contaminated with tainted waste oil (Missouri, USA) and industrial effluent (Seveso, Italy).

Chloracne

Chloracne is the most widely recognized dermal effect elicited by exposure to 2,3,7,8-TCDD-contaminated substances. This persistent acne-like condition is characterized by comedones, keratin cysts, and inflamed papules with hyperpigmentation and a unique anatomic distribution, occurring as a result of an acute and/or chronic exposure to a variety of chlorinated aromatic compounds (Crow *et al.*, 1978; Moses and Prioleau, 1985). Chloracne symptoms were reported in a few workers following an accidental exposure in a 2,4,5-trichlorophenol (TCP) production plant (Zober at al., 1990) and among at least 193 (0.6%) Seveso residents, mostly children (Ideo *et al.*, 1985; Mocarelli *et al.*, 1986; Assennato *et al.*, 1989).
Bond *et al.* (1989)'s analysis of 325 individuals occupationally espoused to TCDD found that risk of chloracne was highest among workers who were exposed at younger ages, among those who had the longest length of exposure to 2,4,5-trichlorophenol or pentachlorophenol production operations, and among jobs rated at the highest intensity of exposure (Ott *et al.*, 1987). In the Seveso incident, Mocarelli *et al.* (1991) described chloracne in persons from zone A who had very high serum 2,3,7,8-TCDD levels ranging from 820 to 56,000 pg/g measured within 1 year of the chemical plant fire. However, other individuals from zone A, without chloracne had serum 2,3,7,8-TCDD levels ranging from 1,770 to 10,400 pg/g.
Other dermal effects less frequently diagnosed following TCDD exposure include: hyperpigmentation and hirsutism (also known as hypertrichosis or abnormal distribution of hair), actinic or solar elastosis, red and irritated eyes, conjunctivitis, and blepharitis (inflammation of the eyelids) (U.S. EPA, 2000)

Hepatic effects

As for animal studies of TCDD-induced hepatic structural and functional alterations (Kociba *et al.*, 1978; Gasiewicz *et al.*, 1980; DeCaprio *et al.*, 1986), human TCDD-induced hepatic effects are also subject to great variability in the type and degree of response. Transient liver enlargement was observed in 5 of 22 residents who suffered severe chloracne in the Seveso incident (Reggiani, 1980). However, little evidence of hepatomegaly was found in studies on TCP production workers (Moses *et al.*, 1984; Calvert *et al.*, 1992) and Vietnam veterans of the Ranch Hand unit (Roegner *et al.*, 1991),
Changes in hepatic enzymes (gamma glutamyl transferase (GGT)) level were observed after exposure to TCDD contamination in TCP production workers and among Seveso residents (Mocarelli *et al.*, 1986; Calvert *et al.*, 1992; Ott *et al.*, 1994). Increased levels of GGT may suggest activity such as cholestasis, liver regeneration, or drug or xenobiotic metabolism. There was also some indication of abnormal level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) following acute and severe exposure to TCDD contamination but these changes in hepatic enzymes were transient (Seveso children, British and Czechoslovakian TCP production workers) (May, 1973; Jirasek *et al.*, 1974; Caramaschi *et al.*, 1981; Mocarelli *et al.*, 1986). Elevation of serum ALT and AST is mainly indicative of liver cell damage. D-glucaric acid-creatinine changes was also observed in TCDD-exposed individuals. D-glucaric acid-creatinine urinary excretion is a valid although indirect indicator of enzymes induction. In the Seveso incident, D-glucaric acid-creatinine was significantly elevated in adults and children residing in zone A (the zone closest to the fire and most contaminated zone) at the time of the chemical plant fire when compared to population of uncontaminated communities (Ideo *et al.*, 1985).
Porphyrin metabolism was clearly shown to be altered in rats and mice following exposure to TCDD (Goldstein *et al.*, 1982; Smith *et al.*, 1982; DeVerneuil *et al.*, 1983; Cantoni *et al.*, 1981). However, in

human, the association between TCDD exposure and porphyrin metabolism (porphyria, porphyria cutanea tarda) is not as clear (U.S. EPA, 2000).

Endocrine effects

In animal studies serum thyroxin (T_4) level was decreased by a single high dose of 2,3,7,8-TCDD, indicating hypothyroidism; however, no consistent findings were reported for alterations in 3,5,3'-triiodothyronine (T_3) (Pazdernik and Kozman, 1985; Potter *et al.*, 1986; Henry and Gasiewicz, 1987; Roth *et al.*, 1988; Muzi *et al.*, 1989). Only a few human studies examined the relationship between 2,3,7,8-TCDD exposure and thyroid function in adult, and the results of these studies are inconsistent. Studies like the Ranch Hand (Roegner *et al.*, 1991; Grubbs *et al.*, 1995) and the NIOSH (Calvert *et al.*, 1999), which measured serum 2,3,7,8-TCDD concentrations, suggest that in adults there are few long-term effects on adult thyroid function. TCDD exposure in these studies involved chronic exposure at level lower than in animal studies. On the other hand, infants appear to be more susceptible to altered thyroid function elicited following lactational expose to dioxin TEQ (Pluim *et al.*, 1993; Koopman-Esseboom *et al.*, 1994). Altered development is among the most sensitive endpoints of 2,3,7,8-TCDD toxicity. Mixtures containing both TCDD-like congeners and non-TCDD-like congeners were reported to cause developmental and reproductive toxicity in the Yusho and Yu-Cheng poisoning incidents in Japan and Taiwan (Kuratsune, 1989; Hsu *et al.*, 1985; Rogan, 1989). In the incident of Yusho and Yu-Cheng an increased perinatal mortality and low birth weight were observed in infants born to mothers who had been exposed to the contaminated rice oil. Rocker bottom heal was observed in Yusho infants, and functional abnormalities have been reported in Yu-Cheng children. In addition, hyperpigmentation, deformation of the fingernails and toenails, conjunctivitis, gingival hyperplasia, and abnormalities of the teeth were also reported in the Yu-Cheng and Yusho episodes

Decreased testosterone level was reported following exposure to high doses of 2,3,7,8-TCDD. That decrease was in part attributed to dioxin inhibition of testosterone synthesis (Kleeman *et al.*, 1990; Mebus *et al.*, 1987; Moore and Peterson, 1988). Men exposed to 2,3,7,8-TCDD-contaminated materials from daily exposure and industrial accidents were reported to complaint of decrease libido. In the NIOSH study of TCP production workers, prevalence of abnormally low testosterone was two to four times higher among workers with serum 2,3,7,8-TCDD levels of 20-75 pg/g (Observed ratio (OR) = 3.9, 95% CI = 1.3, 11.3), 76-243 pg/g (OR = 2.7, 95% CI = 0.9, 8.2), or > 244 pg/g (OR = 2.1, 95% CI = 0.8, 5.8) than the unexposed control group (4.8%) (mean serum 2,3,7,8-TCDD = 7 pg/g) (Egeland *et al.*, 1994). Serum 2,3,7,8-TCDD was also positively and significantly related to serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) but inversely related to total testosterone. Ranch Hand veterans with current serum dioxin levels exceeding 33.3 pg/g were reported to have a lower mean total serum testosterone level (515.0 ng/dL) when compared to the nonexposed control group (525.2 ng/dL). The difference was not statistically significant (Roegner *et al.*, 1991). Altered male reproductive system was associated with important TCDD occupational exposure. In women, there is no convincing evidence linking TCDD-TEQ exposure with endometriosis (U.S. EPA, 2000).

Immunotoxicity

Numerous immunological effects have been reported in laboratory animals following exposure to TCDD and related chemicals. In human, the data linking TCDD exposure with altered immunological functions are inconsistent. For instance, a population of TCDD-exposed chemical workers exhibited increased natural killer cell (NK) level when examined 17 years after exposure was ended (Jennings *et al.*, 1988). However, studies on workers occupationally exposed to TCDD such as the Ranch Hand veterans (Roegner *et al.*, 1991; Michalek *et al*, 1998), the BASF accident cohort (Ott *et al.*, 1994), the NIOSH cohort (Halperin *et al.*, 1998) or the Hamburg cohort (Jung *et al.*, 1998; Ernst *et al.*, 1998) did not corroborate these findings. In the Vietnam War veterans, Operation Ranch Hand units, responsible for handling the herbicide Agent Orange (contaminated with dioxin), no immune function deficiencies could be associated with current or initial serum dioxin level. (Roegner *et al.*, 1991; Wolfe *et al.*, 1992). In the most recent examination of Operation Ranch Hand unit cohort, Michalek *et al.* (1999) also concluded that there was no relationship between dioxin exposure and immune system alteration in Ranch Hand veterans. In a retrospective study of 11 workers occupationally exposed to high level of TCDD and other PCDDs between 1966 and 1976, Tonn *et al.* (1996) found no difference in cell surface marker distribution (i.e. CD3, CD4, etc.) or mitogen induced lymphocyte proliferation responses. These workers involved in

production and maintenance operation at a German chemical factory producing 2,4,5-trichlorphenol had TCDD body burdens as high as 43 to 874 pg/g blood (corresponding to an average level 10 times higher than the general German population) after 20 years exposure. However, Tonn *et al.* (1996) concluded that TCDD exposure cause long-term immunosuppressive effect on T helper cells based on the reduced lymphoproliferation in response to human lymphocyte antigen-allogeneic lymphocytes (e.g., MLR) and IL-2 stimulation.

One of the most important cases of human accidental exposure was the PCBs/PCDFs contaminated rice oil episode in Japan (1968) and Taiwan (1979). Symptoms from these two human poisoning episodes known as Yusho or Yu-Cheng (oil disease) included acne-form eruptions and follicular accentuation, pigmentation of the skin and nails, swelling of the eyelids and increased discharge, nausea, headaches, numbness of the limbs, decreased serum concentration of α-globulin and decreased delayed type hypersensitivity (DTH) responses (Chang *et al.*, 1980). Yu-Cheng patients also exhibited increased frequency of various kinds of infection, especially of the respiratory tract and skin (Nakanishi *et al.*, 1985; Lu and Wu, 1985). The U.S. EPA (2000) report on dioxin reviews other inconsistencies between studies on the impact of TCDD exposure on immununologic functions in human.

The maturing immunologic system appears to be a far better target for dioxin-like compounds. Comparison of perinatally exposed children born of Yu-Cheng mothers with marched controls revealed an increase incidence of middle-ear disease (Chao *et al.*, 1997). Furthermore, children with middle ear disease had higher serum levels of 2,3,4,7,8-pentachloro- and 1,2,3,4,7,8-hexachloro-dibenzofurans than did children with no middle-ear disease. In Seveso, Italy (1976), a fire in a chemical plant released into the air an estimated 1.7 kg TCDD (Pocchiari *et al.*, 1979). Although 21 of the 45 children aged 3 to 7 year of age living in the most contaminated zone (zone A) at the time of the accident had chloracne, no evidence of immunological symptoms was detected (Pocchiari *et al.*, 1979). The immunological parameters examined were: serum immunoglobulin concentrations, levels of circulating complement, lymphoproliferative responses to T and B cell mitogens or alloantigens in the mixed leukocytes (MLR), or peripheral blood lymphocytes T and B cell populations. On the other hand, a follow-up study on a different cohort of TCDD-exposed children 6 years after the explosion, reported a significant increase in complement protein levels, which correlated with increased numbers of peripheral blood lymphocytes and increased lymphoproliferative responses (Tognoni and Bonaccorsi, 1982; Mocarelli *et al.*, 1986, 1991). However, no specific health problem aside from chloracne was correlated with dioxin exposure. In a follow-up study of the Rotterdam, Netherlands, of 207 healthy infant-mother pairs, Weisglas-Kuperus *et al.* (2000) reported an association between perinatal background exposure to PCBs and dioxins and a greater susceptibility to infectious diseases at preschool age. Infants/children exposed *in utero* or via lactation to dioxins and related compounds have also been shown to present suppressed immune functions and increased susceptibility to infectious diseases (Nagayama *et al.*, 1998; Weisglas-Kuperus *et al.*, 2000).

Neurotoxicity

Neurotoxicologic symptoms in individuals following acute exposure in the occupational environment, and chronic exposure to TCDD include: headache, insomnia, nervousness or irritability, depression and anxiety, loss of libido, and encephalopathy (U.S. EPA, 2000).

In the West Virginia chemical plant study, significant excess for the following symptoms: insomnia, decreased libido, and difficulties with ejaculation or erection were found

among workers with chloracne compared to those without lesions (Moses *et al.*, 1984). Workers with chloracne also exhibited decreased sensitivity to pinprick, whereas none of the subjects without chloracne had decreased pinprick sensation ($p<0.01$). No other differences in performance of the neurological examination were reported. Furthermore, when examined by Suskind and Hertzberg (1984), no significant differences were noted in the conduction velocities of sural sensory and peroneal motor nerve fibers between exposed and nonexposed workers. There was also no difference between the two groups for the symptoms of fatigue, irritability, nervousness, depression, or personality changes. Similarly, no association between current serum levels of 2,3,7,8-TCDD and current depression were reported among a population of workers highly exposed to TCDD (Alderfer *et al.*, 1992). This conclusion was supported by the study of Roegner *et al.*, (1991) of Ranch Hand personnel who applied Agent Orange during the Vietnam War; serum 2,3,7,8-TCDD was not associated with the depression subscale score. Moreover, in the 1987 reanalysis (Roegner *et al.*, 1991), there was no significant difference between groups or relationship with serum 2,3,7,8-TCDD levels in the reported data on lifetime psychological illness or sleep disorders.

In the Seveso, Italy chemical plant fire episode, Seveso, residents who had clinical indication of 2,3,7,8-TCDD exposure (chloracne or elevated liver enzymes GGT, AST, ALT), or who had risk factors for neuropathy (alcoholism, inflammatory disease, diabetes, or potential occupational exposure to neurotoxins) were found to have significantly greater prevalence risk ratio (PRR) of neuropathy than residents without either manifestation (PRR exposure to TCDD = 2.8, 95% CI = 1.2-6.5; PRR for possible 2,3,7,8-TCDD-predisposing factors = 2.6, 95% CI = 1.2-5.6) (Filippini *et al.*, 1981). However, in a follow-up study of the Seveso incident (1976), no increases in the prevalence of abnormal electrophysiologic measures were observed in the chloracne group when compared with controls without chloracne (Assennato *et al.*, 1989). These observations on conduction velocities of the median motor, peroneal motor, and sural sensory fibers were conducted in 1982-1983 and 1985.

Overall, these case reports and epidemiological studies demonstrate that exposure to 2,3,7,8-TCDD-contaminated materials is associated with toxic symptoms of the central and peripheral nervous systems shortly following exposure and, in some cases, the symptoms last many years. Generally, the scientific literature suggests that, in adults, no long-term neurological effects are caused by TCDD exposure, even at high level of exposure to 2,3,7,8-TCDD-contaminated materials.

Developmental neurobehavioral effects in infants perinatlly exposed to PCDDs, PCDFs and PCBs have been reviewed by OEHHA (2001). It appears that *in utero* exposure to these contaminants is a major component in the onset of impaired neurobehavioral functions in infants. Also, non-dioxin-like PCBs, (PCBs acting by a mechanism other than the Ah receptor pathway) could be the congeners most likely to produce neurodevelopmental deleterious effects (OEHHA, 2001).

Summary

In summary, in adults, chloracne, elevated GGT levels, and altered testosterone levels appear to be long-term consequences of exposure to 2,3,7,8-TCDD. These endpoints

were positively related to TCDD exposure. Other dermatological endpoints other than chloracne, which can be more readily characterized as acute effects are eyelid cyst, hypertrichosis, hyperpigmentation, actinic keratosis, and Peyronie's disease. For liver diseases, those are: cirrhosis, liver enlargement, and hepatic enzyme levels (LDH, AST, ALT, and D-glucaric acid). Porphyrias, thyroid function, renal, neurologic, and pulmonary disorders are other endpoints mostly elicited as acute effect and for which only a few epidemiologic studies are available on chronic exposure to TCDD. The relationship between TCDD exposure and heart diseases, diabetes and glucose metabolism, reproductive and developmental outcomes, and immunologic disorders require further study to better established this relationship. However, for *in utero*/lactational exposure to TCDD and related chemicals, numerous recent studies have identified a possible positive relationship in infants/children with outcomes such as immunologic, thyroid hormones neurobehavioral and developmental disorders. These studies are reviewed in the OEHHA's document Prioritization of Toxic Air Contaminants - Children's Environmental Health Protection Act - Final Draft (OEHHA, 2001)

Carcinogenic effects

Table 19: Health Assessment Values for Carcinogenicity

Congener	Unit Risk $(\mu g/m^3)^{-1}$	Slope Factor $(mg/kg/day)^{-1}$
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	3.8 E+1	1.3 E+5
1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin	1.9 E+1	6.5 E+4
1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin	3.8 E+0	1.3 E+4
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	3.8 E+0	1.3 E+4
1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin	3.8 E+0	1.3 E+4
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	3.8 E-1	1.3 E+3
1,2,3,4,5,6,7,8-Octachlorodibenzo-*p*-dioxin	3.8 E-2	1.3 E+2
2,3,7,8-Tetrachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,7,8-Pentachlorodibenzofuran	1.9 E+0	6.5 E+3
2,3,4,7,8-Pentachlorodibenzofuran	1.9 E+1	6.5 E+4
1,2,3,4,7,8-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,6,7,8-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,7,8,9-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
2,3,4,6,7,8-Hexachlorodibenzofuran	3.8 E+0	1.3 E+4
1,2,3,4,6,7,8-Heptachlorodibenzofuran	3.8 E-1	1.3 E+3
1,2,3,4,7,8,9-Heptachlorodibenzofuran	3.8 E-1	1.3 E+3
1,2,3,4,5,6,7,8-Octachlorodibenzofuran	3.8 E-2	1.3 E+2

[Linearized multistage procedure (GLOBAL79), fitted to male mouse hepatic adenoma and carcinoma data (NTP, 1982), body weight scaling, cross-route extrapolation (CDHS, 1986).]
(Source: OEHHA, 1999)

Human studies

There are only a few documented cases of dioxin exposure of the general population; one of these is the incident in Seveso, Italy. In 1976, a chemical plant producing 2,4,5-trichlorophenol experienced an explosion and fire releasing several chemicals including TCDD into the atmosphere near Seveso. The Seveso incident represents a unique event in the sense that exposure to dioxins was not limited to occupational exposure by workers but the whole population was affected by the TCDD release in the area surrounding the chemical plant. The population was exposed to different degrees depending on the distance and direction from the origin of the plume. Fifteen years after the industrial accident, Bertazzi *et al.* (1997) examined the cancer mortality among residents (20 to 74 years old) of Seveso by comparing populations living in dioxin contaminated areas (divided into three zones: highest, lower and lowest zone of exposure to dioxin, zone A, B, and R, respectively) with a population from neighboring uncontaminated areas (zone nonABR). No increase for all-cancer mortality, or major specific sites like respiratory cancer among males and breast cancer among females, was found. However, elevation in other specific cancer mortality was observed, and could be associated with dioxin exposure. Table 20 summarizes cancer mortality for men and women living in zone B.

Table 20: Female and male deaths in zone B for selected causes, 1976-1991, greater than ten years since first exposure (latency) and duration of exposure (length of stay in contaminated area)*

		Latency > 10 years		Length of stay > 10 years	
		Female	Male	Female	Male
All cancers	OBS	23	31	20	29
	RR	1.4	1.0	1.4	1.1
	(95% CI)	(0.9 –2.1)	(0.7 –1.4)	(0.8 –2.1)	(0.7 – 1.6)
Digestive cancer	OBS	10	12	9	12
	RR	1.5	1.0	1.6	1.2
	(95% CI)	(0.7 – 2.7)	(0.5 – 1.8)	(0.7 – 2.9)	(0.6 – 2.1)
Stomach cancer	OBS	5	X	4	
	RR	2.4	X	2.3	
	(95% CI)	(0.8 – 5.7)		(0.6 – 6.0)	
Lymphatic and hemopoietic	OBS	4	4	3	4
	RR	2.8	2.5	2.4	3.0
	(95% CI)	(0.7 – 7.1)	(0.7 – 6.4)	(0.5 – 7.1)	(0.8 – 7.7)
Multiple myeloma	OBS	3		2	
	RR	15.9		11.0	
	(95% CI)	(3.2 – 46.5)		(1.2 – 39.6)	
Rectal cancer	OBS		4		4
	RR		6.2		7.2
	(95% CI)		(1.7 – 15.9)		(1.9 - 18.4)
Leukemia	OBS		2		2
	RR		3.4		3.9
	(95% CI)		(0.4 – 12.3)		(0.4 – 14.1)

* OBS = observed deaths.
(Source : Bertazzi *et al.*, 1997)

Increased mortality from stomach cancer (RR = 2.4; 95% CI = 0.8-5.7) was reported 10 years after the accident in women living in zone B although this was not statistically significant. In men, increased mortality from rectal cancer (RR = 6.2; 95% CI = 1.7-15.9) was observed. Leukemia in men represented one of the highest risks seen in zone B for hematologic neoplasms (RR = 3.4; 95% CI = 0.4 – 12.3). Elevated rates of multiple myeloma in women (RR = 15.9; 95% CI = 3.2 - 46.5), and Hodgkin's disease in both genders (RR = 3.3; 95% CI = 0.4-11.9 in men; and RR = 6.5; 95% CI = 0.7-23.5 in women) were also noted in that zone.

In the young population (20,000 subjects aged 0 to 19 years old), some cases of cancer were also found (Pesatori *et al.*, 1993), including two ovarian cancers and Hodgkin's

lymphoma; myeloid leukemia was elevated although not statistically significant (RR = 2.7; 95% CI = 0.7-11.4). Two cases of thyroid cancer were also reported (RR = 4.6; 95% CI = 0.6-32.7) in younger people. None of the elevated cancer incidences in zone A, the area with the highest exposure, were statistically significant; however, this area also had the smallest population. Additionally, it should be noted that the Seveso population was exposed to 2–3 orders of magnitude the level of dioxin normally experienced by the general population of industrialized countries. In 1997, individuals living in the contaminated area at the time of the accident still experienced high level of plasma TCDD 20 years after the industrial accident in Seveso. Geometric means for plasma TCDD concentration for individuals who lived in zone A, B and nonABR (control zone) in 1976 were 53.2, 11.0 and 4.9 ppt, respectively. Women in these three groups had higher plasma TCDD contamination than men (Landi *et al.*, 1997). The authors concluded that the results indicate a positive association between dioxin exposure and certain cancers, but further study is needed to clarify this association.

Animal studies

van Miller *et al.* (1977 a,b) reported the results of a study in which rats were fed diets containing from 1 ppt to 1 ppm of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) for 78 weeks. Surviving rats were killed after 95 weeks. Laparotomies were performed on all surviving rats at 65 weeks and all tumors were biopsied. Rats in the three highest dose groups, receiving 50 ppb or more, died early. A variety of tumors were found in rats receiving 5 ppt to 5 ppb while no-neoplasms were found in the control or low-dose groups. The absence of tumors in these two groups is unusual in this strain of rats. In addition, because of the small number of animals in each group (10) the study was inadequate to determine the carcinogenic potential of TCDD.

Toth *et al.* (1979) administered TCDD to male Swiss/H/Riop strain mice by gavage once a week for a year, then followed them for their lifetime. The weekly doses were 0.007, 0.7, and 7.0 µg/kg. Analysis of the results from this study focused on the incidence of liver tumors. A significant increase in the incidence of liver tumors was observed in the intermediate-dose group compared to the four separate control groups. The high-dose group, however, had an incidence of liver tumors that was similar to the control group. This finding may be explained by the early mortality in the high-dose group. The average life span was 424 days for this group, compared to average life spans of between 577 and 651 days for the control groups. If the treated animals had lived it is possible that more tumors may have formed.

Kociba *et al.* (1978) conducted a two-year feeding study in male and female Sprague-Dawley rats given diets containing 2200, 210, or 22 parts per trillion (w/w) TCDD for two years. Consumption of these diets resulted in daily doses of 0.1, 0.01, and 0.001 µg/kg body weight, respectively. There were 50 male and 50 female rats in each treatment group and 86 animals of each sex in the control group. There was a statistically significant ($p < 0.05$) increase in cumulative mortality for the high-dose female group in the latter half of the study. Body weights of the male and female high-dose groups were significantly ($p < 0.05$) reduced for the last three quarters of the study; however, food intake was not altered. The combined incidence of hepatocellular carcinomas and hepatocellular neoplastic nodules in the intermediate and high-dose groups of female rats was increased above the control group. Statistically significant increased incidences of

stratified squamous cell carcinomas of the hard palate and/or nasal turbinates were observed in both male and female high-dose groups. The male group also had an increased incidence of squamous cell carcinoma of the tongue, while the female group had an increased incidence of keratinizing squamous cell carcinoma of the lung.

US EPA (1981) reviewed this study and had an independent pathologist, Robert Squire, review the tissue pathology. The incidences of significant tumors reported by Kociba *et al.* (1978) and by Squire (US EPA, 1981) are given in Table 5 for male and female rats. The results of Squire's review did not differ greatly from those reported by Kociba *et al.* (1978).

Table 21: Tumor incidences in rats receiving 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) in the diet for two years (US EPA, 1984)

Tumor type, sex	Tumor incidence[a]			
	Dose level (µg/kg-day)			
	0	0.001	0.01	0.1
Tongue, stratified squamous cell carcinoma				
Male	0/76 (0/77)	1/49 (1/44)	1/49 (1/49)	4/42 ($p = 0.015$) (3/44) ($p = 0.046$)
Nasal turbinates/hard palate, squamous cell carcinoma				
Male	0/51 (0/55)	1/34 (1/34)	0/27 (0/26)	4/30 ($p = 0.017$) (6/30) ($p = 0.002$)
Female	1/54 (0/54)	0/30 (0/30)	1/27 (1/27)	5/24 ($p = 0.009$) (5/22) ($p = 0.001$)
lung, keratinizing squamous cell carcinoma				
Female	0/86 (0/86)	0/50 (0/50)	0/49 (0/49)	7/49 ($p < 0.001$) (8/47) ($p < 0.001$)
Liver, hepatocellular hyperplastic nodules, carcinomas				
Female	9/86 (16/86)	3/50 (8/50)	18/50 ($p < 0.001$) (27/50) ($p < 0.001$)	34/48 ($p < 0.001$) (33/47) ($p < 0.001$)

P values determined using Fisher's exact test.

a Number of animals with tumor over number of animals examined (incidence reported by Kociba *et al.*, 1978). Numbers in parentheses give the incidence reported by Squire (US EPA, 1984).

(Source: OEHHA, 1999)

Reviewers (CDHS, 1986; IARC, 1982; EPA, 1984) concluded that the study reported by Kociba *et al.* (1978) was an adequately conducted chronic carcinogenicity bioassay of TCDD, with significant effects observed at the two higher dose levels.

The National Toxicology Program (NTP 1982a) conducted an oncogenicity bioassay of TCDD in male and female Osborne-Mendel rats. They were administered TCDD in a 9:1 corn oil:acetone vehicle by gavage at dose levels of 0.005, 0.025, or 0.25 µg/kg twice a week for 104 weeks. The treatment groups consisted of 50 rats of each sex and a vehicle control group that was made up of three subgroups of 25 rats of each sex. An untreated control group, also made up of three subgroups of 25 rats of each sex, was included in the study, but not in the statistical analysis of the results by NTP. At the dose levels used, TCDD did not have a significant effect on survival of any treatment group. The high-dose group of male rats did have a statistically-significant increased incidence of subcutaneous

tissue fibromas, but it was not considered biologically significant because of the variability found. All male treatment groups had significantly ($p < 0.05$) increased incidences of thyroid follicular cell adenomas or adenomas and carcinomas, although the low- and intermediate-dose level group incidences were not significant when compared to the untreated control group by CDHS staff. The female high-dose group had significantly ($p < 0.05$) increased incidences of several tumor types, including subcutaneous tissue fibrosarcomas, liver neoplastic nodules or hepatocellular carcinomas, and adrenal cortical adenomas. Of these 3 tumors, NTP considered only the liver tumors to be related to TCDD administration. The incidences of these tumors are given in Table 22. Toxic hepatitis was found in 14 male and 32 female high-dose level rats.

Table 22: Tumor incidences in male and female Osborne-Mendel rats given 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) by gavage for two years (NTP, 1982a)

	Tumor incidence[a]			
Sex, tumor type	**Dose level (µg/kg-week)**			
	0	0.01	0.05	0.5
Males				
Thyroid:				
Follicular cell adenoma	1/69	5/48 ($p = 0.042$)	6/50 ($p = 0.021$)	10/50 ($p = 0.001$)
Follicular cell adenoma/carcinoma	1/69	5/48 ($p = 0.042$)	8/50 ($p = 0.004$)	11/50 ($p < 0.001$)
Females				
Subcutaneous tissue: fibrosarcoma	0/75	2/50	3/50	4/49 ($p = 0.023$) [3][b]
Liver:				
Neoplastic nodules/ hepatocellular carcinoma	5/75	1/49	3/50	14/49 ($p = 0.001$)
Adrenal:				
Cortical adenoma or adenoma NOS	11/73	8/49	4/49	14/46 ($p = 0.039$)

[a] Number of animals with tumor over number of animals examined.
[b] Number of animals with hepatocellular carcinoma.
NOS Not otherwise specified
P values determined using Fisher's exact test.

NTP (1982a) also conducted an carcinogenicity bioassay with TCDD in male and female B6C3F$_1$ hybrid strain mice. The protocol was similar to that used in the rat study with male mice receiving the same doses of TCDD. Female rats, however, received larger doses of 0.02, 0.1 or 1.0 µg/kg twice a week. These dose levels did not have a statistically significant effect on survival of any treatment group.
Male mice in the highest dose group had a significantly increased incidence of hepatocellular carcinomas. The high dose female group had significantly increased

incidences of subcutaneous tissue fibrosarcomas, hepatocellular adenomas or carcinomas, and thyroid follicular-cell adenomas. NTP considered only liver tumors and thyroid tumors to be related to TCDD administration. NTP also considered histiocytic lymphomas to have been increased in the high-dose female group; however, CDHS (1986) did not consider that these lymphomas were increased when the incidences in all control subgroups were considered. The observed tumor incidences in both male and female mice are given in Table 3. Toxic hepatitis was observed in 44 male and 34 female high-dose group animals. It was also observed in several animals of the other treatment groups.

Table 3: Tumor incidences in male and female B6C3F$_1$ mice given 2,3,7,8-Tetrachloro-dibenzo-*p*-dioxin (TCDD) by gavage for two years (NTP, 1982a).

	Tumor incidence[b]			
Sex, tumor type	**Dose level (µg/kg-week)**[a]			
	0	0.01 (0.04)	0.05 (0.2)	0.5 (2.0)
Males				
Liver:				
Hepatocellular carcinoma	8/73	9/49	8/49	17/50 ($p = 0.002$)
Hepatocellular adenoma or carcinoma	15/73	12/49	13/49	27/50 ($p < 0.001$)
Females				
Subcutaneous tissue, fibrosarcoma	1/74	1/50	1/48	5/47 ($p = 0.032$)
Liver:				
Hepatocellular carcinoma	1/73	2/50	2/48	6/47 ($p = 0.014$)
Hepatocellular adenoma or carcinoma	3/73	6/50	6/48	11/47 ($p = 0.002$)
Thyroid, follicular cell adenoma	0/69	3/50	1/47	5/46 (p - 0.009)

P values determined using Fisher's exact test.
[a] Dose administered to male mice; dose administered to female mice in parentheses.
[b] Number of animals with tumor over number of animals examined.

Both rat and mouse carcinogenicity bioassays conducted by NTP appear to have been done in an adequate manner. The number of treatment groups and the large dose range used in the studies are not typical of NTP bioassays, although it was similar to that used by Kociba *et al.* (1978). However, it may not have been large enough to include a dose level which produced no effect. Most significantly increased tumor incidences only occurred in the high-dose level groups, but a statistically significant dose-related trend was found in all groups.

NTP (1982b) also conducted a dermal oncogenicity bioassay on TCDD in male and female Swiss-Webster mice. TCDD in an acetone suspension was applied to the skin three days per week for 104 weeks. The male rats received 0.001 µg per application and the females received 0.005 µg per application. Separate groups of male and female mice were treated with one application of 50 µg 7,12-dimethylbenz(*a*)anthracene (DMBA) one week prior to the start of TCDD treatments. The only significantly ($p = 0.01$) increased incidences of tumors observed were among female mice. Both the TCDD- and

DMBA/TCDD-treated groups had a similar incidences of fibrosarcoma in the integumentary system (8/27 and 8/29, respectively), compared to the vehicle control of 2/41. In NTP's judgement, the results of this experiment indicated that TCDD was carcinogenic.

HexaCDDs have been tested for carcinogenicity by NTP (1980a) in both Osborne-Mendel rats and B6C3F$_1$ mice. The bioassay tested a mixture of HexaCDDs containing 31 percent 1,2,3,6,7,8-HexaCDD and 67 percent 1,2,3,7,8,9-HexaCDD. Lower chlorinated PCDDs made up the remaining 2% of the mixture, including 0.04 percent TetraCDDs. Male and female rats and male mice received weekly doses of 1.25, 2.5 or 5 µg/kg, administered by gavage twice a week. The female mice were administered doses of 2.5, 5.0, or 10 µg/kg/week.

A dose-related "toxic hepatitis", which was noninflammatory and consisted of degenerative changes in the liver, was observed in treated rats. The treated groups of female rats had significantly increased incidences of liver neoplastic nodules. Four high-dose animals were diagnosed as having hepatocellular carcinoma. The mice also had a dose-related incidence of "toxic hepatitis" and the high-dose male and female mouse groups had statistically significant increased incidences of hepatocellular adenomas and combined incidences of hepatocellular adenomas and carcinomas. The incidences of these tumors are given in Table 23.

Table 23: Tumor incidences in female Osborne-Mendel rats and male and female B6C3F$_1$

Mice given HexaCDD by gavage for two years (NTP, 1980a)

	Tumor incidence			
Sex, species, tumor type	**Dose level (µg/kg-week)**			
	0	1.25 (2.5)	2.5 (5.0)	5.0 (10)
Female rats				
liver, neoplastic nodule or hepatocellular carcinoma	5/75	10/50 (p = 0.026)	12/50 (p = 0.007)	30/50 (p < 0.001)
Male mice				
liver, hepatocellular adenoma	7/73	5/50	9/49	15/4 (p = 0.003)
liver, hepatocellular adenoma or carcinoma	15/73	14/50	14/49	24/48 (p = 0.001)
Female mice				
Liver, hepatocellular adenoma	2/73	4/48	4/47	9/47 (p = 0.003)
liver, hepatocellular adenoma or carcinoma	3/73	4/48	6/47	10/47 (p = 0.004)

P values determined using Fisher's exact test.

[a] Dose administered to male mice; dose administered to female mice in parentheses.

[b] Number of animals with tumor over number of animals examined.

Several pathologists have independently evaluated the slides made from the female rat livers in this bioassay. The re-evaluations found fewer neoplastic nodules and carcinomas than did the original evaluation. Although the incidences of neoplastic nodules and carcinomas are probably lower than originally reported, the incidence is still significant in the high-dose group. The results of four separate evaluations of the liver pathology of the female rats are given in Table 24.

Table 24: Incidence of liver tumors based on four separate pathological evaluations of female rats given HexaCDD by gavage for two years[a] (CDHS, 1986)

	Tumor incidence[b]			
Pathologist and Diagnosis	**Dose level (μg/kg-week)**			
	0	1.25	2.5	5
NTP (1980) Neoplastic nodules or hepatocellular carcinoma	5/75	10/50 $p = 0.026$	12/50 $p = 0.007$	30/50 (4)[c] $p < 0.001$
Squire (1983) Neoplastic nodules	1/75	4/50	7/50 $p = 0.007$	7/50 $p = 0.007$
Haberman and Schueler (Schueler 1983) Neoplastic nodules or hepatocellular carcinoma	NA	NA	NA	17/50 (3)[d]
Hildebrandt (1983) Neoplastic nodules or hepatocellular carcinoma	1/75	5/50 $p = 0.037$	7/50 $p = 0.007$	18/50(2) $p < 0.001$

[a] Chi-square test for trend in proportions for NTP, Squire, and Hildebrandt studies significant at $\alpha = 0.05$ level.
[b] Number of animals with tumor over number of animals examined.
[c] Number of animals diagnosed with hepatocellular carcinoma is shown in parentheses.
[d] The diagnosis for nine of the animals with neoplastic nodules was considered a matter of judgment by the pathologist.
NA = Not available.

A dermal application carcinogenicity bioassay of the same mixture of HexaCDD in male and female Swiss-Webster mice was also conducted by NTP (1980b). This study was similar to the TCDD dermal oncogenicity bioassay in its protocol. Thirty mice of each sex were treated with 0.005 μg of the dioxin mixture three times per week for the first 16 weeks, which was increased to 0.01 μg thereafter. A similar group was initially treated once with 50 μg DMBA before being treated with the HexaCDD mixture. Thirty untreated and 45 vehicle-treated mice of each sex were used as controls. Although there was a slight increase in fibrosarcomas of the integumentary system, this was not considered by NTP to be a significant carcinogenic response. DMBA pretreatment had no additional effect.

CDHS (1986) agreed with IARC (1982) that there is adequate evidence to support a conclusion that TCDD is carcinogenic to rats and mice and that TCDD should be considered a potential carcinogen to humans. The NTP bioassays (NTP 1980a) of HexaCDDs also indicated that the mixture used was tumorigenic.

It has been suggested that dioxin is a potent potentiator but a weak initiator of cancer processes, in which case exposure early in life theoretically should have less impact than when exposed later. However, Brown *et al.* (1998) suggested that prenatal exposure to dioxin and related compounds may increase sensitivity in adulthood to other chemical carcinogens. In an investigation of predisposition to mammary cancer, Brown *et al.* (1998) treated pregnant Sprague-Dawley rats on gestational day 15 with 1 μg/kg TCDD. Results indicate that prenatal TCDD exposure significantly increased terminal end buds and decreased lobules II in 50-day-old offspring. No alterations in mammary gland differentiation were observed in 21-day old offspring. Additionally, prenatal TCDD treatment was associated with an increased number of chemically induced (by DMBA) mammary adenocarcinomas in rats. These authors concluded that prenatal exposure to TCDD increased susceptibility to mammary cancer that correlated with alteration of mammary gland differentiation, based on the increased number of terminal end buds.

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ACUTE TOXICITY SUMMARY

TOLUENE

(methyl benzene, methyl benzol, phenyl methane, toluol)

CAS Registry Number: 108-88-3

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**37,000 µg/m³**
Critical effect(s)	headache, dizziness, slight eye and nose irritation
Hazard Index target(s)	Nervous System; Eyes; Respiratory System; Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

Description	colorless liquid
Molecular formula	C_7H_8
Molecular weight	92.13
Density	0.861 g/cm³ @ 25°C (Low *et al*, 1988)
Boiling point	111°C
Melting point	-95°C
Vapor pressure	28.1 mm Hg @ 25°C (USEPA, 1984)
Flashpoint	4° C, closed cup
Explosive limits	upper = 7% lower = 1.27%
Solubility	miscible in organic solvents
Odor threshold	1.6 ppm (geometric mean) (AIHA, 1989)
Odor description	sour, burnt (AIHA, 1989)
Metabolites	hippuric acid
Conversion factor	1 ppm = 3.75 mg/m³ @ 25°C

III. Major Uses or Sources

Toluene occurs naturally as a component of crude oil and is produced in petroleum refining and coke oven operations. It is used in household aerosols, nail polish, paints and paint thinners, lacquers, rust inhibitors, adhesives, and solvent based cleaning agents. Toluene is also used in printing operations, leather tanning, and chemical processes. Benzene and other polycyclic aromatic hydrocarbons (PAHs) are common contaminants of toluene. Toluene is considered a sentinel chemical for benzene exposure.

IV. Acute Toxicity to Humans

Dysfunction of the central nervous system and narcosis are the major effects of acute exposure to toluene (ATSDR, 1989). Irritation of the skin, eye, and respiratory tract can also result. Inhalational abuse of toluene with high level exposure for long periods of time has produced progressive and irreversible changes in brain structure and function (Spencer and Schaumberg, 1985).

Two separate workplace incidents involving acute inhalation exposure to toluene in several workers resulted in effects of euphoria, drunkenness, dizziness, nausea, confusion, incoordination, drowsiness, and loss of consciousness (Longley *et al.*, 1967). The toluene concentrations were estimated at 10,000 to 30,000 ppm (40,000 to 110,000 mg/m^3) although no actual measurements were made. No long-term follow-up of the exposed workers was conducted.

Reaction time and perceptual speed were studied in 12 young male subjects exposed by inhalation to toluene concentrations ranging from 100 to 700 ppm (400 to 3,000 mg/m^3), each for a 20-minute interval (Gamberale and Hultengren, 1972). Statistically significant impaired reaction time was apparent following exposure to 300 ppm (1,000 mg/m^3) toluene. A statistically significant impairment in perceptual speed was observed at 700 ppm toluene. No effects were observed at 100 ppm.

Two groups of middle aged workers, one with previous occupational exposure to solvents and one without, were exposed once to 100 ppm (400 mg/m^3) of toluene for 6.5 hours (Baelum *et al.*, 1985). Fatigue, sleepiness, a feeling of intoxication, and eye, nose and throat irritation were reported. Decrements in manual dexterity, color discrimination, and accuracy in visual perception were also observed. Greater sensitivity to toluene was noted for those subjects with previous solvent exposure.

Nasal mucus flow, lung function, psychometric performance, and subjective responses were studied in 16 young healthy males exposed to toluene concentrations ranging from 10 to 100 ppm (40 mg/m^3 to 400 mg/m^3) for 6 hours (Andersen *et al*, 1983). Headaches, dizziness, a feeling of intoxication, and slight eye and upper respiratory irritation were reported at 100 ppm. The subjects also reported that it became more difficult to participate in the battery of psychometric tests and that their reaction time felt impaired at 100 ppm. No significant objective changes compared to control exposures were observed in the performance test results. No symptoms were reported at 10 and 40 ppm.

A battery of neurobehavioral and performance tests was conducted among 42 young men and women exposed by inhalation for 7 hours to 0, 75, and 150 ppm (0, 280, and 560 mg/m^3) toluene (Echeverria *et al.*, 1989). Statistically significant decrements in visual short term memory, visual perception, and psychomotor skills were observed at 150 ppm compared to control exposures. A dose-dependent increase in subjective symptoms of headache and eye irritation was also observed.

Wilson (1943) reported that workers exposed to concentrations of commercial toluene ranging from 50 to 200 ppm (200 to 750 mg/m^3) for periods of 1 to 3 weeks experienced

headaches, lassitude, and loss of appetite. At 200 to 500 ppm (750 to 2,000 mg/m^3), symptoms of nausea, bad taste in the mouth, slightly impaired coordination and reaction time, and temporary memory loss were also observed. Exposure to 500 to 1,500 ppm (2,000 to 5,600 mg/m^3) resulted in palpitations, extreme weakness, pronounced loss of coordination, and impaired reaction time. Red blood cell counts were decreased and there were 2 cases of aplastic anemia. The hematologic effects were most likely caused by benzene impurities (ACGIH, 1986).

Three volunteer subjects exposed by inhalation to toluene concentrations ranging from 50 to 100 ppm (200 to 400 mg/m^3), 8 hours per day, 2 times per week over 8 weeks experienced fatigue, drowsiness, and headaches (von Oettingen *et al.*, 1942). At 200 to 800 ppm (750 to 3,000 mg/m^3), symptoms of muscular weakness, confusion, impaired coordination, paresthesia, and nausea were also reported. After exposure to 800 ppm, all 3 subjects reported considerable after-effects (severe nervousness, muscular fatigue, and insomnia) lasting several days.

Predisposing Conditions for Toluene Toxicity

Medical: Since toluene is metabolized by the liver, persons with liver disease may be sensitive to its acute effects (ATSDR, 1993). Persons with preexisting neurologic or heart disease may also be at increased risk for adverse effects resulting from exposure to toluene (Reprotext, 1999).

Chemical: Because salicylates and alcohol competitively inhibit toluene metabolism, concurrent use of these substances may increase susceptibility to toluene toxicity (ATSDR, 1993). Persons using over-the-counter bronchial dilators containing epinephrine might be more sensitive to arrhythmogenic effects (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The 1-hour LC_{50} for toluene in the rat is 26,700 ppm (100,000 mg/m^3) (Pryor *et al*, 1978). The 6-hour LC_{50}s in rats and mice are 4,618 ppm (17,320 mg/m^3) and 6,949 ppm (26,060 mg/m^3), respectively (Bonnet *et al.*, 1982). The 8-hour LC_{50} is 5,300 ppm (19,900 mg/m^3) in the mouse (Svirbely *et al*, 1943).

Attention deficits and impairment of visual-motor abilities were observed in 6 macaque monkeys exposed by inhalation for 50 minutes to 2,000-4,500 ppm (7,500-17,000 mg/m^3) toluene (Taylor and Evans, 1985). Expired carbon dioxide increased in a dose-dependent manner from 100 to 3,000 ppm (400 to 11,000 mg/m^3). The investigators stated that changes in expired carbon dioxide may provide evidence of combined behavioral, respiratory, sensory, and metabolic effects.

Dose-dependent decreases in behavioral performance and central nervous system depression were observed in mice and rats exposed by inhalation to toluene at concentrations ranging from 2,600 to 12,000 ppm (9,800 to 45,000 mg/m^3) for up to 3

hours (Bruckner and Peterson, 1981). Younger animals were more susceptible to toluene toxicity and mice were more sensitive than rats of the same age.

Kishi *et al.* (1988) used the shock avoidance response test to study behavioral effects in rats. Inhalation exposure to 125 ppm (469 mg/m^3) toluene for 20 minutes resulted in a considerable decrease in the effective avoidance response rate.

Hearing loss was observed in rats after exposure to 1,000 ppm (4,000 mg/m^3) toluene, 14 hours per day for 2 weeks (Pryor *et al.*, 1984).

VI. Reproductive or Developmental Effects

Toluene is listed under the California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. Most of the information concerning the adverse developmental effects of toluene in humans comes from case reports among children of deliberate toluene "sniffers." Children whose mothers had inhaled large quantities of toluene during pregnancy were found to have microencephaly, facial and limb abnormalities, attention deficits, hyperactivity, developmental delay with greater language impairment, and growth retardation (Hersch *et al.*, 1985; Hersch, 1989). Multiple solvent and/or other substance abuse may have contributed to the observed abnormalities. Growth retardation, craniofacial abnormalities, and hyperchloremic acidosis were observed in the children of women with severe renal tubular acidosis induced by chronic paint sniffing (Goodwin, 1988). Preterm delivery, perinatal death, and growth retardation were significantly increased among 21 newborns exposed to toluene as a result of maternal inhalation abuse (Wilkins-Haug and Gabow, 1991). A case-referent study of women occupationally exposed to organic solvents, including toluene, reported increased incidences of urogenital, gastrointestinal, and cardiac anomalies in their children (McDonald *et al.*, 1987). Although toluene was considered to be the most likely teratogenic agent, concurrent exposures to other developmental toxicants make this conclusion difficult to support.

There are several animal studies of varying quality on the reproductive and developmental toxicity of toluene. A complete review of the developmental toxicology of toluene is available (Donald *et al.*, 1991). Selected studies are summarized below.

Shigeta *et al.* (1982) reported statistically significant increases in the number of fetal resorptions observed in the offspring of mice exposed by inhalation to 100 ppm (400 mg/m^3) toluene for 6 hours per day on days 1-17 of gestation. Exposure at 1,000 ppm (4,000 mg/m^3) resulted in a statistically significant increase in the incidence of extra ribs.

A statistically insignificant increased incidence of extra ribs was observed in rats exposed by inhalation to 1,000 mg/m^3 toluene for 24 hours per day on days 7-14 of gestation (Tatrai *et al.*, 1980). Fused sternebrae and extra ribs were observed in rats exposed to 400 ppm (1,500 mg/m$^{3)}$ toluene for 24 hours per day on days 9-14 of gestation (Hudak and Ungvary, 1978). Skeletal retardation was observed in rats exposed to 266 ppm (1,000 mg/m^3) toluene for 8 hours per day on days 1-21 of gestation and to 400 ppm

(1,500 mg/m^3) 24 hours per day on days 1-8. This same group exposed mice to 400 ppm (1,500 mg/m^3) or to 133 ppm (500 mg/m^3) toluene for 24 hours per day on days 6-13 of gestation. All dams died at the higher dose and a statistically significant decrease in fetal weight was observed at the lower dose.

Skeletal retardations were observed in the offspring of pregnant rabbits exposed by inhalation to concentrations of toluene ranging from 30 to 300 ppm (100 to 1,000 mg/m^3), 6 hours per day on days 6-18 of gestation (Klimisch *et al.*, 1992). These results were not dose-dependent and were not reproduced in two additional groups of rabbits exposed to 100 and 500 ppm (400 and 2,000 mg/m^3) toluene.

A statistically significant increase in the number of animals showing a 13/13 rib profile (which is considered normal) was observed in mice exposed to 400 ppm (1,500 mg/m^3) toluene, 7 hours per day on days 7-16 of gestation (Courtney *et al.*, 1986). An increased number of resorptions was observed in mice exposed to 400 ppm toluene on days 6-15 of gestation (Gleich and Hofman, 1983); the daily exposure duration was not specified.

These preceding animal studies support the association between toluene exposure and effects on somatic development of the fetus. However, the value of these studies is limited by issues such as unknown or unconventional exposure durations, inadequate descriptions of maternal toxicity, use of individual offspring instead of litters for statistical analyses, and purity of toluene used (Donald *et al.*, 1991).

The best available study relating toluene exposure and retardation of somatic development is one in which adult rats of 2 generations were exposed for 6 hours per day to 0, 100, 500 or 2,000 ppm (0, 375, 1,875, or 7,500 mg/m^3) toluene during an 80-day premating period and a 15 day mating period (IRDC, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weights of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. Exposure at this level to the male parent only did not result in any adverse effects. The NOAEL for fetotoxic effects in this study was 500 ppm.

In a recent teratogenicity study by inhalation, Ono *et al.* (1995) exposed pregnant Sprague-Dawley rats to 600 or 2000 ppm toluene for 6 h/day from day 7 to day 17 of pregnancy. The control group inhaled "conditioned" clean air. Maternal exposure to 2000 ppm caused significant toxic effects such as body weight suppression in dams and offspring, high fetal mortality, and embryonic growth retardation. However, no external, internal, or skeletal anomalies were observed in the fetuses of any treated group. In addition, there were no differences in the results of pre- and post-weaning behavioral tests of the offspring. No changes which could be related to toluene were apparent in the 600 ppm group. Thus 600 ppm is a NOAEL is this study.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 9.8 ppm (37,000 $\mu g/m^3$)

Study	Andersen *et al.*, 1983
Study population	16 young, healthy males
Exposure method	inhalation
Critical effects	impaired reaction time and symptoms of headache, dizziness, a feeling of intoxication and slight eye and nose irritation
LOAEL	100 ppm
NOAEL	40 ppm
Exposure duration	6 hours
Extrapolated 1 hour concentration	98 ppm (40^2ppm* 6 h = C^2 * 1 h) (see Table 12 for information on "n")
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	9.8 ppm (37 mg/m^3; 37,000 $\mu g/m^3$)

Level Protective Against Severe Adverse Effects

In a 2-generation study, adult rats were exposed for 6 hours per day to 0, 100, 500, or 2,000 ppm (0, 375, 1875, or 7,500 mg/m^3) toluene during an 80-day premating period and a 15 day mating period (International Research and Development Corporation, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weights of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. The NOAEL for fetotoxic effects in this study was 500 ppm. The NOAEL reported in the study, a chronic exposure study, was in the same concentration range as the LOAELs reported in other acute exposure studies addressing reproductive and developmental toxicity, summarized above. However, because the IRDC study was judged to be methodologically the most sound of all the studies considered for this endpoint (Donald *et al.*, 1991), it was chosen as the basis for the severe adverse effect level. An uncertainty factor of 100 was applied to the NOAEL to account for animal to human extrapolation and for intraindividual variability. The 6-hour exposure serves as the basis for the level protective against severe adverse effects. This yields a 6-hour level protective against severe adverse effects of 5 ppm (19 mg/m^3).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) reports an IDLH for toluene of 500 ppm. According to NIOSH, "It has been reported that extreme fatigue, mental confusion, exhilaration, nausea, headache and dizziness resulted from exposures to 600 ppm by the end of 3 hours [von Oettingen *et al.* 1942]. In addition, the following observations have been made: some workers will tolerate concentrations ranging up to 200 ppm for 6 to 8 hours daily with no demonstrable ill effects; 200 to 500 ppm for 6 to 8 hours will cause tiredness and lassitude in most workers; and concentrations over 500 ppm for 1 to 3 hours are definitely dangerous and will cause symptoms attributable to depression of the central nervous system and the bone marrow [Wilson 1943]. It has also been reported that exposure to concentrations greater than 4,000 ppm for more than 5 minutes might limit self rescue ability [ANSI 1973]. After 20 minutes, exposures to concentrations at 300, 500, or 700 ppm resulted in significant increases in reaction times; a significant decrease in perceptual speed resulted after a 20-minute exposure to 700 ppm [Gamberale and Hultengren 1972]. .... The revised IDLH for toluene is 500 ppm based on acute inhalation toxicity data in humans [Gamberale and Hultengren 1972; von Oettingen *et al.* 1942; Wilson 1943]." Based on its documentation, the IDLH of 500 ppm, designed for a 30 minute exposure, does not appear to be low enough to protect the general public, especially sensitive individuals, from life-threatening effects for 1 hour. Therefore, no recommendation for a level protective against life-threatening effects is made at this time.

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CHRONIC TOXICITY SUMMARY

TOLUENE

(Methyl benzene; methyl benzol; phenyl methane; toluol)

CAS Registry Number: 108-88-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**400 µg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC.
Critical effect(s)	Neurological disturbances in human workers
Hazard index target(s)	Nervous system; alimentary system; teratogenicity

II. Physical and Chemical Properties (HSDB, 1995 except as noted)

Description	Colorless liquid
Molecular formula	C_7H_8
Molecular weight	92.13 g/mol
Density	0.861 g/cm^3 @ 25°C (Low *et al.*, 1988)
Boiling point	111° C
Vapor pressure	28.1 mm Hg @ 25°C (U.S. EPA, 1984)
Solubility	miscible in most organic solvents
Conversion factor	1 ppm = 3.77 mg/m^3 @ 25°C

III. Major Uses or Sources

Toluene occurs naturally as a component of crude oil and is produced in petroleum refining and coke oven operations (HSDB, 1995). It is used in household aerosols, nail polish, paints and paint thinners, lacquers, rust inhibitor, adhesives and solvent based cleaning agents. Toluene is also utilized in printing operations, leather tanning and chemical processes. Benzene and other polycyclic aromatic hydrocarbons are common contaminants of toluene. Toluene is considered a sentinel chemical for benzene in the context of air and water sample monitoring.

IV. Effects of Human Exposures

Case studies of solvent abusers have shown that high doses of toluene (e.g., 425 mg/day) can cause neurobehavioral changes and degeneration of cerebellar, cortical, and brainstem functions.

A battery of neurobehavioral tests was performed in 30 female workers exposed to toluene vapors in an electronic assembly plant (Foo *et al.*, 1990). The average number of years worked was 5.7 ± 3.2 for the exposed group and 2.5 ± 2.7 years for the controls. The exposed group of workers inhaled a time-weighted average of 88 ppm (330 mg/m^3) toluene while the control workers inhaled 13 ppm (49 mg/m^3). A significant decrease in neurobehavioral performance was observed in the exposed workers in 6 out of 8 tests. Irritant effects were not examined, and concurrent exposures to other chemicals were not addressed. In this study, 88 ppm was considered a LOAEL for central nervous system effects.

Workers exposed to lesser concentrations have shown some impairment of CNS endpoints, however, controls and exposed individuals have not been well matched in many of these studies (Hanninen *et al.*, 1987; Iregren, 1982; Cherry *et al.*, 1985).

Solvent workers were exposed to 42.8 ppm toluene (estimated as a time-weighted average) for an average duration of 6.8 years (Yin *et al.*, 1987). No significant differences from controls were noted in treated individuals in questionnaires, hematology, or urinalyses. This study did not account for confounding variables, such as smoking and alcohol consumption.

Subjective symptoms of headache, sore throat and dizziness were reported by workers exposed to approximately 100 ppm toluene (time-weighted average, duration unspecified) (Lee *et al.*, 1988). The prevalence of these symptoms was concentration-dependent. A similar study examined the psychomotor, manual dexterity, and visual perception abilities of college students exposed to 0, 74, or 151 ppm (0, 278, or 566 mg/m^3) toluene 7 hours/day for 3 days (Echeverria *et al.*, 1989). In addition to the above objective measures, subjective symptoms of eye irritation, headache, and somnolescence were noted at 151 ppm. Visual perception and manual dexterity performances both decreased, while reported symptoms increased in the 151 ppm group. No effects of toluene on psychomotor tests were observed. In this study, 74 ppm was a NOAEL.

Baelum *et al.* (1985) found that subjects exposed to 0 or 100 ppm (375 mg/m^3) toluene for 6.5 hours experienced a loss of color discrimination, regardless of their prior solvent exposure history. Other signs of toxicity included visual perception and visual motor function, although these signs were only observed in the occupationally-exposed individuals.

Liver toxicity has been documented in toluene solvent abusers (Fornazzari *et al.*, 1983). In a cross-sectional study of 289 printing workers exposed to an estimated 53 ppm (200 mg/m^3) for 8 hours/day, 8 workers had significantly elevated serum enzymes (ALT/AST

ratio) indicative of liver damage (Guzelian *et al.*, 1988). However, another cross-sectional study by Boewer *et al.* (1988) showed no significant effects on serum enzymes in 181 printing workers exposed to concentrations below 53 ppm (200 mg/m^3).

Toluene was identified as the principal solvent associated with an increased incidence of urinary tract birth defects in a retrospective cohort study of 301 cases compared with 301 referent controls (McDonald *et al.*, 1987). The cohort was matched for age, employment, date of delivery, and educational level.

V. Effects of Animal Exposures

Rats (20 per group) exposed for 2 years to 0, 600, or 1200 ppm (0, 2261, or 4523 mg/m^3) toluene 6.5 hours/day, 5 days/week for 103 weeks were examined for hematological and histopathological effects in addition to gross observations of toxicity (NTP, 1990). Significant erosion of the olfactory epithelium was observed in male rats while degeneration of the respiratory and nasal epithelium was observed in both sexes at 600 ppm.

A study of the chronic effects of toluene in rats (5-20 animals per group) exposed for 106 weeks to 0, 30, 100, or 300 ppm (0, 113, 375, or 1125 mg/m^3) toluene showed no treatment-related effects on histopathology of major organs, including the nasal turbinates (CIIT, 1980). In this study, the samples taken for nasal histopathology examination may have been inadequate to substantiate the nasal lesions reported by the NTP (1990).

Reproductive toxicity to maternal rats was observed during exposure to 1500 ppm toluene, 24 hours/day on days 9 to 14 of gestation (Hudak and Ungvary, 1978). Two dams out of 19 died during exposure. Fetuses from the 1500 ppm group showed increased incidence of sternebral alterations, extra ribs and missing tails. The same concentration given on days 1 through 8 of gestation resulted in 5 deaths out of 14 dams. Fetuses in this regimen showed increased incidence of hydrocephaly and growth retardation compared to controls. A third regimen that exposed maternal rats to 1000 ppm on days 1 through 21 of gestation resulted in no maternal deaths or toxicity, and an increase in the incidence of skeletal variations in the fetuses. When exposed to 1500 ppm continuously, maternal mice died within 24 hours of exposure whereas exposure to 500 ppm had no apparent effect. Examination of the fetal mice showed significant growth retardation in the 500 ppm group.

Inhalation of 0 or 800 mg/m^3 toluene for 6 hours/day on gestation days 14-20 (rats), or days 6-11 (hamsters) showed significant exposure-related decrease in birth weight of the rats compared with controls (Da Silva *et al.*, 1990). In addition to low birth weight, the numbers of live pups was significantly lower in the 800 ppm group. No deficits in any parameter were noted in the hamsters. In this study, no neurobehavioral effects were noted in the offspring.

A 2-generation study of the effects of 0, 100, 500, or 2000 ppm (0, 377, 1885, or 7538 mg/m^3) toluene in rats (males, 10-40 per group; females, 20-80 per group) (API, 1985). Rats were exposed for 6 hours/day, 7 days/week for 80 days and a 15 day mating period. The mated females were then exposed to the same concentrations during days 1-20 of gestation and days 5-20 of lactation. After weaning, the F1 pups were exposed 80 times to the appropriate exposure level and then randomly mated to members of the same exposure group. The F1 generation showed significantly decreased body weight which remained throughout lactation. No effects were observed on histopathology. No data were presented for the F2 generation.

Mice exposed chronically to 0, 120, 600, or 1200 ppm (0, 452, 2261, or 4523 mg/m^3) toluene 6.5 hours/day, 5 days/week, for 2 years (NTP, 1990). The only treatment-related effect was a significant increase in the number of animals with hyperplasia of the bronchial epithelium in the 1200 ppm exposure group.

No significant effects of 1481 ppm toluene exposure were noted in rats (15/sex/group) after 26 weeks exposure (API, 1985). Examined in this study were neurohistopathological responses, hematology, serum enzymes and urinalyses.

Ototoxicity in the form of hearing loss was observed in rats exposed to 1000 ppm 14 hours/day for 2 weeks (Pryor *et al.*, 1984). In this study, the auditory brainstem reponse and behavioral changes both indicated hearing loss. A lower concentration of 700 ppm for 14 hours/day for 16 weeks did not result in any significant hearing loss.

VI. Derivation of U.S. EPA RfC

Study	Foo *et al.*, 1990; NTP, 1990; U.S. EPA, 1994
Study population	30 Female workers in an electronic assembly plant
Exposure method	Occupational inhalation
Critical effects	Neurobehavioral deficits in 6 out of 8 tests
LOAEL	88 ppm
NOAEL	Not observed
Exposure continuity	10 m^3/day occupational inhalation rate, 5 days/week
Average occupational exposure	31.4 ppm (88 x 10/20 x 5/7)
Exposure duration	5.7 ± 3.2 years (exposed group); 2.5 ± 2.7 years (controls)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Modifying factor	3 (database deficiencies including the lack of animal neurotoxicity and irritation studies)
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.1 ppm (100 ppb; 0.4 mg/m^3; 400 $\mu g/m^3$)

The major strength of the U.S. EPA RfC is the use of human exposure data from workers exposed over a period of years. The major weaknesses are the uncertainty in estimating exposure, the potential variability in exposure concentration, and the lack of a NOAEL observation and of dose-response information.

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ACUTE TOXICITY SUMMARY

XYLENES

(technical xylene (o-, m-, p-), xylol)
(o-xylene, ortho-xylene, 1,2-dimethylbenzene, 2-xylene)
(m-xylene, meta-xylene, 1,3-dimethylbenzene, 3-xylene)
(p-xylene, para-xylene, 1,4-dimethylbenzene, 4-xylene)

CAS Registry Numbers: 1330-20-7 (technical), 95-47-6 (o-), 108-38-3 (m-), 106-42-3 (p-)

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**22,000 µg/m³**
Critical effect(s)	eye irritation in healthy human volunteers
Hazard Index target(s)	Eyes; Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	C_8H_{10}
Molecular weight	106.2
Density	0.881 g/cm³ (o-); 0.860 (m-); 0.861 (p-) @ 20°C
Boiling point	144.4°C (o-); 139.1°C (m-); 138.4°C (p-)
Melting point	-25°C (o-); -47.87°C (m-); 13.3°C (p-)
Vapor pressure	6.6 (o-); 8.39 (m-); 8.87 (p-) mm Hg at 25°C
Flashpoint	17.2°C (o-); 25°C (m-); 25°C (p-) (closed cup)
Explosive limits	unknown
Solubility	insoluble in water; soluble in ethanol, acetone, ether
Odor threshold	1 ppm (Carpenter *et al.*, 1975)
Metabolites	methylbenzoic acids
Conversion factor	1 ppm = 4.34 mg/m³ @ 25°C

III. Major Uses or Sources

As nonexplosive aromatic hydrocarbons, mixtures of the three (technical xylene) isomers are heavily used in the chemical industry and in the petroleum industry as a solvent and gasoline "antiknock" additives. Of the three isomers, p-xylene is produced in the highest quantities in the U.S. for use in the synthesis of terephthalic acid for polymer fibers such as mylar and dacron (HSDB, 1994). However, m-xylene is the most abundant isomer in the environment (Silverman and Schatz, 1991).

IV. Acute Toxicity to Humans

Despite its structural similarity to benzene, xylene does not influence hematopoiesis. The principal systemic effects of acute xylene exposure are on the central nervous system (CNS) but it is also a respiratory and eye irritant. Nelson *et al.* (1943) exposed 10 healthy human volunteers for periods of 3 to 5 minutes to estimated concentrations of 100 or 200 ppm technical grade xylene. The subjects reported eye, nose, and throat irritation at 200 ppm but not at 100 ppm. A significant area of uncertainty arising from the Nelson *et al.* (1943) study is the use of estimated rather than measured exposure concentrations. Carpenter *et al.* (1975) evaluated eye irritation in 7 human volunteers exposed for 15 minutes to 460, 1,000, 2,000, or 3,000 mg/m^3. One volunteer noted mild throat discomfort at 460 mg/m^3, but not at 2,000 mg/m^3. No subjects reported eye irritation at 460 mg/m^3 (106 ppm). Hastings *et al.* (1984) exposed 50 healthy individuals to 100, 200, or 400 ppm mixed xylenes for 30 minutes to evaluate eye, nose, and throat irritation. The percent of subjects reporting eye irritation was 56 for controls (clean air), 60 at 100 ppm, 70 at 200 ppm, and 90 at 400 ppm. The authors concluded there was no effect on eye irritation at 100 ppm because the incidence of irritation was as low as the control group. The data from Nelson *et al* (1943), Carpenter *et al.* (1975), and Hastings *et al.* (1984) taken together are consistent with a human NOAEL for eye irritation of about 100 ppm for at least a 30-minute exposure.

Exposure of sedentary or exercising subjects to a 10-minute peak concentration of 400 ppm (1,736 mg/m^3) resulted in significantly increased uncontrolled body sway in these subjects. Exposure to 200 ppm (868 mg/m^3) xylene for up to 5 hours did not result in CNS disturbances measured by increased body sway (Laine *et al.*, 1993). Riihimaki and Savolainen (1980) reported that a single 5-minute exposure to 400 ppm xylene (isomeric form unknown) resulted in lightheadedness and inebriation similar to alcohol intoxication. Deleterious effects on EEG, reaction time, body balance, and manual dexterity were found in 8 healthy volunteers following exposure to 100 ppm (434 mg/m^3) m-xylene for 6 hours/day for 6 days (Savolainen *et al.*, 1980). Exposure of 15 volunteers to 100 ppm technical xylene mixed with 20% ethylbenzene for 70 minutes, including 30 minutes of exercise, resulted in significant impairments in short-term memory and other CNS performance tests (Gamberale *et al.*, 1978). Because ethylbenzene may have contributed to the CNS effects, definitive conclusions about the effects of xylene cannot be drawn from this study.

Nine healthy male volunteers were exposed to 200 ppm m-xylene 4 hours a day, with or without exercise for 10 minutes at the beginning of each session (Savolainen *et al.*, 1985). There were no changes in reaction times, but average and maximal body sway were decreased in a concentration-dependent manner. Exercise had a sway reducing effect. Male volunteers were exposed to 200 ppm m-xylene vapor for 4 hours a day, either sedentary or with 10 minutes periods of exercise twice a day (Savolainen *et al.*, 1984). The body balance of the subjects was impaired in the anteroposterior direction. Nine healthy male students were exposed to 200 ppm m-xylene for 4 hours per day at 6-day intervals over 6 consecutive weeks (Savolainen *et al.*, 1982). Body sway tended to decrease with exposure. Only minor electroencephalographic effects were noted on 4

hour exposures to 200 ppm m-xylene exposure, and no other adverse effects were noted (Seppalainen *et al.*, 1991).
Five volunteers were exposed to 40 ppm xylene for 7 hours/day, 3 consecutive days/week in an inhalation chamber. There was an 11-day break between each 3-day session (Mergler and Beauvais, 1992). Individual differences in olfactory perception thresholds for toluene were noted, but there was no effect of exposure duration.

Predisposing Conditions for Xylene Toxicity

Medical: Unknown

Chemical: In rats, exposure to 300 ppm (1,302 mg/m^3) m-xylene mixed with 600 ppm methyl ethyl ketone (MEK) for 6 hours resulted in synergistic effects on liver enzyme induction and glutathione depletion compared to MEK exposure alone (Liira *et al.*, 1991). Xylene may therefore accelerate the metabolism and clearance of some other xenobiotics. However, in the presence of MEK, xylene metabolism was strongly inhibited; this was accompanied by elevation of xylene concentrations in blood and fat. Thus, exposure to xylene in the presence of other solvents may result in increased toxicity.

V. Acute Toxicity to Animals

Six-hour inhalation LC_{50} values in mice for each xylene isomer are: 4,595, 5,267, and 3,907 ppm (19,942, 22,859, 16,956 mg/m^3) for o-, m-, and p- xylene, respectively (Bonnet *et al.*, 1979). A 4-hour LC_{50} for mixed xylenes was estimated as 6,700 ppm (29,078 mg/m^3) in rats; and a 2-hour LC_{50} was calculated as 9,500 ppm (41,230 mg/m^3) in cats (Carpenter *et al.*, 1975).

An increase in liver weight and cytochrome P450 (P450) content was observed in rats exposed to 1,600 ppm (6,944 mg/m^3) p-xylene for 6 hours (Simmons *et al.*, 1991). Rats exposed for 6-hours to 300 ppm (1,302 mg/m^3) m-xylene showed increased specific liver P450 enzyme activity and depleted liver glutathione concentrations. These effects were enhanced by simultaneous exposure to 600 ppm MEK (Liira *et al.*, 1991).

Pulmonary effects following exposure to 300 ppm (1,302 mg/m^3) p-xylene for 6 hours include microsomal membrane damage and decreased lung P450 enzyme content (Silverman and Schatz, 1991). The destruction of rat lung but not liver P450 enzymes by p-xylene has been described by Patel *et al.* (1978), and has been attributed to the formation of a toxic aldehyde metabolite of p-xylene. Single 6-hr exposures of rats to m-xylene caused inhibition of aryl hydrocarbon hydroxylase and CYP2B1 activities in the lung but not the liver (Foy *et al.*, 1996).

VI. Reproductive or Developmental Toxicity

Exposure of pregnant rats for 6 hours/day on days 4-20 of gestation to 200 ppm (868 mg/m^3) technical (mixed) xylene resulted in significantly increased incidence of delayed ossification of the skull in the offspring (Hass and Jakobsen, 1993). The rat pups exposed prenatally to 200 ppm xylene displayed significantly decreased motor performance during adolescence. However, a study using p-xylene showed no significant embryotoxic or developmental effects on the CNS as measured by acoustic startle response in rats following exposure to 7,000 mg/m^3 (1,613 ppm) throughout gestation (Rosen *et al.*, 1986).

All three isomers of xylene cause maternal toxicity and are fetotoxic but not teratogenic at near lethal concentrations in rats (Hudak and Ungvary, 1978; Ungvary *et al.*, 1980). Ungvary and Tatrai (1985) showed that exposure of both rats and mice to technical xylene as well as specific isomers resulted in fetotoxic effects such as fetal weight loss and delayed skeletal ossification. Of the 3 isomers, p-xylene exposure is the most toxic to the fetus, since it results in the least maternal toxicity and the greatest fetotoxicity (Barlow and Sullivan, 1982); m-xylene has been shown to cause the greatest maternal toxicity (Hood and Ottley, 1985).

Persistence of neurobehavioral effects was noted in offspring of female rats (Mol:WIST) exposed to 500 ppm technical xylene for 6 hours per day on days 7-20 of prenatal development. The dose was not maternally toxic and did not decrease viability of offspring. Learning and memory abilities with spatial navigation on a water maze were impaired at 16, 28 and 55 weeks of age. However, differences were not significant at 55 weeks. The authors suggested these results were compatible with two different conclusions: 1) the effect was partly reversible over a long time period, or 2) practice at solving the problem led to compensation over unresolved neurotoxic effects (Hass *et al.*, 1997). Rats of the same strain (Mol: WIST) exposed prenatally to the same regimen did not show any differences from control rats in synaptosomal cytosolic calcium concentration (Edelfors *et al.*, 1996).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 22,000 μg/m^3

Study	Hastings *et al.*, 1984 (with support from Carpenter et al., 1975; Nelson *et al.*, 1943)
Study population	50 healthy human volunteers
Exposure method	30 minute exposures to 430, 860 or 1720 mg/m^3 xylene (technical grade)
Critical effects	subjective reports of eye, nose, and throat irritation
LOAEL	860 mg/m^3
NOAEL	430 mg/m^3 (100 ppm)
Exposure duration	30 minutes

Equivalent 1 hour concentration	50 ppm (C^1 * 60 min = 100 ppm * 30 min)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	5 ppm (22 mg/m^3, 22,000 µg/m^3)

With the possible exception of inconsistently observed developmental endpoints, irritation is the lowest reported human health effect for xylene.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

The NAS Committee on Toxicology (NRC, 1984) reviewed the toxicological literature for xylene and determined that the CNS was the main target for xylene toxicity. The Committee concluded that the CNS disturbances in humans (Ogata *et al.*, 1970; Gamberale *et al.*, 1978) were reversible and were similar to those produced by alkyl benzenes and other related compounds. Irritation of the eyes and mucous membranes (Carpenter *et al.*, 1975; Nelson *et al.*, 1943) was considered, but the purpose of the EEGL is to protect against CNS toxicity in military personnel . Based on these findings, the Committee recommended a NAS-EEGL of 200 ppm (870 mg/m^3). However, it is not clear that an adequate margin of safety is incorporated into this EEGL for use for the general public.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

The IDLH is 900 ppm, based on animal LC_{50} and LC_{lo} estimates divided by a 10-fold uncertainty factor (NIOSH, 1995). The data cited include several 4 hour studies: (1) an 8,000 ppm m-xylene LC_{lo} for rats (Smyth *et al.*, 1962); (2) a 4,550 ppm rat LC_{50} for p-xylene (Harper *et al.* 1977); and (3) a 5,000 ppm rat LC50 for xylenes (NPIRI, 1974). The IDLH appears to be based on the Harper *et al.* (1977) data with an extrapolated 30-minute LC_{50} estimate of 9,100 ppm.

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XYLENES

(Xylol or commercial xylenes (mixture of 60-70% m- and remaining percentage is mix of o- and p- xylenes), technical grade xylenes or mixed xylenes (20% o-xylene, 40% m-xylene, 20% p-xylene, 20% ethyl benzene, and traces of toluene and C9 aromatics), o-xylene (1,2-dimethylbenzene or 2-xylene), m-xylene (1,3-dimethylbenzene or 3-xylene), p-xylene (1,4-dimethylbenzene or 4-xylene), also noted as methyltoluene, benzene-dimethyl, dimethylbenzene)

CAS Registry Numbers.: 1330-20-7 (technical mixture of o-, p-, and m-xylene); 95-47-6 (o-xylene); 108-38-3 (m-xylene); 106-42-3 (p-xylene)

I. Chronic Toxicity Summary

Inhalation reference exposure level	**700 µg/m^3** (for technical or mixed xylenes or sum of individual isomers of xylene)
Critical effect(s)	CNS effects in humans; irritation of the eyes, nose, and throat
Hazard index target(s)	Nervous system; respiratory system

II. Physical and Chemical Properties (ATSDR, 1995; HSDB, 1995)

Description	Colorless liquid
Molecular formula	C_8H_{10}
Molecular weight	106.16 g/mol
Density	0.864 g/cm^3 @ 20°C(technical mixture); 0.881 (o-); 0.860 (m-); 0.861 (p-)
Boiling point	137-140°C @ 760 mm Hg (technical mixture); 144.4°C (o-); 139.1°C (m-); 138.4°C (p-)
Vapor pressure	6.6 mm Hg (o-); 8.39 mm Hg (m-); 8.87 mm Hg (p-) all @ 25°C.
Solubility	Practically insoluble in water; miscible with absolute alcohol, ether and many other organic solvents
Conversion factor	1 ppb = 4.34 µg/m^3

III. Major Uses or Sources

Mixtures of o-, p-, and m-xylenes are extensively used in the chemical industry as solvents for products including paints, inks, dyes, adhesives, pharmaceuticals, and detergents (HSDB, 1995). In the petroleum industry xylenes are used as antiknock agents in gasoline, and as an intermediate in synthetic reactions. Of the three isomers, p-xylene is produced in the highest quantities in the U.S. for use in the synthesis of

phthalic, isophthalic, and terephthalic acid used in manufacture of plastics and polymer fibers including mylar and dacron.

IV. Effects of Human Exposure

Information on the toxicity of xylenes to humans is almost exclusively limited to case reports of acute exposures and studies of occupational exposures in which persons often inhaled a mixture of hydrocarbon solvents 8 hours per day, 5-6 days per week. These studies often have incomplete information on the airborne concentrations of xylene and other hydrocarbons. One study examining chronic effects in humans from inhalation of predominantly mixed xylenes was identified (Uchida *et al.*, 1993) and one study examining subchronic effects of p-xylene exposure was identified (Hake *et al.*, 1981). No studies examining the chronic effects of oral or dermal xylene exposure in humans were identified.

Pharmacokinetic studies have documented the absorption of xylene in humans through inhalation, oral, and dermal routes of exposure. Approximately 60% of inspired xylene is retained systemically (Sedivec and Flek, 1979). The majority of ingested xylene (~90%) is absorbed into the systemic circulation (ATSDR, 1995). Xylene is also absorbed dermally; the rate of absorption of xylene vapor is estimated as 0.1-0.2% of that by inhalation (Riihimaki and Pfaffli, 1978). Measurement of the rate of absorption through direct contact with the skin produced variable results ranging from 2 $\mu g/cm^2/min$ (Engstrom *et al.*, 1977) to 75-160 $\mu g/cm^2/min$ (Dutkiewicz and Tyras, 1968).

Xylene exposure has been associated with effects in a number of organ systems including the lungs, skin and eyes; neurological system; heart and gastrointestinal system; kidney; and possibly the reproductive system.

Pulmonary effects have been documented in occupational exposures to undetermined concentrations of mixed xylenes (and other solvents) and include labored breathing and impaired pulmonary function (Hipolito 1980; Roberts *et al.*, 1988). High levels of xylene exposure for short periods are associated with irritation of the skin, eyes, nose and throat (ATSDR, 1995). Chronic exposure to xylenes has been associated with eye and nasal irritation (Uchida *et al.*, 1993).

The central nervous system is affected by both short term and long term exposure to high concentrations of xylene with: 100-200 ppm associated with nausea and headache; 200-500 ppm with dizziness, irritability, weakness, vomiting, and slowed reaction time; 800-10,000 ppm with lack of muscle coordination, giddiness, confusion, ringing in the ears, and changes in sense of balance; and >10,000 ppm with loss of consciousness (HESIS, 1986). Other documented, neurological effects include impaired short term memory, impaired reaction time, performance decrements in numerical ability, and impaired equilibrium (dizziness) and balance (Carpenter *et al.*, 1975; Dudek *et al.*, 1990; Gamberale *et al.*, 1978; Riihimaki and Savolainen, 1980; Savolainen and Linnavuo, 1979; Savolainen and Riihimaki 1981; Savolainen *et al.*, 1979; 1984; 1985).

Chronic exposure to xylenes (with other hydrocarbons) has been associated with cardiovascular and gastrointestinal effects. Heart palpitations, chest pain, and abnormal electrocardiogram were noted (Hipolito, 1980; Kilburn *et al.*, 1985) as were effects on the gastrointestinal system producing nausea, vomiting and gastric discomfort in exposed workers (Goldie, 1960; Hipolito, 1980; Uchida *et al.*, 1993; Klaucke *et al.*, 1982; Nersesian *et al.*, 1985).

Results of studies of renal effects of xylene are mixed and come from case reports and occupational studies where multiple chemical exposures are common. The effects from subchronic exposure documented by Hake *et al.* (1981) and from chronic exposure documented by Uchida *et al.* (1993) did not include renal effects. However, Morley *et al.* (1970) found increased BUN and decreased creatinine clearance; Martinez *et al.* (1989) found distal renal tubular acidemia; Franchini *et al.* (1983) found increased levels of urinary β-glucuronidase; and Askergren (1981, 1982) found increased urinary excretion of albumin, erythrocytes, and leukocytes.

Reproductive effects were documented by Taskinen *et al.* (1994) who found increased incidence of spontaneous abortions in 37 pathology and histology workers exposed to xylene and formaldehyde in the work place. The multiple chemical exposures and the small number of subjects in this study limit the conclusions that can be drawn as to reproductive effects of xylene in humans.

No hematological effects have been identified in studies where exposure was to xylene only. Previous studies identifying hematological effects included known or suspected exposure to benzene (ATSDR, 1995; ECETOC, 1986). One series of case reports identified lowered white cell counts in two women with chronic occupational exposure to xylene (Hipolito, 1980; Moszczynsky and Lisiewicz, 1983; 1984), although they may also have had multiple chemical exposures.

The Uchida *et al.* (1993) study included a relatively large number of workers studied, exposure for an average of 7 years to xylenes predominately and a comprehensive set of medical examinations to document potential effects. A survey of 994 Chinese workers involved in the production of rubber boots, plastic coated wire and printing processes employing xylene solvents was carried out. The survey consisted of fitting individual workers with diffusive samplers for an 8 hour shift. At the end of the 8 hour shift the samplers were recovered for analysis of solvent exposure, and urine samples were collected for analysis of xylene metabolites. The following day workers answered a questionnaire concerning subjective symptoms, and blood and urine were collected for analysis. Out of this group of xylene-exposed workers, 175 individuals (107 men and 68 women) were selected for further study and analysis based on completion of their health examinations and on results from diffusive samplers showing that xylene constituted 70% or more of that individual's exposure to solvents in the workplace. The control population consisted of 241 (116 men and 125 women) unexposed workers from the same factories or other factories in the same region, of similar age distribution, of similar time in this occupation (average of 7 years), and having a similar incidence of alcohol

consumption and cigarette usage. The xylene-exposed and unexposed groups were given health examinations which evaluated hematology (red, white, and platelet cell counts, and hemoglobin concentration), serum biochemistry (albumin concentration, total bilirubin concentration, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, leucine aminopeptidase, lactate dehydrogenase, amylase, blood urea nitrogen, creatinine), and subjective symptoms (survey of symptoms occurring during work and in the previous three months).

Results of analysis of the diffusive samplers showed that workers were exposed to a geometric mean of 14.2 ± 2.6 ppm xylene (arithmetic mean of 21.3 ± 21.6 ppm). This was broken down into geometric means of 1.2 ppm o-xylene, 7.3 ppm m-xylene, 3.8 ppm p-xylene, 3.4 ppm ethyl benzene, and 1.2 ppm toluene. n-Hexane was rarely present and no benzene was detected. Analysis of data from the health examinations found no statistically significant difference ($p<0.10$) between hematology and serum biochemistry values for xylene-exposed and unexposed populations. The frequency of an elevated ratio of aspartate aminotransferase to alanine transferase and of elevated ratio of alkaline phosphatase to leucine aminopeptidase was significantly ($p<0.01$) higher in exposed men than in the control population of men. Results of the survey of subjective symptoms found differences in symptoms occurring during work and over the previous three months, apparently related to effects on the central nervous system and to local effects on the eyes, nose and throat. The frequency of five symptoms experienced during work were significantly ($p<0.01$) elevated in either xylene-exposed men or women including: dimmed vision, unusual taste, dizziness, heavy feeling in the head, and headache. The frequency of four symptoms experienced during work were significantly ($p<0.01$) elevated in both men and women including irritation in the eyes, nasal irritation, sore throat, and floating sensation. Ten subjective symptoms occurring in the previous three months were significantly ($p<0.01$) elevated in exposed men and women including nausea, nightmare, anxiety, forgetfulness, inability to concentrate, fainting after suddenly standing up, poor appetite, reduced grasping power, reduced muscle power in the extremities, and rough skin. Dose dependency appeared to exist for 3 subjective symptoms noted during work: irritation in the eyes, sore throat, floating sensation, and one symptom occurring in the last three months, poor appetite.

V. Effects of Animal Exposure

A limited number of chronic toxicity studies are available for xylene including two inhalation studies with o-xylene (Tatrai *et al.*, 1981; Jenkins *et al.*, 1970) and one oral chronic study with mixed xylenes (NTP, 1986). No chronic dermal studies could be identified. A spectrum of adverse effects has been documented in shorter term studies which potentially could occur with chronic exposure. These studies are presented here along with a brief description of the three chronic studies identified. Xylene affects a number of organ systems including the pulmonary system, the cardiovascular system, the gastrointestinal system, the hepatic system, the renal system, the dermis, and the eye, and it has numerous neurological effects and developmental effects.

Animal data are consistent with human data in documenting respiratory effects from xylene exposure. Acute and subacute exposures in mice, rats, and guinea pigs have been associated with decreased metabolic capacity of the lungs; decreased respiratory rate; labored breathing; irritation of the respiratory tract; pulmonary edema; and pulmonary inflammation (Carpenter *et al.*, 1975; De Ceaurriz *et al.*, 1981; Elovaara *et al.*, 1987; 1989; Furnas and Hine, 1958; Korsak *et al.*, 1988; 1990; Patel *et al.*, 1978; Silverman and Schatz, 1991; Toftgard and Nilsen, 1982).

Limited evidence is available in animal studies for cardiovascular effects resulting from xylene exposure. Morvai *et al.* (1976; 1987) conducted two studies. The first study observed rats following acute and intermediate duration inhalation exposure to very high (unspecified) levels of xylene and recorded ventricular repolarization disturbances, atrial fibrillation, arrhythmias, occasional cardiac arrest and changes in electrocardiogram (Morvai *et al.*, 1976). In a subsequent study morphological changes in coronary microvessels were seen in rats exposed to 230 ppm xylene (isomer composition unspecified) (Morvai *et al.*, 1987). However the chronic toxicity studies conducted by the National Toxicology Program (NTP, 1986) and by Jenkins *et al.* (1970), as well as other shorter term studies (Carpenter *et al.*, 1975; Wolfe, 1988), have not identified histopathological lesions of the heart.

Studies identifying adverse gastrointestinal effects, hematological effects, or musculoskeletal effects in animals were not identified. Studies reporting no hematological effects include Carpenter *et al.* (1975) (rats exposed to 810 ppm of mixed xylenes for 10 weeks, 5 days/week, 6 hours/day and dogs exposed for 13 weeks to 810 ppm mixed xylenes, 5 days/week, 6 hours/day) and Jenkins *et al.* (1970) (rats, guinea pigs and dogs exposed for 6 weeks to 780 ppm o-xylene, 5 days/week, 8 hours per day). Carpenter *et al.* (1975) and the NTP (1986) reported no effects on the musculoskeletal system.

Hepatic effects have been documented after acute exposure to high concentrations of xylene (2,000 ppm) or subacute exposure to lower concentrations (345-800 ppm) of mixed xylene or individual isomers. These effects include increased cytochrome P-450 and b5 content, increased hepatic weight, increased liver to body weight ratios, decreased hepatic glycogen, proliferation of endoplasmic reticulum, changes in distribution of hepatocellular nuclei, and liver degeneration (Bowers *et al.*, 1982; Condie *et al.*, 1988; Elovaara, 1982; Elovaara *et al.*, 1980; Muralidhara and Krishnakumari 1980; Patel *et al.*, 1979; Pyykko 1980; Tatrai and Ungvary, 1980; Tatrai *et al.*, 1981; Toftgard and Nilsen, 1981; 1982; Toftgard *et al.*, 1981; Ungvary *et al.*, 1980).

Renal effects have been identified in studies with rats, guinea pigs, dogs, and monkeys exposed to 50-2,000 ppm of xylenes. These effects include increased cytochrome P-450 content and increased kidney to body weight ratios (Condie *et al.*, 1988; Elovaara 1982; Toftgard and Nilsen, 1982). Condie *et al.* (1988) also noted tubular dilation, atrophy, and increased hyaline droplets in the kidney of Sprague-Dawley rats administered 150 mg/kg/day orally of mixed xylenes. This response is consistent with early nephropathy.

Xylene has been found to affect the dermis and eyes of animals. Hine and Zuidema (1970) found skin erythema and edema, epidermal thickening, and eschar formation in response to xylene exposure. Direct instillation of xylenes into the eyes of rabbits produces eye irritation (Hine and Zuidema, 1970; Smyth *et al.*, 1962)

Numerous neurological effects have been documented in response to acute and subchronic xylene exposures ranging between 160 to 2,000 ppm. This is consistent with effects on neurofunction documented in humans. These effects include narcosis, prostration, incoordination, tremors, muscular spasms, labored respiration, behavioral changes, hyperactivity, elevated auditory thresholds, hearing loss, and changes in brain biochemistry (Andersson *et al.*, 1981; Carpenter *et al.*, 1975; De Ceaurriz *et al.*, 1983; Furnas and Hine, 1958; Ghosh *et al.*, 1987; Kyrklund *et al.*, 1987; Molnar *et al.*, 1986; NTP, 1986; Pryor *et al.*, 1987; Rank 1985; Rosengren *et al.*, 1986; Savolainen and Seppalainen, 1979; Savolainen *et al.*, 1978; 1979a; Wimolwattanapun *et al.*, 1987).

Developmental effects have been documented in pregnant animals exposed to xylenes. ATSDR (1995) concluded that the body of information available for developmental effects is consistent with the hypothesis that xylene is fetotoxic and many of the fetotoxic responses are secondary to maternal toxicity. However, the ATSDR also observed that there was a large variation in the concentrations of xylene producing developmental effects and of those producing no developmental effects. The ATSDR thought that these differences were influenced by a number of factors (strain and species of animal, purity of xylene, method of exposure, exposure pattern and duration, etc.). The two most common test species have been the rat and the mouse.

With respect to rats, Mirkova *et al.* (1983) exposed groups of pregnant rats (unspecified strain of white rats) to clean air or 2.3, 12, or 120 ppm of xylene (unspecified composition) for 6 h/day on days 1-21 of gestation. They reported increased postimplantation losses and fetotoxicity (reduced fetal weights) as well as a statistically increased incidence of visceral abnormalities (including ossification defects in bones of the skull) at xylene air concentrations of 12 ppm and above. The ATSDR has suggested that the Mirkova *et al.* (1983) study results may have been influenced by poor animal husbandry as indicated by the low conception rates and the high incidence of fetal hemorrhages seen in the controls. Hass *et al.* (1993) attempted to replicate the findings of Mirkova et al. (1983). Hass *et al.* (1993) exposed groups of 36 pregnant Wistar rats to clean air or 200 ppm of xylene for 6 h/day on days 4-20 of gestation. Unlike Mirakova *et al.* (1983), there was no sign of maternal toxicity and no decrease in fetal weights and no increase in soft-tissue or skeletal malformations. A large increase in the incidence of delayed ossification of the *os maxillare* of the skull, however, was observed (53% of experimental fetuses as opposed to 2% of the controls). Potential neurological/muscular changes measured as performance on a rotorod were also noted upon testing of 2-day-old rat pups.

Ungvary *et al.* (1985) exposed CFY rats by inhalation to air concentrations of xylene (60 ppm, 440 ppm, 800 ppm) for 24 h/day on days 7-15 of gestation. Maternal toxicity was described as moderate and dose-dependent. They observed weight retarded fetuses at all

air concentrations. However, there was no increase in malformations, and an increase in minor anomalies and resorbed fetuses occurred only at the highest concentration. In a separate study investigating the interactions between solvents and other agents, Ungvary (1985) exposed CFY rats to either 140 ppm or 440 ppm of xylene on days 10-13 of gestation and also reported increases for either condition in weight retarded and skeletal retarded fetuses without any increase in malformations. Hudak and Ungvary (1978) had earlier examined the effect of 230 ppm xylene (24 h/day, days 9-14 of pregnancy) in the CFY rat and reported effects on skeletal development (e.g., fused sternebrae). In contrast to the other Ungvary findings, no effect on fetal weight was observed. Bio/dynamics (1983) conducted an inhalation exposure study in the rat (CrL-CD (SD) BR strain). Rats were exposed 6 h/day during premating, mating, gestation and lactation. Exposure concentrations were 0, 60, 250, and 500 ppm. Most measures for adverse effects on fetal development were not significantly increased. Mean fetal weights at the highest exposure level were lower than controls, but this difference was significant only for the female fetuses. These depressed weights were, however, still significant on day 21 of lactation. Other adverse effects (such as increased soft tissue and skeletal abnormalities, increased fetal resorptions) were not increased significantly at any of the test concentrations.

Ungvary *et al.* (1980a) tested by inhalation the individual ortho, meta, and para isomers of xylene in the CFY rat. Pregnant rats were exposed 24 h/day on days 7 –14 of pregnancy to 35, 350, or 700 ppm of each isomer. An increased incidence of weight retarded fetuses was observed for each isomer at the 700 ppm level, and for the ortho isomer at the 350 ppm level. Post implantation losses were increased only at the 700 ppm level in the para-xylene exposed group. Skeletal anomalies were increased only at the 700 ppm level for the meta and para isomers of xylene. Rosen *et al.* (1986) evaluated the effects of prenatal exposure to para-xylene in the rat. They exposed pregnant Sprague-Dawley rats by inhalation to either 800 ppm or 1600 ppm of p-xylene from days 7-16 of gestation. Despite the high concentrations, no effects were seen on litter size or weight at birth or on the subsequent growth rates of the pups.

With respect to mice, Ungvary *et al.* (1985) exposed CFLP mice by inhalation to air concentrations of xylene (120 ppm, 230 ppm) for 24 h/day on days 7-15 of gestation. In the mouse, they observed increased incidences of weight-retarded fetuses and increased skeletal retarded fetuses at 230 ppm. Shigeta *et al.* (1983) exposed pregnant ICR mice to approximately 0, 120, 230, 460, and 920 ppm of xylene in an exposure chamber for 6 h/day on days 6-12 of gestation. Shigeta *et al.* (1983) reported significant decreases in fetal weight in the 460 ppm and 920 ppm dose groups only. There was no difference in the number of live or dead fetuses. Decreased weight gains and delayed development of body hair and teeth were observed at the 920 ppm exposure level. Dose-response relations were reported for delayed ossification of the sternebrae. Marks *et al.* (1982) noted that 2060 mg/kg/day of mixed xylene administered orally is associated with cleft palate and decreased fetal weight in the mouse.

Ungvary *et al.* (1985) also tested the individual ortho, meta, and para isomers of xylene at 120 ppm in the CFLP mouse. Each isomer of xylene also increased the incidence of

weight-retarded fetuses and skeletal retarded fetuses at 120 ppm. There was no increase in malformations.

Of the three chronic studies available (Tatrai *et al.*, 1981; Jenkins *et al.*, 1970; NTP 1986) none comprehensively examined systemic effects. The study by Tatrai *et al.* (1981) exposed rats for one year, 7 days/week, 8 hours per day to 1096 ppm o-xylene. This exposure was a LOAEL for body weight gain in males and a NOAEL for hepatic effects in male rats. Jenkins *et al.* (1970) exposed rats, guinea pigs, squirrel monkeys, and beagle dogs for 90-127 days continuously to 78 ppm of o-xylene. The study examined body weight gain; hematological parameters including white cell counts, red blood cell counts, and hematocrit; serum biochemistry including bromosulfalein retention, blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and creatinine and liver function including alkaline phosphatase, tyrosine aminotransferase, and total lipids. No effects were observed in any of the parameters examined in this study. This study found a NOAEL for all effects examined of 78 ppm o-xylene. The NTP (1986) study administered 0, 250, or 500 mg/kg/day doses of mixed xylene in corn oil by gavage 5 days/week for 103 weeks to groups of F344/N rats of both sexes, 50 animals per group. B6C3F1 mice were treated in a similar manner but given 0, 500 or 1000 mg/kg/day of mixed xylenes in corn oil by gavage. A complete histopathological examination of all tissues was made as well as determination of body weight gain. Based on histopathology of all organ systems, a NOAEL of 500 mg/kg/day was observed for rats and a NOAEL of 1000 mg/kg/day was observed for mice.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Uchida *et al.* (1993)
Study population	175 xylene-exposed factory workers and control population of 241 factory workers
Exposure method	Inhalation
Critical Effects	Dose related increase in the prevalence of eye irritation, sore throat, floating sensation, and poor appetite.
LOAEL	14.2 ppm (geometric mean of exposure concentrations)
NOAEL	Not applicable
Exposure continuity	Occupational exposure for an average of 7 years
Average exposure concentration	5.1 ppm for LOAEL group (14.2 x 10/20 x 5/7)
Human equivalent concentration	5.1 ppm for LOAEL group
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.17 ppm (170 ppb; 0.7 mg/m^3; 700 $\mu g/m^3$) for mixed xylenes or for total of individual isomers

A number of issues are important in considering the uncertainty associated with this REL. ATSDR (1995) concludes that animal and human toxicity data suggest that mixed xylenes and the different xylene isomers produce similar effects, although different isomers are not equal in potency for producing a given effect. Therefore exposure of workers to a mix of xylenes in the Uchida *et al.* (1993) study would be expected to generate a similar spectrum of responses as exposure to single isomers, however the intensity of particular effects could be different. The use of a neurological endpoint for derivation of a REL is supported by the large number of inhalation and oral studies associating neurological effects with xylene exposure. ATSDR (1995) indicates that neurological effects are a sensitive endpoint. The observation that floating sensation is apparently related to dose further supports the concept that this subjective symptom related to neurological effects was due to xylene exposure. The use of a factor of 3 for using a LOAEL as the basis for the REL should serve to protect populations from neurological effects as should the use of a factor of 10 for sensitive individuals within the population. Another issue is the use of diffusive samplers in the Uchida *et al.* (1993) study. These samplers provide a time weighted average concentration of hydrocarbon and cannot indicate the maximum concentrations a worker is exposed to. It is unknown whether peak concentrations alter the response to xylenes in humans.

The strengths of the inhalation REL include the use of human exposure data from workers exposed over a period of years. Major areas of uncertainty are the uncertainty in

estimating exposure, the potential variability in exposure concentration, and the lack of observation of a NOAEL.

VII. References

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Appendix B
Air Resources Board Westley Tire Fire Air Monitoring Data.

Air Resources Board

Alan C. Lloyd, Ph.D.
Chairman
2020 L Street • P.O. Box 2815 • Sacramento, California 95812 • www.arb.ca.gov

Winston H. Hickox
Agency Secretary

Gray Davis
Governor

MEMORANDUM

TO: Michael P. Kenny
Executive Officer

FROM: James J. Morgester, Chief
Compliance Division

DATE: January 24, 2000

SUBJECT: Filbin (Westley) Tire Fire Emergency Response

On September 22, 1999, at the request of the Stanislaus County Department of Environmental Health and the State Office of Emergency Services (OES), Air Resources Board staff responded to a tire fire located just west of the town of Westley in Stanislaus County. The Air Resources Board Compliance Division Emergency Response Team was requested to assist in this emergency by conducting onsite ambient air monitoring of pollutants in the smoke plume that could possibly impact nearby residents.

Filbin (Westley) Tire Fire

Owner/Operator

The Filbin (Westley) Tire Facility is located just south of the San Joaquin County line, 1/4 mile west of I-5 near Westley in Stanislaus County, 20 miles west of Modesto. Five million tires were reportedly involved in the fire at the facility. The facility, operated by the Oxford Tire Re-cycling Co., is on approximately 30 acres (the burning area was initially about 15 acres) owned by the Cal-Neva Ranch Company, LLC, and also known as the Filbin Land and Cattle Co. The facility supplies tires to fuel the Modesto Energy LP tire burning cogeneration plant located near the pile. Figure 2 shows a map of the fire area.

In addition, the Monitoring and Laboratory Division (MLD) was asked to set up fixed air monitoring equipment at several sites requested by the Incident Command. The MLD staff who participated in the emergency response effort were:

MLD Division Office
Michael Poore
Jane Park

Engineering & Laboratory Branch

Organic Laboratory
Hieu Le
Ben Chang
Dave Hartmann
Bruce Joab
Ferry Niyati

Evaluation Section
Bob Okamoto

Inorganic Laboratory
Russell Grace
Bill Davis
Lyman Dinkins
George Dunstan
Karen Fletcher
Jose Orozco
Samantha Scola
Dan Tackett

Air Quality Surveillance Branch
Bill Oslund
Marlene Ramatici

Air Monitoring – North
Larry Molek
Ken Breitwieser
Lowell Jarvis
John Lawson
Bob Caselton
John Crumpler
Joe Rohr
Johnny Foston

Air Monitoring - Central
Peter Ouchida
Diane Arnold
Ron Lewis
Steve Rider
Jack Romans

Special Purpose Monitoring
Ken Stroud
Reggie Smith
Ron Barros
James Frasche
Greg Frye
Harlan Quan
Klaus Scott
Mac McDougall
Pat Vaca
Chateau Vaughn

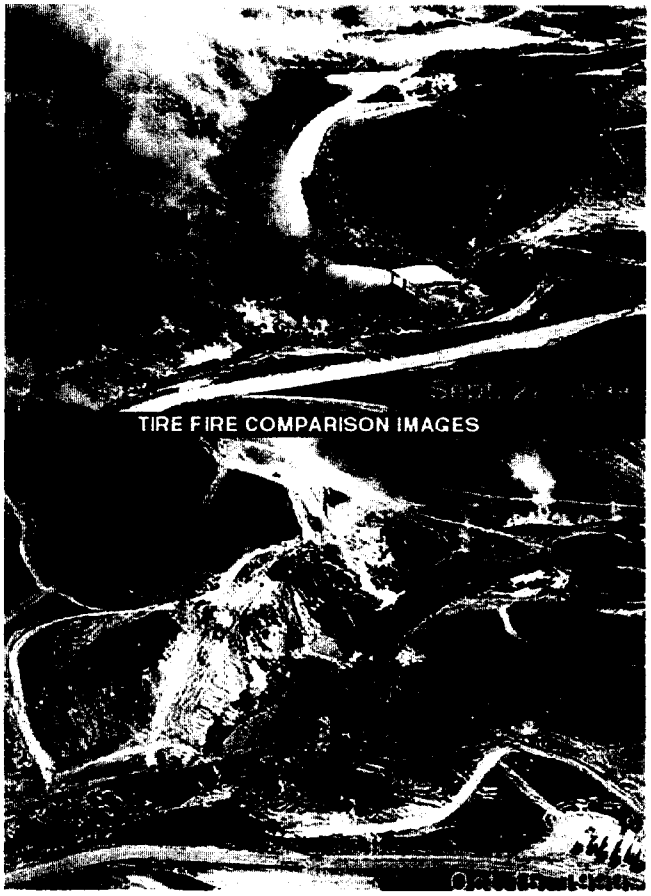
The fire was finally put out on October 27, 1999 by the unprecedented efforts of a U.S. EPA contractor. The fire was initially predicted to burn for months, but after a pool of pyrolitic oil distilled from the burning tires caught fire, the EPA called in an oil fire fighting specialist contractor from Texas. Using a new technique of smothering the fire with massive amounts of foam and carefully separating the individual tires with bulldozers, the EPA contractor quelled the fire in less than three weeks.

Pyrolytic Oil Accumulated in Pond

Foamed Tires

Background

The tire fire started as a result of lightning strikes during an early morning storm on September 22, 1999. The fire was initially reported at 3:59 a.m. from a call to 911 dispatch, with the West Stanislaus Fire Department responding to the remote scene by 4:12 a.m.



Aerial View of Tire Pile Before and After

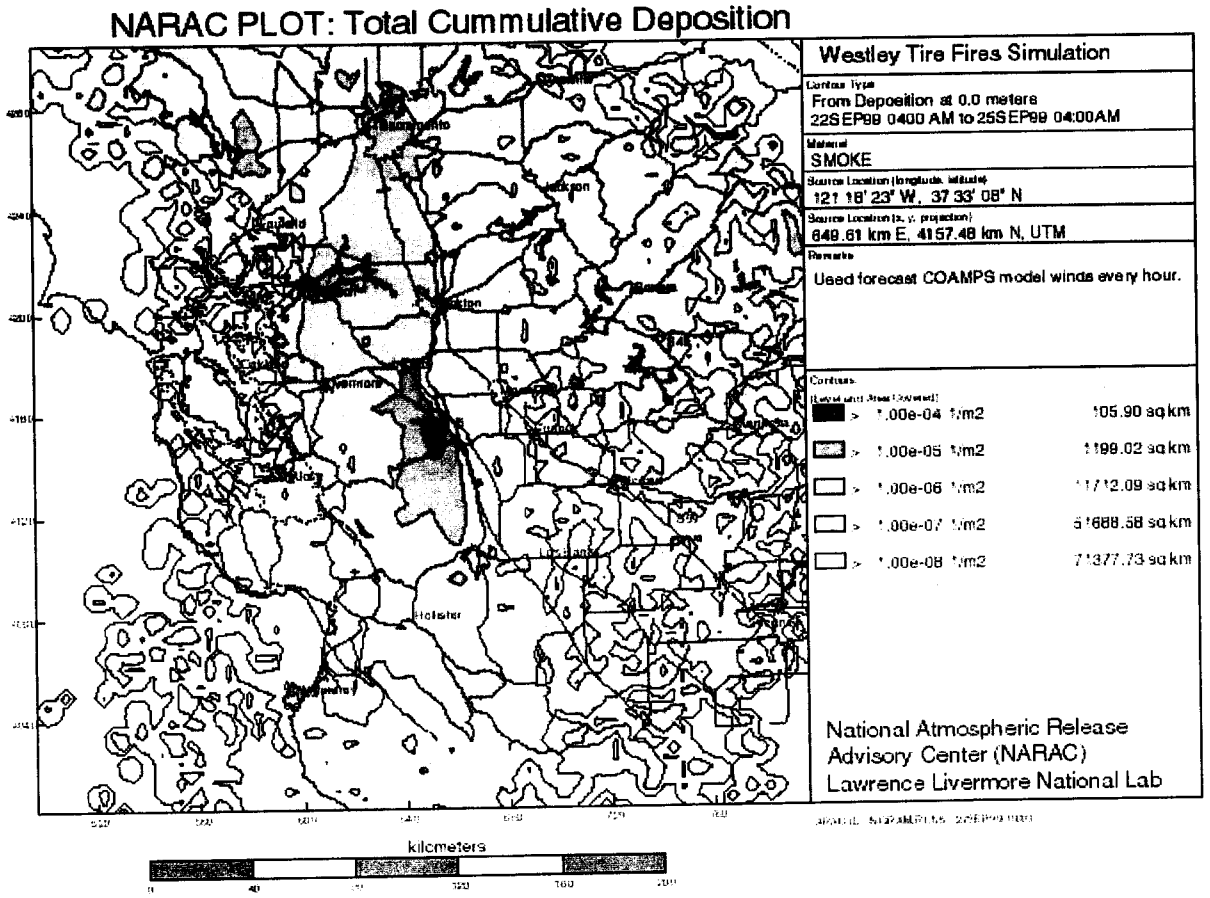
I was contacted by the State Office of Emergency Services at approximately 8 a.m. on September 22 and asked to respond to a request from the Stanislaus County Environmental Health Department for emergency air monitoring at and near a fire involving a large used tire dump near Westley, California. The ARB Emergency Response Team (ERT) was immediately activated. Gary Zimmerman and John Marconi of the CD staff deployed and coordinated two-person crews with Miran 1B real-time infrared portable analyzers monitoring for CO and total hydrocarbons (THC). The two-person teams were directed by the Incident Command to observe the plume, conduct surveys of the general area around the fire and respond to reported smoke in populated areas. During the course of the response, Miran 1B monitoring in the area of the tire fire was conducted around the clock by these two-person teams working eight-hour shifts. They reported the monitoring results directly to the Incident Command (IC), and monitored around the fire area as directed by the IC. In addition, during off-hours the teams checked the fire site at least once each hour. The Compliance Division staff who participated in the field monitoring were:

Hardip Ahluwalia	Basharat Iqbal	Simion Okoroike	Raak Veblen
Kerry Albert	Britt Floyd	Eric Patton	Sue Wyman
Trevor Anderson	Walter Gothberg	Terone Preston	
Pete Campos	Herman Lau	Fred Schmidt	
Nestor Castillo	Francis Mateo	Mark Tavianini	

Lawrence Livermore National Lab NARAC Plume Modeling

At the request of the Stanislaus County Office of Emergency Services (OES), the National Atmospheric Release Advisory Center (NARAC) predicted the locations of smoke from the tire fire. NARAC predicted the winds and the dispersion of smoke from the fire, and provided the first set of plots to the Stanislaus OES at approximately 2:15 p.m. on 9/22. Additional requests for plots were fulfilled for the California Air Resources Board, the Bay Area Air Quality Management District, the Governor's Emergency Operations Center, and several media representatives. Later sets of plots extended the forecast period farther into the future. The final plot shown in Figure 1 indicates the calculation of smoke particles deposited on the ground over the entire initial 72-hour period of the fire.

Figure 1



NARAC meteorologists used the U.S. Navy's COAMPS model to predict high-resolution winds over the area of concern; then NARAC's own dispersion models were used to predict the areas covered by smoke. NARAC assumed that the smoke plume rose 2500 meters (about 7,500 feet) above the fire for the first 18 hours after ignition, and then lowered to 600 meters (about 1,800 feet) for the remainder of the simulation period. Because the exact quantity of material emitted by the fire into the atmosphere is

unknown, the plot is contoured in relative concentrations, with contour intervals specified in factors of ten (smoke within the innermost, darkest shaded contour is at least ten times more concentrated than smoke within the next surrounding contour). Therefore, these plots do not show health effects; rather they show the relative density of smoke near the ground.

ARB Ambient Air Monitoring Response

MLD's Rover Monitoring Platform Near Grayson School (Westley-Livingston)

Our 24-hr surveillance and air monitoring at the Westley tire fire continued until October 27, 1999 when the fire was declared to be extinguished. Ambient carbon monoxide and total hydrocarbon concentrations were essentially zero or at typical background levels at all locations surveyed with the Miran 1B. The field staff observed few incidents of the smoke plume laying down on the ground or fumigating. However, many local residents complained of adverse health effects from periodic ground-level impacts by the smoke. From September 22 until October 8 we had three, two-person teams at the fire working eight-hr shifts around the clock, and an on-call supervisory coordinator. From October 8 to October 27, field surveillance was reduced to one person working an eight-hour shift, but on-call for 24 hours.

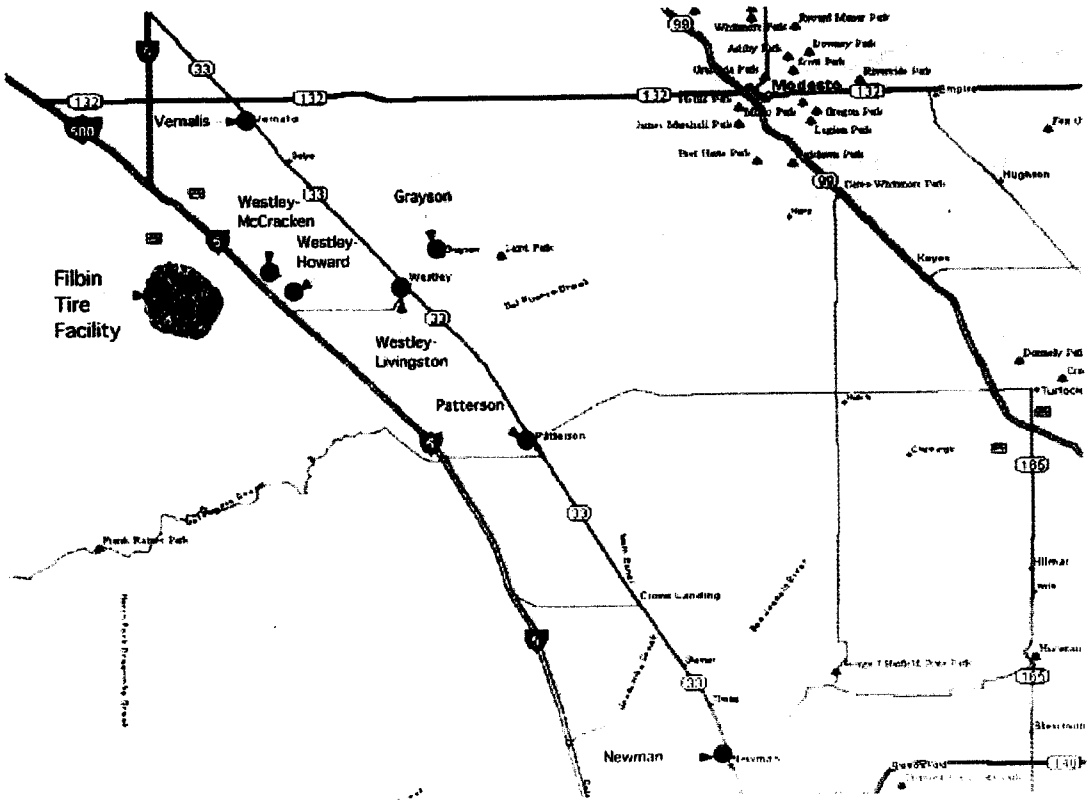
MLD's Air Quality Surveillance Branch initially deployed its "Rover" air monitoring station to the Grayson Elementary School in Westley, about 5.5 miles east of the fire site to determine exposures to the population in Wesley. The Rover provided extensive monitoring capabilities, including criteria and toxic air pollutants. The following pollutants were monitored:

Continuous PM_{10} mass by TEOM (Taper Element Oscillating Microbalance)
Continuous black carbon (soot) concentration by Aethalometer
Continuous carbon monoxide
24-hour composite monitoring for:
Benzene
Polyaromatic Hydrocarbons (i.e., benzo(a)pyrene)
PM 10 mass
Total metals by XRF
Total Carbon

In response to a request from the Incident Command for additional monitoring stations around the fire, on September 25, MLD deployed four PM_{10}/saturation filter samplers at the I-5 & Howard Rd. exit, Vernalis, Grayson and Neuman. (During a teleconference with the responding agencies late afternoon Friday (9/24), DHS and OEHHA requested 5-6 additional Rover-type monitoring stations be deployed around

the fire. MLD staff verified that they had no more such monitoring resources available, but could probably field some additional PM_{10} samplers. State OES representative Tracy Vardas stated that Stanislaus Co. Environmental Health staff wanted any additional samplers to be set up at the above priority sites.)

Figure 2 - Area Map Showing Air Monitoring Sites (● = site)



In response to public demands for more monitoring sites, MLD later set up additional sampler sites at Patterson High School and near a truck stop across I-5 from the fire site. The fixed monitoring sites are shown mapped out in Figure 2.

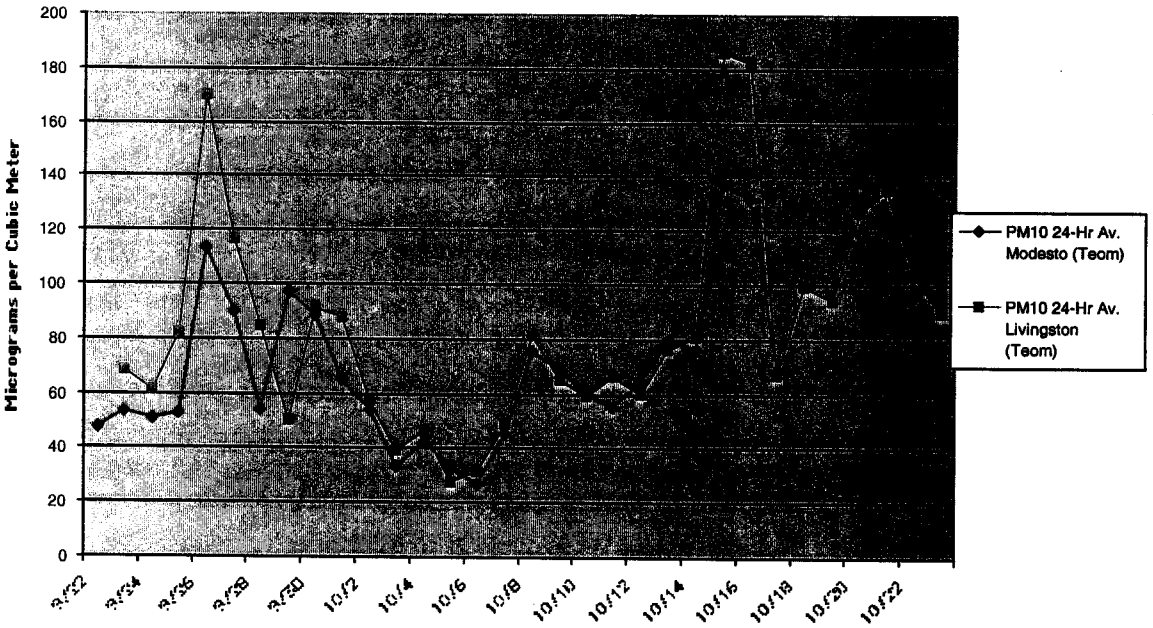
The final MLD monitoring results are shown in Appendix 1. Detailed descriptions of the monitoring sites follow in Appendix 2. An analysis of the pyrolitic oil headspace constituents is shown in Appendix 3.

In addition, a U. S. EPA contractor at ARB's request obtained canister samples of the smoke in the fire plume. Those samples showed 570 ppb and 338 ppb of butadiene, and 930 ppb and 557 ppb of benzene, respectively. For comparison, the OSHA Permissible Exposure Levels (8-hr. average) for butadiene and benzene are 1000 ppm and 1 ppm, respectively.

The air monitoring data shows slightly elevated PM_{10} and toxic (benzene/butadiene) air contaminant concentrations occurred at the start of the fire. Overall, no extraordinarily high readings (for the area) occurred for any pollutants monitored. Typically, for the San Joaquin Valley air basin, 24-hour PM_{10} concentrations monitored during most of the fire exceeded the State ambient air quality standard of 50 $\mu g/m^3$. As shown in Figure 3, during most of the same time period PM_{10} readings near

Figure 2

PM10 Concentrations
Westley-Livingston and Modesto
9/22 - 10/23/99



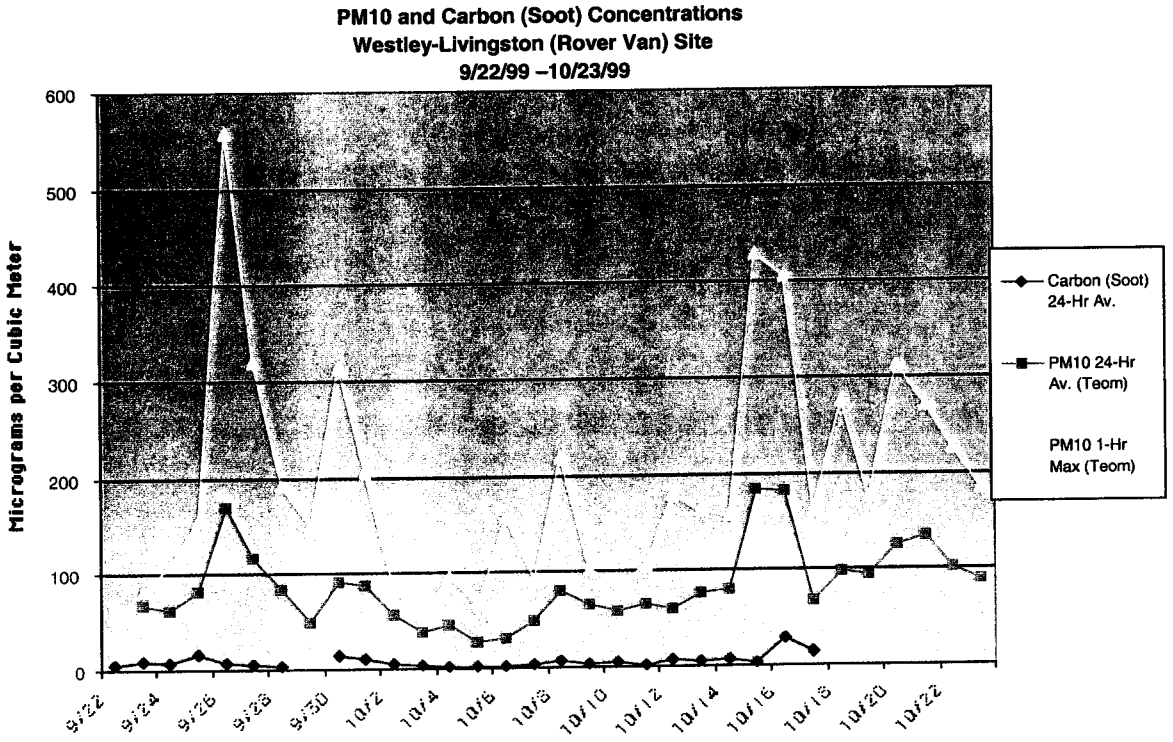
the fire were comparable at Modesto (as well as Fresno, Visalia and Bakersfield). However, all air monitoring conducted, particularly the Total Carbon (soot) data collected at the fixed monitoring sites, does not show any significant ground-level impacts that could be clearly attributable to the fire. The peak PM_{10} and Total Carbon concentrations monitored near the fire actually occurred from 10/16-17 when the fire was 75-80% extinguished. At that time, several large forest fires in Colusa and Shasta Counties sent heavy smoke into the San Joaquin Valley, held low to the ground by a strong inversion layer. The smoke was so thick that cars in Sacramento were covered with ash. Total Carbon monitored at the Westley-Livingston site peaked at 29.5 $\mu g/m^3$ on 10/16, reflecting the sensitivity of Total Carbon sampling to ambient smoke. The next highest PM_{10} concentration was monitored on 9/26 at the Livingston site, and may have been biased by nearby construction and strong winds causing visible blowing dust as reported by the sampling site operator.

From our experience in the Tracy tire fire last year, Total Carbon, rather than total or PM_{10} particulate matter, is the best indicator of any fire's actual impact.

Atmospheric particulate matter, a complex mixture of chemicals, is partially made up of organic and elemental carbon. The elemental carbon (soot) is a product of combustion, and typical emissions sources are agricultural burning, wildfires, motor vehicles, wood stoves, fireplaces, charcoal broilers, etc. The Total Carbon (organic and elemental) contributions to total PM_{10} concentrations in the northern San Joaquin Valley are generally between 5 - 10 $\mu g/m^3$ during the summertime, and 40 - 80 $\mu g/m^3$ during the wintertime. The higher wintertime concentrations are due to lower temperatures, inversions and the use of fireplaces.

Figure 3 graphically compares the daily Total Carbon and total PM_{10} concentrations monitored during the height of the fire, and illustrates little, if any, impact

Figure 3



of the fire smoke on particulate matter levels at the sampling site. However, as can be seen in the 1-hr. maximum PM_{10} readings, this does not mean that the tire fire smoke did not cause short-term impacts or impacts in other areas where we didn't have a monitoring site. Regardless of our monitoring results, many local residents scattered around the area reported adverse health effects from periodic ground-level impacts by the smoke that may not have shown up in our data.

ARB's Emergency Response Costs

The total estimated cost of ARB's response to this emergency is $145,000.

APPENDIX 1
AIR RESOURCES BOARD LABORATORY RESULTS

WESTLEY TIRE FIRE

Sample results include the following compounds:

Compound	Abbreviation	Federal Standards	Annual Average Comparison
Carbon Monoxide	CO	20 ppm (1Hr)	
Black Carbon	Black Carbon		
High Volume SSI PM10 Mass	Hi-Vol SSI PM10 Mass		
High Volume SSI PM10 Total Carbon	PM10 Total Carb		
Mini Vol Saturation Sampler PM10 Mass	Mini-Vol PM10 Mass Sat		
TEOM PM10	PM10 Teom	150 ug/m3 (24 Hr)	
	Ambient Toxic Volatile Organic Compounds	VOC	
Butadiene	Buta		1997 Modesto Max. 0.6/Avg. .155
Benzene	Benz		1997 Modesto Max. 2.2/Avg. .462
Polycyclic Aromatic Hydrocarbons	PAH		
Benzo (b) fluoranthene	BbF		1997 Modesto Max. 3.3/Avg. .270
Benzo (k) fluoranthene	BkF		" " Modesto Max. 1.30/Avg. .115
Benzo (a) pyrene	BaP		" " Modesto Max. 2.20/Avg. 191
Dibenz (a,h) anthracene	DahA		" " Modesto Max. 0.25/Avg. .034
Benzo (ghi) perylene	BghiP		" " Modesto Max. 5.00/Avg. .543
Indeno (1,2,3-cd) pyrene	IcdP		" " Modesto Max. 3.10/Avg. .293
	Resultant Wind Speed	RWS	
Resultant Wind Direction	RWD		

All PAH Results are reported in ng/m3
All VOC Results are reported in ppb

All Mini Volume PM10 Results are reported in ug/m3
All High Volume PM10 Results are reported in ug/m3
All TEOM PM10 Results are reported in ug/m3
All Carbon Monoxide Results are reported in ppm
All Black Carbon Results are reported in ug/m3
All Resultant Wind Speed Results are reported in knots
All Resultant Wind Direction Results are reported in degrees
All PAH's are 24-hour Average Results except for sampling date 9/22/99 results from approximately 4-hr average.

	SAMPLING DATE											
COMPOUNDS/ ELEMENTS	9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30	10/1	10/2	10/3
Westley-Liviningston												
Black Carbon												
24-Hr Average	NA	NA	NA	NA	NA	NA	NA	NA	NA	3	1	1
1-Hr Maximum	NA	NA	NA	NA	NA	NA	NA	NA	NA	8	3	3
Westley-McCracken												
Black Carbon												
24-Hr Average	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	3
1-Hr Maximum	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	6
Westley-Livingston												
Carbon Monoxide												
24-Hr Average	0.0	0.3	0.2	0.7	0.2	0.1	0.1	0.1	0.3	0.1	0.0	0.0
1-Hr Maximum	0.0	0.4	0.4	0.4	0.5	0.2	0.3	0.2	0.1	0.3	0.1	0.1
METEOROLOGY												
Westley-Livingston												
RWS												
24-Hr Average	2	4	4	4	11	15	9	4	4	5	4	3
1-Hr Maximum	3	9	9	11	17	18	17	6	5	8	8	5
RWD												
24-Hr Average	146	282	272	235	294	301	279	251	253	258	259	251

	SAMPLING DATE													
COMPOUNDS/ ELEMENTS	10/4	10/5	10/6	10/7	10/8	10/9	10/10	10/11	10/12	10/13	10/14	10/15	10/16	10/17
Westley-Livininingston														
Black Carbon														
24-Hr Average	1	1	1	1	1	2	1	1	1	1	2	0	1	1
1-Hr Maximum	3	2	1	1	4	5	3	3	2	4	4	2	5	2
Westley-McCracken														
Black Carbon														
24-Hr Average	2	2	2	2	2	2	1	1	1	1	1	1	1	1
1-Hr Maximum	4	5	11	4	8	7	4	4	8	6	10	4	8	4
Westley-Livingston														
Carbon Monoxide														
24-Hr Average	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1-Hr Maximum	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.4	0.1	0.1	0.1	0.1
METEOROLOGY														
Westley-Livingston														
RWS														
24-Hr Average	5	5	6	7	2	3	2	4	5	4	3	12	12	8
1-Hr Maximum	10	12	17	14	4	6	4	5	10	9	9	18	17	13
RWD														
24-Hr Average	302	240	270	261	160	236	150	191	293	295	228	308	313	308

	SAMPLING DATE													
COMPOUNDS/ ELEMENTS	10/18	10/19	10/20	10/21	10/22	10/23	10/24	10/25	10/26	10/27	10/28	10/29	10/30	10/31
Westley-Livininingston														
Black Carbon														
24-Hr Average	2	1	2	2	1	3	1							
1-Hr Maximum	3	4	6	3	3	3	2							
Westley-McCracken														
Black Carbon														
24-Hr Average	1	1	2	3	1	2	0							
1-Hr Maximum	6	4	5	4	4	4	2							
Westley-Livingston														
Carbon Monoxide														
24-Hr Average	0.1	0.1	0.1	0.1	0.1	0.1	0.0							
1-Hr Maximum	0.1	0.2	0.2	0.2	0.1	0.1	0.1							
METEOROLOGY														
Westley-Livingston														
RWS														
24-Hr Average	3	2	2	2	2	4	4							
1-Hr Maximum	7	5	4	4	4	8	6							
RWD														
24-Hr Average	207	171	242	164	263	287	276							

	SAMPLING DATE											
COMPOUNDS/ ELEMENTS	9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30	10/1	10/2	10/3
Westley-McCracken												
RWS												
24-Hr Average	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3	2
1-Hr Maximum	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7	6
RWD												
24-Hr Average	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	229	160
Westley-Livingston												
PAH												
BbF	<.05	<.05	<.08	<.38	<.05	<.05	<.05	NA	.59	0.85	<.05	<.05
BkF	<.05	<.05	<.05	<.12	<.05	<.05	<.05	NA	0.07	0.15	<.05	<.05
Bap	<.05	<.05	<.05	<.24	<.05	<.05	<.05	NA	0.15	0.12	<.05	<.05
DahA	<.05	<.05	<.05	<.05	<.05	<.05	<.05	NA	<.05	<.05	<.05	<.05
BghiP	<.05	<.05	<.06	<.36	<.05	<.05	<.05	NA	0.32	0.41	<.05	<.05
IcdP	<.05	<.05	<.08	<.27	<.05	<.05	<.05	NA	0.71	0.78	<.05	<.05
Westley-Livingston												
Hi-Vol SSI PM10 Mass												
24-Hr Average Except * 4-Hr Avg.	95.8*	78.1	81.1	180.5	180.4	95.2	135.9*					
Patterson H.S.												
Hi-Vol SSI PM10 Mass												
24-Hr Average Except * 4-Hr Avg.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	SAMPLING DATE													
COMPOUNDS/ ELEMENTS	10/4	10/5	10/6	10/7	10/8	10/9	10/10	10/11	10/12	10/13	10/14	10/15	10/16	10/17
Westley-McCracken														
RWS														
24-Hr Average	4	4	6	12	4	6	4	4	6	6	5	16	15	10
1-Hr Maximum	9	12	17	19	8	12	11	7	13	9	11	21	20	16
RWD														
24-Hr Average	234	192	202	283	139	210	169	232	267	271	201	315	310	305
Westley-Livingston														
PAH														
BbF	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<1.5	<1.5	<1.5
BkF	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<1.5	<1.5	<1.5
Bap	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.1.5	<1.5	<1.5
DahA	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<1.5	<1.5	<1.5
BghiP	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<1.5	<1.5	<1.5
IcdP	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<.05	<1.5	<1.5	<1.5
Patterson H.S.														
PAH														
Bbf	NA	NA	0.56	0.13	0.34	NA	NA	NA	NA	0.32	0.33	0.70	NA	NA
BkF	NA	NA	0.16	<.05	0.09	NA	NA	NA	NA	0.09	0.09	0.20	NA	NA
Bap	NA	NA	0.24	0.06	0.12	NA	NA	NA	NA	0.13	0.17	0.37	NA	NA
DahA	NA	NA	<.05	<.05	<.05	NA	NA	NA	NA	<.05	<.05	<.05	NA	NA
BghiP	NA	NA	0.34	0.10	0.22	NA	NA	NA	NA	0.23	0.27	0.43	NA	NA
IcdP	NA	NA	0.39	0.08	0.27	NA	NA	NA	NA	0.23	0.26	0.58	NA	NA
Hi-Vol SSI PM10 Mass														
Patterson H.S.														
24-Hr Average Except * 4-Hr Avg.	NA	NA	42.7	67.2	61.5	NA	NA	NA	NA	NA	179.6	135.7	NA	NA

	SAMPLING DATE													
COMPOUNDS/ ELEMENTS	10/18	10/19	10/20	10/21	10/22	10/23	10/24	10/25	10/26	10/27	10/28	10/29	10/30	10/31
Westley-McCracken														
RWS														
24-Hr Average	4	4	5	4	4	3	4							
1-Hr Maximum	8	9	10	10	8	7	10							
RWD														
24-Hr Average	192	187	206	174	198	239	197							
Westley-Livingston														
PAH														
BbF														
BkF														
Bap														
DahA														
BghiP														
IcdP														
Patterson H.S.														
PAH														
Bbf	0.89	0.35	0.24											
BkF	0.23	0.08	0.05											
Bap	0.35	0.10	0.11											
DahA	0.09	<.05	<.05											
BghiP	0.58	0.27	0.24											
IcdP	0.61	0.23	0.18											
Hi Vol SSI PM10 Mass														
Patterson H.S.														
24-Hr Average Except * 4-Hr Avg.	110.6	118.8												

	SAMPLING DATE											
COMPOUNDS/ ELEMENTS	9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30	10/1	10/2	10/3
Mini-Vol PM10 Mass Saturation												
24-Hr Average												
Westley-Livingston	NA	NA	NA	NA	NA	NA	NA	NA	82.9	59.7	52.4	53.3
Westley-Grayson	NA	NA	NA	NA	79.2	10.5	123.6	51.8	81.1	89.5	61.6	38.1
Westley-I5/Howard	NA	NA	NA	NA	57.3	98.7	6.6	73.1	65.8	58.7	59.8	57.2
Westley-Newman	NA	NA	NA	NA	NA	14.1	122.5	56.2	74.2	59.8	59.5	29.6
Westley-Vernalis	NA	NA	NA	NA	58.4	17.6	53.3	72.4	55.4	54.9	57.2	20.1
Westley-Livingston												
PM10 Total Carb												
24-Hr Average Except * 4-hr Avg,	5.4*	9.7	7.9	17.3	8.0	4.6	4.3*	NA	14.9	10.4	5.1	3.9
Westley-Livingston												
PM10 Teom												
24-Hr Average	NA	68.2*	61.3	81.6	169.4	116.3	84.2	50	90.7	87.4	57.3	38.8
* 11-Hr Avg.												
1-Hr Maximum	NA	82.0	110	155	557.4	319.9	191.7	150	314.1	205.7	82.9	55.4
Westley-McCracken												
PM10 Teom												
24-Hr Average	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	24.6	28.7
1-Hr Maximum	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	40.1	79.2
Westley-Livingston												
VOC												
Butadiene	0.48	<.04	<.04	<.04	<.04	<.04	<.04	NA	0.04	<.04	0.04	<.04
Benzene	2.88	0.35	0.34	0.40	<.2	<.2	0.66	NA	.70	.64	0.36	0.31

	SAMPLING DATE													
COMPOUNDS/ ELEMENTS	10/4	10/5	10/6	10/7	10/8	10/9	10/10	10/11	10/12	10/13	10/14	10/15	10/16	10/17
Mini-Vol PM10 Mass Saturation														
24-Hr Average														
Westley-Livingston	81.6	25.2	22.9	51.7	23.9	88.8	50.4	12.6	Invalid	51.8	23.5	43.1	82.9	54.7
Westley-Grayson	34.1	25.7	23.2	34.4	60.2	42.0	83.2	79.4	71.4	73.9	76.2	70.7	107.7	113.3
Westley-I5/Howard	39.0	23.3	45.6	62.5	48.1	33.9	9.6	23.8	109.3	76.9	106.5	47.4	105.4	49.6
Westley-Newman	38.3	24.2	25.9	51.7	34.0	28.9	46.7	49.6	181.4	77.6	18.9	57.7	150.8	65.4
Westley-Vernalis	27.1	15.6	18.5	16.3	13.2	56.0	56.5	51.8	35.6	52.2	64.5	74.2	118.0	52.0
Westley-Livingston														
PM10 Total Carb														
24-Hr Average Except * 4-hr Avg,	<1	<1	<1	2.8	8.2	3.8	6.0	<1	7.2	5.7	8.2	2.8	29.5	14.9
Patterson H.S.	NA	NA	3.8	6.3	8.7	NA	NA	NA	NA	NA	16.4	4.3		
PM10 Total Carb														
Westley-Livingston														
PM10 Teom														
24-Hr Average	46.1	27.2	31.4	48.6	81.0	65.2	59.2	66.1	59.5	76.0	80.6	185.5	182.1	66.9
1-Hr Maximum	97.3	65.2	158	94.2	219	102.8	87.6	106.3	179.3	162.7	157.3	430.5	406.0	162.4
Westley-McCracken														
PM10 Teom														
24-Hr Average	37.1	22.1	51.5	145	93.1	73.5	63.0	91.8	98.9	108.3	107.2	312.7	212.3	62.9
1-Hr Maximum	76	58.5	138	574	205	145	95.3	197.8	295.5	215.7	287.3	643.5	499.6	103.7
Westley-Livingston														
VOC														
Butadiene	<.04	<.04	0.007	0.056	0.030	0.043	<.04	<.04	0.05	<.04	<.04	<.04	0.05	0.04
Benzene	<.2	0.20	.111	0.32	0.68	0.56	0.66	0.29	0.70	0.46	0.48	<.2	0.41	0.68

	SAMPLING DATE													
COMPOUNDS/ ELEMENTS	10/18	10/19	10/20	10/21	10/22	10/23	10/24	10/25	10/26	10/27	10/28	10/29	10/30	10/31
Mini-Vol PM10 Mass Saturation														
24-Hr Average														
Westley-Livingston	82.6	99.4	133.2	129.5	52.0	63.6								
Westley-Grayson	102.4	287.1	169.4	145.4	103.6	67.1								
Westley-I5/Howard	78.3	80.3	114.2	90.0	87.2	53.6								
Westley-Newman	92.7	105.0	116.5	104.7	105.0	61.6								
Westley-Vernalis	85.7	83.4	98.7	80.6	NA	46.1								
Westley-Livingston														
PM10 Total Carb														
24-Hr Average Except * 4-hr Avg,														
Westley-Livingston														
PM10 Teom														
24-Hr Average	99.2	94.3	126.9	135.1	103.3	89.8	34.5							
1-Hr Maximum	275.3	175.1	312.4	271.5	227.5	185.0	79.9							
Westley-McCracken														
PM10 Teom														
24-Hr Average	101.2	94.8	134.0	97.8	88.1	60.9	19.8							
1-Hr Maximum	228.5	354.6	267.2	206.3	198.2	140.5	60.4							
Westley-Livingston														
VOC														
Butadiene	0.04	0.17	0.063	0.064	<.04	0.050								
Benzene	0.80	0.98	1.11	0.81	0.83	0.54								

WESTLEY TIRE FIRE
Total Metals
September

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Westley-Livingston								
			9/22	9/23	9/24	9/25	9/26	9/27	9/28	9/29	9/30
Aluminum	2750	1237									4377
Silicon	7500	3313									10475
Phosphorus	100	58									148
Sulfur	523	1203									1100
Chlorine	439	1666									216
Potassium	875	514									1019
Calcium	1157	1141									1296
Titanium	175	108									184
Vanadium	<10	<10									17
Chromium	5	6									6
Manganese	38	21									43
Iron	1738	1316									1893
Cobalt	<16	<16									<16
Nickel	3	5									4
Copper	28	34									8
Zinc	33	75	55	50	49	72	42	21			206
Arsenic	<3	<3									5
Selenium	<2	<2									4
Bromine	4	8									19
Rubidium	4	2									3
Strontium	17	16									12
Yttrium	<2	<2									<2
Zirconium	4	5									<2
Molybdenum	<4	<4									<4
Tin	<4	5									12
Antimony	<5	<5									<5
Barium	45	62									<25
Mercury	<3	<3									<3
Lead	6	19									9
Uranium	<2	<2									<2

WESTLEY TIRE FIRE
Total Metals
September

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Grayson					I-5/Howard				
			9/26	9/27	9/28	9/29	9/30	9/26	9/27	9/28	9/29	9/30
Aluminum	2750	1237	7471	1056	10837	4070	4194	4435	5342	5198	4686	3480
Silicon	7500	3313	18464	2554	25805	9735	10273	12762	15579	11996	12608	9576
Phosphorus	100	58	144	21	233	93	129	87	123	164	118	75
Sulfur	523	1203	263	48	535	369	963	171	471	509	666	861
Chlorine	439	1666	380	59	303	308	156	353	327	342	152	123
Potassium	875	514	1362	190	2039	812	927	1040	1058	1056	1013	796
Calcium	1157	1141	1340	182	1793	954	1046	1017	1267	1241	1283	1069
Titanium	175	108	310	45	413	182	157	180	188	213	173	129
Vanadium	<10	<10	<10	<10	19	28	<10	11	<10	11	12	10
Chromium	5	6	10	<2	16	11	8	9	9	8	7	5
Manganese	38	21	89	15	121	53	43	56	70	57	59	45
Iron	1738	1316	3384	436	4519	1691	1818	2030	2465	2241	2087	1535
Cobalt	<16	<16	<16	<16	1	<16	<16	<16	<16	0	<16	<16
Nickel	3	5	10	<2	11	10	5	6	6	7	4	3
Copper	28	34	4	4	18	28	10	5	<2	9	6	8
Zinc	33	75	54	4	199	27	217	67	280	109	149	197
Arsenic	<3	<3	<3	<3	4	<3	4	4	<3	6	<3	7
Selenium	<2	<2	<2	2	<2	7	3	4	<2	2	2	3
Bromine	4	8	4	<2	11	<2	18	5	16	14	15	17
Rubidium	4	2	7	<2	11	<2	3	3	4	5	5	3
Strontium	17	16	13	3	23	12	9	8	11	16	10	9
Yttrium	<2	<2	<2	<2	3	3	<2	2	<2	<2	<2	<2
Zirconium	4	5	10	<2	9	5	2	4	4	5	6	4
Molybdenum	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4
Tin	<4	5	<4	6	7	<4	5	<4	<4	6	<4	13
Antimony	<5	<5	<5	<5	6	<5	<5	<5	<5	<5	<5	<5
Barium	45	62	76	<25	117	<25	59	<25	60	26	42	30
Mercury	<3	<3	4	<3	4	11	<3	8	<3	<3	<3	<3
Lead	6	19	6	<4	8	25	<4	<4	6	<4	6	<4
Uranium	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2

WESTLEY TIRE FIRE
Total Metals
September

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Newman				Vernalis				
			9/27	9/28	9/29	9/30	9/26	9/27	9/28	9/29	9/30
Aluminum	2750	1237	956	3967	3614	4906	4130	1222	3447	5447	2593
Silicon	7500	3313	2460	10454	9012	11585	10468	3102	8148	13137	6529
Phosphorus	100	58	23	106	105	134	88	32	97	132	73
Sulfur	523	1203	100	527	566	833	223	136	440	683	874
Chlorine	439	1666	124	238	152	190	509	276	383	1020	235
Potassium	875	514	213	741	839	1159	828	272	671	963	618
Calcium	1157	1141	234	1020	1003	1202	839	285	983	1445	776
Titanium	175	108	42	152	145	196	188	46	145	162	99
Vanadium	<10	<10	<10	12	<10	11	<10	<10	<10	<10	12
Chromium	5	6	<2	6	7	7	8	<2	3	6	4
Manganese	38	21	13	51	43	49	48	14	46	52	26
Iron	1738	1316	417	1765	1604	2172	1996	489	1520	2196	1156
Cobalt	<16	<16	<16	2	<16	<16	<16	<16	3	<16	<16
Nickel	3	5	2	5	3	6	7	<2	3	<2	3
Copper	28	34	4	7	5	9	4	<2	6	<2	8
Zinc	33	75	73	307	73	64	43	11	91	35	242
Arsenic	<3	<3	<3	<3	3	<3	<3	<3	3	3	5
Selenium	<2	<2	<2	3	<2	3	2	<2	<2	<2	4
Bromine	4	8	4	15	10	13	5	<2	6	<2	23
Rubidium	4	2	<2	3	4	6	4	2	3	11	<2
Strontium	17	16	<2	9	9	14	9	3	9	15	8
Yttrium	<2	<2	<2	<2	<2	3	<2	<2	<2	11	<2
Zirconium	4	5	<2	<2	5	6	4	2	<2	10	2
Molybdenum	<4	<4	<4	<4	<4	<4	<4	<4	<4	11	<4
Tin	<4	5	<4	<4	<4	5	<4	<4	5	<4	10
Antimony	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5
Barium	45	62	<25	38	34	35	25	<25	<25	101	<25
Mercury	<3	<3	4	3	<3	<3	<3	<3	<3	11	<3
Lead	6	19	<4	5	<4	12	<4	<4	<4	<4	6
Uranium	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2

Total Metals

WESTLEY TIRE FIRE

October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Grayson					I-5/Howard				
			10/01	10/02	10/03	10/04	10/05	10/01	10/02	10/03	10/04	10/05
Aluminum	2750	1237	2690	1882	1315	1403	1395	2725	1710	1586	1921	1327
Silicon	7500	3313	7767	4694	3415	3390	3418	8170	4509	4705	5280	4142
Phosphorus	100	58	31	84	49	38	43	65	50	39	38	24
Sulfur	523	1203	883	1244	891	779	391	1018	1285	1422	857	288
Chlorine	439	1666	705	982	625	1636	600	266	968	693	1405	422
Potassium	875	514	690	548	392	371	315	663	503	464	481	282
Calcium	1157	1141	706	679	422	447	362	878	602	595	632	452
Titanium	175	108	32	76	57	52	59	103	80	65	71	34
Vanadium	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Chromium	5	6	23	<2	3	3	3	3	<2	2	3	<2
Manganese	38	21	20	19	16	15	17	35	31	21	25	16
Iron	1738	1316	1356	870	647	644	648	1311	799	791	859	618
Cobalt	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16
Nickel	3	5	<2	3	3	2	2	3	3	3	2	<2
Copper	28	34	19	2	<2	4	7	6	<2	5	5	2
Zinc	33	75	43	34	22	46	11	258	190	173	125	24
Arsenic	<3	<3	24	<3	<3	<3	4	<3	6	5	<3	4
Selenium	<2	<2	18	<2	<2	4	3	2	<2	5	6	4
Bromine	4	8	<2	10	5	8	4	16	15	18	13	<2
Rubidium	4	2	<2	<2	<2	<2	3	2	2	<2	3	<2
Strontium	17	16	13	6	2	5	4	7	6	6	8	4
Yttrium	<2	<2	<2	<2	<2	<2	<2	<2	3	<2	<2	<2
Zirconium	4	5	<2	<2	<2	<2	<2	4	7	3	3	2
Molybdenum	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4
Tin	<4	5	33	<4	<4	<4	4	<4	<4	<4	4	<4
Antimony	<5	<5	101	<5	<5	<5	<5	<5	<5	6	<5	<5
Barium	45	62	395	<25	29	<25	<25	34	<25	<25	<25	40
Mercury	<3	<3	40	<3	<3	<3	5	<3	<3	<3	4	7
Lead	6	19	<4	<4	<4	<4	<4	5	<4	<4	5	<4
Uranium	<2	<2	<2	<2	2	<2	<2	<2	<2	<2	<2	<2

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Newman					Vernalis				
			10/01	10/02	10/03	10/04	10/05	10/01	10/02	10/03	10/04	10/05
Aluminum	2750	1237	2855	2515	1017	1519	1371	2528	1489	529	1094	1036
Silicon	7500	3313	7385	5955	2429	3861	3295	6295	3572	1273	2725	2359
Phosphorus	100	58	117	95	40	57	48	58	45	<15	29	22
Sulfur	523	1203	1017	1277	782	850	453	922	1167	589	789	291
Chlorine	439	1666	286	894	409	1288	672	330	716	330	1673	471
Potassium	875	514	703	679	302	468	351	633	411	173	306	237
Calcium	1157	1141	828	695	290	556	410	784	461	202	440	249
Titanium	175	108	136	93	39	66	65	99	55	21	35	32
Vanadium	<10	<10	<10	<10	<10	<10	<10	11	<10	<10	<10	<10
Chromium	5	6	8	4	4	3	4	2	3	<2	<2	4
Manganese	38	21	27	26	10	17	16	27	18	6	12	12
Iron	1738	1316	1234	1121	454	708	611	1204	688	232	519	473
Cobalt	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16
Nickel	3	5	<2	4	3	2	<2	5	<2	<2	2	<2
Copper	28	34	24	3	3	4	4	5	3	2	3	4
Zinc	33	75	52	38	31	54	24	63	41	24	44	13
Arsenic	<3	<3	<3	3	<3	<3	5	<3	<3	<3	<3	<3
Selenium	<2	<2	7	3	<2	2	<2	3	<2	<2	7	<2
Bromine	4	8	18	13	8	10	5	10	11	4	9	3
Rubidium	4	2	<2	<2	<2	3	<2	2	<2	<2	<2	<2
Strontium	17	16	5	7	5	7	4	7	4	<2	5	5
Yttrium	<2	<2	10	<2	<2	<2	<2	<2	<2	<2	<2	<2
Zirconium	4	5	<2	3	3	3	<2	3	5	<2	3	<2
Molybdenum	<4	<4	9	<4	<4	<4	<4	<4	<4	<4	<4	<4
Tin	<4	5	6	4	<4	<4	5	8	<4	8	<4	7
Antimony	<5	<5	11	<5	<5	<5	<5	5	<5	9	<5	<5
Barium	45	62	<25	57	25	<25	<25	30	<25	<25	<25	<25
Mercury	<3	<3	<3	<3	<3	<3	5	<3	<3	<3	<3	<3
Lead	6	19	5	<4	<4	<4	<4	8	4	<4	<4	<4

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Westley – Livingston										
			10/01	10/02	10/03	10/04	10/05	10/06	10/07	10/08	10/09	10/10	10/11
Aluminum	2750	1237	2763	1840	1674	2138	1249	1586	4465	3133	2740	2883	2001
Silicon	7500	3313	6819	4822	4091	5350	3151	3911	11181	7329	6564	6912	4883
Phosphorus	100	58	88	72	54	18	46	31	84	72	67	89	51
Sulfur	523	1203	1007	1228	1302	2052	386	327	199	612	647	859	807
Chlorine	439	1666	335	842	680	942	756	435	155	173	220	165	134
Potassium	875	514	646	514	454	588	311	374	883	663	561	619	434
Calcium	1157	1141	749	550	485	742	382	392	829	619	601	668	583
Titanium	175	108	99	89	71	<10	55	74	185	131	101	117	79
Vanadium	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Chromium	5	6	4	<2	2	10	<2	<2	9	7	<2	2	<2
Manganese	38	21	30	22	20	27	16	20	49	31	25	28	21
Iron	1738	1316	1221	896	782	994	595	707	2060	1305	1159	1255	939
Cobalt	<16	<16	<16	<16	<16	17	<16	<16	<16	<16	<16	<16	<16
Nickel	3	5	3	4	2	3	3	<2	6	4	3	4	3
Copper	28	34	7	5	2	55	4	3	6	3	4	6	4
Zinc	33	75	214	51	50	473	9	8	70	301	141	159	31
Arsenic	<3	<3	<3	<3	<3	34	4	<3	7	4	6	3	4
Selenium	<2	<2	5	3	<2	42	3	<2	<2	3	<2	4	2
Bromine	4	8	18	12	11	43	4	4	5	13	11	15	7
Rubidium	4	2	<2	<2	2	<2	2	<2	4	<2	<2	3	<2
Strontium	17	16	5	5	5	<2	5	3	10	7	6	9	5
Yttrium	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2
Molybdenum	<4	<4	<4	<4	<4	16	<4	<4	<4	<4	<4	<4	<4
Antimony	<5	<5	<5	<5	8	13	8	<5	<5	<5	<5	<5	10
Barium	45	62	48	<25	<25	337	<25	<25	48	<25	33	<25	32
Mercury	<3	<3	6	<3	<3	50	<3	<3	<3	<3	<3	<3	<3
Lead	6	19	9	<4	<4	<4	<4	<4	<4	<4	<4	<4	<4
Uranium	<2	<2	<2	<2	<2	3	<2	<2	<2	<2	5	<2	<2

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Grayson						I-5/Howard					
			10/06	10/07	10/08	10/09	10/10	10/11	10/06	10/07	10/08	10/09	10/10	10/11
Aluminum	2750	1237	1718	2434	5590	3997	4334	3691	3397	4551	3441	2727	2953	2990
Silicon	7500	3313	4281	6010	13638	9778	10441	8941	10233	12506	9226	7113	7860	8513
Phosphorus	100	58	17	73	141	124	123	85	57	82	80	53	74	69
Sulfur	523	1203	374	167	800	818	1073	927	542	410	610	584	945	811
Chlorine	439	1666	811	168	335	328	293	205	758	284	186	112	152	163
Potassium	875	514	394	537	1168	890	911	780	640	931	715	529	631	605
Calcium	1157	1141	360	544	1160	914	1008	899	854	1006	796	705	820	888
Titanium	175	108	86	119	236	146	165	152	115	171	122	85	122	107
Vanadium	<10	<10	<10	<10	<10	<10	<10	<10	<10	11	<10	<10	<10	<10
Chromium	5	6	7	5	7	5	5	3	3	7	6	3	6	3
Manganese	38	21	22	26	61	39	48	40	43	54	42	27	33	34
[illegible]on	1738	1316	800	1113	2543	1782	1908	1697	1481	2033	1568	1149	1262	1375
Cobalt	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16
Nickel	3	5	2	<2	6	4	5	5	5	6	5	2	3	<2
Copper	28	34	<2	6	4	5	7	<2	5	8	4	<2	5	<2
Zinc	33	75	12	18	252	134	221	32	746	392	379	111	252	171
Arsenic	<3	<3	3	<3	4	4	8	<3	<3	<3	<3	3	<3	<3
Selenium	<2	<2	4	<2	2	2	5	<2	<2	<2	5	<2	3	2
Bromine	4	8	<2	4	15	12	20	9	28	16	16	9	17	13
Rubidium	4	2	<2	2	5	5	4	3	2	4	2	3	<2	3
Strontium	17	16	2	5	13	11	11	8	6	10	5	7	7	9
Yttrium	<2	<2	2	<2	<2	3	<2	<2	<2	<2	<2	2	3	<2
Molybdenum	<4	<4	<4	<4	<4	<4	<4	4	<4	<4	<4	<4	<4	<4
Antimony	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	8	<5	<5	<5
Barium	45	62	<25	<25	62	39	43	29	38	31	56	58	<25	32
Mercury	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3	<3
[illegible]ead	6	19	<4	4	<4	<4	<4	<4	10	8	6	<4	10	<4
Uranium	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2	<2

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Newman						Vernalis					
			10/06	10/07	10/08	10/09	10/10	10/11	10/06	10/07	10/08	10/09	10/10	10/11
Aluminum	2750	1237	2348	3629	3365	2494	2803	3695	1054	1439	3043	2734	3048	4027
Silicon	7500	3313	5469	9233	8065	6361	6716	8924	2824	3740	7579	6903	7132	9796
Phosphorus	100	58	60	122	122	306	118	101	29	37	75	67	91	105
Sulfur	523	1203	498	281	708	773	756	937	288	113	504	708	946	1017
Chlorine	439	1666	676	184	149	237	227	223	379	91	129	166	139	253
Potassium	875	514	547	946	911	684	720	864	282	368	694	572	697	827
Calcium	1157	1141	491	1034	832	701	868	965	296	297	662	674	725	1045
Titanium	175	108	88	147	116	100	122	162	35	51	131	114	110	142
Vanadium	<10	<10	<10	<10	<10	<10	<10	13	<10	<10	12	<10	<10	11
Chromium	5	6	4	7	5	6	3	4	<2	<2	7	8	4	6
Manganese	38	21	25	36	34	28	26	36	12	16	33	28	28	4
Iron	1738	1316	1005	1646	1479	1072	1154	1657	481	666	1365	1192	1333	1935
Cobalt	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16	<16
Nickel	3	5	5	4	3	2	2	5	<2	<2	3	2	4	4
Copper	28	34	13	6	9	<2	<2	4	<2	6	8	3	9	5
Zinc	33	75	43	22	56	78	41	33	12	57	146	87	162	94
Arsenic	<3	<3	<3	<3	<3	4	<3	<3	<3	<3	<3	5	<3	4
Selenium	<2	<2	<2	2	3	<2	<2	<2	4	<2	6	<2	4	<2
Bromine	4	8	<2	5	8	10	11	11	3	5	10	8	16	15
Rubidium	4	2	5	5	4	4	<2	3	<2	<2	3	4	5	5
Strontium	17	16	7	12	9	6	9	14	5	17	8	7	7	11
Yttrium	<2	<2	<2	<2	<2	5	2	3	<2	<2	<2	<2	<2	<2
Antimony	<5	<5	<5	8	<5	<5	12	<5	<5	<5	<5	<5	<5	<5
Barium	45	62	58	44	47	34	<25	<25	<25	33	<25	<25	35	49
Mercury	<3	<3	15	<3	<3	<3	<3	<3	<3	6	5	<3	5	<3
Lead	6	19	10	<4	<4	<4	5	<4	<4	4	7	<4	11	<4
Uranium	<2	<2	<2	<2	<2	<2	<2	<2	4	<2	<2	<2	<2	<2

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Westley – Livingston										
			10/12	10/13	10/14	10/15	10/16	10/17	10/18	10/19	10/20	10/21	10/22
Aluminum	2750	1237	NA	3522			4134	2547	4026	4794			
Silicon	7500	3313	NA	8361			9938	6087	9824	11548			
Phosphorus	100	58	NA	98			117	55	110	113			
Sulfur	523	1203	NA	738			395	374	788	926			
Chlorine	439	1666	NA	175			353	216	202	174			
Potassium	875	514	NA	717			1242	680	1040	1200			
Calcium	1157	1141	NA	856			1184	660	982	1127			
Titanium	175	108	NA	137			127	96	152	189			
Vanadium	<10	<10	NA	12			<10	<10	11	11			
Chromium	5	6	NA	4			5	5	5	6			
Manganese	38	21	NA	38			67	33	47	55			
Iron	1738	1316	NA	1493			1685	1056	1727	2099			
Cobalt	<16	<16	NA	<16			<16	<16	<16	<16			
Nickel	3	5	NA	4			4	3	4	5			
Copper	28	34	NA	7			<2	4	5	4			
Zinc	33	75	NA	80			105	95	118	107			
Arsenic	<3	<3	NA	<3			<3	<3	4	6			
Selenium	<2	<2	NA	4			<2	2	3	2			
Bromine	4	8	NA	8			8	9	13	12			
Rubidium	4	2	NA	2			3	<2	2	4			
Strontium	17	16	NA	5			<3	7	9	11			
Yttrium	<2	<2	NA	<2			<2	2	<2	<2			
Molybdenum	<4	<4	NA	<4			<4	<4	<4	<4			
Antimony	<5	<5	NA	<5			8	<5	<5	<5			
Barium	45	62	NA	<25			88	28	<25	43			
Mercury	<3	<3	NA	<3			<3	<3	<3	<3			
Lead	6	19	NA	4			13	8	<4	<4			
Uranium	<2	<2	NA	<2			<2	<2	<2	<2			

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Grayson						I-5/Howard					
			10/12	10/13	10/14	10/15	10/16	10/17	10/12	10/13	10/14	10/15	10/16	10/17
Aluminum	2750	1237	5005	4059			5713	7413	4639	5222			3802	1680
Silicon	7500	3313	12370	10139			13622	17822	12880	15063			9066	4449
Phosphorus	100	58	116	126			166	139	87	98			133	65
Sulfur	523	1203	800	787			479	533	707	839			995	470
Chlorine	439	1666	230	185			481	337	134	108			851	158
Potassium	875	514	1013	938			1558	1573	912	1037			1382	590
Calcium	1157	1141	1188	1169			1482	1466	1170	1434			1380	648
Titanium	175	108	190	161			203	296	176	192			129	70
Vanadium	<10	<10	<10	16			<10	19	<10	11			<10	<10
Chromium	5	6	7	3			9	6	7	10			6	3
Manganese	38	21	52	49			94	93	49	66			81	27
Iron	1738	1316	2191	1793			2429	3279	2008	2410			1587	7
Cobalt	<16	<16	<16	<16			<16	<16	<16	<16			<16	<16
Nickel	3	5	6	5			5	8	5	6			8	3
Copper	28	34	4	6			<2	10	4	9			9	7
Zinc	33	75	162	44			124	168	159	111			1063	96
Arsenic	<3	<3	4	4			<3	5	4	<3			4	<3
Selenium	<2	<2	<2	3			<2	3	<2	5			3	4
Bromine	4	8	12	10			10	15	12	12			44	9
Rubidium	4	2	5	<2			4	9	4	4			3	<2
Strontium	17	16	12	9			16	19	11	12			9	6
Yttrium	<2	<2	<2	<2			<2	<2	<2	3			<2	<2
Molybdenum	<4	<4	<4	<4			<4	<4	<4	<4			<4	<4
Antimony	<5	<5	<5	<5			<5	<5	<5	<5			<5	<5
Barium	45	62	39	<25			83	66	37	58			90	<25
Mercury	<3	<3	<3	<3			<3	5	<3	<3			<3	6
Lead	6	19	<4	8			16	5	<4	5			29	<4
Uranium	<2	<2	<2	<2			<2	<2	<2	<2			<2	<2

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Newman						Vernalis					
			10/12	10/13	10/14	10/15	10/16	10/17	10/12	10/13	10/14	10/15	10/16	10/17
Aluminum	2750	1237	4974	5636			8191	2938	3122	3436			6041	1845
Silicon	7500	3313	11665	13942			19833	6875	7963	8721			14560	4581
Phosphorus	100	58	146	169			247	93	65	80			171	76
Sulfur	523	1203	811	849			673	502	596	828			463	461
Chlorine	439	1666	382	319			599	392	88	87			440	124
Potassium	875	514	1072	1277			2207	895	646	721			1634	608
Calcium	1157	1141	1325	1422			2259	1033	733	858			1719	736
Titanium	175	108	186	227			343	109	134	138			240	60
Vanadium	<10	<10	<10	17			17	<10	14	16			<10	<10
Chromium	5	6	11	7			16	6	2	3			9	3
Manganese	38	21	46	59			132	46	33	37			103	28
Iron	1738	1316	2150	2497			3729	1223	1354	1564			2645	787
Cobalt	<16	<16	<16	<16			<16	<16	<16	<16			<16	<16
Nickel	3	5	5	7			12	4	3	3			7	<2
Copper	28	34	4	7			11	6	<2	3			4	5
Zinc	33	75	61	45			118	71	22	37			129	65
Arsenic	<3	<3	5	<3			5	4	<3	3			<3	<3
Selenium	<2	<2	2	<2			3	3	2	<2			<2	<2
Bromine	4	8	17	11			14	13	8	6			10	10
Rubidium	4	2	5	5			9	3	4	3			6	2
Strontium	17	16	16	15			21	9	8	7			13	6
Yttrium	<2	<2	3	<2			<2	<2	<2	<2			<2	<2
Molybdenum	<4	<4	<4	<4			<4	<4	<4	<4			<4	<4
Barium	45	62	56	42			82	39	<25	<25			85	33
Mercury	<3	<3	<3	<3			<3	4	<3	<3			<3	<3
Lead	6	19	6	6			9	4	<4	<4			14	6
Uranium	<2	<2	3	<2			<2	<2	<2	<2			<2	<2

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Grayson						I-5/Howard					
			10/18	10/19	10/20	10/21	10/22	10/23	10/18	10/19	10/20	10/21	10/22	10/23
Aluminum	2750	1237	6190	20371					3900	3869				
Silicon	7500	3313	15291	48446					11272	10154				
Phosphorus	100	58	161	263					84	81				
Sulfur	523	1203	853	991					739	940				
Chlorine	439	1666	312	337					124	135				
Potassium	875	514	1439	3960					1011	1025				
Calcium	1157	1141	1342	2987					1208	1072				
Titanium	175	108	232	913					134	132				
Vanadium	<10	<10	13	41					<10	<10				
Chromium	5	6	8	26					8	6				
Manganese	38	21	76	259					56	49				
Iron	1738	1316	2726	10089					1806	1658				
Cobalt	<16	<16	<16	18					<16	<16				
Nickel	3	5	6	24					3	3				
Copper	28	34	8	16					4	6				
Zinc	33	75	160	273					99	135				
Arsenic	<3	<3	4	7					4	8				
Selenium	<2	<2	4	6					3	4				
Bromine	4	8	18	25					9	16				
Rubidium	4	2	6	21					<2	2				
Strontium	17	16	16	49					8	11				
Yttrium	<2	<2	<2	8					<2	5				
Molybdenum	<4	<4	<4	<4					<4	5				
Antimony	<5	<5	<5	<5					<5	<5				
Barium	45	62	58	209					91	35				
Mercury	<3	<3	<3	6					<3	<3				
Lead	6	19	4	12					<4	<4				
Uranium	<2	<2	<2	<2					<2	<2				

WESTLEY TIRE FIRE
Total Metals
October

Element	Modesto Sept. Avg '96-'98	LA - N. Main Annual Avg	Newman						Vernalis					
			10/18	10/19	10/20	10/21	10/22	10/23	10/18	10/19	10/20	10/21	10/22	10/23
Aluminum	2750	1237	4627	5593					4754	4555				
Silicon	7500	3313	11239	12919					11651	10971				
Phosphorus	100	58	146	142					135	88				
Sulfur	523	1203	870	982					707	854				
Chlorine	439	1666	428	302					116	113				
Potassium	875	514	1416	1455					1212	1081				
Calcium	1157	1141	1342	1368					1259	1042				
Titanium	175	108	182	205					172	160				
Vanadium	<10	<10	<10	10					12	<10				
Chromium	5	6	7	9					5	5				
Manganese	38	21	45	58					58	50				
[illegible]on	1738	1316	1978	2362					2066	2015				
Cobalt	<16	<16	<16	<16					<16	<16				
Nickel	3	5	5	5					4	4				
Copper	28	34	9	8					3	7				
Zinc	33	75	70	60					84	64				
Arsenic	<3	<3	<3	<3					5	5				
Selenium	<2	<2	4	4					<2	5				
Bromine	4	8	23	25					9	11				
Rubidium	4	2	4	6					6	4				
Strontium	17	16	12	16					12	12				
Yttrium	<2	<2	<2	3					2	<2				
Molybdenum	<4	<4	<4	<4					<4	<4				
Antimony	<5	<5	<5	<5					7	<5				
Barium	45	62	27	63					<25	63				
Mercury	<3	<3	<3	<3					<3	<3				
Lead	6	19	7	8					<4	<4				
[illegible]anium	<2	<2	<2	2					<2	<2				

APPENDIX 2
Westley Tire Fire Monitoring Activities

The following document describes ongoing monitoring efforts by the Air Resources Board Monitoring and Laboratory Division for the tire fire in Westley, California. Monitoring activities are described on a site by site basis and list instruments and analyses being performed and when sampling began at each monitoring location.

Westley-Livingston: This monitoring station is located adjacent to seasonal worker housing and a daycare center on Livingston Circle in Westley, CA. The site is approximately 4 to 5 miles due southeast of the tire fire. Currently the following instruments are operating at the site: Surface meteorology (wind speed/direction, outside temperature), an aethalometer for continuous black carbon analysis, a carbon monoxide (CO) analyzer, a Xontech 910A toxics sampler (collects 24 hour samples into 6L stainless steel canisters and are analyzed for benzene and 1,3-butadiene), a Tapered Element Oscillating Microbalance (TEOM) for continuous PM10 mass, and two portable battery operated MiniVol particulate samplers collecting 24 hour PM10 samples (one teflon filter for total PM10 mass and total metals (30 different elements analyzed); and one quartz filter for PAH and total carbon analyses). Sampling at this site began on September 22.

Westley-McCracken: This monitoring station is located at a Super 8 Motel on McCracken Road near the I-5 freeway in Westley, CA. The site is approximately ¾ to 1 mile due southeast of the tire fire. Currently the following instruments are operating at the Super 8 Motel: Surface meteorology (wind speed/direction, outside temperature), an aethalometer for continuous black carbon analysis, and a TEOM for continuous PM10 mass. Sampling at this site began on October 2.

Westley-Howard Road: This monitoring site is located near a McDonald's restaurant on Howard Road and the I-5 freeway in Westley, CA.. Currently operating at this location is one portable battery operated MiniVol particulate sampler collecting 24 hour PM10 samples (one teflon filter for total PM10 mass and total metals). The sampler is attached to a utility pole and is approximately 1 mile due southeast of the tire fire. Sampling at this site began on September 26.

Vernalis: This monitoring site is located in the parking lot of an unoccupied warehouse on Welty Road in Vernalis, CA. Currently operating at this location is one portable battery operated MiniVol particulate sampler collecting 24 hour PM10 samples (one teflon filter for total PM10 mass and total metals). The sampler is attached to a utility pole and is approximately 15 miles north/northeast of the tire fire. Sampling at this site began on September 26.

Grayson: This monitoring site is located at the intersection of Minnie and River Roads in Grayson, CA. Currently operating at this location is one portable battery operated MiniVol particulate sampler collecting 24 hour PM10 samples (one teflon filter for total PM10 mass and total metals). The sampler is attached to a utility pole and is approximately 7-10 miles east of the tire fire. Sampling at this site began on September 26.

Newman: This monitoring site is located at the Newman library on Kern street in Newman, CA. Currently operating at this location is one portable battery operated MiniVol particulate sampler collecting 24 hour PM10 samples (one teflon filter for total PM10 mass and total metals). The sampler is attached to a utility pole in the parking lot of the Newman library, and is approximately 30 miles south/southeast of the tire fire. Sampling at this site began on September 27.

Patterson: This monitoring site is located at the Patterson High School on 7th Avenue in Patterson, CA. Currently operating at this location is a High Volume Sampler with Size Selective Inlet collecting 24-hour PM10 samples for total PM10 mass, PAH, and total carbon analysis. The site is approximately 20 miles southeast of the tire fire. Sampling at this site began on October 6.

APPENDIX 3

MLD Analysis of the Pyrolitic Oil Headspace

Project:	WESTLEY TIRE
Sample ID:	101499-01A
Sampling Date:	10/25/99
Analysis Date:	10/25/99
Report Date:	10/29/99
GC Number:	GC#4

CAS Number	Compound	Concentration (ppbC)*
-	-	-
00074-98-6	Propane	16
00075-28-5	methylpropane	22
00106-97-8	Butane	19
00115-11-7	2-methylpropene	93
00513-35-9	2-methyl-2-butene	24
00109-66-0	Pentane	20
00071-43-2	benzene	50
10574-36-4	3-methyl-cis-2-hexene	16
00565-75-3	2,3,4-trimethylpentane	16
00108-88-3	Toluene	43
00100-41-4	ethylbenzene	17
	Total	336

*parts per billion concentration

APPENDIX 3

MLD Analysis of the Pyrolitic Oil Headspace (cont.)

Project:	WESTLEY TIRE
Sample ID:	101499-01A
Sampling Date:	10/25/99
Analysis Date:	10/25/99
Report Date:	10/29/99
GC Number:	GC#4

CAS Number	Hydrocarbon	Volume Percent
-	-	-
00074-98-6	propane	7.78
00115-07-1	propene	0.00
00075-28-5	methylpropane	8.03
00106-97-8	butane	6.93
00115-11-7	2-methylpropene	33.93
00513-35-9	2-methyl-2-butene	7.01
00109-66-0	pentane	5.84
00071-43-2	benzene	12.16
10574-36-4	3-methyl-cis-2-hexene	3.34
00565-75-3	2,3,4-trimethylpentane	2.92
00108-88-3	toluene	8.97
00100-41-4	ethylbenzene	3.10
Total		100

APPENDIX 3

MLD Analysis of the Pyrolitic Oil Headspace (cont.)

Project:	WESTLEY TIRE
Sample ID:	101499-01A
Sampling Date:	10/25/99
Analysis Date:	10/25/99
Report Date:	10/29/99
GC Number:	GC#4

CAS Number	Hydrocarbon	Mass Percent
-	-	-
00074-98-6	propane	5.05
00075-28-5	methylpropane	6.87
00106-97-8	butane	5.93
00115-11-7	2-methylpropene	28.02
00513-35-9	2-methyl-2-butene	7.23
00109-66-0	pentane	6.20
00071-43-2	benzene	13.98
10574-36-4	3-methyl-cis-2-hexene	4.82
00565-75-3	2,3,4-trimethylpentane	4.91
00108-88-3	toluene	12.16
00100-41-4	ethylbenzene	4.85
	Total	100.00

Appendix C

Westley Tire Fire Vegetable Monitoring Data.

Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director

Headquarters • 301 Capitol Mall, Rm. 205 • Sacramento, California 95814-4308

Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

...on H. Hickox
...ncy Secretary

Gray Davis
Governor

October 28, 1999

Mr. Donald O. Cripe
Agricultural Commissioner
Department of Agriculture
3800 Cornucopia Way Suite B
Modesto, California 95358

Dear Mr. Cripe:

Dr. Joan Denton, Director of the Office of Environmental Health Hazard Assessment (OEHHA), has asked me to respond to your letter of October 27, 1999. In your letter you mention that the residents of West Stanislaus County are concerned that chemicals in particles generated by the Westley tire fire may have contaminated local crops. In addition, concern has been raised about long term effects on the soil from airborne particles.

The types of chemicals of potential concern on particles from the fire include metals, dioxins, furans and polycyclic aromatic hydrocarbons (PAHs). These chemicals can potentially cause cancer and other long-term health effects. The fire undoubtedly generated particles containing these chemicals, particularly before the oil runoff from the fire was extinguished. The question is could enough particles deposit on plants to harm the health of people if eaten or affect the soil and future crop productivity.

There is some evidence that very little particulate matter was deposited on the crops. I understand that Stanislaus County Agricultural Officials inspected tomatoes and other crops at multiple sites around Westley two weeks after the tire started and could find no particulate residues. The smoke plume was reported mostly to have risen straight up, then to have dispersed over a wide area to the north or south. The air modeling results from Lawrence Livermore National Labs also indicate that smoke from the fire was dispersed over a very wide area, which would tend to dilute the chemicals below levels that would have health impacts.

The air monitoring results for metals from the Air Resources Board (ARB) monitoring stations around the tire fire indicate that, with the exception of zinc, metal concentrations were similar to concentrations normally found in the air in Modesto and Los Angeles prior to the fire. Zinc is not very toxic to either plants or people. PAH concentrations at the monitoring stations around the fire were also similar to those found in Modesto and Los Angeles before the fire. OEHHA believes it is unlikely that enough particles were deposited on crops to cause health effects. It should be noted that if individuals or commercial processors wash crops, particle chemical residues would be removed. It is our understanding from discussions with you that much of the tomato harvest was completed before the tire fire started. Nuts are covered with a shell, which protects the edible portion from particulate contamination.

OEHHA is not aware of any studies indicating that that PAHs, metals, dioxins and furans deposited in the soil by the fire would have any long-term effects on the soil or crop productivity. PAHs, dioxins and furans are not taken up by plants and are already present in the soil at very low concentrations from diesel exhaust and other combustion sources. Metals deposited in the soil are taken up by plants, but ARB air monitoring results indicate that the amounts that could have been deposited were probably much lower than levels already in the soil.

Stanislaus County has collected crop samples from the West Side and these samples were analyzed for metal content. In addition, samples for comparison from the East Side were collected. OEHHA will assist Stanislaus County in the interpretation of these results and continue to investigate the questions raised by the community. We have requested additional studies published in the literature, which may help in our evaluation.

Sincerely,

Robert J. Blaisdell

Robert J. Blaisdell, Ph.D.
Staff Toxicologist

CC: Joan E. Denton, Ph.D.
Director of OEHHA

George V. Alexeeff, Ph.D.
Deputy Director for Scientific Affairs, OEHHA

12-5-99

The Office of Environmental Health Hazard Assessment's Interpretation of Stanislaus County's Produce Metal Analysis Data

Stanislaus County officials, in response to public concern, collected samples of persimmons, lima beans, tomatoes and walnuts (Table 1). The Hazardous Materials Laboratory of the Department of Toxic Substances Control analyzed the samples. The public was concerned with contamination of crops and possible contamination of soil affecting future crop yields.

Samples were collected on October19, 1999 from various places on the West Side of the valley and a few samples were collected from the East Side away from the proximity of the fire (figure 1). A formal sampling plan was not employed. There was some difficulty in locating samples because most of the crops had already been harvested. The samples from the East Side included tomatoes, persimmons and walnuts. The whole sample in each case was homogenized and then analyzed. All of the samples were analyzed for arsenic, barium, beryllium, cadmium, cobalt, chromium, copper, molybdenum, nickel, lead, selenium, thallium, vanadium, and zinc. Of these metals chromium, cadmium and lead are of potential public health concern because they can be emitted by burning tires in appreciable amounts and have considerable toxicity by the oral route. Zinc is the metal emitted in the highest amount by burning tires but it is not very toxic. It is useful to look at the zinc levels because contamination with zinc should occur at the highest levels if the tire fire was depositing significant amounts of metals.

Zinc levels in Stanislaus County Samples vary from slightly below the average value cited in the literature for dried tomatoes to near the higher of the two values found in the literature for fresh tomatoes (Table 1). The values for persimmons also appear to be about 21/2 times reported literature values. The values measured in other produce are close to the literature average values. The zinc levels did not seem to vary in any obvious way with the distance from the fire. The zinc content of the tomatoes and persimmons is likely due to the zinc content of the local soil and/or fertilizer. It is possible that the fire could have contributed to the zinc content of the produce, but it would be very difficult to establish a causal link. Zinc content of any produce can be expected to vary. Also the USDA average levels in different types of produce vary quite a bit as shown in Table 1. To provide perspective, the United States Department of Agriculture's Reference Daily Intake for zinc is 15 mg/day. This level is a suggested daily intake because zinc is a required nutrient. The United States Environmental Protection Agency (USEPA) has a zinc oral RfD (Reference Dose) of 0.3 mg/kg/day[1]. The RfD is the amount below which no health effects would be expected. The RfD for zinc corresponds to 21 mg/day for a 70 kg person over an extended period of time. Consumption of zinc above this level would result in an increased risk of health effects. The zinc levels measured in the produce do not pose a public health threat.

Chromium, cadmium and lead were below the limit of detection in these samples in all but one case where chromium was found at 2.11 mg/kg in persimmons collected in

In summary, OEHHA has concluded that there is no gross cadmium, lead chromium or zinc contamination of the limited number of produce samples collected by Stanislaus County and analyzed by the Hazardous Materials Lab. The possibility exists, given the limits of detection of the screening method selected by Stanislaus County and the Hazardous Materials Lab, that contamination of produce below the limit of detection could have occurred. OEHHA concludes given the circumstances of the fire it is unlikely that contamination below the detection limit poses a threat to public health. It should be noted that fresh produce from this harvest would be consumed over a relatively short period of time perhaps a month or so at most, thus limiting human exposure. If contamination of the produce had occurred, it would be primarily due to deposition onto the produce surface. Such contamination would be removed by washing. Produce such as tomatoes for canning are washed before the canning process, according to Stanislaus County Agricultural Officials. It is possible for the Hazardous Materials Laboratory to do a more sensitive analysis with a lower limit of detection on the remaining portions of the samples. However, OEHHA does not believe that further analyses would reveal abnormal quantities of chromium, lead or cadmium in samples collected by Stanislaus County.

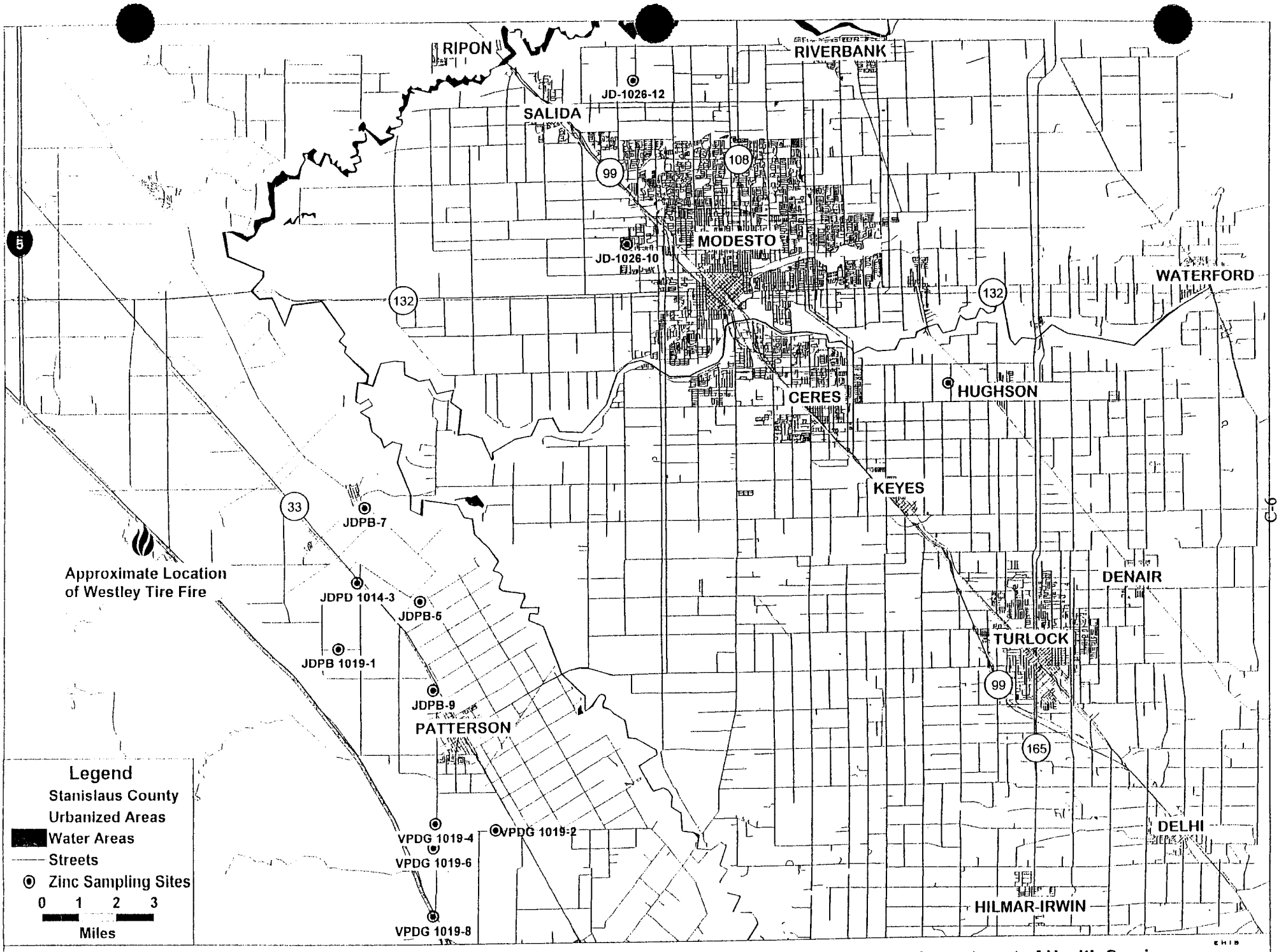
[1] Integrated Risk Information System, USEPA, November 1999.

[2] Recommended dietary allowances; National Academy of Sciences. National Research Council. National Academy Press: Washington DC; 10th ed., 1989.

[3] CAPCOA Air Toxics "Hot Spots" Program, Revised 1992 Risk Assessment Guidelines, October 1993

[4] Health Assessment Document for Cadmium, Environmental Protection Agency, 1981.

[5] IARC; Monograph Some Metals and Metallic Compounds 23: 325-415 (1980) as cited by the Hazardous Substances Data Bank, November 1999.



C-6

Westley Tire Fire: Zinc Concentration in Produce - Sampling Sites

California Department of Health Services
Environmental Health Investigations Branch

Note: Sampling locations are digitized from paper descriptions. Locations are approximate.

Appendix D

Stanilaus County Public Health Recommendations.
And
Health Data From the Westley Tire Fire Collected by Stanislaus County Health Department.

Air Quality Index Category	PM_{10} ($\mu g/ m^3/24$ hr)	Potential Health Effects	Health Protective Action
Good	0-49	Unlikely	None advised
Moderate	50-100	Sensitive persons may experience respiratory symptoms	Sensitive persons should limit outdoor exertion
Unhealthy for Sensitive* Groups	101-150	Increased likelihood of symptoms in sensitive persons, some may require medical attention; likelihood of early symptoms in others	Sensitive persons should remain mostly indoors; others should limit outdoor exertion
Unhealthy	151-249	Many people, healthy and sensitive, likely to experience respiratory symptoms	Sensitive persons should avoid outdoor activity; others should restrict outdoor activity
Very unhealthy	250-424	Significant increased respiratory symptoms and aggravation in sensitive people; increased likelihood of respiratory effects in others	Everyone should avoid outdoor activity and remain indoors; sensitive persons should consider relocation
Hazardous	425+	Serious risk of respiratory symptoms and aggravation in sensitive people; respiratory effects likely in others	Everyone should avoid any outdoor activity and remain indoors or relocate

*Sensitive groups: people with chronic lung or heart disease, such as asthma, emphysema, chronic bronchitis, angina, congestive heart failure; also elderly and young children.

Note: sensitive and other people can vary broadly in sensitivity and symptoms to effects of air pollution.

Westley Tire Fire: Nurse of the Day Calls Summary, Stanislaus County – 09/07/00

There were 86 calls related to health concerns received by the nurse of the day. Almost 56% of the calls were received on September 30 and October 1, 1999 (See Table 1). A few calls were in regards to more than one person. And some individuals called more than once.

Table 1: Frequency of calls received by the nurse of the day about the tire fire by date, Stanislaus County.

Date of Call	Freq	Percent
09/29/99	4	4.7%
09/30/99	29	33.7%
10/01/99	19	22.1%
10/04/99	8	9.3%
10/05/99	1	1.2%
10/06/99	1	1.2%
10/07/99	5	5.8%
10/08/99	2	2.3%
10/11/99	5	5.8%
10/12/99	2	2.3%
10/13/99	3	3.5%
10/14/99	4	4.7%
10/19/99	1	1.2%
10/20/99	1	1.2%
10/25/99	1	1.2%
Total	86	100.0%

Symptoms:

The most common symptoms complained about were headache, coughing and difficulty breathing.

Table 2: Symptoms that callers complained about to the nurse of the day, Stanislaus County. Some people had more than one symptom.

Symptoms	Freq	Percent
Headache	41	47.7%
Coughing	30	34.9%
Difficulty Breathing	25	29.1%
Burning Eyes	18	20.9%
Sore Throat	18	20.9%
Wheezing	17	19.8%
Stuffy Nose	13	15.1%
Nausea	11	12.8%
Nose Discomfort	6	1.2%
Vomiting	5	5.8%
Chest Discomfort	4	2.3%
Bronchial Problems	2	1.2%
Runny Nose	2	2.3%
Joint Pain	2	1.2%
Water Eyes	2	1.2%
Dizzy	2	1.2%

Complaint of: Congestion, Tired, Chills, Dry Throat, Ribs, Sinus Infection, Smell, Taste, Weak

Location:

The majority of the calls received came from individuals living on the West side of the county; Patterson, Newman, Crows Landing, Westley, (and Tracy) etc (See Table 3). Other calls came from as far away as Lathrop and one (not included in the analysis) came from West Hollywood.

Table 3: General area from which calls are originating.

Area of Call	Freq	Percent
Other	31	36.0%
West County	55	64.0%
Total	86	100.0%

Prior Conditions:

Asthma was the most common prior condition followed by allergies among those who called to ask questions about the air quality. Only 26% of the callers had been to see a physician before they called. (Table 5) Several more had plans to see one in the next few days.

Table 4: Prior health conditions among those who called about the tire fire, Stanislaus County.

Prior Conditions	Freq	Percent
Asthma	25	19.8%
Allergies	6	4.7%
Preexisting Respiratory Prob.	4	1.2%
Pregnant	2	1.2%
Bronchitis	1	1.2%
Brain Tumor	1	1.2%
Eye Surgery	1	1.2%
Heart Disease	1	1.2%
Hx Of Mua	1	1.2%
Hypogammaglobinemia	1	1.2%
Mouth Sore	1	1.2%
Parishiners Have Symptoms	1	1.2%
Total	86	100.0%

Table 5: Number of callers who had seen a health care provider about their concerns.

Seen a Doctor	Freq	Percent
N/A	12	14.0%
Yes	22	25.6%
No	52	60.5%
Total	86	100.0%

Appendix E

Everett Washington Tire Fire Risk Assessment.

U.S. ENVIRONMENTAL PROTECTION AGENCY
REGION 10
1200 SIXTH AVENUE
SEATTLE, WASHINGTON 98101

OCT 8 1986

REPLY TO
ATTN OF: M/S 532

Mr. Arthur Dammkoehler
Air Pollution Control Officer
Puget Sound Air Pollution Control Agency
P.O. Box 9863
Seattle, WA 98109

Dear Mr. Dammkoehler:

As you requested in your letter of November 20, 1985, we have evaluated the long term health risk from the Everett tire fire. We have confined our health assessment to estimating the increased cancer risk from inhalation exposure to airborne particulates emitted during the fire. The specific contaminants evaluated were benzo(a)pyrene (B(a)P) and a class of compounds called Products of Incomplete Combustion (PIC). Attached is a report summarizing the results of that assessment.

Using EPA risk assessment methods, the analysis indicated that those individuals (4 of them) calculated to have the highest exposure to the tire fire emissions may have an increased lung cancer risk from 2 in one million to 2 in ten thousand. Since exposure for other residents living in the vicinity of the fire was less, their estimated lung cancer risks are also less (substantially less for most).

Because of the methodologies used these estimates represent a likely upper bound of lung cancer risk - the actual risk is somewhere between zero and these numbers. It should also be stressed that there are many uncertainties and assumptions involved in deriving these lung cancer estimates. These are summarized in the report.

The U.S. EPA has not defined a cancer risk level which is considered to be significant. However, excess cancer risk levels above 1 in a million to 1 in 100,000 (10^{-6} to 10^{-5}) generally give some cause for concern and suggest that exposures should be reduced. To put these numbers in perspective, however, a lung cancer risk of 10^{-6} to 10^{-5} is equivalent to smoking about 5 to 50 cigarettes in a lifetime.

We appreciate the support your staff provided in performing this assessment. Should you have any questions about the results or methodologies, please contact Dana Davoli at 442-1757.

Sincerely,

George Adef for

Gary O'Neal, Director
Air and Toxics Division

Attachment

cc: Dave Peterson, Snohomish Health District

AN ASSESSMENT OF LUNG CANCER FROM THE 1984 TIRE FIRE IN EVERETT, WASHINGTON

On September 24, 1984 a fire broke out in a scrap tire dump east of Everett which contained more than a million tires. The tires burned for more than two months. The Puget Sound Air Pollution Control Agency requested that EPA perform a risk analysis using data gleaned from selected ambient particulate matter samples from stations in Everett and North Seattle operated by that agency. These samples were analyzed for selected products of incomplete combustion (including benzo(a)pyrene). These data coupled with emission parameter estimates were then used to estimate risk to the exposed population. This document presents the results of the risk analysis.

October, 1986

U.S. Environmental Protection Agency
Region 10
1200 Sixth Avenue
Seattle, Washington 98101

On September 24, 1984, a tire fire began burning at the old City of Everett Landfill in Everett, Washington. During the first few weeks of the fire large quantities of smoke were released. This fire continued to smolder for about two months emitting smoke at gradually decreasing levels. The City of Everett, which is west of the fire, was at times heavily impacted by the plume. Smoke was also dispersed to the east and to the south toward Seattle.

Limited air monitoring for organic vapors was done around the tire fire by the U.S. Environmental Protection Agency's (U.S. EPA) Technical Assistance Team on September 28, 1984. ("Tire Fire Investigation, TAT Activities Report", U.S. EPA, Region 10, October, 1984). The results from this one day of monitoring showed that high levels of some compounds (e.g., benzene) were present in or very near the fire but dropped off rapidly in concentration within a half mile. At the request of the Snohomish Health District, the Centers for Disease Control (CDC) reviewed these data. CDC concluded that "concentrations of some chemicals in the immediate vicinity of the fire were high enough to pose a potential immediate health threat to individuals within 200 feet of the fire." Personnel at the scene of the fire (e.g., firemen) were of most concern. Persons living beyond the immediate area of the fire may have received transient exposure, according to CDC, resulting in a "temporary increased risk of acute short term health effects" (e.g., respiratory impairment; eye, throat and respiratory irritation). CDC also stated that "we do not anticipate any significant increased risk of long term health effects nor can we conclude that chemicals in the smoke reached the public in sufficiently high concentration to significantly affect health."

The Puget Sound Air Pollution Control Agency (PSAPCA) has monitors located in Seattle and Everett to measure levels of particulates in the air. A sample collected from the Everett monitor on September 28, 1984 (about 1.2 miles from the fire) was analyzed for selected particulate organics by a lab at the University of Washington in January,1985. The results showed levels of polycyclic aromatic hydrocarbons (PAHs) that were above background. Several members of this class of compounds are known or suspected of causing cancer. At the request of PSAPCA, the U.S. EPA's Region 10 laboratory analyzed 24 additional samples collected by PSAPCA at the Everett station and at two stations in Seattle (approximately 20 and 25 miles south of the tire fire) during the first few months after the tire fire began. These results also showed elevated levels of PAHs in Everett and at both Seattle locations during the fire which lasted about 2 months. Because of these results PSAPCA requested that EPA quantitatively "assess the long-term health risk from the tire fire emissions."

In response to PSAPCA's request, EPA has estimated the lung cancer risk that may result from emissions of benzo(a)pyrene (B(a)P) and Products of Incomplete Combustion (PIC) from the fire. B(a)P is a polynuclear aromatic hydrocarbon (PAH) that is a suspected human cancer causing agent (carcinogen). PICs are loosely defined as a complex mixture of compounds which includes PAH (polynuclear aromatic hydrocarbons) and possibly other organic compounds that are released during the combustion of organic material.

We limited our risk analyses to B(a)P and PIC for several reasons:

(1) Although increased levels of particulates were detected on PSAPCA's samplers more than a mile from the tire fire, the limited sampling data collected by EPA for gaseous organics suggest that levels of these gaseous compounds dropped off quickly within a short distance of the fire. CDC concluded from these data that these gaseous organics did not reach the public in sufficiently high concentrations to cause a long term health risk.

(2) Although other particulate organics were detected on PSAPCA's samples, toxicity and potency (unit risk numbers) data are available only for B(a)P and the generic class of incomplete combustion products, PICs. (see below).

(3) Data from the literature are available to make rough estimates of the amounts of B(a)P emitted from the fire. These data were used in a computer dispersion model to estimate ambient air exposure for residents in the Everett-Seattle area. These modeled ambient air results could also be compared to those levels measured by PSAPCA.

The scientific data now available make it extremely difficult, if not impossible, to identify a level of exposure to cancer-causing agents that is safe. Therefore, EPA and other federal agencies have taken the position that cancer may occur at any level of exposure no matter how low. EPA has also assumed that the risk of cancer increases as exposure increases and that this relationship is linear (e.g., when exposure doubles so does risk). Thus, although a "safe" exposure can't be defined, estimates can be made of the risk of getting cancer if exposure to a cancer-causing substance is known. To estimate the risk from the tire fire, EPA has combined two different types of data: data on the B(a)P exposure for the populations living within about 30 miles of the fire and data on the cancer potency of B(a)P and PIC.

As a first step in calculating exposure levels, emission levels of B(a)P from the fire were estimated from data on the number of tires consumed during the fire and from literature data on the amounts of B(a)P released per pound of burning tire. A mathematical (dispersion) model used these emission data as well as data on weather and geographic conditions to estimate the concentrations of B(a)P at about 250 points around the fire within a 30 mile radius. This information was then combined with Bureau of Census population figures to provide an estimate of the number of people exposed to a given level of B(a)P (see the Attachment for a more detailed explanation of this methodology).

The other type of data needed to estimate the public lung cancer risk from the fire is that on the potency of B(a)P-this potency is expressed as a unit risk number. The unit risk number is defined as the lifetime cancer risk that would occur in a population which is exposed throughout their lifetime (70 years) to one microgram per cubic meter of B(a)P in the air they breathe. The unit risk number for B(a)P, which was derived using experimental data on animals, is about 3×10^{-3} per ug/m^3 (micrograms of B(a)P per cubic meter of air).

The unit risk number for B(a)P and the estimated B(a)P exposure for people living around the fire site were multiplied to give the estimated lung cancer risk if exposure to the fire had occurred for 70 years (over an entire lifetime). This risk number was then divided by 420, the number of two month periods in 70 years, to adjust it for the fact that exposure occurred only for the tire fire duration (i.e., about 2 months). For the persons with the highest exposure to B(a)P emitted by the tire fire, their increased lifetime cancer risk is approximately 2×10^{-6}. That is, their estimated risk of getting cancer as a result of the fire is 2 in 1 million (see Table 3 in the Attachment). This risk decreases significantly as distance from the fire increases.

This level of risk could be compared to the average expectation of dying of all types of cancer which is about 1 in 5 and the lifetime risk of dying from lung cancer for cigarette smokers (pack a day) which is about one in 10. Another way of stating this is that a risk of 2×10^{-6} is equivalent to smoking about 10 cigarettes over a lifetime.

Another way of estimating risk from exposure to B(a)P utilizes a different unit risk number, that for Products of Incomplete Combustion or PIC. During combustion of organic material many compounds in addition to CO_2 and water can be released because the combustion is not 100% efficient and because of impurities in the materials being burned. These may include the original organic material or other more or less complex compounds formed during combustion. As previously mentioned, this complex mixture of compounds is loosely defined as PIC and includes PAH (polynuclear aromatic hydrocarbons) and possibly other organic compounds.

A unit risk number for PIC has been derived using B(a)P as a surrogate. As an example, workers exposed to products of incomplete combustion (e.g., roofers, gas workers) have higher lung cancer rates than non-exposed workers. Although PICs are a complex mixture of compounds, most of the worker exposure data are expressed in B(a)P concentrations since B(a)P is a suspected carcinogen and is fairly easy to measure. Therefore, in these studies, B(a)P serves as a surrogate or indicator of the PICs, and cancer risk is expressed in excess cancers per unit measure (e.g., ug/m^3) of B(a)P. Results from many studies such as these (occupational and non-occupational) were combined to estimate the PIC unit risk number. The B(a)P exposure levels estimated to be produced as a result of the tire fire can be used with the PIC unit risk number (4×10^{-1} per ug/m^3) to estimate lung cancer risk resulting from exposure to PICs emitted by the tire fire. This results in an estimated lifetime cancer risk for those persons with the highest exposure of 2×10^{-4} or about 2 in 10,000. This is significantly higher than the estimate using the B(a)P unit risk number, 2 in one million.

It should be kept in mind that the risk estimates given here for both B(a)P and PICs are for those few people with the highest exposure to emissions from the tire fire. According to the model used by EPA, only 4 persons are living in this area of highest exposure (0.26 ug/m^3 of B(a)P). Exposures for other people living around the fire were less as can be seen in Figures 1 and 2 (isopleth maps) of the Attachment. In the area

west of the fire and within about 0.6 miles, the model we used predicts a population of roughly 1200 residents. Their estimated exposure ranges from about 0.023 ug/m^3 B(a)P to 0.26 ug/m^3 B(a)P. People living in Snohomish, Monroe, and Lynnwood were exposed to B(a)P levels between 0.0002 ug/m^3 and 0.002 ug/m^3. Therefore their risk is substantially less than that of the highest exposure group.

It must also be stressed that there are many assumptions and uncertainties involved in this type of risk estimate. For example, for carcinogens, EPA assumes that a linear relationship exists between exposure and cancer risk (e.g., a person who inhales one microgram of B(a)P per cubic meter of air is one-tenth as likely to get cancer as a person who inhales 10 micrograms per cubic meter). A mathematical model based upon this assumption is used to estimate the unit risk number; the model relies upon laboratory data in animals (B(a)P) or studies of workers or community exposures (PIC). Because this model is conservative, the risk numbers generated represent upper bounds of risk rather than an actual expected level of risk. The actual level of risk in terms of excess cancers is somewhere between zero and the risk value calculated here (2 in one million for B(a)P and 2 in 10,000 for PIC). Other assumptions and uncertainties are discussed below:

(1) Modeling - In Attachment A, Table 2, a comparison is made between the ambient levels of B(a)P predicted from the dispersion model and those measured (observed) by PSAPCA. The discrepancies between these two numbers are likely a result of several factors including:

° Emission estimates of B(a)P from the fire were based upon emission rates obtained from the literature not measured data from the fire

° The dispersion model that estimates the ambient levels of B(a)P at various points is limited in dealing with complex geographic and meteorological conditions as well as non-constant emissions of pollutants as was the case with the tire fire

° The number of ambient air samples analyzed by EPA were too few in number to consider them a very good representation of an average concentration over the two-month period of the fire. Additionally, these samples were analyzed more than 10 months after collection; volatilization and decomposition of substances on the filter may have occurred.

(2) Exposure

° Much of the information available on carcinogens, including development of potency numbers such as the unit risk numbers, are from laboratory or occupational studies where exposure occurred over a long time period. The use of such numbers for a two month exposure to B(a)P as occurred with the tire fire may not be appropriate.

° Exposure to B(a)P and PICs from inhalation of contaminated dust or from ingestion of contaminated soils and dusts by children has not been considered.

(3) Unit Risk Numbers

° There is a even more uncertainty with the PIC unit risk number than with other unit risk numbers, in part because of the way it was derived and because B(a)P is used as a surrogate. For example, the PIC unit risk number is derived from studies of workers and communities. The types of chemicals present in these situations may be very different from those emitted from the tire fire.

Conclusion

This assessment of the long term health effects from the tire fire emissions was limited to estimating lifetime lung cancer risk for the reasons already discussed. Using conservative assumptions, this increased lifetime cancer risk may approach 2 in one million for B(a)P and 2 in 10,000 for PIC for a limited number of people (about 4) with the highest exposure to emissions from the tire fire. It should be kept in mind that there are many assumptions and uncertainties involved in this type of risk assessment (e.g., assuming that a linear relationship between exposure and cancer risk exists, estimating B(a)P emissions using literature values, using "lifetime" unit risk numbers to estimate risk from a two month exposure to the tire fire emissions). It should also be stressed that these risk estimates represent upper bounds of lung cancer risk rather than an actual expected level of risk; that is, the true risk is expected to be somewhere between zero and the risk values calculated.

ATTACHMENT

Modeling Analysis to Assess Risk from Everett Tire Fire Emissions

The purpose of this attachment is to briefly document a modeling analysis of the air emissions from the Everett tire fire and the development of risk estimates. The modeling approach employed the Industrial Source Complex (ISC) Model to estimate concentrations, which were then input to the Human Exposure Model (HEM) to estimate risk.

Emissions estimates for benzo-a-pyrene [B(a)P] employed in the risk assessment analysis were developed based on the following information:

- 807,000 tires burned in 60 days
- 20 pounds per tire
- 18 grams of B(a)P emitted per ton of tires burned *

This yielded an average B(a)P emission rate during the fire of 0.02802 grams per second. The fire was simulated in the ISC model as a volume source with horizontal dimensions of 100 meters by 100 meters, and a vertical height of 20 meters. This accounts for initial dilution of the emissions caused by the spreading out of the fire as it progressed. It also accounts for the minimal rise of the plume during most of the two-month period. The source was located at a latitude of 47° 57' 56" north, and a longitude of 122° 11' 30" west.

Meteorological data was supplied by the Puget Sound Air Pollution Control Agency (PSAPCA). The data consisted of joint frequency distributions of wind speed, wind direction, and stability class for the two-month period from September 24 to November 23, 1984. Two distributions were developed using the wind data from PSAPCA's monitoring stations at the Medical-Dental Building on Colby Avenue in Everett, and at North 98th Street and Stone Way in North Seattle. Stability classes were developed from concurrent cloud cover and ceiling height observations at Seattle-Tacoma Airport. After preliminary model runs were completed, it became evident that the Everett wind data yielded higher modeled concentrations than the North Seattle data. Furthermore, owing to the close proximity of the Everett station to the fire location, the Everett wind data are judged to be more representative of the conditions which affected the fire than the North Seattle data. Thus, all subsequent modeling analyses utilized the Everett meteorological data set.

Other meteorological data input to the ISC model are documented in Table 1. The values are listed as a function of stability class. The temperatures and mixing heights are based on historical climatological data for the Seattle area. The vertical potential temperature gradients and the vertical wind profile exponents are normal default values.

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* "Atmospheric Emissions from Open Burning," Richard Gerstle and Douglas Kemnitz, Journal of the Air Pollution Control Association, Volume 7, Number 5, May 1967, page 324.

Concentrations were estimated using the rural mode of the long-term version of the ISC model (EPA-450/4-79-030). ISC is a standard gaussian model intended for use in flat or gently rolling terrain. Deviations in plume trajectories resulting from wind flows which are altered by complex terrain are not simulated by ISC. Elevated stable plume impact on high terrain is also not modeled by ISC. However, because of the minimal plume rise during most of the fire, stable plume impact should not be a significant factor in this analysis. ISC does not, as all gaussian models do not, simulate very low wind speed conditions well. Light and variable winds were reported about 4% of the time during the fire. In spite of these limitations, the ISC model is judged to be adequate for this analysis.

Receptors in the modeling analysis were set in a polar grid with the fire at the center of the grid. Sixteen grid radials were spaced at azimuths of 22.5° around a 360° circle. Concentric rings of receptors were located at ranges from the fire in kilometers of 0.5, 1.0, 1.5, 2, 3, 4, 5, 7, 9, 12, 15, 20, 25, 30, 40, and 50. This grid layout yields 256 receptors.

ISC was used to calculate average concentrations of B(a)P at all receptor locations. The results are displayed in Figures 1 and 2. Figure 1 contains the predicted spatial distribution of B(a)P within a few kilometers of the fire location, while the predicted concentrations over the entire receptor grid are shown in Figure 2. These figures show how concentration decreases significantly with increasing distance from the fire. For example, the highest concentration estimate (0.26 micrograms per cubic meter) was one-half kilometer to the northwest of the fire, near the I-5 freeway. Further into Everett near the intersection of Hewitt and Broadway, the average concentration was only about one-fifth of the maximum. And, near Oak Harbor on Whidbey Island, the average concentration estimate dropped by about a factor of 300 from the maximum. The concentration drops even more rapidly in other directions from the fire.

Measured ambient concentration data collected by PSAPCA at their Everett and North Seattle monitoring stations were obtained. The measured values were averaged over the duration of the fire for comparison with the model estimates. The model estimated concentrations were interpolated from the grid receptors to the monitoring locations so that a rough comparison of predicted and observed concentrations could be made. The results of this comparison are listed in Table 2.

There are several factors which suggest that this comparison is crude at best, and may in part explain some of the discrepancies between the predicted and observed concentrations. While the emissions estimates are based on the best information available, they must be considered very approximate. The plume from the Everett tire fire was not sampled, so that emission factors had to be obtained from the literature. ISC assumes that the fire emissions are constant, while in reality the fire emissions were obviously not constant with time. No background concentration was subtracted from the measurements, so that the measured values include contributions from sources other than the tire fire. No measurements of ambient concentrations were available for November. The numbers of 24-hour averaged samples for B(a)P at the Everett and North Seattle monitors are really too small to

consider them a very good representation of an average concentration over the two-month period of the fire. Finally, the limited ability of the ISC model to handle complex terrain and low wind speeds is also a factor in the comparison.

It is not possible to draw any firm conclusions from the comparison. Statistical significance of the differences (or similarities) between the measurements and the model estimates can not be established. From this limited evaluation it appears that the modeled concentration estimates are probably good enough for order-of-magnitude risk estimates.

The output concentration estimates from the ISC model were input to the HEM developed by Systems Applications, Inc. under contract to EPA. A draft user's manual for HEM (October 1985) was obtained from the Pollutant Assessment Branch at the EPA Office of Air Quality Planning and Standards. HEM uses the ISC concentration estimates and the population data from the 1980 census to estimate exposures. Risk estimates were developed with HEM using two different unit risk factors: the B(a)P unit risk factor of 0.0033 per microgram per cubic meter, and the unit risk factor for products of incomplete combustion (PIC) of 0.42 per microgram per cubic meter. The HEM assumes a lifetime (70-year) exposure. Therefore, the risk estimates were adjusted for the shorter two-month exposure resulting from the fire. This amounted to dividing the lifetime values by 420, the number of two-month periods in 70 years.

The results from the HEM are listed in Table 3. The maximum individual risk estimates due to emissions from the fire are for people who live very close to the fire location. These analyses extended to a radial distance of 50 kilometers from the fire. The total number of people within this area is approximately 1.23 million. The minimum risk is the lowest risk value to which the entire population was exposed.

Table 1

Meteorological Data Input to the ISC Model

Stability Class	Temp. (deg K)	Mixing Height (meters)	Potential Temp. Grad. (deg K / m)	Wind Profile Exponent
A	286	950	0.0	0.10
B	285	850	0.0	0.15
C	284	750	0.0	0.20
D	282	750	0.0	0.25
E	280	10000	0.020	0.30
F	279	10000	0.035	0.30

Table 2

Comparison of Estimated and Measured B(a)P Concentrations

Monitoring Station	ISC Estimate (micrograms per cubic meter)	Average Measured Concentration	Number of 24-Hour Samples
Everett	0.0484	0.0142	8
North Seattle	0.000276	0.0032	2

Table 3

Risk Estimates for B(a)P Emissions from the Everett Tire Fire Calculated by the Human Exposure Model

Unit Risk Factor Employed	0.0033 [for B(a)P]	0.42 [for PIC]
Maximum Risk to an Individual as a Result of Exposure	2.1×10^{-6}	2.4×10^{-4}
Number of People at Maximum Risk	4	4
Minimum Risk Level	3.5 x 10-10	4.4 x 10^{-8}

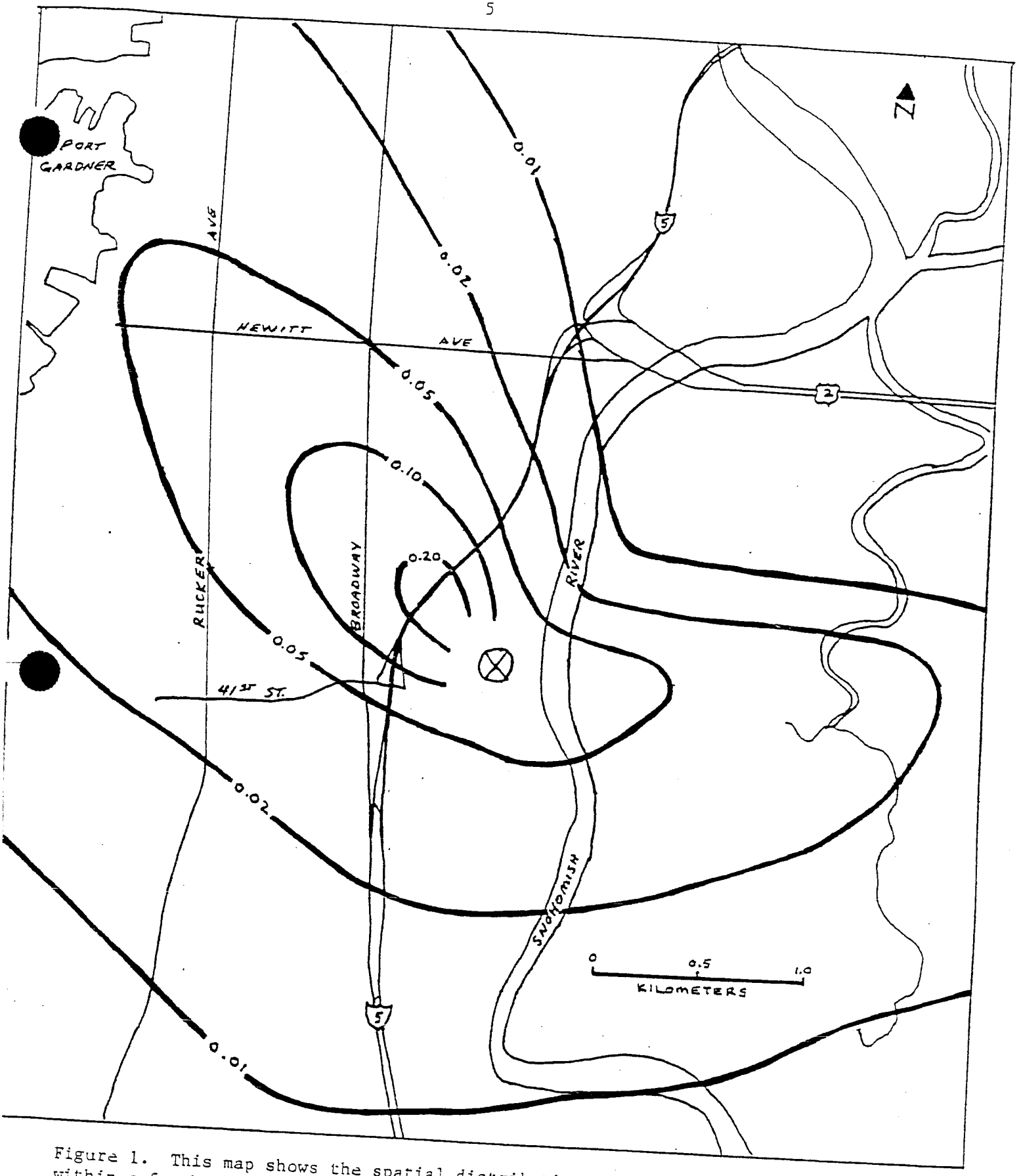

Figure 1. This map shows the spatial distribution of predicted concentrations within a few kilometers of the fire location at ⊗. The concentrations are in units of micrograms of B(a)P per cubic meter of air averaged over the two-month period of the fire.

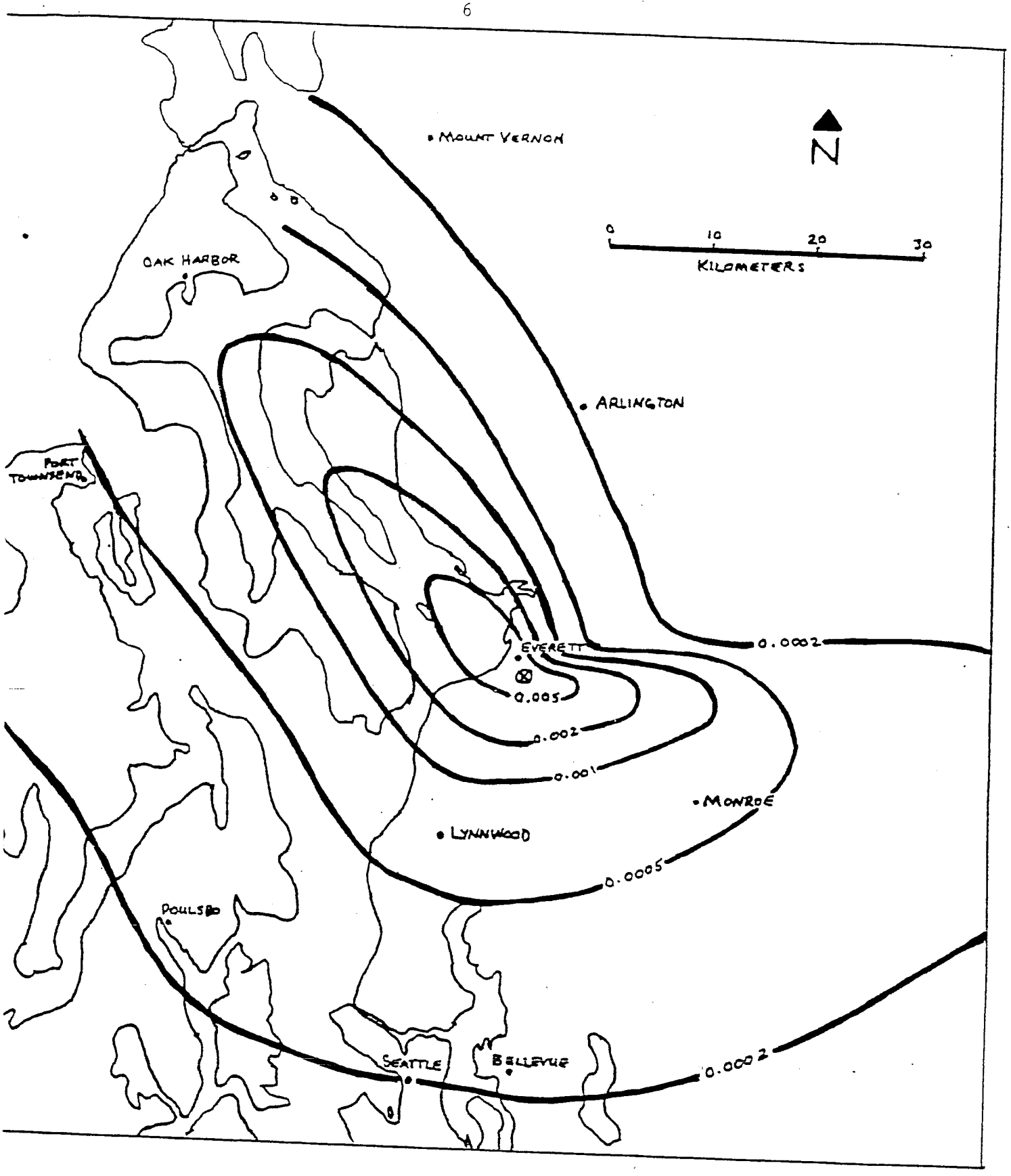

Figure 2. This map shows the spatial distribution of predicted concentrations over the entire modeling grid, within 50 kilometers of the fire location at ⊗. The concentrations are in units of micrograms of B(a)P per cubic meter of air averaged over the two-month period of the fire.

Appendix F

Air Resources Board Tracy Tire Fire Air Monitoring Data.

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Air Resources Board

John D. Dunlap, III, Chairman
2020 L Street • P.O. Box 2815 • Sacramento, California 95814 • www.arb.ca.gov

Pete Wilson
Governor

MEMORANDUM

TO: Michael P. Kenny
Executive Officer

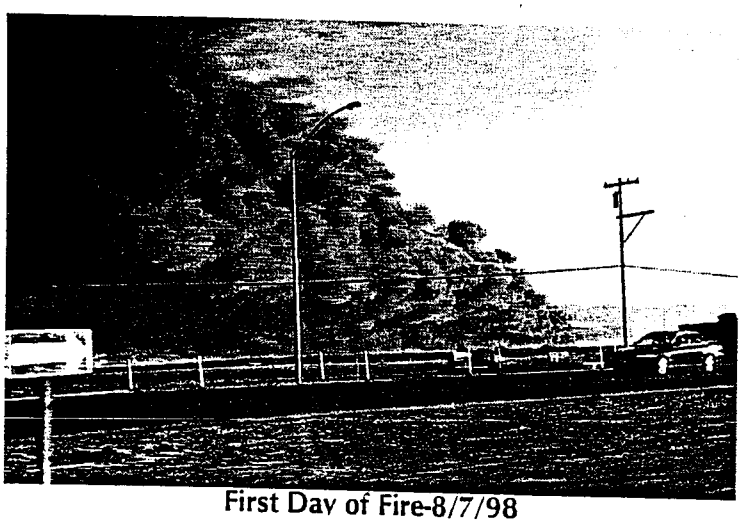
FROM: James J. Morgester, Chief
Compliance Division

DATE: September 3, 1998

SUBJECT: Tracy Tire Fire Emergency Response

Chairman Dunlap (via Tim Gergen) has requested this final memo on the ARB's emergency response to the Tracy tire fire.

At the request of the San Joaquin County and State Office of Emergency Services (OES) Cal/EPA Air Resources Board staff responded to a tire fire located just south of the city of Tracy in San Joaquin County. The Air Resources Board Compliance Division Emergency Response Team was requested to assist in this emergency by conducting onsite ambient air monitoring of pollutants in the smoke plume that could possibly impact nearby neighborhoods.



First Day of Fire-8/7/98

Owner/Operator

The Royster Tire Re-cycling Facility is located at 29245 MacArthur Blvd. on approximately 30 acres (the burning tire pit is about 3 acres) and is now owned and operated by the estate of the late Mr. S. F. Royster. Two and a half million tires

Table 2
ARB Monitoring and Laboratory Division
Total Carbon Sampling Results
Royster Tire Recycling Facility Fire

Date	Location	Carbon, µg/m³
8/8/98	0.25 mi SE of fire	69.3
8/8/98	1.5 mi SE of fire	7.9
8/9/98	0.25 mi SE	12.8
8/9/98	1.5 mi SE	9.4
8/11/98	0.25 mi SE	20
8/11/98	1.5 mi SE	17
8/11/98	0.25 mi NW	15
8/12/98	0.25 mi SE	17
8/12/98	1.5 mi SE	10
8/12/98	0.25 mi NW	11
8/13/98	0.25 mi SE	22
8/13/98	1.5 mi SE	11
8/13/98	0.25 mi NW	14
8/14/98	0.25 mi SE	11
8/14/98	1.5 mi SE	5
8/14/98	0.25 mi NW	11
8/17/98	0.25 mi SE	12
8/17/98	1.5 mi SE	7
8/17/98	0.25 mi NW	15
8/18/98	0.25 mi SE	12
8/18/98	1.5 mi SE	11
8/18/98	0.25 mi NW	7
8/19/98	0.25 mi SE	3
8/19/98	1.5 mi SE	6
8/19/98	0.25 mi NW	15
8/20/98	0.25 mi SE	27
8/20/98	1.5 mi SE	9
8/20/98	0.25 mi NW	15

Table 1 (cont.)
ARB Compliance Division Monitoring Results
Royster Tire Recycling Facility Fire
(Miran 1B Results)

Monitoring Location	Time Monitored	Instrument Reading, ppm	Comments
1985 Tahoe Circle Site #32	8-13-98 1645	CO = 0 THC = 2.8 Toluene = 1.2	Wind 2.5 mph NW
Mt. Diablo Park Site #21	8-13-98 1730	CO = 0 THC = 1.6 Toluene = 0.7	Wind 2.2 mph NW
Teichert Const. Site #8	8-14-98 0750 - 0852	CO = 0.8 THC = 5.1 Toluene = 0.6	Below plume, upwind of fire. Wind NW
MacArthur (by canal) Site #34	8-14-98 1030 - 1130	CO = 1.0 THC = 0.5 Toluene = 0.3	Background
MacArthur Dr. 0.75 miles S of Linne Site #2	8-14-98 1250 - 1350	CO = 0.7 THC = 2.0 Toluene = 0.7	Next to house where smoke is settling. Downwind of fire.
RMC Lonestar Site #35	8-14-98 1430 - 1530	CO = 1.1 THC = 4.2 Toluene = 0.8	~30 ft. west of fire pit.

Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Winston H. Hickox
Agency Secretary

Gray Davis
Governor

February 4, 2003

Mr. Mark Leary
Executive Director
1001 I Street
Sacramento, California 95814

Dear Mr. Mark Leary:

Pursuant to the provisions required in Chapter 838, Section 42889(k) of the Public Resources Code, as amended by Senate Bill 876 (Statutes of 2000), enclosed are two copies of the report entitled "Tire Fire Smoke: Major Constituents and Potential for Public Health Impacts."

The report describes what is known about the constituents of tire smoke and the potential public health impacts of exposure. Should you have any questions or need further assistance, please do not hesitate to contact Melanie Marty, Ph. D., Section Chief of the Air Toxicology and Epidemiology Section at the Office of Environmental Health Hazard Assessment. Dr. Marty may be reached at (510) 622-3150. You may also contact Allan Hirsch, Deputy Director of External and Legislative Affairs at (916) 324-0955.

Sincerely,

Joan E. Denton, Ph.D.

Joan Denton, Ph.D.
Director

Enclosure

cc: See next page

cc: Mr. Mike Gotch
Legislative Secretary
Governor's Office
State Capitol Building
Sacramento, California 95814

Ms. Elizabeth G. Hill
Legislative Analyst
925 L Street, Suite 1000
Sacramento, California 95814

Mr. Steve Peace
Department of Finance
State Capitol, Room 1145
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Mr. Kevin Starr
State Librarian
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Allan Hirsch
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Melanie Marty, Ph.D., Chief
Air Toxicology and Epidemiology Section
1515 Clay Street, 16th Floor
Oakland, California 94612

Mandated Report Coordinator
California Integrated Waste Management Board
1001 I Street
Sacramento, CA 95814

State of California

California Environmental Protection Agency

MEMORANDUM

To: Board Members **Date:** February 27, 2003

From:

Mark Leary, Executive Director
CALIFORNIA INTEGRATED WASTE MANAGEMENT BOARD

Subject: **OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT (OEHHA) REPORT TO LEGISLATURE ON "TIRE FIRE SMOKE: MAJOR CONSTITUENTS AND POTENTIAL FOR PUBLIC HEALTH IMPACTS"**

Attached is a cover letter from Joan Denton, Ph.D., Director of OEHHA, transmitting a report to the Legislature entitled "Tire Fire Smoke: Major Constituents and Potential for Public Health Impacts." The report concludes that the "most significant public health risk from exposure to tire fire smoke appears to be to people with asthma, heart or lung disease who are particularly affected by exposure to irritating components of smoke including PM10" (i.e. particulates less than 10 microns in diameter). The report also notes that "it is unlikely that exposure to tire fire smoke will result in a significant increased cancer risk to the public." The report lends credence to established procedures and practices of the Board of controlling tire disposal so as to avoid tire fires and rapidly extinguishing any fires that do occur as quickly as possible to minimize smoke generation. The report notes the desirability of additional toxicological research to fill in "data gaps" and allow for a comprehensive analysis of the health effects of tire smoke.

A copy of the Executive Summary of the report is attached for your use and consideration. It is also our plan to invite Dr. Denton and her staff to make a presentation to the Board in the near future on the report findings.

If you have any questions or comments, please call me at 341-6544 or Jim Lee at 341-6455.

Attachment

Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
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Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Winston H. Hickox
Agency Secretary

Gray Davis
Governor

February 4, 2003

Mr. Mark Leary
Executive Director
1001 I Street
Sacramento, California 95814

Dear Mr. Mark Leary:

Pursuant to the provisions required in Chapter 838, Section 42889(k) of the Public Resources Code, as amended by Senate Bill 876 (Statutes of 2000), enclosed are two copies of the report entitled "Tire Fire Smoke: Major Constituents and Potential for Public Health Impacts."

The report describes what is known about the constituents of tire smoke and the potential public health impacts of exposure. Should you have any questions or need further assistance, please do not hesitate to contact Melanie Marty, Ph. D., Section Chief of the Air Toxicology and Epidemiology Section at the Office of Environmental Health Hazard Assessment. Dr. Marty may be reached at (510) 622-3150. You may also contact Allan Hirsch, Deputy Director of External and Legislative Affairs at (916) 324-0955.

Sincerely,

Joan E. Denton, Ph.D.

Joan Denton, Ph.D.
Director

Enclosure

cc: See next page

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1.0 Executive Summary

A number of tire fires have occurred in the United States and elsewhere over the years. There have been major tire fires at Panoche, Tracy and Westley within the last few years in California. The latest major tire fire occurred in September 1999 in Westley, California. Approximately five million tires caught fire and burned for 36 days. The California State Legislature subsequently requested a report from the Office of Environmental Health Hazard Assessment (OEHHA) that identified the major chemical constituents of smoke from burning tires, the toxicity of those chemicals, and the potential effects on human health from exposure to smoke from tire fires. This report will not discuss site remediation or potential ground water contamination issues from tire fires. The Integrated Waste Management Board, Department of Toxic Substances Control and the State Water Resources Board have expertise in these areas.

Currently, there are limited data available to evaluate the constituents of tire fire smoke and the potential health effects of exposure. The United States Environmental Protection Agency has sponsored studies to identify the major chemical constituents of tire smoke. These studies involve igniting chunks of tires in a laboratory, collecting the smoke and then identifying the chemicals that can be measured. Combustion generates thousands of different chemical constituents and many of these are not readily identifiable using current analytical techniques. In addition, toxicology studies must be available in order to estimate the potential health effects of exposure to a chemical that is identified from the source testing. However, toxicological studies are not available for the majority of chemicals identified in source testing. Only eight of the 78 chemicals identified in the source tests have health values for acute or chronic endpoints.

We have taken two approaches to provide information on potential health impacts of exposure to tire fire smoke. The first is to identify chemicals known to occur in tire fire smoke and describe what is known about the toxicity of those chemicals. Although, identification of individual constituents provides useful information this approach does have limitations. Not all identified constituents have been tested for toxicological properties. Furthermore, without information on concentrations to which people are exposed, it is not possible to state with certainty what health effects might result. The second approach is to consider the information available on exposure to the entire mixture (smoke). This second approach has important limitations also. Information on exposure to tire fire smoke is limited so exposure to other types of smoke must be used instead. The use of both approaches gives the best available picture of tire fire smoke toxicity.

All smoke contains toxic chemicals, different types of smoke can vary in the proportions of individual toxic constituents and toxicant classes. However, there is enough similarity between smoke types to make comparisons useful. Each tire contains about 2 gallons of oil that is similar to heating oil. Therefore tire fire smoke is probably most like an uncontrolled oil fire. Tire fire smoke is particularly irritating probably in part because sulfur dioxide is generated from the sulfur in tires.

There are a number of irritating chemicals that have been identified or are also most certainly present in tire fire smoke such as sulfur dioxide, xylenes, aldehydes, toluene, and styrene. Respirable small particles composed of a carbon core with numerous chemicals attached are also a major component of smoke. Some smoke constituents (e.g. irritants and small particles) are known to trigger asthma attacks in people with preexisting asthma. Stanislaus County data on clinic visits and phone calls seems to indicate that asthmatics did experience exacerbation of symptoms. People who have been exposed to tire fire smoke, for example at the Westley tire fire, have reported symptoms that would result from exposure to irritants. Forest fire smoke and second-hand tobacco smoke exposure have also been associated in a number of studies with exacerbation of asthma.

As noted above, tire fire smoke contains many tiny particles small enough to be inhaled into the deep lung. Those particles small enough to be inhaled into the lung are referred to as PM_{10} because they are 10 μm (10 millionths of a meter) or less in diameter. PM_{10} is known to cause increased emergency admissions to hospitals for patients with lung and heart disease. Each 10 $\mu g/m^3$ increase in 24 hour average PM_{10} concentration has been associated with a 1% increase in daily mortality in epidemiological studies conducted in a number of cities, primarily in elderly people who have pre-existing heart and/or lung disease. In London in the early 1950's, there were days when the PM_{10} concentrations were extreme (several thousand $\mu g/m^3$) and thousands of people died.

A concern of many people is the possibility of contracting cancer because of exposure to tire fire smoke. Tire fire smoke contains a number of known cancer-causing chemicals (carcinogens). The major carcinogens of concern are the polycyclic aromatic hydrocarbons (PAHs), a large group of fused six carbon ring structures that are formed with virtually all types of combustion sources to a greater or lesser extent. These combustion sources include, for example, wood burning, automobile and diesel engines and tobacco smoke. Tire fire smoke contains more PAHs than other commonly encountered types of smoke such as wood smoke. In addition to the PAHs, the carcinogens benzene and 1,3-butadiene are present in tire fire smoke. These two chemicals are common in vehicular exhaust. To put the risks in perspective, the chances of developing some kind of cancer over a lifetime are about 1 in 5. The assumption with carcinogens is that there is no threshold and that each exposure can cause some increased risk. Many regulatory agencies consider cancer risks below 1 in a million, or 10 in a million, and infrequently 100 in a million to be below a level of public health concern. The USEPA conducted a cancer risk assessment of the Everett, Washington tire fire. They concluded that the cancer risks from PAH exposure were not large. The risk from exposure to other carcinogens in tire fire smoke such as benzene and 1,3-butadiene are likely to be small relative to everyday exposure to these chemicals from other combustion sources.

Monitoring data indicate that tire fires emit trace quantities of polychlorinated dibenzo-p-dioxins and dibenzofurans, commonly known as dioxins. Although these compounds are in general initially emitted into the air, the major source of dioxin exposure to the public turns out to be through consumption of animal fat and not through

breathing contaminated air. This is because dioxins have a long environmental half life and are deposited onto vegetation. Animals consume contaminated vegetation and accumulate dioxins in their fat. When contaminated animal fat is consumed dioxins are in turn stored in human fat and slowly accumulate in most people over a lifetime. They are very slowly eliminated from the body.

The levels of dioxins found in air at some distance downwind from a tire fire are several times greater than the normal airborne levels. However, the amount of dioxins inhaled during the days to weeks that many tire fires burn is not likely to be a significant contribution to the total exposure of an individual relative to normal ongoing exposures. Dioxins are carcinogenic and have noncancer health effects as well. Any additional exposure from breathing tire smoke is undesirable but not likely to be a source of significant individual exposure relative to other sources.

PAHs and dioxins are at least partially associated with particles in the air and so can be deposited onto vegetation, including food crops. Monitoring at tire fires indicates that some surface contamination can occur especially in close proximity to tire fires. The amounts deposited a kilometer or more away from a tire fire would probably not represent a significant exposure for people consuming the crops. Metals are present in tires as a significant fraction of the total weight and could potentially be deposited onto crops since they are also in the form of particles in the atmosphere. However, the source test data from USEPA does not indicate that tire fires release significant quantities of metals into the air. The available ambient air monitoring data also indicate that public exposure to airborne metals, as the result of a tire fire is not likely to be significant.

It is true that public exposure to tire fire smoke will cause some increased risk of cancer. There is reason for concern because smoke from burning tires is about 16 times more mutagenic than residential wood smoke and about 8 times more mutagenic than open burning of plastic on a weight basis. However, it is useful to compare the exposures to these chemicals commonly experienced from other sources of combustion with the levels that have been measured during tire fires. The levels of carcinogens detected at monitoring stations, for example at the Westley tire fire, did not exceed levels commonly found in Modesto prior to the tire fire. The carcinogens measured included PAHs, benzene, and 1,3-butadiene. The favorable meteorology and prompt extinguishing of the oil part of the tire after one week played a role in reducing emissions and thus influenced the monitoring results at Westley. The increased risk of cancer experienced by fire fighters also provides useful insight. Firefighters are exposed to smoke during their entire working lives and according to some studies do experience an increased risk of cancer. The exposure that firefighters receive is much greater than public exposure over a period of days to weeks. It is unlikely that exposure to tire fire smoke will result in a significant increased cancer risk to the public.

The most significant public health risk from exposure to tire fire smoke appears to be to people with asthma, heart or lung disease who are particularly affected by exposure to irritating components of smoke including PM_{10}. The elderly with these diseases are particularly at risk. Children may be somewhat more vulnerable than healthy adults

because they breath more on a body weight basis, are more active and spend more time outdoors, all of which increases their exposure to airborne contaminants including particulate matter. Tire fires produce large quantities of smoke and depending on meteorological conditions, concentrations of irritating smoke constituents including particulate matter concentrations could become extreme. Extreme levels of particulate matter were not reached in the Westley tire fire, according to monitoring data but levels during the fire were above the state health standard of 50 $\mu g/m^3$ (24 hour average) for a number of days. Twenty-four hour average levels of PM_{10} detected during the tire fire ranged from 10.5 to 180.5 $\mu g/m^3$. In addition, on several days the Federal standard of 150 $\mu g/m^3$ (24 hour average) was exceeded. The Federal standard is not considered by California to be health protective (OEHHA and CARB, 2000a). The average PM_{10} concentration for the permanent Modesto monitoring site at I Street for 1997 (prior to the tire fire) was 32.3 $\mu g/m^3$ and the maximum value was 119 $\mu g/m^3$ (California Air Resources Board, 2001). It is important to note that monitors at a tire fire may not necessarily be located where short-term or daily average maximum concentrations would have occured.

In summary, tire fire smoke contains irritating chemicals, particulate matter and carcinogens. The acute health effects of exposure result from the irritating compounds and include eye, nose and throat irritation, exacerbation of asthma and respiratory conditions and potential exacerbation of pre-existing heart disease. The effects seen would obviously depend on the concentrations to which people are exposed. Irritation and exacerbation of asthma apparently occurred during the Westley tire fire. The available scientific information on tire fire smoke constituents and studies of exposure to other types of smoke point to the need to control tire disposal so as to avoid tire fires. In addition, the data point to the need to rapidly extinguish any tire fires that do occur. Extinguishing the oil part of the Westley tire fire at the end of the first week reduced the volume of smoke by a large percentage and the entire fire was extinguished after 36 days. If meteorological conditions had not been favorable and the fire had not been rapidly extinguished, more severe and more wide spread respiratory and cardiovascular health effects might have occurred.

The lack of toxicological studies on combustion product chemicals is a serious data gap when evaluating the health impacts of exposure to tire fire smoke. In particular there is a need for studies to better characterize the irritating properties of these chemicals. These chemicals are commonly found in urban air due to controlled and uncontrolled combustion sources such as automobiles, trucks and wood burning. Such research would also aid in understanding the effects of urban air pollution. Research studies are needed on the effects of short-term high exposures to particulates so that better public health recommendations can be developed. Research is also needed on ways to establish clean air shelters so that sensitive subpopulations can be protected when smoke concentrations become excessive. These research studies would be useful for protecting public health during tire fires. The studies would also be useful for protecting the public from forest fire smoke exposure, which is likely to be more common. In addition, research into understanding risks from additional PAHs might help clarify the relative importance of exposure to this class of compounds.