THE CONTROL OF AIR TOXICS:

TOXICOLOGY MOTIVATION AND HOUSTON IMPLICATIONS

FINAL REPORT

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1.0: Introduction and Background

1.1 Overview

Houston has long had a reputation of poor air quality. As a giant in the petrochemical industry, a major port, and a large metropolitan center, Houston has numerous sources of air pollution.

Air pollution can be defined as the presence of an airborne contaminant at sufficient concentration to have a negative impact on human health, welfare, or the environment. While negative impacts on welfare (such as visibility reduction) or the environment (such as acid rain) are important, most air pollution regulations are motivated by the desire to protect human health.

In the United States (US), the Clean Air Act and its amendments define the federal response to the control of air pollution. Initial regulations, called the National Ambient Air Quality Standards (NAAQS), focused on common air pollutants including ozone, carbon monoxide, lead, sulfur dioxide, nitrogen dioxide, and atmospheric particles, which have widespread sources and are found in relatively large concentrations in ambient air.

However, there are many other compounds present in air that can be hazardous in even at low concentrations. In 1990, the Clean Air Act Amendments designated 189 compounds to be regulated as hazardous air pollutants (HAPs).[1] These so-called air toxics are regulated by emission standards that apply the maximum achievable control technology (MACT) to different emission sources. Although these standards are designed to give the maximum protection achievable to reduce emissions to the environment, there is no guarantee that the ambient concentration of air toxics will not impact human health.

In a source-rich region like Houston, there is concern that MACT emission standards are not sufficiently protective of human health and that an unacceptable level of residual health risk exists. Data gathered over the last few decades suggest that the ambient levels of HAPs in Houston have decreased as a result of the implementation of various control strategies. Increased monitoring has also uncovered previously unrecognized "hot spots" where localized concentrations are much higher than area average concentrations. Monitoring has found that concentrations of many pollutants are still substantially higher than the levels measured in other cities across the US (Tables 1 and 2).

Table 1: A comparison of the 2004 annual average concentration of three hazardous air pollutants at the single highest monitoring location in four US cities [1].

	Benzene	1,3-Butadiene	Formaldehyde
Chicago	0.5 ppb	0.08 ppb	2.0 ppb
Los Angeles	0.9 ppb	0.2 ppb	7.2 ppb
St. Louis	0.5 ppb	0.07 ppb	4.2 ppb
Houston	1.7 ppb	4.0 ppb	7.9 ppb

[1] This list of federally recognized HAPs was later amended to include only 188 compounds.

Table 2: A comparison of the maximum 24-hour average concentration during 2004 of three hazardous air pollutants as observed in four US cities [1].

	Benzene	1,3-Butadiene	Formaldehyde
Chicago	2.7 ppb	0.5 ppb	8.1 ppb
Los Angeles	2.9 ppb	0.5 ppb	15.5 ppb
St. Louis	1.1 ppb	0.3 ppb	35.6 ppb
Houston	73.5 ppb	37.4 ppb	20.1 ppb

From these observations, it is noted that the concentrations observed in the Houston area are generally substantially higher than those measured in other cities across the US. The degree to which these concentrations affect human health is of particular concern to the population of Houston.

In order to better understand the risk that exists, information about how these air pollutants affect human health and at what pollutant concentration these impacts occur in different individuals is necessary. To determine what concentrations pose a significant health risk, detailed toxicology data are needed for individual compounds because each one has a unique dose-response relationship in the human population. This is because compounds are processed by a variety of metabolic pathways, create various metabolites which may or may not be harmful in and of themselves, and an individual's sensitivity to them also varies. The level of effort put into understanding these relationships is evident by the thousands of different studies investigating the long- and short-term impacts of different air contaminants and concentrations.

This study evaluated the existing toxicology and risk assessments in order to provide relevant data for four HAPs of particular concern to the Houston region: benzene, 1,3-butadiene, formaldehyde, and diesel particulate matter (PM). These four pollutants were identified by the Mayor's Task Force on the Health Effects of Air Pollution as being definite risk pollutants, which means that there is "compelling and convincing evidence of significant risk to the general population or vulnerable subgroups at current ambient concentrations" [2].

Benzene and 1,3-butadiene are key components of the petrochemical industry that is centered in Houston and are emitted from motor vehicles. Formaldehyde is emitted from industrial sources and motor vehicles and is also formed in atmospheric chemistry from the photo-oxidation of many volatile organic compounds. Diesel particulate matter (diesel PM) has been identified as a possible carcinogen by the US Environmental Protection Agency (US EPA) and is already partially regulated as a criteria pollutant with other particulate matter.

The Clean Air Act and its amendments have charged the US EPA with managing residual health risks like those that exist in Houston. To date, such regulations for HAPs are non-existent and, in their absence, some states have enacted regulations to try to manage the risk. This work will also review the standards, guidelines, or permissible levels that exist in other states and international jurisdictions.

1.2 Regulation of Hazardous Air Pollution in the Clean Air Act

1.2.1 History of the Regulation of HAPs – The Change to Technology Based Standards

The main focus of the Clean Air Act is the regulation of the so-called criteria air pollutants (CAPs). These pollutants, such as NO_2, SO_2, and CO, result primarily from combustion and, at least theoretically, are not dangerous under a certain threshold, the National Ambient Air Quality Standards. Criteria air pollutants are generally found in relatively large quantities in our lower atmosphere, particularly in populated urban areas. Their abundance threatens human health and the environment across broad regions of the country but also makes them easier to measure and subsequently regulate. The criteria pollutants are regulated under Title I of the Clean Air Act which sets a national health standard for each pollutant. The burden is on the state to set up monitoring networks, monitor the air continuously for each pollutant, and report the data to the United States Environmental Protection Agency (US EPA). States must also submit emission summaries and control plans for each pollutant which demonstrate to the US EPA that state controls and regulations will both achieve and maintain the standards.

However, there are other dangerous air contaminants that may be produced on a smaller scale. These pollutants, many of them synthetic chemicals, can be hazardous or even toxic in very small quantities. There is a large amount of uncertainty with regard to air toxics in terms of what kind of risk and the degree of risk they pose. And, because even low levels of exposure to air toxic substances frequently poses a risk, safe thresholds for human exposure are quite difficult to establish. These unique characteristics of air toxics make regulation a difficult and controversial process. Toxic air pollutants are regulated under Title III of the Clean Air Act. Toxic air pollutant regulations focus on the air emissions from targeted industries and the control technology used to limit those emissions. In general, the burden is on industries to report emissions of toxic air pollutants and to demonstrate to the state agency that the control technology in place meets MACT standards. The details of this regulation are discussed in this section.

1.2.1.1 The Pre-1990 Risk-only Approach

The 1970 amendments to the Clean Air Act first established a strict regime for reducing emissions of hazardous air pollutants (HAPs). The US EPA was required to list as a HAP an air pollutant "which might reasonably have been anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible illness" [3] and once listed, "to establish health based emission standards which provide an ample margin of safety to protect the public health" [4]. Substances listed as CAPs were not considered under this category.

The question of the US EPA's ability to consider cost in standard setting arose early. In *Natural Resources Defense Council v. EPA*, 824 F2d 1146 (DC Cir. 1987), the Natural Resources Defense Council (NRDC) argued that once the US EPA had concluded that the

emission of vinyl chloride created an adverse health effect, even if it was unable to determine a safe threshold, Section 112 of the Clean Air Act required the US EPA to establish a threshold of zero which would effectively shut down the industry. The US EPA disagreed and adopted a standard based solely on the level attainable by the best available control technology (BACT). The Court held that neither the NRDC nor the US EPA was correct and remanded the case to the US EPA with instructions that the US EPA set a standard that takes into account the effect the chosen emission standard has on health in making the initial determination of what is "safe".

Effectively, the Court read Section 112 as requiring the US EPA to do a two-step process. It must first determine what is "safe" solely on the basis of risk to health at a particular emission level. However, the Court stated that "safe" did not mean risk free but rather that the Administrator is to determine what is an acceptable risk to health. If the Administrator cannot find an acceptable risk at any level, then he or she was to set the initial standard at zero emissions. Once this initial level was set, the Administrator was then required to set the actual standard at a level that ensures an ample margin of safety to protect the public. Only at this point was the Administrator free to take into account other factors, including technology and economics, in lowering the initial standard to the actual standard or the lowest feasible level. Feasibility thus could include economics, technology, etc., but was supposed to ensure the acceptable risk level found initially.

This standard, which arguably followed Congress' intent, presented unusual problems for the US EPA. Unlike the CAPs, many of the HAPs are harmful in extremely small doses, effectively banning certain chemicals that play an important part in some economies. The US EPA became involved in many legal, scientific, and policy debates over which pollutants to regulate and how stringently to regulate them. Debates focused on risk assessment methods and assumptions, the amount of health risk data needed to justify regulation, analyses of the costs to industry and benefits to human health and the environment, and decisions about "how safe is safe" [5].

As a result, and despite litigation and pressure from Congress, between 1970 and 1990 the US EPA identified only eight of the hundreds of HAPs already listed by state agencies and many of these were spurred by litigation against the agency. The first HAP listed was asbestos, which was listed in 1971 with regulations established in 1973. Later the US EPA added benzene, beryllium, coke oven emissions, inorganic arsenic, mercury, radionuclides, and vinyl chloride to the list of regulated HAPs.

In 1989, in response to the NRDC case, the US EPA promulgated new criteria for establishing national emission standards for hazardous pollutants that established a risk-based approach. This approach allowed the US EPA to set the standard at a level that "(1) protects the greatest number of persons possible to a lifetime risk level no higher than 1 in 1 million and (2) limiting to no higher than 1 in 10 thousand the estimated risk that a person living near a plant would have if they were exposed for 70 years." In undertaking this analysis, the US EPA stated that it would first consider the extent of the estimated risk to an individual who is exposed for a lifetime; if it is less than 1 in 10 thousand, that risk would be acceptable. This is the maximum individual risk (MIR), which establishes the baseline. To ensure an ample margin of safety, the US EPA would then determine whether the risk is above or below that baseline. In this second step, the US EPA would strive to provide protection to the greatest number of persons to an individual lifetime risk level no higher than 1 in 1 million [6].

1.2.1.2 1990 Clean Air Act Amendments: Technology First, then Risk Approach

In spite of passing new regulations defining how it would determine the appropriate threshold for a standard, the US EPA continued to delay setting standards. As a result of the US EPA's failure to act, in 1990 Congress imposed a technology-based and performance-based approach to significantly reduce emissions of air toxics from major sources of air pollution followed by a risk-based approach to address any remaining, or residual, risks.

Under the technology-based approach, the US EPA was to develop standards for controlling the routine emissions of air toxics from each major type of facility within an industry group (or source category). These standards, known as maximum achievable control technology (MACT) standards, are based on emissions levels that are already being achieved by the better-controlled and lower-emitting sources in an industry. It was believed that this approach provided a level economic playing field by ensuring that facilities that employ cleaner processes and good emission controls are not disadvantaged relative to competitors with poorer controls. In setting MACT standards, US EPA would not generally prescribe a specific control technology. Instead, whenever feasible, the agency set a performance level based on technology or other practices already used by the industry, allowing the facilities the freedom to achieve these performance levels in whatever way is most cost-effective for them.

Congress imposed strict requirements that limited the US EPA's discretion and imposed short timelines for compliance with the technology-based approach. Congress set out a detailed plan that the US EPA was required to implement in order to reduce emissions of HAPs. As a first step, rather than asking the US EPA to develop a list, Congress itself listed 189 substances as HAPs. Congress compiled the list from information furnished by companies in compliance with the Emergency Planning and Community Right to Know Act [7].

The US EPA was then required to review the list, either on its own initiative or in response to a petition,[2] on a continuous basis and was mandated to add a pollutant to the list if it presents, or may present, a threat of adverse human health affect or adverse environmental effect [8]. This effectively lowered the threshold for inclusion of a pollutant on the list[3].

The US EPA was then given 12 months, until November 15, 1991, to publish a list of the sources of the listed HAPs. The sources were required to be classified as major, i.e., a stationary source that emits 10 tons per year or more of any HAP or 25 tons per year of any combination of HAPS; or area, which includes all other stationary sources that emit HAPs.[4]

Once sources were listed, Congress established a two-phase process. In Phase I, the US EPA was required to establish technological standards [9] for each category of major sources and area sources that had been listed in accordance with the established schedules [10]. In Phase

[2] Third parties were given the right to petition the US EPA to have a pollutant added or removed from the list. Within 18 months of receipt of the petition, the US EPA Administrator is required to either accept or deny the petition.

[3] The US EPA was no longer required to find that the pollutant caused a "serious" illness in humans.

[4] In an attempt to remove impediments to speedy implementation, Congress chose to set standards for a source rather than by pollutant.

II, the US EPA was to apply a risk-based approach to assess how these technology-based emission limits reduced health and environmental risks. Based on this assessment, the US EPA might be required to implement additional standards to address any significant remaining, or residual, health or environmental risks.

To ensure that there would be no delays in implementing controls, Congress stipulated that if the US EPA failed to set a MACT standard for a major source within the specified time, each source in the category would be required to submit a Title V permit application.[5] Title V permit was required to contain emission limits that were to be determined on a case-by-case basis to be equivalent to the limit that would apply to such source if an emission standard had been promulgated in a timely manner [11].

Congress established specific deadlines by which the US EPA was to promulgate the MACT standards [12]. By 1992, the US EPA was to issue MACT standards for the 40 most harmful HAPs, followed by an additional 25% of the listed HAPs by 1994, an additional 25% by 1997, and the rest by 2000. Although the regulations set benchmarks with regard to individual HAPs, the MACT standards actually addressed them by industry (source) since the maximum achievable controls depend on the process as well as the compound. By 1996, the US EPA had issued 17 MACT standards covering 29 major sources [13].

Congress also provided an incentive for companies to strive for early compliance. If a source had met 90% of the emission standard before it was required to do so, the source was given an additional six years to attain the final 10% compliance.

Although all major sources, new and existing,[6] were required were required to implement MACT, in determining which devices could be required, the US EPA Administrator could take into consideration the cost, and any non-air quality health, environmental, or energy impacts or requirements [12].

However, Congress effectively set the MACT as a floor or minimum control by requiring that any MACT deemed achievable for a new major source could not be less stringent than the emission control that is achieved in practice by the best controlled similar source [14]. In contrast, the MACT standard for existing major sources was to be "less stringent than standards for new sources but not less stringent then the average emission limitation achieved by the best performing 12 percent of the existing sources or the average emission limitation achieved for the best 5 sources in a category with fewer than 30 sources." [15]

With respect to area sources, i.e. all other sources that emit one of the listed HAPs, the US EPA Administrator was permitted to enact standards that provide for the use of generally available control technologies or management practices to reduce emissions [16, 17].

Between 1990 and 1996, a number of companies claimed that additions or changes to their facilities did not meet the test for "modification" under the statute and avoided compliance with the MACT standards. Although the US EPA did not prosecute these companies in 1996 the US EPA attempted to clarify the statute by promulgating a rule that allowed facilities to make reasonable modifications without triggering MACT requirements.

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[5] Of interest is the fact that Congress felt compelled to state that although the Administrator had discretion in how he developed the emission standards, "there shall be no delay in the compliance date for any standard applicable to any source under subsection (i) of this section" as a result of the discretionary authority conveyed.

[6] Applying the Clean Air Act to existing sources was a new feature of the 1990 amendments.

1.2.1.3 Health Based Standards

By focusing the US EPA's attention on technology standards, Congress intended that the US EPA would be able to quickly enunciate the applicable pollution control mechanisms, thereby effecting a noticeable reduction in emissions of HAPs. However, Congress did not eliminate the desire for ensuring that health also be protected if the technology controls did not adequately do so. The 1990 Clean Air Act also directed the US EPA to determine whether the emission control standards were successful in protecting health and required the US EPA to report to Congress on any residual risk which continued after application of MACT. The report would enable Congress to enact legislation before the Phase II requirements were scheduled to begin eight years after implementation of MACT standards. Congress has not yet enacted legislation to further manage the reduction of HAPs emissions although the US EPA and third parties have accumulated evidence that HAPs continue to pose a substantial health risk. The federal law does not explicitly pre-empt individual states from enacting their own standards [3, 4, 10-12, 14, 15, 17].

In Phase II, the US EPA is to assess whether the MACT standards for a category of sources emitting a known, probable, or possible carcinogen reduced lifetime excess cancer risks to the most exposed population to less than one in one million (1×10^{-6}). If not, the US EPA is required to prepare standards that would address the residual risks created by emission of the particular HAP. This second phase is referred to as the health-based standards.

Because Congress has not enacted legislation to address residual risks as required after the US EPA's report on these risks, the US EPA is required to do so within 8 years after the establishment of MACT for major HAP sources. In most cases, the US EPA has fallen behind the mandated timeline for developing the MACT standards, control of area sources, and the control of residual health based risks in the absence of Congressional action.

1.2.2 Regulation of HAPs Impacting Houston

Of particular interest to the Houston area, refineries are subject to a number of MACT standards that have been developed since the 1990 Clean Air Act amendments. These include standards called Refinery MACT1, Refinery MACT2, Organic Liquids Distribution MACT, Boiler and Process Heater MACT, and Turbines and Engine MACT [18]. Of these, the Refinery MACT1 was promulgated in August 1995, meaning that residual risk standards were required by law in August of 2003 [3, 4, 10-12, 14, 15, 17]. To date, no residual risk regulations have been established.

The US EPA's initial assessment of the residual health risk following implementation of the Refinery MACT1 rules concluded that there were risks above 1×10^{-6} associated with most refineries and that the primary risk driver was benzene [3, 4, 10-12, 14, 15, 17]. The petroleum industry believes this test to be a crude one that overstates the risk [3, 4, 10-12, 14, 15, 17]. Currently, a US EPA/API (American Petroleum Institute)/NPRA (National Petroleum Refiners Association) work group has been formed to do a more accurate risk analysis [3, 4, 10-12, 14, 15, 17]. This work group is anticipated to suggest controls in addition to MACT, as well as additional controls for area sources that will be put out for

comment in the Federal Register. Note, however, that the US EPA is not bound by statute to utilize 1 x 10^{-6} as its threshold for determining when additional controls are necessary. Nevertheless, this is currently its position for assessing risks from air toxics [3, 4, 10-12, 14, 15, 17].

The legal framework for control of residual health risks from air toxics is procedurally complex and requires both the establishment of direct emissions controls as well as assessment and implementation of residual risk controls. Due to additional procedural requirements on all new federal rules, as well as pressure from industry, the process is behind schedule. Several lawsuits have already been initiated and the US EPA is trying to comply with these requirements.

This means that at some point the US EPA should address concerns over residual risk in the southeastern Houston area. Although litigation might accelerate this process, it is also possible, since the US EPA has already begun an assessment of the primary industries associated with risk in Houston, that litigation could also slow the process down. It is unclear whether more direct participation in the administrative arena or legal action will lead to better or quicker residual risk control.

2.0: Toxicology

2.1 Toxicological Methods to Support Risk Assessment and Regulation

2.1.1 Goals of Toxicological Research

Information needed to support risk assessments and regulatory decisions for toxic agents in the environment is obtained by pursuing several research goals. The first goal of research is to establish whether a chemical agent being investigated induces toxic effects in biological systems and, if so, to determine the types of effects that are manifested. Initial discoveries of toxic effects may occur through anecdotal clinical observations in human subjects or through systematic experimental studies in a variety of different biological systems. Such screening studies may be performed because the chemical of interest is related structurally to other known toxicants, because of concerns based on widespread release into the environment, or because of high levels of human exposure.

Once evidence of a potential toxic effect has been established, the second goal of research is to determine the relationship between exposure level and toxicity. Quantitative risk assessments in toxicology are based primarily on the dose-response relationship. These relationships are typically determined using experimental studies in animal models, typically rodents, and in human epidemiological studies when circumstances allow the needed data to be collected. Both the slope of the derived dose-response curve and its shape may be important in conducting risk assessments. The shape of the curve, combined with information about the known health effects and mechanisms of action of the chemical, is used to decide whether to assume that a threshold concentration (i.e., a concentration below which there is no toxic effect) exists or to assume a no-threshold model (i.e., there is no threshold below which there is no toxic effect).

The third goal of research is to understand the mechanism by which the toxic agent induces injury to a biological system. Mechanistic research investigates the chain of events by which a chemical exposure results in the manifestation of toxic effects in a biological system. The processes by which a chemical is absorbed, distributed, metabolized, and excreted must be understood in order to appreciate how a chemical exposure is related to its toxicity. In addition, the response of the organism to the toxicant is important in understanding the injury manifested after exposure. Mechanistic research in toxicology seeks to explain why an exposure to a chemical produces a toxic effect. Mechanistic information can assist in predicting or understanding the shape and slope of the dose-response curve. Such information can be very useful in the comparison of effects between humans and laboratory animals and in characterizing the relevance of effects seen in animal experiments to human risk. Thus, an understanding of the mechanism of action of a chemical can help to predict the outcome of an exposure to a toxic substance under specific conditions and can help to predict other factors that might modify the toxicity of the chemical. These factors might include co-exposure to other agents, the genetic characteristics of the exposed individual, or the physiological state of the individual when exposed.

The fourth goal of toxicological research, which is related to understanding mechanisms of toxicity, is to characterize special situations that may contribute to the toxic effects of exposure. One example is the role of co-exposure to other chemicals with the primary toxic agent. Other chemicals can, for example, produce additive or synergistic effects with a primary agent that would influence the slope and shape of the dose-response curve. The metabolic status of the individual may also modify the response to toxic chemical exposure. Insufficiency of specific amino acids or vitamins in the diet, for example, may impair the ability of the organism to respond adaptively to a toxic chemical. High rates of respiration that are associated with strenuous activity may increase the volume of air inhaled and thus increase the dose of an inhaled toxicant. The modifying effects of variations in genetic background have been a subject of intense research in recent years. Predispositions to illness or to toxic responses that are associated with exposure to specific toxins in individuals with particular variant alleles of polymorphic genes have been described.

Overall, risk assessment and the management of toxic chemicals in the environment are driven by information generated through epidemiological studies and experimental toxicological research.

2.1.2 Different Methods of Research in Human Populations

A well conduced epidemiological study based on adequate data is the gold standard for associating an environmental exposure with an adverse health effect. Such studies, when they demonstrate an association between exposure to a chemical and a significant health effect, are more likely to result in higher hazard classifications for the chemical and more stringent regulation. Epidemiological studies directly investigate human experience. The exposure levels are generally representative of human experience, although they may have been higher in the past than at present. Epidemiological studies that are conducted to investigate environmental chemical exposures usually are based on one of three basic study designs [19].

Cohort studies begin with the identification of an exposed population and look forward in time to determine rates of disease or mortality. Frequently the exposed cohort is defined as it existed at some time in the past so the outcome experience can be determined as it exists in the present. Records that allow this to be done sometimes exist for occupational groups but almost never for studies in the general community. Exposures must often be estimated because actual data were not collected in the past and the availability of medical records is very limited. Health outcomes, usually mortality, are typically used for study of chronic diseases such as cancer. The chosen health outcome for the cohort is compared to national statistics or other population data to obtain a ratio comparing the cohort experience to the expected disease rate. Adjustments of the data to avoid biases in population selection or confounding factors, such as age or lifestyle factors, must be made. When all of the information required is available, a cohort study can provide a robust result associating a specific exposure with an adverse health outcome. It can provide population-specific rates of adverse health outcomes that can be very useful in assessing risk.

Case-control studies are initiated by defining a group with a particular disease. The subjects with the disease are matched to appropriate control subjects who do not have the disease and then the history of exposure to potential causative factors is determined. This approach works well for the investigation of potential causes of relatively rare diseases, including some types

of cancers. The outcome, called an odds ratio, is the ratio of the odds of exposure in the case group compared with the odds of exposure in the control group. An odds ratio greater than 1 indicates that the odds of exposure were greater in the cases than in the controls. The odds ratio can approximate the disease rate if the control population is a representative sample of the underlying population. In that situation, the data may be useful for risk assessment.

Cross-studies investigate the prevalence of disease in a group that is exposed at the time of study or the prevalence of exposure in a group with a disease. This is a useful approach for obtaining information about acute effects of exposure, but it may be of more limited value in the investigation of diseases that manifest slowly unless the currently exposed population is representative of past exposure as well. A population is identified and both the exposure of interest and health status is characterized at the same time. Cross-sectional studies have been used to measure acute effects of exposure to air pollutants.

Molecular epidemiology is a variation on traditional epidemiological approaches that substitutes the use of biological indicators of exposure and biological effect in place of health outcomes. These indicators, commonly referred to as biomarkers, allow exposures to be measured directly at the biological level and to then be correlated with specific biological outcomes. These biomarkers of exposure and effect are now also being correlated with molecular information about polymorphic genetic variants that may modify response to toxicant exposures. This approach has two significant advantages when investigating etiological factors in diseases that occur with a low frequency and require long periods of time to develop. First, the use of biomarkers of exposure and effect allow the relationship between an exposure and an outcome to be observed very quickly, eliminating the latency period because the biomarkers that are typically used respond to exposure within days to weeks. Second, biomarkers of effect, such as chromosome aberrations, respond to exposures in a much larger proportion of an exposed population than the fraction that ultimately develops a disease such as cancer. Consequently, a much smaller population can be investigated than is required for a traditional epidemiological study. A third advantage of this approach is that investigating the combination of exposure, biological effect, and genetic factors that modify susceptibility provides valuable information directly in humans about the mechanisms of action of a chemical. This provides an interface between epidemiology and mechanistic toxicology [20].

Exposure trials are used on occasion to investigate the effects of toxicant exposures in human subjects. Ethical concerns about deliberately exposing human subjects to toxic agents limit the use of this approach in environmental health research. It is a common approach in clinical studies that are designed to evaluate specific treatment methods or new drugs. Such trials are experiments in which a treatment is administered under controlled conditions and the outcome is compared with the response of matched subjects who are either not treated or receive an alternative treatment.

Both traditional and molecular epidemiological methods can be used in investigations of exposures that occur at the community level in addition to an occupational or clinical setting. The same types of study designs are applicable. Typically, ambient exposure levels in communities are at low concentrations so studies must be designed to maximize the sensitivity of the methods used and the contrast between exposed and non-exposed populations to be studied. The health effects of exposure to particulate matter have been the subject of many traditional and molecular epidemiology studies which serve as excellent

examples of the application of these methods to community-level population exposures [21, 22].

2.1.3 Animal-Based Toxicology

Epidemiological studies observe final health outcomes in most cases but cannot investigate the intermediate processes that lead to disease. Molecular epidemiological studies allow some of the intermediate effects to be investigated but are limited to a few body fluids and tissues that can be obtained without invasive methods.

Most studies in human populations are observational. Animal models allow controlled experimental studies to be performed that can better capture the complex nature of responses to toxicant exposures that occur in humans but that cannot be studied in detail.

Different types of animal-based studies allow both the disease outcomes and the intermediate steps to be investigated under controlled experimental conditions and with full access to all tissues. The most widely used animals in toxicological research are rodents. While they are not perfect models for humans, they are anatomically, physiologically, and genetically similar enough to provide useful information to characterize toxic effects that are likely to occur in humans. The rodent lifetime bioassay for carcinogenic effects of chemicals provides the basis for risk assessment for many environmental chemicals. The limitations of epidemiological studies make human studies inappropriate for the investigation of many chemicals. In many cases, well defined, large populations are not available for study. Also, the time period of human exposure may not be long enough for carcinogenic effects to have become manifested.

The standard protocol for the animal lifetime bioassay involves treatment of mice and rats of both sexes with three concentrations of the test agent and a vehicle control by an appropriate route of exposure, based on normal pathways of human exposure. Typically 50-60 animals are included in each exposure group. The highest exposure dose is usually established based on the maximum tolerated dose in a preliminary sub-chronic study. The animals are exposed from weaning until either death or the end of the normal lifespan for the animals, about 24 months. Detailed information is kept on the condition of the animals, survival, and causes of death. At the termination of the study, the animals are dissected and all organs are evaluated for the presence and frequencies of tumors. The types of tumors and frequencies of animals bearing specific tumors in the treated groups are compared with the control groups.

Conservative statistical tests are used to identify significant increases in tumor frequency and to minimize misclassification due to multiple comparisons. The high doses used are required to raise the frequencies of tumors to a detectable level. Most positive chemicals increase tumor frequency at lower doses as well as at the maximum tolerated dose [23]. There are several variations on the basic study design including the use of mice with various genetic modifications that may alter the neoplastic transformation process or modify sensitivity to the agent being used [24]. The animal lifetime bioassay has been an effective tool in identifying and characterizing carcinogenic chemicals. Essentially all of the chemicals classified as human carcinogens by the International Agency for Research on Cancer (IARC) are carcinogenic in the animal bioassay as well.

Animal testing methods are also used to evaluate other types of toxic effects including reproductive toxicity, damage to the genetic apparatus, and organ-specific toxicity. The value of animal-based toxicology is that it integrates the entire response of the organism as it would occur in human subjects. This allows issues of absorption, distribution, metabolism, and excretion of chemicals and their metabolites to be investigated experimentally. Biological responses that range from tissue necrosis to subtle changes in signaling pathways can be investigated. The sequential metabolism of chemicals in multiple tissues and organ-specific toxicity can also be investigated. These experimental approaches would not be practical in cell-culture or biochemical systems.

2.1.4 Mechanistic Research

The objective of mechanistic research in toxicology is to determine the chain of events linking exposure to a toxic substance to a biological outcome [25]. Working out the mechanism by which a chemical induces toxicity provides valuable information that can be used in modifying risk assessments and gaining a clearer understanding of the relevance to toxicology in humans from toxicological data developed in animals or isolated cells. Types of information that are obtained in the course of mechanistic studies can include an understanding of the processes of absorption, distribution, storage, and release of the agent. These processes are the foundation for determining the pharmacokinetics of the agent. Understanding the metabolism of agents and the balance between bioactivation, detoxification, and elimination is also an important aspect of mechanistic research. The interaction of an agent, or its critical metabolites, with cellular structures such as the plasma membrane, mitochondria, or DNA is also important. Intracellular processes that result from these interactions are a critical part of the mechanism of action. These might include forming adducts with DNA, oxidative damage to DNA, stimulating or antagonizing plasma membrane or cytoplasmic receptors, altering the transcriptional control of the expression of key genes, or altering proteins so that their activities or stabilities are changed. By using either animals or specific types of cell cultures the differential actions of specific chemicals on different types of target cells can be determined. The roles of several factors in the modifications of responses to a toxic agent can provide important information about the vulnerability of cells to toxic effects. These modifiers may include the presence or absence of specific genetic polymorphisms that can alter the ability of cells or whole organisms to metabolize agents or to respond adaptively to damage that the agents produce. The physiological state of the organism is also important and may be modified by co-exposures to other agents, nutritional status, or other factors. Mechanistic studies can be carried out using cell-free extracts, isolated cells, or whole organisms, including rodents. Molecular epidemiological studies can involve measures to provide mechanistic information in human subjects. These might include determination of the levels of expression of specific genes in exposed individuals or specific mutagenic changes that might be induced in target cells, such as lymphocytes. The levels of different metabolites of an agent in body fluids, such as urine, can provide information about metabolic processes as well as a measure of exposure. Mechanistic studies are not used directly in performing risk assessments, but they contribute significantly to understanding the relevance of data from animal studies, or other experiments, to human risk.

2.1.5 Risk Assessment

2.1.5.1 Definition and Purpose of Risk Assessment

Risk assessment is an analytical methodology that uses toxicological data (obtained using the methods described in sections 2.1.2–2.1.4) to develop statements describing the probability of disease that could be ascribed to exposures to environmental agents. Exposure to most toxic agents in the environment occurs at relatively low levels and adverse health effects may become manifested only after an extended period of time. Thus, it is necessary to determine the probability that an exposed individual will actually be adversely affected. Statements about probable risks may take the form of a categorization of disease risks associated with particular hazards, or they may be quantitative estimates of the probability of disease in a population that are based on a defined set of conditions. Risk assessments provide a consistent and scientifically defensible means to estimate risks for individual chemicals, mixtures, or sometimes specified environments. This allows decisions to be made about appropriate strategies for limiting human exposures in a manner that is predicted to minimize the risk of disease. These strategies can include the establishment of guidelines or standards for maximum allowable concentrations of a specified toxic chemical in ambient air. Beginning in section 2.2, the toxicology of benzene, 1,3-butadiene, formaldehyde, and diesel particulate matter will be reviewed and the risk assessments used to estimate the disease risks attributable to each of them will be described.

2.1.5.2 Qualitative and Quantitative Risk Assessment Approaches

Risk assessment approaches fall into two broad categories: qualitative and quantitative. Qualitative methods are typically based on a "weight of evidence" approach in which all of the available qualifying information on a specific agent is gathered and then reviewed by scientific experts in that area. Typically, information that qualifies must have been published in peer-reviewed scientific journals or study reports and must meet criteria for completeness and scientific integrity. After reviewing the available information, a panel of scientists makes a judgment to place the agent into a particular risk category. A widely respected qualitative risk categorization process is the one used by the IARC, which is a subsidiary organization of the World Health Organization of the United Nations.

The approach used by the IARC is detailed in the preface of each of the monographs it has published, such as its most recent evaluation of benzene [26, 27]. Carcinogens are placed into categories based on the weight of evidence from human epidemiologic studies and animal bioassays. Mechanistic data are considered in making a final classification. The classifications are based on the sufficiency of data to identify a chemical as a carcinogen in humans or rodents. Agents for which there is sufficient evidence of carcinogenicity in humans are placed in class 1. If there is sufficient evidence in animals, but not humans, they are placed in class 2A or 2B depending on the strength of human data. If the data are inconclusive in both animals and humans they are placed in class 3 and if the data strongly indicate that the agent is not carcinogenic it is placed in class 4. Benzene and formaldehyde are class 1 carcinogens whereas 1,3-butadiene and diesel exhaust are in class 2A. Other organizations use similar approaches to place carcinogens into categories of concern. These include the annual report of the National Toxicology Program (NTP) on carcinogens [28] and similar lists developed by the United States Environmental Protection Agency (US EPA) and the California EPA. These expert assessments are not always in agreement. For example, 1,3-

butadiene is classified as a human carcinogen by the NTP but only as a probable human carcinogen by the IARC [29]. These categorical lists are useful in setting priorities for further action and for public education. However, this approach does not provide any quantitative data that can be used in setting numerical standards or guidelines. This categorical approach has been used almost entirely for characterizing the carcinogenic activity of environmental agents but has seldom been applied to non-carcinogenic effects.

Quantitative methods are used extensively to derive risk probabilities for human populations by utilizing epidemiological or experimental data on the toxic effects of environmental agents. Two different approaches are taken, depending on whether the toxic effect is assumed to occur only after a threshold exposure level has been reached or whether a finite risk is assumed to be present at any exposure level. For most types of toxic effects, it is assumed that an organism can tolerate exposure up to a certain point because of detoxification or reparative mechanisms. In most cases the presumed injury is either derangement of cellular function or cell death. In the former case, termination of exposure is assumed to allow cell function to return to normal. In the latter case, lost cells can usually be replaced by replication of undamaged cells in the affected tissue. This conceptual approach is applied to most types of injurious effects associated with damage to specific organs. This would include injury to specific organs, such as the liver, or most types of embryonic or fetal injury. As long as compensatory mechanisms are not overwhelmed and the cells in a tissue can recover or be replaced, a threshold-based model for risk assessment is assumed to apply. The exception is the risks related to exposure to mutagenic carcinogens. This is because mutations in the DNA of cells, once they have formed, are essentially irreversible and are heritable so that the progeny of the originally altered cell will also harbor the mutation. Although there are mechanisms to detoxify mutagens and to repair DNA damage or trigger programmed cell death, it is assumed that each “hit” by a mutagenic carcinogen carries a finite probability of inducing a mutation. Thus, even though the effect of a very low dose would be immeasurably small, there is a risk that it could result in an alteration in genetic information which could lead to cancer.

2.1.5.2.1 Threshold-Based Risk Assessment

Quantitative risk assessments are based on the analysis of dose-response curves. There is an extensive literature on the methods used. Useful summaries may be found in several documents [30-33]. The first step is to identify and evaluate studies that can provide dose-response data of adequate quality to make a risk assessment. The objective is to estimate risks under relevant exposure conditions based on data obtained through human epidemiologic studies or studies on experimental animals. Typically, the exposure conditions under which those studies were performed would be as high as or higher than those exposures of interest to risk assessors. The objective will then be to extrapolate levels of risk from the available dose-response data to the levels of concern. In the case of the development of ambient air standards, risks must be estimated for exposures that may be three to four orders of magnitude below the levels that were involved in occupational epidemiologic studies, and they may be even lower than the doses used in animal bioassays.

For analyses based on non-carcinogenic effects, the US EPA describes a two-step process of analysis [31]. The first step is to evaluate a dose-response curve to establish a point of departure (POD). The second is to extrapolate from the POD to the lower environmentally

relevant levels. The original approach for doing this involved identifying either the highest dose at which no adverse effect was observed (no observed adverse effect level, or NOAEL) or the lowest dose at which an adverse effect was seen (lowest observed adverse effect level, or LOAEL). These two points set a boundary around the threshold dose below which no adverse effect is anticipated. The NOAEL is used as a POD to calculate a chronic exposure dose below which no adverse effect would be expected. A reference dose or reference concentration (RfD or RfC) is calculated by dividing the NOAEL by uncertainty factors and modifying factors. These factors adjust the RfD to compensate for differences in human sensitivity, between humans and laboratory animals, in exposure circumstances, and in relation to other factors [30]. The RfD provides a level of exposure that can be used as a basis for setting guidelines or standards for allowable exposure levels. The major weakness of this approach is that it makes no use of the shape of the dose-response curve. The metabolic processes and mechanisms by which a chemical or its metabolites induce injury may influence the shape of the dose-response curve in ways that can be very significant at low exposures. Selecting a simple threshold point on which to base the POD may result in significant over- or under-estimation of the RfD value.

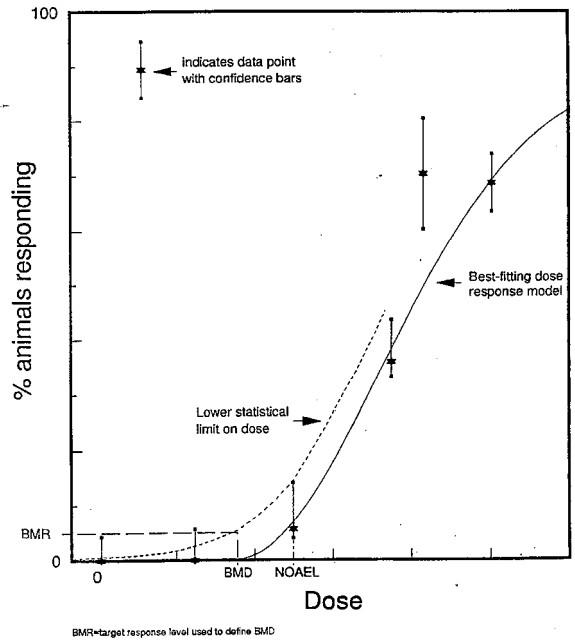

Figure 1. Graphical representation of the determination of a NOAEL (or BMD) and a BMDL (labeled BMD here) from a dose response curve. [30].

A more modern variation on this approach is the Benchmark Dose method [30]. This approach is based on selecting the POD by identifying a level of response that would be considered biologically significant, such as an excess frequency of an adverse effect of 10%. This would be a benchmark response at 10% (BMR_{10}). The dose at which the BMR is reached is determined from the dose-response data, using a mathematical model to generate a curve using all of the data points. Selection of an appropriate mathematical model may be based on obtaining the best fit curve of the data or may take into account biological information about the metabolism of the agent and the mechanisms of toxicity. The dose at which the lower confidence interval curve crosses the BMR is defined as the lower bound benchmark dose or BMDL (labeled BMD in Figure 1) [30]. The dose at which the curve crosses the BMR is defined as the benchmark dose or benchmark concentration (BMD or BMC). The BMDL (or BMCL) is used as the POD and the same types of uncertainty and modifying factors are applied to determine the RfC or RfD. These factors are based to some extent on scientific judgments. It is not uncommon for different risk assessors to apply different values as uncertainty factors

so that the RfD values derived are different, sometimes by an order of magnitude. Also, the terminology used to describe these reference levels differs among organizations that conduct these risk assessments. For example, while the US EPA uses the term Reference Dose, the California EPA's Office of Environmental Health Hazard Assessment (OEHHA) uses the term reference exposure level (REL).

Whether it is calculated from the NOAEL or the BMCL, the RfD is a level of exposure that can be used as a basis for setting exposures guidelines or standards.

2.1.5.2.2 Non-Threshold-Based Risk Assessment (Genotoxic Carcinogens)

The basic approach for quantitative risk assessment of genotoxic carcinogens is similar to the approach used for non-carcinogens. The significant difference is in the models used to extrapolate risk to relevant exposure levels. Because mutagenic agents are viewed as having a linear dose-response with no threshold at low exposure levels, linear, non-threshold models are used. The first step in the risk assessment process for genotoxic carcinogens is to identify a suitable study to use as a source of data for the analysis. Human epidemiological studies are preferred if they are of adequate quality. In the absence of adequate human data, well conducted animal bioassays are used. Carcinogen risk assessment guidelines from the US EPA recommend comparing results from more than one study to evaluate the consistency of the analysis [34]. The data are analyzed to establish a POD to use in extrapolating the dose response to lower exposure levels. When possible, an understanding of the mode of action of the agent is used in selecting the model to be used for the extrapolation. From the modeled dose-response curve an effective dose (ED) or effective concentration (EC) that is associated with a chosen excess cancer rate (such as 1%) is determined. This value, an EC_x, where X is the response level, is analogous to the benchmark response selected for use in the benchmark dose methodology, as shown in Figure 1. The lower 95% confidence interval of the point estimate for the EC is calculated and then converted to a continuous lifetime exposure [34]. From this value a risk at an exposure level of interest is calculated. For ambient air exposures to carcinogens a concentration of 1 $\mu g/m^3$ or 1 ppb is typically used. This value is termed a unit risk (UR) and the unit of the value is in the form of a rate of predicted disease. For example, the UR for 1,3-butadiene after a lifetime of continuous exposure to 1 $\mu g/m^3$ is 3 in 100,000 individuals [35]. The UR is typically converted into ambient environmental concentrations that would pose specified levels of risk such as one per 1,000,000 or one per 100,000. These ambient concentrations can then be considered as a basis for setting guidelines or standards for exposure. The product of the risk assessment for genotoxic carcinogens differs from the product for non-carcinogens in that the UR defines a level of risk that exists at a selected exposure concentration. The RfD or RfC determined for a non-carcinogenic effect defines a level at which induced disease is not expected to occur [33].

2.2 Toxicology of Selected Air Toxics

2.2.1 Benzene

2.2.1.1 Introduction

The toxicology of benzene has been the subject of intense investigation for more than 20 years at the time of this writing. The literature resulting from these investigations is voluminous. This assessment of the basis for regulatory guidelines for ambient air levels of benzene will summarize this information but will not attempt to report it in detail. Many peer-reviewed summaries of benzene toxicology have been published and can serve as a more complete guide to the literature on benzene. These include reviews by the United States Environmental Protection Agency (US EPA), the Agency for Toxic Substances and Disease Registry (ATSDR), the International Agency for Research on Cancer (IARC), the California Environmental Protection Agency (CA EPA), Health Canada, and the Occupational Safety and Health Administration (OSHA), as well as numerous reviews on specific topics in the scientific literature.

2.2.1.2 Production and Use

Benzene (CAS Registry No. 71-43-2) is a volatile aromatic chemical with a molecular weight of 78.11 and chemical formula of C_6H_6. Structurally, it is a six-carbon ring with three double bonds (Figure 2). It is used industrially as a solvent and as a precursor in the manufacture of many aromatic chemicals. It is found naturally in petroleum products and is present in gasoline at a concentration of 1 to 2% in the US [36]. Production in the US was almost 8.8 million liters (2.3 million gallons) in 2004 [37] making it one of the highest volume chemicals in use.

Figure 2: Benzene

2.2.1.3 Means of Exposure

The primary source of human exposure to benzene is by inhalation. Benzene has low solubility in water allowing some exposure orally by contaminated water. Exposure by inhalation is the route that is most relevant to community exposures in Houston. Sources of benzene in the ambient air include gasoline, emissions from internal combustion engines, environmental tobacco smoke, mainstream tobacco smoke, and industrial emissions [38]. Significant exposures from industrial emissions appear to be concentrated in locations adjacent to specific facilities.

2.2.1.4 Exposure in Houston

The average annual benzene levels in 2004 reported by the Texas Council on Environmental Quality (TCEQ) were 1.7 parts per billion by volume (ppb) at the Baytown/Lynchburg Ferry monitoring site and 1.6 ppb at the Clinton Drive/Galena Park monitoring site, based on 24-hour canister samples. Automated gas chromatography (autoGC) reported an average annual concentration of 1.6 ppb at the Texas City site. The annual average at Baytown/Lynchburg Ferry, based on hourly autoGC data, was 2.4 ppb in 2004 which was in good agreement with canister sampling results from the first nine months of 2003, which was 2.7 ppb. These

values exceeded the TCEQ's annual Effects Screening Level (ESL) of 1 ppb for benzene. The Texas ESLs, discussed in section 3.1, are used primarily as guidance for permitting facilities. Figure 3 illustrates the location of these monitoring sites.

Based on the directionality of the autoGC data, a possible source of benzene near the Baytown/Lynchburg Ferry site was a barge facility. Tanks in a nearby facility are a likely source at the Clinton Drive/Galena park site and a pipeline facility is a probable source at the Texas City station [39].

Figure 3: Map of referenced benzene monitoring site locations.

2.2.1.5 Summary of Significant Health Concerns

The primary health concerns associated with human exposure to benzene are a consequence of its toxicity to bone marrow and its effects on hematopoiesis. Metabolites formed from benzene are toxic to all types of hematopoietic stem cells in the bone marrow. This results in a decrease in cell numbers in the marrow, cell death, and effects on stem cell differentiation and maturation. The consequent health effects include anemia and leukemia. High or prolonged exposures to benzene can produce aplastic anemia. At lower concentrations, benzene exposure can inhibit colony formation from progenitor cells. This can result in immune suppression and increased susceptibility to infections. A voluminous literature describes these effects in humans and in animals. They are reviewed by Snyder [40] and the ATSDR [41] among other sources. Benzene exposure is also associated with adverse effects on the nervous system and on reproduction and development. These effects are less well documented in humans and appear to require higher levels of exposure to be observed [41]. The adverse health effect which drives risk assessments and exposure standards is the ability of benzene to induce leukemia in humans.

2.2.1.6 Disposition and Metabolism of Benzene

Benzene must be metabolized in order to exert its toxic effects. The metabolism of benzene has been the subject of extensive research and numerous publications. Studies of benzene metabolism date back to the 1920s and 1930s [40] and entered the modern era of biochemistry with the use, by Parke and Williams, of ^{14}C benzene as a tracer in the 1950s [42]. Snyder published a general review of benzene toxicity [40] and also a more focused review of the relationship between benzene metabolism and toxicity [43]. A detailed critical review of the role of metabolism in benzene toxicity has been written by Ross [44]. The metabolism of benzene is complex as shown in Figure 4, a summary of benzene metabolism taken from Ross' review [44].

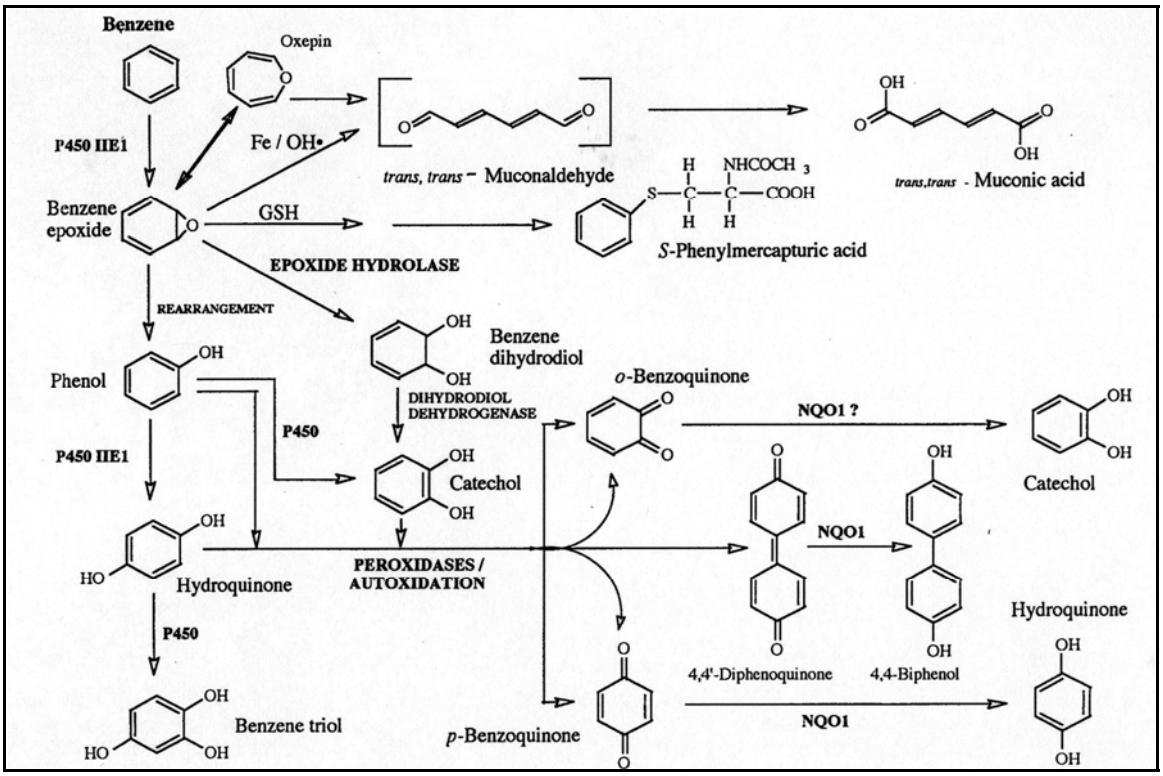

Figure 4: Metabolic pathways of benzene reproduced from a review by Ross [43]. Ross omitted the glucuronidation and sulfation pathways for clarity.

As shown in Figure 4, the initial step in benzene metabolism is its oxidation to benzene oxide. Several lines of evidence indicate that cytochrome P450 2E1 (CYP2E1) is the primary mediator of this process [44]. Subsequent to that initial step, benzene oxide may rearrange non-enzymatically to phenol which can then be further oxidized to polyphenolic metabolites such as hydroquinone, catechol, and benzene triol. These may form conjugates with glutathione, sulfate, or glucuronic acid (not shown in Figure 4). They may also be reduced to less toxic hydroxybenzenes by NAD(P)H:quinone oxidoreductases (NQO1). Benzene oxide may be hydrolyzed by microsomal epoxide hydrolase to benzene dihydrodiol which may then be further metabolized to the same polyphenolic compounds derived from phenol. Benzene oxide may also undergo spontaneous rearrangement to the oxepin and/or a non-enzymatic ring-opening process to yield a straight chain six-carbon dialdehyde, trans,trans-muconaldehyde (MA). MA may be further oxidized to muconic acid. Benzene oxide may also conjugate with glutathione to form phenylmercapturic acid. Thus, the oxidation of benzene to benzene oxide is a critical first step leading to the subsequent metabolism of benzene to numerous products, some of which are toxic and some not.

The organ sites at which benzene is metabolized to toxic products are still not clearly understood. Only slight CYP2E1 activity can be demonstrated in bone marrow from humans or rodents suggesting that the initial oxidation to benzene oxide may occur primarily in other tissues, such as the liver and lungs [44]. How toxic metabolites are then transported to target tissues is not certain. Benzene oxide adducts of hemoglobin and albumin have been detected

in the blood of occupationally exposed workers [45] and these could be transported to the bone marrow. Sulfate phenolic conjugates could be transported to target tissues and released by sulfatases [44]. Target tissues in rats have high sulfatase levels but low sulphonotransferase levels. Thus, it is plausible that mechanisms may exist for facilitating the transfer of benzene oxide, polyphenolic metabolites, or MA from the liver, where these compounds form in abundance, to target tissues, including the bone marrow [44].

2.2.1.7 Toxicity of Metabolic Products

Among the polyphenolic products formed through the subsequent metabolism of phenol or benzene dihydrodiol, hydroquinone, catechol, and benzene triol appear to be the most significant toxicants. Hydroquinone induces chromosome damage in lymphocytes. Hydroquinone and benzene triol induce oxidative damage in the bone marrow which is the primary target tissue for benzene toxicity. Catechol has been found to stimulate peroxidase-mediated activation of hydroquinone.

The biological plausibility for the polyphenols to act as the primary toxicants resulting from benzene metabolism is strengthened because bone marrow contains high levels of myeloperoxidase. Target tissues in rats and mice, other than bone marrow, also have high peroxidase levels [44]. Occupationally exposed workers who have a low-activity polymorphism for NQO1 are more sensitive to genotoxic effects and bone marrow toxicity from benzene. This suggests that they are less able to reduce the reactive polyphenolic compounds and detoxify them [46].

The ring open product, MA, has been shown to be associated with toxicity and chromosome damage in mice exposed to benzene [47], but has not been directly detected in bone marrow from humans or rodents [44]. Combinations of metabolites, including combinations of polyphenolic compounds and the combination of MA and hydroquinone, produce greater bone marrow toxicity than individual compounds [44].

2.2.1.8 Mechanisms Leading to Health Effects

The two most significant health effects associated with benzene exposure are bone marrow toxicity, leading to loss of cellularity and anemia, and disorders of growth and differentiation of bone marrow stem cells, leading to myelodysplastic disease and leukemias that can originate in several progenitor cell lines. Although acute myelogenous leukemia (AML) was the type of leukemia most often observed in epidemiologic studies, a broad review of studies concluded that evidence linking benzene exposure with elevated risks of several other types of leukemia was as strong as for AML [48].

Benzene exposure is also associated with chromosome aberrations both in human occupational studies and in rodents. Whysner et al. [49] reviewed a large number of genetic toxicity studies that demonstrated that benzene forms DNA adducts very weakly, but that a variety of chromosome aberrations including chromosome breaks, micronuclei aneuploidy, and sister chromatid exchanges are induced in humans, non-human primates, rodents, and human cells in vitro. Reviewing in vivo studies in humans and rodents, Eastmond similarly concluded that the genetic toxicity of benzene was primarily expressed as chromosome breaks, with translocations and aneuploidy also being observed [50]. In addition, specific

translocations that are associated with AML were found at elevated rates in lymphocytes from exposed workers [51, 52].

Recent research has modified our understanding of the mechanisms by which benzene metabolites induce hematotoxicity and leukemogenesis. Originally, toxicity was thought to be due to direct genetic damage induced by the formation of DNA adducts with reactive metabolites of benzene or by the induction of oxidative DNA damage as a result of oxidation-reduction reactions of the metabolites. The binding of benzene metabolites to DNA in target tissues has proven to be rather limited whereas proteins in tissues serve as major sinks for metabolite binding [43]. DNA adduct formation by benzene in vivo occurs at only very low levels [49]. Although much of the binding to proteins appears to be non-specific, several studies have identified effects of benzene metabolites on the functions of specific proteins that may play a role in the mechanisms of toxicity. This type of binding affects mitochondrial DNA polymerase, topoisomerase II, and calpain-mediated conversion of pre-interleukin-1α to interleukin-1α [43]. Benzene exposure in mice and exposure to its metabolites in in-vitro studies in cells have been shown to inhibit topoisomerase II [53, 54]. This enzyme plays a key role in the maintenance of the structural integrity of DNA and is required for replication. Topoisomerase II inhibitors, when used as cancer chemotherapeutic agents, are associated with the induction of AML as a secondary cancer. The pattern of genetic damage induced by these drugs is very similar to the pattern seen following exposure to benzene [49].

Hirabayashi et al. [55] recently reviewed work on the effects of benzene exposure in the cycling of progenitor cells. Short-term exposure to benzene reduced bone marrow cellularity. This, however, was rapidly reversed following cessation of exposure. The cycling fraction of progenitor cells was reduced during exposure but recovered rapidly after cessation. This effect appears to be associated with p53-mediated up-regulation of p21. The authors hypothesize that repeated exposures to benzene result in oscillations in hematopoiesis that ultimately lead to genetic instability and leukemogenesis. They found that exposure of p53-knockout mice did not produce these oscillatory changes in hematopoiesis but did produce cumulative DNA damage leading to aberrant expression of oncogenes.

Martyn Smith proposed an overall hypothesis for the toxicity of benzene indicating that multiple factors are determinants of its toxicity. These include benzene's biotransformation to phenolic metabolites, which are transported to the bone marrow where they are converted to semiquinone radicals. He identified several mechanisms by which metabolites induced toxic effects. These include oxidation-reduction cycling of phenolic metabolites, damage to several proteins including tubulin, histones, and topoisomerase II with key roles in DNA metabolism, and damage to DNA. Interference with these proteins, which results in abnormal DNA processing during replication and at mitosis, produces the variety of observed cytogenetic abnormalities. He hypothesized that the occurrence of these changes in bone marrow stem or progenitor cells could produce clones of leukemic cells in which chromosomal rearrangements activate oncogenes and inactivate tumor-suppressor genes [56]. Subsequent study of workers in the National Cancer Institute's (NCI's) Chinese cohort found that exposed, but non-symptomatic, workers had elevated frequencies of circulating lymphocytes that were hyperdiploid for chromosomes 8 or 21 or contained chromosome 8:21 translocations that are associated with AML [52].

In conclusion, the mechanisms by which benzene induces hematotoxicity and leukemia are still not clearly understood. They appear to be complex, probably involving the combined effects of multiple metabolites. In addition, the role of direct genetic damage leading to mutations appears to be limited. The impairment of physiological responses to DNA damage, as a result of damage to proteins and derangement of signaling processes, may play a significant role in the induction of the observed chromosomal abnormalities and in interference with normal hematopoietic stem cell differentiation. These effects may well be responsible for the hematotoxicity and the leukemias that occur as a result of benzene exposure.

2.2.1.9 US EPA IRIS Risk Assessment and Evidence

Most of the state guidelines for benzene use the US EPA Integrated Risk Information System (IRIS) risk assessment or the California risk assessment. These assessments are based on the epidemiologic literature, with supporting analyses of animal studies. Rather than review this large volume of literature, the studies considered for use in the risk assessments will be summarized.

2.2.1.9.1 Risk Assessment Evidence for Non-Cancer Endpoints from Epidemiology Studies

The US EPA IRIS evaluation of benzene used only one study in establishing a reference concentration (RfC) based on non-cancer effects. This was the epidemiologic study by Rothman et al. published in 1996 [57]. Animal studies were used for comparison and are discussed in the next section.

The Rothman study was a component of a very large study involving 75,000 workers in China conducted jointly by investigators from the Chinese Academy of Preventive Medicine, the US NCI, and scientists from several US universities and institutes. This study focused on the effects of benzene exposure on benzene metabolite formation and hematotoxicity. The exposed workers were from three workplaces, a natural rubber processing plant, an adhesive manufacturing facility, and a facility where benzene-based paints and varnishes were used to paint toys, and were matched for age, gender, smoking and alcohol consumption with controls from two workplaces that used neither benzene nor other chemicals associated with hematotoxicity. Personal exposure monitoring was performed using the 3M 3500 organic vapor monitor. Participating workers wore the monitors on five full work shifts over a 1- to 2-week period prior to blood sample collection. Blood counts were measured using an electronic blood cell counter. Urine specimens were collected from 43 of the exposed workers and analyzed for several benzene metabolites. During the study, the exposed cohort of 44 workers was exposed to a median concentration of 31 ppm of benzene. The exposed workers were subdivided into two equal groups based on exposure level. The median exposure in the low-exposure subgroup was 13.6 ppm and in the high-exposure subgroup it was 91.9 ppm. The concentrations of the urine metabolites correlated with the measured air exposures. A second subdivision, referred to as the restricted low exposure group, consisted of 11 workers who had no exposure measurements exceeding 31 ppm, the entire group median. Their median exposure was 7.6 ppm.

The US EPA assessment focused on decreased values for several of the blood cell count parameters in the high- and low-exposure groups compared with the controls. Mean

corpuscular volume of erythrocytes increased with exposure. The most sensitive parameter was absolute lymphocyte count (ALC), which is the ratio of total white blood cell count to the proportion of lymphocytes. This parameter, which was not ascertained in most of the other benzene studies, could be determined because of the use of an electronic particle counter to analyze the blood samples. ALC was also the only parameter that declined in a dose-related fashion when it was correlated with individual exposures among the entire exposed group. The ALC was also the only parameter that was reduced in the restricted low-exposure group when compared with the control group. The major conclusions of the study were that, over a wide range of exposures, workers experienced reduced blood cell counts, ALC was the most sensitive parameter, and workers with a range of exposures between 1 and 20 ppm were affected. The strengths of this study were that it included the use of gender- and age-matched controls, the exposed group included a broad range of exposures, confounding exposures were minimized, exposures were directly measured by both air monitoring and urine metabolite analysis, and a spectrum of hematological endpoints were assessed, including ALC.

Although the study just described was the only study used to determine the RfC included in the US EPA IRIS, additional research was published in 2004 [58]. In this study, part of the Chinese benzene study, many of the same investigators analyzed the effects of even lower occupational exposures to benzene using a cohort of 250 exposed workers and 140 controls. Exposed workers were divided into three groups based on exposure: (1) less than 1 ppm, (2) 1–10 ppm and, (3) greater than 10 ppm. These investigators again found a significant decline in blood cell counts for several cell types and a significant trend in this decline with individual exposure among the exposed subjects. In addition, they determined the ability of bone marrow progenitor cells to form colonies. They found that this parameter was more sensitive to benzene exposure than peripheral lymphocyte counts, suggesting that bone marrow cells are more sensitive than mature blood cells. Significant effects on both stem cell colony formation and lymphocyte counts were observed in even the lowest, <1 ppm, exposure group as compared with the controls. These findings suggest that it may be appropriate to recalculate the RfC based on these effects at lower doses.

2.2.1.9.2 Risk Assessment Evidence for Non-Cancer Endpoints from Animal Studies

For the determination of the RfC, the US EPA used the rodent exposure study by Ward and his colleagues [59]. In this study, CD-1 mice and Sprague-Dawley rats were exposed to benzene for 6 hours/day 5 days/week for 91 days at doses of 0, 1, 10, 30, or 300 ppm. Hematological endpoints were measured and decreased hematocrit was selected as the critical endpoint. Male mice were found to be more sensitive than females and the lowest observed adverse effects level (LOAEL) and no observable adverse effects level (NOAEL) were observed at 300 ppm and 30 ppm, respectively. This study was selected for use in calculating risk estimates because of the relatively long duration of exposure, adequate sample size, and availability of dose-response data [60]. Other animal studies that were cited, but not used in the analysis, were reports by Baarson et al. [61] and Cronkite et al. [62].

2.2.1.9.3 US EPA IRIS Risk Assessment of Non-Cancer Endpoints

The RfC was calculated based on the hematoxicity observed in the Rothman human occupational study. Two approaches were used. First, benchmark concentration (BMC) modeling [31] was used with the ALC data from the Rothman [57] study. Because the dose-response was supralinear (slope decreasing at higher doses), the data were transformed and fit to a continuous linear model. Because there was no clear definition of an adverse effect, a one standard deviation change from the control mean was selected as the benchmark response. The calculated lower 95% confidence interval of the BMC, the BMCL, was converted back to the original scale and determined to be 7.2 ppm for an 8-hr time-weighted average. The RfC was derived from this value by converting it to units of mg/m^3 and adjusting the exposure period from 8 to 24 hours. The adjusted value of 8.2 mg/m^3 was further adjusted by an uncertainty factor of 300 to determine the RfC of 3×10^{-2} mg/m^3, which is 9.4 ppb.

A second calculation was made using the LOAEL that was determined based on the median exposure concentration (7.6 ppm) for the subpopulation with measured exposures below 31 ppm. The same calculations were made, except that an uncertainty factor of 1000 was used to add uncertainty to account for the lack of a NOAEL. The resulting RfC was 9×10^{-3} mg/m^3, or 2.82 ppb, which is in good agreement with the value derived from the BMC analysis (3×10^{-2} mg/m^3; 9.4 ppb).

The results of the animal study [59] were used to calculate a comparative RfC using decreased hematocrit as the critical effect. A BMC of 100.7 ppm and BMCL of 85.0 ppm were determined. The BMCL, adjusted for continuous exposure, was 48.5 mg/m^3, and the RfC, with an uncertainty factor of 1000, was 5×10^{-2} mg/m^3 or 15.7 ppb. When the calculation was repeated using the NOAEL of 30 ppm and an uncertainly factor of 300, the result was an RfC of 6×10^{-2} or 19 ppb. These values are in good agreement with the values derived from the Rothman study. Thus, the benzene concentrations at which no adverse effect on hematopoietic parameters would be expected from long-term exposure would be at or below about 10 ppb based on the human study and slightly higher based on the mouse study.

2.2.1.9.4 Risk Assessment Evidence for Cancer Endpoints from Epidemiology Studies

The relationship between occupational benzene exposure and cancer, specifically leukemias, has been documented in many epidemiologic studies. These studies have been peer reviewed by several expert panels for the purpose of classifying benzene in its status as a carcinogen. These panels include the IARC that places benzene in its Class I, a chemical for which there is adequate evidence of carcinogenic activity in humans [26] [27], the United States National Toxicology Program (US NTP) and the US EPA which also classify benzene as a known human carcinogen [38, 63], and the ASTDR which has prepared a detailed review on benzene [41].

The US EPA IRIS assessment of the carcinogenic risks associated with benzene cited several epidemiologic studies and selected one, Rinsky et al. [64, 65], as best fitting their criteria for analysis. The following epidemiologic studies were considered in their IRIS analysis.

- The study of Turkish shoe industry workers by Aksoy et al. [66] evaluated 28,500 workers. These workers experienced very high exposures of between 210 and 650 ppm. The study detected about a 2-fold excess of leukemias compared with the general population. It lacked detailed information on exposures and on potential confounding exposures.
- In 1977, Infante et al. [67] conducted the first cohort mortality study in what came to be known as the Pliofilm cohort. They investigated the mortality experience of 748 white male workers who were employed at least one day in the manufacture of rubber products between 1940 and 1949. Vital status, as of 1975, was determined and completed for 75% of the cohort. A statistically significant increase in deaths from leukemia was observed in this group.
- Rinsky et al. [64, 65] extended the study of the Pliofilm cohort with a study published in 1981 and a follow-up in 1987. Vital status was completed for 96% of the cohort and estimates of exposure were made based on small-scale sampling and exposure data collected by the company between 1946 and 1976. This allowed cumulative exposures in ppm*years to be estimated for the different work areas and job descriptions. The overall standardized mortality ratio (SMR) was 560 based on 7 deaths from leukemia. A large percentage of the cohort was exposed for less than one year. For workers who were exposed for five or more years, the SMR was 2100 suggesting an exposure-related increase in mortality. All of the deaths were due to myelogenous or monocytic leukemia. The 1987 update expanded the population to 1165 workers and included 2 additional deaths due to leukemia. The study included a much more detailed estimate of ppm*years of benzene exposure which made it possible to evaluate the relationship between exposure and risk of developing leukemia. The overall SMR for the cohort was 337 and ranged from a low of 109 for less than 40 ppm*years to 6637 for over 400 ppm*years of cumulative exposure. Using a nested case-control study, the investigators were able to create a model calculating the odds of developing leukemia over a range of ppm*years of exposure. At 400 ppm*years it estimated a mean odds ratio (OR) of 154.5. This was equivalent to 40 years of exposure at 10 ppm, the exposure standard at the time. At an exposure of 1 ppm, the current OSHA standard, the OR was estimated to be 1.7.
- In 1978, Ott et al. [68] studied 594 chemical workers and observed a non-significant increase in leukemia (3 deaths). The exposure levels were much lower than in the Pliofilm cohort with time-weighted average exposures ranging from 2 to 25 ppm.
- In 1987, Wong et al. [69] investigated a population of 4602 workers from seven chemical plants. They observed a marginally significant increase in the relative risk of leukemia of 3.93 at 720 ppm*months of exposure (60 ppm*years).
- The largest study by far is the continuing US NCI/Chinese Academy of Preventive Medicine study conducted by Hayes and his colleagues [70]. This investigation provided the data for the Rothman study that the US EPA used to calculate the RfC [57] and for the cytogenetic monitoring and hematotoxicity studies mentioned earlier [52, 58]. For the cancer study, a cohort of 74,828 benzene exposed workers was compared with 35,805 non-exposed controls. The workers were employed between 1972 and 1987 at 1427 work units in 12 cities in China. The subjects worked in several types of occupations including coatings applications and rubber, chemical, and shoe production. Exposures were

estimated and the relative risk of mortality from many causes was determined across a range of exposure categories. Hematopoietic cancers and malignancies of the lung were elevated, with statistical significance, for a dose-response trend. Even in the lowest exposure category (< 10 ppm*years), hematopoietic malignancies were significantly elevated, with a relative risk of 2.5 ($p<0.01$). While this study was large and potentially quite powerful, the US EPA did not find it suitable for use in risk assessment because of concerns about possible co-exposures to other chemicals and limitations in the numbers of exposure measurements on which the estimates were based.

2.2.1.9.5 Risk Assessment Evidence for Cancer Endpoints from Animal Studies

The US EPA considered several of the many rodent cancer studies that have been conducted. Inhalation studies in rodents that support the observation of leukemia in humans are reported in multiple publications from Cronkite et al., Snyder et al., and Maltoni et al., and are reviewed in detail by ATSDR [41].

2.2.1.9.6 US EPA IRIS Risk Assessment Evidence of Cancer Endpoints

The assessment to calculate the unit risk (UR) for leukemia by the inhalation of benzene was based on the updated Pliofilm cohort study by Rinsky et al. [65]. This study was selected because it had the fewest co-exposures and broadest range of exposures among the studies that were considered. The URs were determined by Crump [71, 72]. The factors that the US EPA listed as important in developing their UR were the choice of the extrapolation model and the choice of exposure estimates. The choice of extrapolation model was not straightforward. Based on data from the Chinese study, Hayes et al. [73] indicated that formation of toxic metabolites may saturate above 25 ppm, suggesting that a supralinear model may be important. For estimates at low doses, the US EPA chose to use a linear extrapolation model. Two exposure estimates were used. One was developed by Crump and Allan [74] and the other by Paustenbach et al. [75]. Crump [71] seemed to place more confidence in the Paustenbach analysis. Using a linear model, the US EPA selection of URs fell in a range of 7.1×10^{-3} to 2.5×10^{-2} or 2.2×10^{-6} to 7.8×10^{-6}, depending on whether the exposure data of Crump and Allan or Paustenbach were used. From this range of URs, the lifetime risk levels for an increase in cancer risk of 1 per 100,000 lives is 1.3 to 4.5 $\mu g/m^3$ (0.41 to 1.41 ppb). Thus, the current Texas ESL of 1 ppb would pose a lifetime risk of about 1 per 100,000. To reduce the statistical risk to 1 per million, the range of allowable exposures would have to be reduced ten-fold to 0.04 to 0.14 ppb, which is well below ambient air concentrations in most urban centers, including Houston.

2.2.1.10 California Risk Assessment and Evidence

As mentioned previously, most of the state guidelines for benzene use the US EPA IRIS risk assessment or the California risk assessment. These assessments are based on the epidemiologic literature, with supporting analyses of animal studies. The studies considered in developing the California risk assessment will be summarized here.

2.2.1.10.1 California Risk Assessment Evidence by Non-Cancer Endpoints in Epidemiology Studies

The California chronic reference exposure level (REL) was based primarily on an occupational study by Tsai et al. [76]. This study investigated mortality experience and reported the results of medical surveillance on a cohort of male workers in a large petrochemical refinery in Texas. It was selected because of the extensive medical and exposure monitoring that was done. All of the male workers that were employed at the plant between 1952 and 1978 (n=454) were included in the study. Average age at entry in the cohort was 34 years. They were exposed to benzene for an average of 8 years for white employees and 4.5 years for nonwhite employees. The average number of years of follow-up was 13 years. The cohort was extensively monitored for benzene exposure with a total of 1,394 samples collected between 1973 and 1982. From 1959 to 1973, blood samples were collected yearly, sometimes more often, and analyzed for hematological parameters. Between 1970 and 1979, blood chemistry analyses were also performed. Approximately 1400 hematologic profiles and 900 blood chemistries were analyzed. Benzene exposures were low, with only one unit of the plant, the Cumene unit, having a median exposure that exceeded 1 ppm. For all of the units in which there was benzene exposure, the median exposure was 0.53 ppm.

Only 34 deaths occurred in the cohort and no individual cause of death was significantly elevated. For most causes of death, SMRs were below 1.0, suggesting a healthy worker effect. There were no deaths listed that resulted from leukemia. All of the mean hematological parameters measured were within normal limits. Therefore, this study was considered to be a NOAEL study because no abnormal findings were observed [77]. The measured exposures were very low for the time period of the study and the average follow-up was relatively short for a mortality analysis.

Several other studies were considered in developing the REL. In particular, the hematological analyses of workers in a cohort producing Pliofilm were considered. An initial study of 459 workers in the cohort found significant decreases in white and red cell counts during the 1940s which did not persist in later years. Decreased benzene exposures after this period were considered to be a factor [78]. A reanalysis of this data examined blood cell counts measured in workers over their first year of employment. A subset of 161 workers who had initial counts before or during the first two months of employment was evaluated. When the workers were stratified into groups with exposures above or below the estimated median exposure of 40 to 54 ppm for the time period, a clear decline in blood cell counts was observed over the first six months. The high exposure group had lower counts than the low exposure group at all time points [79]. Exposures in this study were estimates made by Crump and Allen [74].

2.2.1.10.2 California Risk Assessment Evidence by Non-Cancer Endpoints in Animal Studies

Two animal studies were used to calculate comparative REL values based on hematological effects. The study by Baarson et al. [61] observed suppression of bone marrow progenitor cells after exposure at 10 ppm over 6 months. An 8-week study by Farris et al. [80] also documented hematological effects.

2.2.1.10.3 California OEHHA Risk Assessment of Non-Cancer Endpoints

For determination of the REL, the California Office of Environmental Health Hazard Assessment (OEHHA) used the occupational exposure study by Tsai et al. [76]. Hematological effects were considered the critical effects. Since none were observed in this cohort over many years of observation, the median air concentration of 0.53 ppm was used as a NOAEL. Based on an 8-hour workday and an average work duration of 7.4 years, an average occupational exposure was calculated to be 0.19 ppm. Uncertainty factors were 1 for LOAEL uncertainty, 1 for subchronic uncertainty, 1 for interspecies uncertainty, and 10 for cumulative uncertainty. An inhalation reference exposure of 0.02 ppm (20 ppb, 0.06 mg/m^3, or 60 $\mu g/m^3$) was determined. This may be compared with the US EPA IRIS RfC of 9.4 ppb.

For comparison, an REL was calculated from data presented in the Pliofilm cohort study. An analysis based on a LOAEL of 30 ppm produced a calculated REL of 10 ppb which is similar to the value (20 ppb) calculated from the data from the study by Tsai [76]. The two animal studies yielded comparable REL values based on hematological effects. A REL of 6 ppb was calculated based on the Baarson et al. study [61]. While the Farris et al. [80] study documented a LOAEL of 100 ppm and a NOAEL of 10 ppm which yielded a REL of 20 ppb.

2.2.1.10.4 California Risk Assessment Evidence by Cancer Endpoints in Epidemiology Studies

The risk assessment developed by OEHHA [81] was based on evaluations of several human studies including the studies by Infante et al. [67] and Rinsky [64] of the Pliofilm cohort, the series of studies by Aksoy et al. [82, 83], and the study by Ott et al. [68], each described in detail in the US EPA IRIS risk assessment evidence for cancer endpoints.

2.2.1.10.5 California Risk Assessment Evidence by Cancer Endpoints in Animal Studies

In addition, the US NTP rodent bioassay study [84] was used in the California risk assessment. This study followed the standard protocol used by the US NTP. Following a preliminary 17-week study to establish dose tolerance, Fisher 344 rats and B6C3F1 mice were exposed to benzene by oral gavage in corn oil for 103 weeks. The doses used were 0, 50, or 100 mg/kg/day for 5 days per week. Male rats were also administered a dose of 20 mg/kg. Neoplastic and non-neoplastic effects were observed in both rats and mice. In rats, tumors of the zymbal gland, oral cavity, and skin were observed. In mice, frequencies of lymphomas and tumors of the zymbal gland, lung, harderian gland, mammary gland (females), preputial gland (males), forestomach, ovary (females), and liver were related to treatment. The US NTP concluded that there was “clear evidence of carcinogenicity” of benzene in rats and mice.

2.2.1.10.6 California OEHHA Risk Assessment of Cancer Endpoints

The risk assessment developed by OEHHA [81] was based on evaluations of both human and animal studies. The animal studies used were the inhalation and oral gavage administration studies by Maltoni et al. [85] and the US NTP study [84].

The animal results were analyzed using a linearized multistage procedure to fit the dose-response data from the cancer bioassays to a curve. Risks were estimated from the

epidemiological data using a linear non-threshold model. Maximum likelihood estimates of cancer risk/ppb of benzene exposure from different tumor endpoints in the animal studies ranged from 6.4 x 10^{-6} to 170 x 10^{-6}. Based on leukemia as an outcome in the human studies, the range of risks was 15 x 10^{-6} to 48 x 10^{-6}. In 1984, the California Department of Health Services (CDHS) [81] recommended that a range of cancer potencies from 24 x 10^{-6} to 170 x 10^{-6} per ppb be used to estimate low-level risks. Assuming a human respiratory volume of 20 m^3 per day, a weight of 70 kg, and an air concentration equivalency for benzene of 1 ppm=3.25 $\mu g/m^3$, a range of potency values of 0.03 to 0.2 per mg/kg-day was calculated. In 1988, CDHS recommended using a potency value of 0.1 per mg/kg-day, which is equivalent to a UR of 29 x 10^{-6} ($\square g/m^3)^{-1}$. This may be compared to the IRIS range of URs of 2.2 x 10^{-6} to 7.8 x 10^{-6} $(\mu g/m^3)^{-1}$. The California UR is about 6 times greater than the US EPA IRIS value. Based on a UR of 29 x 10^{-6} $(\mu g/m^3)^{-1}$, the benzene level producing a risk of 1 per million corresponds to 0.034 $\mu g/m^3$ or 0.011 ppb. At the Texas annual ESL of 1 ppb, the calculated risk is near 1 in 10,000.

2.2.1.11 ATSDR Risk Assessment

The ATSDR has calculated minimal risk levels (MRLs) for benzene based on two studies. The MRL is defined as "an estimate of daily human exposure to a dose of a chemical that is likely to be without appreciable risk of adverse non-cancerous effects over a specified duration of exposure" [41]. An acute MRL was calculated from data from a study by Rozen et al. [86] in which B6C3F1 mice were exposed to three doses of benzene by inhalation over 6 days. Hematological parameters were used as endpoints. Depression of proliferative activity of bone marrow B-cells and splenic T-cells was observed at the lowest dose used, 10.2 ppm. This value was used as a LOAEL in calculating the MRL. The dose level was corrected for a 24 hour per day exposure and a human-equivalent concentration, based on differences between mice and humans in weight and ventilation volume, of 14.7 ppm was calculated. After applying the uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation to humans, and 10 for human variability), a MRL of 0.05 ppm (50 ppb) was calculated.

An intermediate MRL was calculated based on data from a study by Li et al. [87]. In this case, Kunming mice were exposed to several concentrations of benzene by inhalation for 30 days and a battery of neurotoxicity tests were used to evaluate toxic effects. Changes in spleen and liver weights were also determined. Increased rapid response rates were observed at the lowest dose tested, 0.78 ppm. Other effects were manifested at higher doses. The 0.78 dose was used as a LOAEL (referred to as a less serious minimal LOAEL). The uncertainty factor used was 90 (3 for a minimal LOAEL, 3 for extrapolation from mice to humans, and 10 for human variability). The human equivalent concentration was 0.33 ppm resulting in a MRL of 0.004 ppm (4 ppb).

2.2.1.12 Occupational Exposure Standards

2.2.1.12.1 The OSHA Standard

The risk assessment performed by the Occupational Safety and Health Administration (OSHA) used the Pliofilm cohort study by Rinsky [65] and the study by Wong [69], both described in the US EPA cancer risk assessment section (see Section 2.2.1.6.4). It also used

an additional epidemiologic study by Bond et al. [88], which updated the earlier study by Ott et al. [68] of 594 workers at a chemical plant in Michigan through 1982. As observed by Ott et al., there was a strong healthy-worker effect and there was a significant excess mortality due to skin cancer. Although the number of deaths from leukemia in the cohort had risen from 3 in the Ott et al. study to 5 in the Bond et al. study, this number was still not statistically significant.

The OSHA standard for benzene was last set in 1987 [89]. The rule sets forth a Permissible Exposure Limit (PEL) of 1 ppm for an 8-hour time-weighted average. A Short Term Exposure Limit (STEL) of 5 ppm is allowed as an average for 15 minutes.

2.2.1.12.2 The NIOSH Standard

Related to the OSHA standard, The National Institute of Occupational Safety and Health (NIOSH) has set a recommended exposure limit (REL) for benzene of 0.1 ppm as an 8-hour time-weighted average. The short-term limit recommended by NIOSH is 1 ppm.

2.2.1.13 Summary and Conclusions

The risk assessments that have been cited most widely in developing guidelines for allowable ambient air levels of benzene are the US EPA IRIS analysis and the California OEHHA analysis. ATSDR calculated both acute and intermediate exposure minimum risk levels (MRLs), which have been cited by a few agencies in setting guidelines. Analyses from the US EPA and the California OEHHA have been made, based on both non-cancer and cancer endpoints. Non-cancer adverse effects were based on toxicity to the hematopoietic system while cancer effects were based on leukemias that are attributable to exposure. The reference concentration (RfC) from US EPA IRIS, the recommended exposure limit (REL) from CA OEHHA for non-cancer effects, and the unit risk (UR) for cancer effects are summarized in Table 3. Both RfC and REL values are calculated estimates of exposure levels that would not be expected to produce adverse effects in humans over a lifetime of exposure. URs are calculated risk probabilities for cancer effects at a specified concentration, in this case 1 $\mu g/m^3$ in air. These analyses have produced similar estimates of risk. The non-cancer risks are based on hematopoietic effects, except for the intermediate MRL by ATSDR which is based on neurological effects. The cancer endpoints are based on risk of leukemia in humans. The US EPA IRIS assessment predicts a population risk at the Texas effects screening level (ESL) of about 1 in 100,000 while the California OEHHA assessment predicts a risk of about 1 in 10,000. The 1 in 1,000,000 risk that the US EPA prefers to use for general population exposures would require a much lower limit on ambient air levels than is currently set by the Texas Council on Environmental Quality (TCEQ) or met by actual measured levels in the air in industrialized sections in the Houston area.

Table 3. Summary of risk assessments that are widely used in setting guidelines for benzene

Risk assessment source	**Non-cancer risk**	**Cancer risk**
US EPA IRIS	RfC=32 μg/m^3 9.4 ppb	UR=2.2–7.8x10^{-6} (μg/m^3)$^{-1}$ Risk=1x10^{-5} @ 1.3–4.5 μg/m^3, 0.41–1.41 ppb
California OEHHA	REL=60 μg/m^3 20 ppb	UR=29x10^{-6} (μg/m^3) Risk=1x10^{-4} @ 3.4 μg/m^3, 1.1 ppb
ATSDR	Acute MRL=159.5 μg/m^3, 50 ppb Intermediate MRL=12.76 μg/m^3, 4 ppb	

2.2.2. 1,3-Butadiene

2.2.2.1 Introduction

The toxicology of 1,3-butadiene has been studied intensively since the early 1980s when initial epidemiologic studies suggested that it might be associated with hematopoietic cancers in exposed industrial workers. The literature on the metabolism, toxicity, and carcinogenicity of 1,3-butadiene is voluminous and there are several comprehensive reviews. These reviews are often cited in this summary rather than listing many individual publications.

2.2.2.2 Production and Use

1,3-Butadiene (CAS Registry No. 106-99-0) is a four-carbon straight chain hydrocarbon with two double bonds at the 1 and 3 positions (Figure 5). It is a gas at standard temperature and pressure and has a molecular mass of 54.09. For industrial use, it is purified from a stream of four-carbon compounds generated in petrochemical refining. 1,3-Butadiene is used in the synthesis of polymers, particularly styrene-butadiene rubber (SBR). In 2004, US production was 2,204,000 metric tons, a 15% increase over 2003 [37].

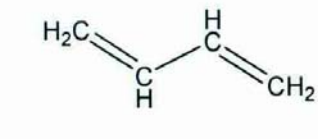

Figure 5: 1,3-Butadiene

2.2.2.3 Means of Exposure

The primary source of human exposure to 1,3-butadiene is by inhalation. Sources of 1,3-butadiene in ambient air include emissions from industrial facilities, gasoline, auto emissions, and environmental tobacco smoke. A compilation of studies of ambient urban air levels in the 1970s and 1980s reported a median level of 0.29 parts per billion (ppb). Suburban air levels were similar [90].

2.2.2.4 Exposure in Houston

In 2004, annual average levels measured in the Houston area by the air monitoring network were similar except for selected sites. The annual average at the Milby Park monitor was 4 ppb, while annual averages at Clinton Drive and Galena Park were near 0.5 ppb. Data from automated gas chromatograph (autoGC) monitors at Milby Park, Cesar Chavez High School, and Clinton Drive indicate that the elevated emissions probably originate at a complex of three plants that are immediately southeast of Milby Park. Figure 6

Figure 6: Map of 1,3-butadiene monitoring site locations refernced in the text.

illustrates the location of these monitoring sites.

Preliminary autoGC data for 2005 suggests a significant decline in emissions from this area [39]. Despite this decline, emissions from this area are still a health concern to the Texas Council on Environmental Quality (TCEQ) and the City of Houston and are a primary stimulus for the preparation of this report.

2.2.2.5 Summary of Significant Health Concerns

The major health concern associated with 1,3-butadiene is an association with hematopoietic cancers in occupationally exposed workers. Several epidemiologic studies have been reviewed in evaluations by the United States Environmental Protection Agency (US EPA) [91], the International Agency for Research on Cancer (IARC) [29], the Agency for Toxic Substances and Disease Registry (ATSDR) [90], the United States National Toxicology Program (US NTP) [28], and others. The major finding has been an elevation in leukemia in SBR workers and an increase in non-Hodgkin's lymphoma in workers in 1,3-butadiene monomer plants. The lack of a plausible explanation for the different types of cancers in different work settings and inconsistencies between dose, duration of exposure, and cancer risk have generated controversies regarding the carcinogenic effects of 1,3-butadiene exposure in humans [92-94].

Animal studies have demonstrated that 1,3-butadiene is a potent carcinogen in mice, inducing lung tumors at the lowest dose tested, 6.25 ppm [95]. 1,3-Butadiene also induced tumors at multiple sites in rats, but at substantially higher doses [96]. In addition, 1,3-butadiene causes reproductive abnormalities in mice, but in human studies, reproductive effects have not been observed [35].

2.2.2.6 Disposition and Metabolism of 1,3-Butadiene

The metabolism and disposition of 1,3-butadiene, as well as the mechanisms of toxicity, have been investigated in detail. A voluminous literature exists, dating back to the late 1980s, and several comprehensive reviews of this literature are available. Matthew Himmelstein and colleagues published a detailed review in 1997 which summarizes the literature up to that time [97]. Jackson et al. published a review of the genetic toxicity and related effects of 1,3-butadiene in 2000 [98]. Several reviews were published in association with risk assessments including the review by Health Canada in 2000 [99], the IARC assessment in 1999 [29], and the US EPA Integrated Risk Information System (IRIS) risk assessment in 2002 [35]. In this current review of the metabolism and toxicity of butadiene, key studies will be cited individually, but one or more of the published reviews will be cited for evidence derived from multiple publications.

Because 1,3-butadiene is a gas, the primary route of exposure is by inhalation. Although 1,3-butadiene itself has low solubility in water, its metabolites are more soluble and distribute to all tissue compartments in the body [97]. The metabolism of 1,3-butadiene is depicted in Figure 7 and is summarized in several reviews [35, 97-99]. The first step in 1,3-butadiene metabolism is oxidation of one double bond producing butadiene monoepoxide (EB or BDO)[7]. The primary enzyme involved is cytochrome P450 2E1 (CYP2E1) although 1,3-

[7] Two systems for abbreviating 1,3-butadiene metabolites are used. Butadiene monoepoxide: BDO or EB, Butadiene diepoxide: BDO_2 or DEB, Butadiene diolepoxide: BDO diol or EB diol.

butadiene is also a substrate for CYP 2A6 [100]. Inhibition of CYP 2E1 in mice still allows some genetic damage to occur after 1,3-butadiene exposure, suggesting that other isoforms play a role in the bioactivation of 1,3-butadiene [35, 98].

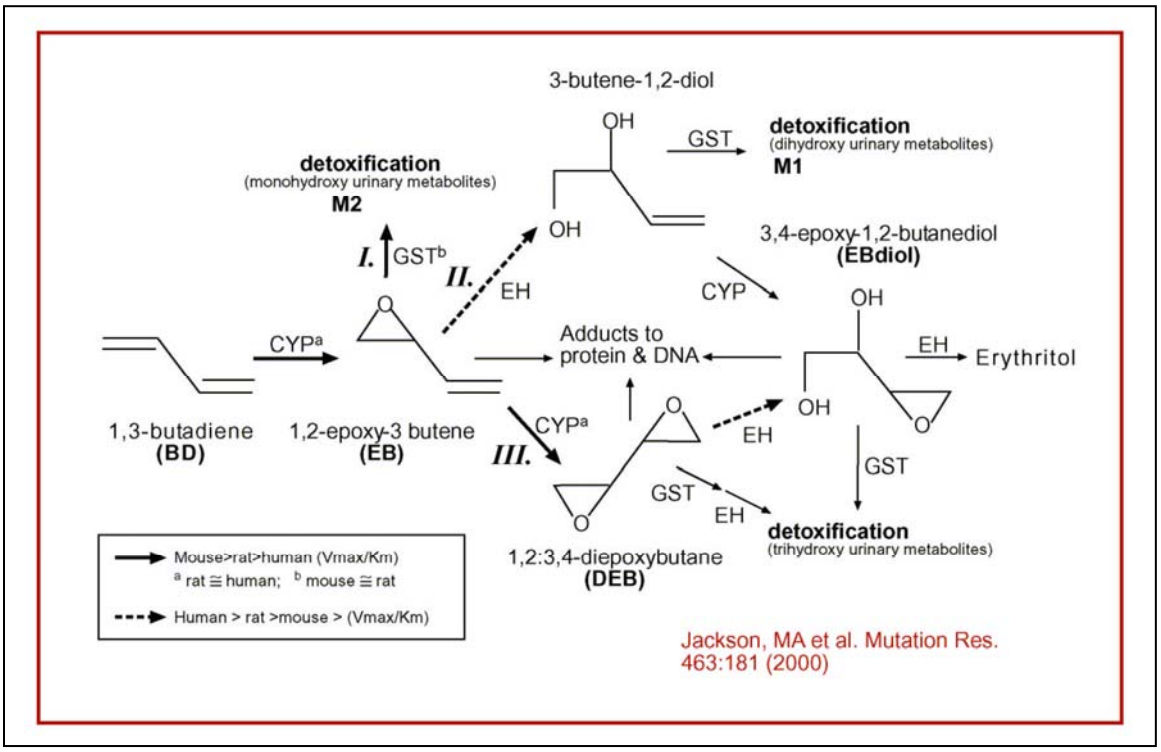

Figure 7: Metabolic scheme for 1,3-butadiene [101].

BDO can react directly with macromolecules including DNA and proteins. It can form a conjugate with glutathione (GSH) mediated by glutathione S-transferase (GST) or can be hydrolyzed by microsomal epoxide hydrolase (mEH) to form 3-butene-1,2-diol. The remaining double bond in BDO can be further oxidized by cytochrome P450s to butadiene diepoxide (DEB or BDO_2)[7]. The glutathione conjugate is processed to a urinary metabolite 1-hydroxy-2-(N-acetylcysteinyl)-3-butene (also referred to as M2) or 2-hydroxy-1-(N-acetylcysteinyl)-3-butene [102]. 3-Butene-1,2-diol can be oxidized to butadiene diolexpoxide (EB diol or BDO diol)[7] which can react with macromolecules or be further hydrolyzed to erythritol. Alternatively, it can conjugate with GSH resulting in the excretion of 1,2-dihydroxy-4-(N-acetylcysteinyl)-butane (also called M1). BDO_2 can react with macromolecules, form GSH conjugates, or be hydrolyzed by mEH to also form BDO diol. Thus, the balance of the formation of metabolites from exposure to 1,3-butadiene is determined by the balance between oxidation of the double bonds in the parent compound to epoxides, the formation of glutathione conjugates, and the hydrolysis of the epoxides. Similar levels of BDO and BDO_2 are found in the blood and tissues of mice after inhalation exposures to moderate 1,3-butadiene doses. In rats, the levels of metabolites are lower and the proportion of BDO_2 is much lower than that of BDO [35, 97, 98].

2.2.2.7 Mechanisms Leading to Health Effects

While the mechanisms by which 1,3-butadiene induces its carcinogenic effects are not precisely known, the genotoxicity of the epoxide metabolites is thought to play a major role. 1,3-Butadiene and its metabolites have been shown to produce genotoxic effects in a variety of organisms including bacteria, yeast, Drosophila, cultured mammalian cells, rodents, and some populations of human workers [98]. The genotoxic effects of 1,3-butadiene and its metabolites in humans was reviewed in 2000 by Jackson et al. for the US EPA [98]. The Health Effects Institute (HEI) has funded extensive research on the genotoxicity of 1,3-butadiene in rodents and in a human population study. The results of these studies are published in two HEI reports, numbered 92 and 116. The focus of genotoxicity studies has been to understand the relationship between the metabolism of 1,3-butadiene to its epoxides and the induction of genotoxic effects. The induction of mutations in cultured mammalian cells by BDO, BDO diol, and BDO_2 has been documented in human lymphoblasts [103]. All three metabolites are mutagenic; however, the potency of BDO_2 is about 100 times greater than that of the other two metabolites. This is presumably because it is a bifunctional alkylating agent capable of generating DNA-DNA crosslinks [104]. In mice, a number of studies have confirmed that 1,3-butadiene is mutagenic. These studies were done with several different mutation assays including the Hprt reporter gene assay in spleen lymphocytes and the transgenic LacI gene assay in several tissues. In an early study, Cochrane and Skopek [105] found that exposures to 1,3-butadiene, BDO, or BDO_2 were mutagenic at the Hprt gene locus in spleen lymphocytes from B6C3F1 mice. These studies have been expanded by several additional studies of the mutagenicity of 1,3-butadiene and its metabolites in mice by Walker and colleagues, by Recio and colleagues, and by Ward and colleagues. To summarize the findings of significance in considering the relevance of these rodent studies to human risk, the following points can be made:

- 1,3-Butadiene exposure by inhalation is uniformly mutagenic in mice over a wide range of dose levels [106-112].
- Three genetic loci have been used as the target for most studies in mice and rats. The endogenous Hprt reporter gene is on the X chromosome in mice, rats, and primates including humans. Consequently, there is only one functional copy of the gene per cell (due to X chromosome inactivation in females) facilitating the selection of mutant cells using purine analogues that are toxic to normal cells. The Hprt gene codes for an enzyme that is required for purine recycling in nucleic acid metabolism. Cells that can grow in culture can be assayed for mutations. Primarily, T-lymphocytes from the spleen or thymus are the cells used. The other two loci are derived from Escherichia coli bacteria and have been integrated into mice and rats, as part of a bacteriophage vector, using recombinant DNA technology. The vector can be recovered from any tissue and assayed for mutants in a bacterial plate assay. The two target genes are LacI and LacZ.
- A study using a large number of mice has documented a statistically significant 1.6-fold increase in Hprt mutant frequency and a decrease in cell growth in spleen lymphocytes in mice exposed to 3 ppm of butadiene for 2 weeks (6 hr/day, 5 days/week) [107]. This exposure level is only 3 times the Occupational Safety and Health Administration (OSHA) permitted exposure limit [108] and is about half the lowest level at which carcinogenic effects have been assessed and observed [109].

- The mutagenic activity of 1,3-butadiene can be detected in bone marrow, in addition to lymphocytes, in the LacI assay [110] and in the lung in the LacZ assay [111].
- The mutagenic potency of 1,3-butadiene was compared in mice and rats by measuring the mutant frequencies in spleen lymphocytes at several time points following exposure to determine the integrated area under the curve of the manifested mutations. At a high dose, 1250 ppm for 2 weeks of exposure, the mutagenic potency of 1,3-butadiene in mice was five-fold greater than in rats [112].
- The mutagenic effects of BDO and BDO_2 have been investigated with both types of mutagenesis assays in rats as well as mice. Mice were exposed by inhalation to levels of each metabolite that were equivalent to the blood levels achieved at 62.5 ppm of 1,3-butadiene. Mutagenic potencies were determined, as described above, with the conclusion that, at low-exposure levels, BDO_2 was primarily responsible for the induction of mutations in mice. At higher doses in mice and in rats, other metabolites played a more significant role [106].
- Investigation of the spectrum of the types of mutations induced by 1,3-butadiene and its metabolites in different biological systems provides insights into the mechanisms by which 1,3-butadiene induces mutations. A specific pattern of changes in the frequency of base substitutions has been seen in several biological systems, as well as an increase in the frequency of deletion mutations. This is consistent with the potential cross-linking activity of BDO_2. There is some overlap between base substitutions induced by 1,3-butadiene and mutations known to active K-ras and H-ras oncogenes in 1,3-butadiene-induced tumors in mice [112].
- In several biological systems, exposure to BDO_2 has been inferred to be associated with the induction of large-scale deletion mutations. Studies using the most rigorous approach for detecting deletions are in progress, including analysis of genomic Hprt gene sequences by multiplex PCR [113].
- The events required for mutagenesis have been documented. The formation of adducts between 1,3-butadiene metabolites and DNA in multiple tissues in rats and mice have been investigated in several studies. Monohydroxy and trihydroxy adducts, primarily with guanine and adenine, have been reported in lung, liver, lymphocytes, and other tissues [98]. The formation of these adducts from the BDO and BDO diol metabolites have been reported [114] and an N7-N7 crosslink derived from exposure of DNA to BDO_2 has also been reported [115]. In addition, adducts with the N-terminal valine of the β-chain of hemoglobin have been measured in several studies documenting the formation of electrophilic metabolites of 1,3-butadiene [98]. The investigation of adduct formation with DNA and hemoglobin by 1,3-butadiene and its metabolites has documented the formation of reactive species in vivo and has provided insights into the relationships between 1,3-butadiene exposure, metabolism, and genotoxic outcomes [116].

Species differences in the metabolism and toxicity of 1,3-butadiene have been the subject of extensive study [35, 97-99]. In general, mice oxidize 1,3-butadiene to BDO more rapidly than do rats, monkeys, or humans [117]. Mice also hydrolyze BDO less rapidly than the other species, allowing BDO_2 to accumulate at higher levels which have been measured in tissues in several studies [97]. The pattern of excretion of metabolites in urine also reflects this difference. The metabolites derived from GHS conjugates M1 and M2 (Figure 7) follow a

pattern across species that reflects the extent to which BDO is hydrolyzed. After a brief exposure to a high dose of 1,3-butadiene, mice excreted 3 to 4 times as much M2 as M1 whereas rats and Syrian hamsters excreted 1.5 times more M2 than M1 and monkeys excreted almost exclusively M1. The proportion of M1 excreted correlated with the activity of hepatic mEH [102]. The relatively low levels of mEH in mice as compared with rats probably accounts for the ability of mice to accumulate higher tissue levels of BDO_2 and contributes to their greater sensitivity to the carcinogenic and mutagenic effects of 1,3-butadiene [97]. Humans have a range of mEH activity, but these are usually at higher levels than are found in mice [102] which correlates with the observation that 1,3-butadiene-exposed workers excrete almost exclusively M1. These species differences are considered to be significant when using data from mouse studies in assessing human risk [93, 94].

Evaluation of workers for effects of exposure to 1,3-butadiene has produced mixed results. Studies of workers at plants in Texas have consistently detected an increase in mutations in the HPRT reporter gene in lymphocytes using the short-term autoradiographic assay. The frequencies of HPRT mutations were related to measures of exposure including personal air monitoring and measurement of the M1 urinary metabolite [118]. No increase in chromosome aberrations were observed, but isolated lymphocytes from the more highly exposed workers that were challenged in vitro with gamma radiation had higher induced chromosome damage than did lymphocytes from workers with low exposures [119]. A major study of workers in China however, did not find any correlation between 1,3-butadiene exposure and the frequency of HPRT mutations in lymphocytes assayed with a cloning assay [120]. Similarly, a large study conducted in the Czech Republic found correlations between exposure measured by personal monitoring and by exposure biomarkers (urine metabolites and hemoglobin adducts), but not with HPRT mutant frequency measured by either the cloning or the autoradiographic method [121]. However, the 1,3-butadiene exposure levels in this study were lower than the average levels detected in the Texas studies [118, 119]. An earlier study in the Czech Republic reported an increase in chromosome aberrations and sister chromatid exchanges in workers exposed to 1,3-butadiene [122]. The later study there did not observe chromosomal effects of 1,3-butadiene exposure [121], nor did the study in China [120]. Human biomonitoring studies have fairly consistently documented biological evidence of exposure to 1,3-butadiene at exposure levels from 0.5 to 5 ppm but have produced inconsistent evidence of genetic effects of exposure over this dose range.

The relationship to 1,3-butadiene genotoxicity of genetic polymorphisms in genes controlling the biotransformation of 1,3-butadiene has also been evaluated with inconsistent results. The Czech cytogenetic study reported a relationship between higher chromosomal damage and the null mutation in glutathione-S-transferase M1 (GSTM1) in exposed workers [122]. In cell cultures, lymphocytes carrying the null mutation for GSTT1 induce higher frequencies of sister chromatid exchanges when exposed to BDO_2 than GSTT1 positive cells. The study of workers in Texas found that 1,3-butadiene exposed workers with low-activity polymorphisms in mEH were the individuals who had dose-related increases in HPRT mutant frequencies [123]. Neither the later Czech Republic Study [121] nor the China study [120] identified relationships between polymorphisms in biotransformation genes and sensitivity to genotoxic effects in exposed workers. Thus, there is equivocal evidence that genetic polymorphisms in genes controlling biotransformation may alter human sensitivity to 1,3-butadiene.

The primary health effect on which risk assessments are based is cancer, both in humans and in mice. The non-cancer health effect that has been used for risk assessment is reproductive effects, which have been documented in mice. Both types of effects are known responses to genetic damage and mutation. The toxicologic data for 1,3-butadiene clearly document mechanisms of biotransformation and cellular responses leading to the formation of electrophilic metabolites that form adducts with DNA and proteins (hemoglobin) and that include mutations and chromosome damage in a variety of biological systems, probably including humans. The inconsistencies in observing genotoxic effects in human molecular epidemiologic studies of 1,3-butadiene exposed workers is probably a function of dose and other confounding exposures rather than a fundamental difference in human response to 1,3-butadiene when compared with the responses seen in laboratory animals.

2.2.2.8 US EPA IRIS Risk Assessment and Evidence

Most state guidelines use the US EPA IRIS risk assessment, the California risk assessment, or the risk assessment associated with the OSHA occupational exposure standard. The studies used for the US EPA 1,3-butadiene risk assessment are the focus of the following analysis.

2.2.2.8.1 Risk Assessment Evidence for Non-Cancer Endpoints from Epidemiologic Studies

There is virtually no information in the scientific literature on purely toxic, in contrast to genotoxic, effects from chronic human exposure to 1,3-butadiene. The acute effect is primarily irritation, which is observed at very high concentrations. Human epidemiologic studies have addressed the health effects of 1,3-butadiene exposure and have found that mortality rates for all causes from occupational exposures are lower than rates for the general public. This is probably reflective of the "healthy worker effect" and does not identify potential non-malignant diseases that may be caused by chronic exposure to 1,3-butadiene. In the study of SBR workers by Delzell et al. [124], standardized mortality ratios (SMRs) for cerebrovascular, vascular, and cardiac diseases were close to the expected number of 100 whereas mortality from other causes occurred at lower rates.

2.2.2.8.2 Risk Assessment Evidence for Non-Cancer Endpoints from Animal Studies

The determination of the reference concentration (RfC) for 1,3-butadiene in the US EPA IRIS analysis was based on reproductive effects in animals. No comparable reproductive effects have been observed in human populations. Data on reproductive effects from acute, subchronic, and chronic exposures were evaluated. The most sensitive endpoint for acute exposure was decreased fetal weight in mice exposed to 40 ppm 1,3-butadiene for 6 hours per day on days 6-15 of gestation. Weights of male fetuses were significantly depressed at 40 ppm, the lowest dose administered, and female fetuses were affected at 200 ppm [125]. The effects seen at 40 ppm represented the lowest observed adverse effect level (LOAEL) for an acute exposure.

The most sensitive reproductive endpoint observed after subchronic exposure was fetal deaths in dominant lethal studies [126]. Two other studies were conducted that produced similar results. In one study, male mice were exposed to 1250 ppm 1,3-butadiene for 10

weeks and bred to unexposed females for 1 week [127]. In the other study, male mice were exposed to 1300 ppm 1,3-butadiene for 5 days and bred to unexposed females for 4 weeks [128]. The 10-week exposure yielded a 28.1% dominant lethality while in the one-week study, dominant lethality was 5.2%, 12.45%, and 5.5% after 1, 2, and 3 weeks of mating, respectively. In the one-week exposure study, the mouse spot test, a method for measuring in utero mutagenicity, was performed on a separate set of mice and was positive at 500 ppm. Thus, 1250 ppm of 1,3-butadiene for 10 weeks served as a LOEAL for a subchronic exposure.

The most sensitive reproductive effects observed following a chronic exposure were ovarian atrophy and testicular atrophy, which were noted in the US NTP lifetime bioassay [95]. Ovarian atrophy was observed in female mice exposed to 6.25 ppm 1,3-butadiene for 2 years. Testicular atrophy occurred only at higher doses. The 6.25 ppm dose was the lowest used in the study and was also the exposure level at which female mice developed lung tumors.

2.2.2.8.3 US EPA IRIS Risk Assessment of Non-Cancer Endpoints

The benchmark concentration (BMC) approach was used to identify an exposure concentration to use as a starting point in developing a risk assessment. The chronic RfC was calculated based on ovarian atrophy in the mouse after chronic exposure [35]. The lower 5% confidence interval for the BMC producing a response in 10% of the mice ($BMCL_{10}$) was calculated to be 0.88 ppm from the US NTP bioassay [95]. Significant increases in ovarian atrophy were seen at all doses tested: 6.25, 20, 62.5, 200, and 625 ppm administered 6 hours per day, 5 days per week for 103 weeks. The highest dose was excluded in calculating the BMC_{10} and $BMCL_{10}$ because of high mortality. Ovarian atrophy was modeled to reflect extra risks only to age 50 because after menopause follicles would not be available to be affected. Exposure concentrations were converted to 24 hour per day equivalents. The calculated BMC_{10} was 1.0 ppm and the $BMCL_{10}$ was 0.88 ppm. An uncertainty factor of 1000 was applied. The modifying factors were 3 for interspecies extrapolation, 10 for intraspecies variability, 3 for incomplete database, and 10 for extrapolation to a level below a 10% effect level (analogous to adjusting a LOAEL to a NOAEL). Because the data were obtained from a chronic exposure study, no factor to correct for acute to chronic was required. Using the above uncertainty and modifying factors, the $BMCL_{10}$ of 0.88 ppm generated an RfC of 0.9 ppb.

The risk assessors considered evidence that ovarian atrophy is likely a result of BDO_2 exposure. They also considered whether the pharmacologically-based pharmacokinetic models available were adequate to estimate BDO_2 tissue concentrations in the mouse and extrapolate to humans. They concluded that they were not. The confidence expressed in the assessment was medium. Although the study from which the data were derived was of high quality, a NOAEL was not achieved; thus, no comparable effect in humans is known.

2.2.2.8.4 Risk Assessment Evidence for Cancer Endpoints from Epidemiologic Studies

The US EPA has classified 1,3-butadiene as “carcinogenic to humans by inhalation” [35], based on the weight of evidence from human epidemiologic studies with the support of chronic exposure studies in mice and rats. The US NTP [95] has also classified 1,3-butadiene as a recognized human carcinogen, as has Health Canada [129]. The IARC last reviewed 1,3-

butadiene in 1999 [29], retaining a 2A classification, probable human carcinogen, for the chemical. The basis of that decision was that there was no comparable confirming study to the one that provided the primary evidence of its carcinogenicity [29].

The weight of evidence for the carcinogenic activity of 1,3-butadiene relies on both human epidemiology and on bioassays of mice and rats exposed chronically to 1,3-butadiene. The US EPA IRIS risk assessment used a large cohort study of workers at eight styrene-butadiene rubber manufacturing plants. The study was conducted by epidemiologists from the University of Alabama at Birmingham [124]. This retrospective cohort study was a continuation of a study initiated by Johns Hopkins University [130] under the sponsorship of the International Institute of Synthetic Rubber Producers (IISRP). Over 17,000 workers who worked at least one year between 1943 and 1991 in eight North American plants were evaluated. A retrospective quantitative exposure estimate was made. Mortality rates were compared with US national, state, and Canadian provincial population rates to calculate SMRs and 95% confidence intervals (CI_{95}). Overall observed mortality from all causes was less than the expected number (SMR=87; CI_{95}=85-90). Deaths from all cancers were also less than expected. This is often seen in occupational epidemiology studies and is attributed to the fact that industrial workers are a select population that, in most respects, is healthier than the general population. However, deaths due to leukemia exceeded the expected number with 48 observed and 37 expected deaths (SMR=131; CI_{95}=97-174). Among workers who had ever worked in the plants on an hourly basis, leukemia deaths were elevated among white workers (SMR=130; CI_{95}=91-181) and more so among black workers (SMR=227; CI_{95}=104-431). The risk increased with time since hire for workers with over 10 years of work experience. The risks were also elevated for workers in polymerization units and laboratories and for general laborers; this correlated with estimates of exposure [124].

Additional epidemiologic evidence was cited in the US EPA IRIS risk assessment. The preceding cohort study [130] was identified as was a nested case-control study within that cohort [131]. Several studies of workers exposed to 1,3-butadiene in monomer plants were also cited. These studies have consistently identified an increase in what was earlier classified as lymphosarcoma and reticulosarcoma [132]. These diseases are currently classified as a single disease, non-Hodgkin's lymphoma (NHL). In some cases, non-significant increases in leukemia deaths were seen, but the significant excesses of NHL were observed.

A concern in interpreting these results is that the cases were largely confined to workers employed during the Second World War. One interpretation was that high exposure rates during that period may have influenced the risk. Another interpretation was that some other factor preceding this work experience, which was not documented, may have been important [97]. The SBR cohort study has continued with a reanalysis of the exposure estimates [133] and updates of the study were published in 1998 [134] and in 2005 [135]. The follow-up studies have continued to observe the same pattern of disease with overall mortality below expected rates, but a unique excess of leukemia deaths. Overall excess leukemia death rates in the highest risk groups have been 2-3 times the expected rate.

2.2.2.8.5 Risk Assessment Evidence for Cancer Endpoints from Animal Studies

Chronic lifetime bioassays in mice and rats have provided further evidence of the carcinogenic activity of 1,3-butadiene. The US NTP conducted two studies in B6C3F1 mice.

In the first study, mice were exposed to 625 and 1250 ppm of 1,3-butadiene. Although the intended duration of the study was to be 103 weeks, the lifetime for mice, the study was ended prematurely at 60 and 61 weeks because of high mortality rates in male and female mice due to malignant lymphomas [136]. A second study, in B6C3F1 mice, was conducted at concentrations of 0, 6.25, 20, 62.5, 200, and 625 ppm for 103 weeks. In this study, the carcinogenic effect observed at the lowest dose was lung cancer in female mice at 6.25 ppm of 1,3-butadiene. At higher concentrations, both male and female mice developed tumors at multiple sites, including lymphomas, hemangiosarcomas of the heart, tumors of the liver and harderian gland, and tumors of the mammary glands and ovaries in females [95, 109]. This investigation included a stop exposure component, to evaluate exposures of shorter duration, followed by observation over the normal lifespan. Even with shorter exposure durations, significant excess numbers of tumors were seen at multiple sites [95, 109].

A two-year chronic study in rats was performed by Hazelton Laboratories [96]. Sprague-Dawley rats were exposed to 0, 1000, or 8000 ppm 1,3-butadiene for 105 to 111 weeks. Survivals were shortened in a dose-dependent manner, with females being slightly more sensitive than males. An increase in exocrine adenomas of the pancreas and in Leydig cell tumors was seen at the high dose in males. In females, increased tumor frequencies were seen in the uterus, mammary gland, zymbal gland, and thyroid gland. Although rats appear to be much less sensitive than mice, the pattern of tumor induction in multiple tissues was observed in both species.

2.2.2.8.6 US EPA IRIS Risk Assessment of Cancer Endpoints

The US EPA IRIS risk assessment [35] was based on the 1996 assessment of cancer in SBR workers by the University of Alabama group [124]. The analysis by Health Canada of the data from this study [129] was used in the risk assessment. Health Canada selected a linear relative-rate model using cumulative exposure in ppm-years as the exposure metric. The results were adjusted for age, calendar period, years since hire, and cumulative styrene exposure. Benzene exposure was examined and eliminated as a confounder. Risks were computed out to 85 years of age. The occupational exposures derived from the study were converted to continuous exposures. The US EPA considered a linear extrapolation from the lower 95% confidence interval for the least effective concentration associated with a 1% risk (LEC_{01}) to zero exposure and risk to be appropriate because of the well established mutagenicity of the metabolites of 1,3-butadiene. Applying the linear model to the data yielded an LEC_{01} of 0.377 ppm. Using that as a point of departure and extrapolating to zero, a unit risk (UR) estimate of 3 in 100 per ppm was calculated. An adjustment was made to base the calculation on incidence, rather than mortality, producing an adjusted LEC_{01} of 0.254 ppm and a UR of 4 in 100 per ppm. An additional adjustment of two was made for use of male data to estimate risk based on the greater sensitivity of female mice. This resulted in a final UR of 8 in 100 per ppm.

The US EPA IRIS analysis discussed the possible use of lung tumor data in the risk assessment, but this was not done because there is no clear evidence for lung cancer risk in the human epidemiologic data and, in the human studies, possible exposures to cigarette smoke and asbestos were viewed as potential confounders.

For comparison, a UR was calculated based on the animal studies. A linearized low-dose extrapolation model was used and exposures were adjusted to 24 hour continuous

equivalents. The URs were 4.3 in 1000 per ppm based on data from male rats and 5.6 in 100 per ppm based on data from female rats. The URs based on the mouse data were 22 in 100 per ppm for males and 30 in 100 per ppm for females which was considered the preferred model. The human UR of 8 in 100 per ppm of 1,3-butadiene lies between estimates from the rat and the mouse data, but they are all in a similar range.

The confidence expressed by the US EPA analysts in these results was moderate. Uncertainties regarding exposure estimates in the SBR worker study and uncertainties with the study itself were cited. Other concerns mentioned were the use of ppm-years as a dose metric, use of the linear extrapolation model, potential confounding factors, and uncertainties related to the choice of the model. Additional concerns about the rodent data, including lack of ability to resolve questions of interspecies differences in sensitivity, were discussed.

The inhalation unit risk converted to a unit more appropriate to ambient exposure was 3 in 100 (3×10^{-2}) per mg/m^3 or 3×10^{-5} per $\mu g/m^3$. One ppb 1,3-butadiene is 2.25 $\mu g/m^3$. Restating this UR in terms of risk intervals produces air concentrations with the following risks: 3 $\mu g/m^3$ (1.33 ppb) implies a risk of 1 in 10,000, 0.3 $\mu g/m^3$ (0.133 ppb) implies a risk of 1 in 10^5, and 0.03 $\mu g/m^3$ (0.013 ppb) implies a risk of 1 in 10^6. Thus, typical urban ambient exposure levels of about 0.3 ppb (including the average for Houston) place the risk near about 1 in 10^5 while the recent hot-spot exposures near Milby Park of about 5 ppb imply a risk of about 1 in 2660. This level is at the current Texas annual effects screening level (ESL) for 1,3-butadiene.

2.2.2.9 California Risk Assessment and Evidence

2.2.2.9.1 California Risk Assessment Evidence for Non-Cancer Endpoints in Epidemiologic Studies

The California analysis of non-cancer effects did not identify any human studies that were suitable for use in risk assessment. Several studies were briefly reviewed that had detected associations between work in the rubber industry or 1,3-butadiene manufacturing with several diseases involving the cardiovascular, pulmonary, and hematopoietic systems. Since workers were exposed to chemical mixtures that included chemicals other than 1,3-butadiene, the studies were not considered suitable for analysis [137].

2.2.2.9.2 California Risk Assessment Evidence for Non-Cancer Endpoints in Animal Studies

The evidence used by the CA Office of Environmental Health Hazard Assessment (OEHHA) for conducting a risk assessment based on non-cancer endpoints after chronic exposure is the same evidence used by the US EPA, ovarian atrophy observed in the second US NTP mouse bioassay. As was done by the US EPA, the study was selected because this effect was observed at the lowest exposure in any chronic study that could be found. In female mice, ovarian atrophy was observed at all four doses used including the lowest dose, 6.25 ppm for 103 weeks [95].

Several other endpoints and studies were mentioned in the review but not considered because the exposure levels were greater. In the same study, testicular atrophy was observed in the male mice but was only significantly increased at exposures of 200 and 625 ppm. Other

effects that were noted in the US NTP study included bone marrow atrophy, uterine atrophy, angiectasis, alveolar epithelial hyperplasia, forestomach epithelial hyperplasia, and cardiac endothelial hyperplasia. Several non-neoplastic effects were also observed in the first US NTP bioassay which only included doses of 625 and 1250 ppm and was ended prematurely [136]. The rat bioassay conducted by Hazelton Laboratories Europe [96] observed some changes in organ weights at the doses used, 1,000 and 8,000 ppm, but no reproductive organ toxicity. A study of young male chickens exposed to 20 ppm of 1,3-butadiene for 16 weeks found significant increases in arterial plaque size but not plaque frequency or location [138]. The CA OEHHA report briefly reviewed several other reproductive studies in rats and mice including the dominant lethality studies, such as the Anderson study [139], discussed in the US EPA IRIS analysis.

2.2.2.9.3 California OEHHA Risk Assessment of Non-Cancer Endpoints

The CA OEHHA determination of a reference exposure level (REL), the equivalent of the US EPA IRIS reference concentration (RfC), was based on ovarian atrophy in mice observed in the US NTP two-year study [95] which was previously described in the US EPA risk assessment. The increasing incidence of ovarian atrophy at all doses allowed the establishment of a LOAEL of 6.25 ppm. A log normal probit analysis using the US EPA benchmark dose software was made using the control and the log of the lowest 3 doses. The highest dose was omitted because the lowest three gave the best fit of the model to the data and because it could be justified based on the lack of induction of a higher frequency of atrophy at the highest dose. The dose of 1,3-butadiene producing the maximum likelihood estimate (MLE) of a 5% response was 1.53 ppm. The 95% lower confidence limit at the MLE provided a BMC_{05} of 1.40 ppm. Converting the average experimental exposure to a continuous exposure produced a concentration of 0.25 ppm, which was also the human equivalent concentration. A cumulative uncertainty factor of 30 was applied (1 for subchronic uncertainty, 3 for interspecies uncertainty, and 10 for intraspecies uncertainty) producing a REL of 8 ppb or 20 $\mu g/m^3$.

The REL of 8 ppb can be compared to the US EPA RfC of 0.9 ppb. Although the same underlying data were used in both calculations, slightly different models were applied. The US EPA calculated a benchmark for a 10% response which came out to 0.88 ppm, which can be compared to the human equivalent concentration of 0.25 ppm. The cumulative uncertainty factor used by the US EPA was 1000 rather than 30. Additional factors of 3 for lack of a NOAEL and 10 for extrapolation to an effect level lower than 10% were applied by the US EPA [35]. The differences in the uncertainty factors applied appear to account for most of the difference between the RfC and the REL.

2.2.2.9.4 California Risk Assessment Evidence by Cancer Endpoints in Epidemiologic Studies

The risk assessment for carcinogenic effects of 1,3-butadiene was based on the US NTP 103-week exposure study in mice [95, 109]. Several human studies involving workers in 1,3-butadiene monomer and polymer plants were cited and briefly reviewed but were not considered adequate for use in conducting a quantitative risk assessment. All of the epidemiologic studies cited were published in the 1970s, 1980s, or early 1990s. The IISRP study conducted by the University of Alabama [124] was not cited. Presumably, the

California assessment was conducted prior to the publication of this research. The studies that were cited included the earlier IISRP study by Matanoski [140] and the monomer plant studies by Downs [141], Meinhardt et al. [142], and Divine [143]. In addition, earlier 1,3-butadiene studies by Checkoway and Williams [144], The National Institute of Occupational Safety and Health [145], McMichael et al. [146], Andjelkovich et al. [147], and Monson and Fine [148], as well as a study of styrene exposure by Ott et al. [149], were cited. The reviewers concluded that a pattern of association between 1,3-butadiene exposure and increased frequencies of hematopoietic cancers was observed, but that it was not possible to distinguish the effects of 1,3-butadiene from other chemicals, such as styrene, present in the work environment. Based on this concern, they chose to use data from the animal bioassay as the basis for the risk assessment.

It should be noted that the California epidemiology-based cancer risk assessment appears to predate the IISRP epidemiology study used by the US EPA, despite the fact that the California assessment appeared in the 2005 technical support document for describing available cancer potency factors.

2.2.2.9.5 California Risk Assessment Evidence by Cancer Endpoints in Animal Studies

The two US NTP studies of the carcinogenic effects of 1,3-butadiene [95, 136] are described as the most detailed evaluations available [150]. These studies are summarized in Section 2.2.2.8.5, above. In the first study, mice were chronically exposed to 0, 625, or 1250 ppm of 1,3-butadiene. As noted earlier, the study was stopped after 60 weeks rather than the standard 103 weeks because of high death rates due to hematopoietic cancers. The second study was performed at chronically administered doses of 0, 6.25, 20, 62.5, 200, and 625 ppm. An excess incidence of cancers was observed in animals at all dose levels, with female mice experiencing an increase in lung tumors at the lowest dose and both genders experiencing multiple types of tumors at 62.5 ppm and higher doses. Tumors of the hematopoietic system, including lymphocytic lymphomas, predominated in both sexes. Tumors of the lungs were observed in excess in males at 62.5 and 200 ppm. At the higher doses, hemangiosarcomas of the heart and tumors of the forestomach were observed, along with ovarian tumors in females. The California assessment also reviewed the Hazelton bioassay of rats [96], which is also discussed in Section 2.2.2.8.5.

2.2.2.9.6 California OEHHA Risk Assessment of Cancer Endpoints

The CA OEHHA calculated cancer potency estimates based on the second mouse US NTP study [95, 109] and on the Hazelton rat study [96]. Continuous internal dose was considered to be the best measure of dose. Using interspecies equivalent dose units based on mg/m^2 of body surface, human equivalent cancer potencies, based on all the rodent assays, ranged from 4.4×10^{-6} to 3.6×10^{-4} $(\mu g/m^3)^{-1}$ with mice and rats differing by two orders of magnitude. The second mouse bioassay was considered to be the most appropriate study for use in the risk assessment based on several factors. These included the use of lower doses, the use of five doses, the presence of two mouse studies, the lack of a second rat study, the consistency of the tumor sites in the two mouse studies, the availability of more detailed data in the mouse studies, and the correspondence with the observed increase in hematopoietic cancers in humans. Using lung alveolar and bronchiolar neoplasms in the female mouse as the basis

for analysis, a cancer potency of 6.0 per mg/kg-day and a cancer unit risk of 1.7×10^{-4} per $\mu g/m^3$ was observed.

2.2.2.10 ATSDR Risk Assessment

ATSDR prepared a toxicological profile for 1,3-butadiene in 1992 [151]. This predated most of the mechanistic, toxicologic, epidemiologic, and chronic animal research reviewed above. ATSDR has not determined a minimum risk level for 1,3-butadiene.

2.2.2.11 OSHA Risk Assessment and Evidence

The Occupational Safety and Health Administration (OSHA) risk assessment addressed cancer risk using data from the second US NTP study [95]. The record of the risk assessment process reflects the full proceedings including the background data considered, the comments of interested parties, the detailed rationale for the approach used in the risk assessment, and the resulting risk values that were determined [108]. The final rule was promulgated in 1996. Other studies were considered as possible sources of data for the risk assessment. These included the first US NTP study of mice [136] and the IISRP study of rats [96], both of which have been described earlier. The second US NTP study was selected for the following reasons.

- Most of the exposure levels used were closer to then-current levels of occupational exposure than levels used in other studies.
- The B6C3F1 mice were randomized to exposure groups and their individual pathology reports were consistently coded.
- Good laboratory practice guidelines were following and audits were performed.
- Clear dose-response relationships were observed for several cancer sites.
- OSHA believed it was appropriate to use the most sensitive animal model known since the mechanism of carcinogenesis was not known for either laboratory animals or humans.
- Risk assessment results for the most recent epidemiologic study [124] were in reasonable agreement with the results based on the US NTP study.

For the risk assessment, OSHA chose to use rates of cancer at four sites: hemangiosarcomas of the heart, lung tumors, lymphomas, and ovarian tumors (in females). Tumor frequencies at the other sites increased with dose in mice of both sexes. The 1,3-butadiene doses considered in the risk assessment were 0, 6.25, 20, 62.5, and 200 ppm. The 625 ppm dose was not included because the response was linear up to 200 ppm, but not at the higher dose, and because pharmacokinetic data suggested that metabolism was becoming saturated at the 625 ppm dose. In extrapolating from doses in the mouse to equivalent doses in humans, a direct first-power calculation of body weight was used. This differed from other risk assessments in which body weights raised to ¾ power was used. The first-power calculation actually produced a lower risk estimate. To calculate equivalent doses, the exposure level in ppm for the mice was converted to an equivalent internal dose based on mg/kg body weight using the difference in mouse and human respiratory volumes and adjusting from continuous exposure to an eight-hour work day. The resultant calculation estimated human occupational exposure to 1 ppm to be the equivalent of a 0.3 mg/kg body weight for an eight-hour day.

OSHA selected a Weibull time-to-tumor multistage model as the basis for the risk calculation. This approach was able to account for competing causes of death, which was important because at some exposure concentrations mice were dying early from one type of tumor precluding the possibility of developing other types of tumors. For each of the four tumor types, and the combination of all of them, the model was fit to the data based on trials using different numbers of stages of tumorigenesis in the models. The model that gave the best fit with the lowest stage was used in each case. Both the maximum likelihood estimate (MLE) and the 95% upper bound of the MLE were determined for the risk of developing tumors in different tissues.

The risk estimates were based on 8-hour time-weighted average exposures for an occupational lifetime working 5 days per week, 50 weeks per year for 45 years. The risks were calculated assuming an exposure to 2 ppm, the proposed PEL at that time, at 1 ppm, as well as at other levels between 0.1 and 5 ppm. Comparative risk based on different tumors that appeared in both sexes, ranked from lowest to highest, are heart hemangiosarcomas < lymphomas < lung tumors. The range of projected excess cancer cases was from 2.7×10^{-4} to 16.2 per 1000 workers at an exposure of 2 ppm. Reducing the exposure reduced the number of cases to between 3.4×10^{-5} and 8.1 per 1000 workers. The estimated cancer risk based on lymphoma in male mice was 1.3 per 1000 workers and based on female mice was 6.0 per 1000 workers at an exposure of 1 ppm. Using lung cancer as the basis, the number of excess cases calculated for female mice at 2 ppm was 16 per 1000 workers or, at 1 ppm, was 8 per 1000. Using male mice, the equivalent numbers were 12.8 or 6.4 excess cases per 1000 workers. The estimate of premature leukemia deaths in workers using a 1-stage Weibull time-to-tumor model based on all lymphoma, lung, and ovarian tumors ranged between 1.3 and 8.1 per 1000 workers. A similar set of estimates made by NIOSH ranged from 0.9 to 30 cases per 1000 workers. A preliminary estimate based on the data available from the IISRP rubber worker study by Delzell et al. was 8 per 1000 workers. Thus, both the animal and human data available at the time were in good concordance.

In using the results of these risk estimations to set the permissible exposure limit (PEL), OSHA considered the risks of premature death associated with other high- and low-risk occupations, technical considerations, and the precedent set by the court in the benzene case that had occurred prior to this regulatory action. Substantial risks over 1 per 1000 workers were viewed by the court as unacceptable so the risks ranging from 2.5 to 16.4 per 1000 that were predicted at 2 ppm were seen as unacceptable. The risks associated with high-risk occupations like mining were in the range of 15 deaths per 1000 workers while the risks from low-risk occupations were about 0.8 per 1000. Technical feasibility issues restricted lowering the PEL below 1 ppm so the risk range of 1.3 to 8.2 per 1000 was seen as a reasonable compromise. OSHA acknowledged that this was still a high level of risk and included measures to encourage employers to lower exposures to an action level of 0.5 ppm.

A UR at 1 ppb could be calculated for comparison to the OSHA PEL by using the upper end of the risk range, about 8 per 1000 workers, by assuming linearity between exposures of 1 ppm and 1 ppb and by converting from the parameters of work exposure to lifetime community exposure. The proportionate risk at 1 ppb can be determined using the total career occupational exposure at 1 ppm and the total lifetime exposure at 1 ppb.

> Cumulative occupational exposure at 1 ppm = 1,000 ppb x 40 hours/wk x 50 wk x 45 years = 9×10^7 ppb*hours.

Cumulative lifetime exposure = 1 ppb x 24 hours/day x 365 days x 75 years = 6.57 x 10^5 ppb*hours (0.008 risk/ 9 x 10^7 ppb*hours) * 6.57 x 10^5 ppb*hours = 5.84 x 10^{-5} per ppb or 2.6 x 10^{-5} per μg/m^3.

This can be compared to the California UR of 1.7x10^{-4} per μg/m^3 or the US EPA IRIS UR of 3x10^{-5} per μg/m^3.

2.2.2.12 Summary and Conclusions

The estimates of risk from exposure to 1,3-butadiene for either non-cancer effects or neoplastic effects developed by the US EPA Integrated Risk Information System, the California Office of Environmental Health Hazard Assessment, and the Occupational Safety and Health Administration are summarized in Table 4. Both the US EPA IRIS and OEHHA determinations of non-cancer risk were based on the observation of ovarian atrophy in the second US NTP mouse bioassay. The development of both the reference concentration (RfC) and the reference exposure level (REL) used the benchmark dose approach which assumes a threshold below which no significant adverse health effect is anticipated.

Table 4. Summary of conclusions from risk assessments of 1,3-butadiene.

Agency	**Non-cancer**		**Cancer**	
	Outcome	Basis	Outcome	Basis
US EPA IRIS [35]	RfC=0.9 ppb (2.03 μg/m^3)	Ovarian atrophy in mice [95]	Inhalation unit risk = 3 x 10^{-5} per μg/m^3 or 8 x 10^{-5} per ppb	Epidemiology [124]
California OEHHA [137]	REL= 8 ppb (20 μg/m^3)	Ovarian atrophy in mice [95]	Inhalation unit risk = 1.7 x 10^{-4} per μg/m^3 or 3.8 x 10^{-4} per ppb	Cancer in mice [95]
OSHA [108]	N/A		Occupational excess risk 1.3–8.2 per 1000 workers at 1 ppm career exposure	Cancer in mice [95]

The cancer URs were calculated from either the IISRP cohort epidemiologic study by Delzell and colleagues or from the second US NTP bioassay. The US EPA and California non-cancer reference doses differ by about an order of magnitude, with the US EPA values being lower. The differences in the risk assessments are due primarily to the way uncertainty and modifying factors were applied. The same primary data were used for both analyses. The URs for cancer at 1 μg/m^3 were determined by the US EPA from epidemiologic data and by the California OEHHA from the US NTP mouse study. The UR calculated by OEHHA is about 5 times higher than the US EPA estimate. The use of different types of studies as data sources accounts for much of the difference. An estimate of UR from the upper end of the OSHA risk assessment is 3 x 10^{-5} per μg/m^3 which is in good agreement with the other two determinations. As noted above, ambient exposure levels of about 0.3 ppb (0.675 μg/m^3)

would be associated with a risk level between 10^{-4} and 10^{-5}. Hot-spot exposure areas in Houston have ambient concentrations that are about 10-fold greater, which would shift the risk up by about an order of magnitude, to between 1 and 10 per 10,000 individuals.

2.2.3 Formaldehyde

2.2.3.1 What is Formaldehyde?

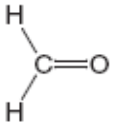

Figure 8: Formaldehyde

Description. Formaldehyde (CAS Registry No. 50-00-0), molecular formula HCHO (Figure 8), is a colorless, flammable, and pungent gas that is sold commercially as 30-50% (by weight) aqueous solutions. It is also known as methanal, methylene oxide, oxymethylene, methyladehyde, and oxomethane. Concentrations of formaldehyde in the air are usually listed as micro- or milligrams per cubic meter ($\mu g/m^3$, mg/m^3) or as parts per billion or parts per million (ppb, ppm). For converting $\mu g/m^3$ to ppb, 1.23 $\mu g/m^3$ = 1 ppb of formaldehyde; 1,000 ppb = 1 ppm. For purposes of this section, most formaldehyde concentrations are given in ppb for easier comparability.

Major Uses. Formaldehyde is used in the production of fertilizer, paper, plywood, urea- and phenol-formaldehyde resins, detergents, cosmetics, and sugar. It is also used in fumigants, soil disinfectants, and embalming fluid; for tanning leather; and in hospitals and laboratories as a tissue preservative.

Sources. Natural sources of formaldehyde in ambient air include forest fires, animal waste, and plants. Man-made combustion sources include power plants, incinerators, refineries, wood stoves, kerosene heaters, and cigarettes. Other man-made sources include vent gas from formaldehyde production, exhaust from motor vehicles, emissions from the use of formaldehyde as a disinfectant or preservative, and off-gassing of formaldehyde resins in plywood, fabrics, and paper.

Formaldehyde is also formed secondarily in the atmosphere by the photochemical oxidation of organic gases. Using ambient measurements, Li et al. have estimated that the amount of formaldehyde directly emitted from eastern North America is 16 times less than that produced by the oxidation of emitted volatile organic compounds (VOCs) [152]. Formaldehyde formation in Houston has been shown to be directly related to oxidation of olefins, including propene and ethene [153]. Concentrations of formaldehyde in plumes from several petrochemical plants were observed to increase dramatically downwind of the plants, despite dilution and consistent with rapid photochemical formation of formaldehyde from emitted VOCs rather than from direct emission from the plants.

The formation of formaldehyde in the atmosphere is counter-balanced by removal processes including direct photolysis and oxidation by photochemically produced hydroxyl and nitrate radicals. Estimates of the half-life for formaldehyde in the atmosphere range from 1.9 to 19 hours depending upon the level of radiant energy and concentrations of other pollutants in the air. The dominant pathway of formaldehyde photolysis produces stable molecular hydrogen and carbon monoxide. The other pathway produces the formyl radical and a hydrogen atom, which react quickly with oxygen to form the hydroperoxyl radical and carbon monoxide [154].

2.2.3.2 Where Does Exposure Occur?

For formaldehyde, inhalation is the primary exposure route. For most people, three scenarios account for nearly all exposure to formaldehyde: (1) outdoor, (2) indoor (e.g., home, school, in-vehicle, and office), and (3) occupational (e.g., chemical processes, embalming). As shown in Table 5, cigarette smoking is a major source of exposure for smokers and for persons exposed to second-hand smoke.

Table 5: World Health Organization's summary of typical formaldehyde concentrations found in outdoor and indoor environments and their contribution to daily exposure [155, 156].

Source	Concentration in mg/m^3 (ppb)	Exposure (mg/day)
Ambient air (10% of time; 2 m^3/day)	0.001–0.02 (0.8–16)	0.002–0.04
Indoor Air		
Home (65% of time; 10 m^3/day)		
Conventional home	0.03–0.06 (24–48)	0.3–0.6
Mobile home	0.1 (80)	1.0
Environmental tobacco smoke	0.05–0.35 (40–280)	0.5–3.5
Workplace (25% of time; 8 m^3/day)		
Without occupational exposure[a]	0.03–0.06 (24–48)	0.2–0.5
With occupational exposure	1.0 (800)	8.0
Environmental tobacco smoke	0.05–0.35 (40–280)	0.4–2.8
Smoking (20 cigarettes/day)	60–130 (48,000–104,000)	0.9–2.0[b]

[a] Assumes average indoor formaldehyde concentration
[b] Total amount of formaldehyde in smoke from 20 cigarettes

Outdoor Air. Air in rural areas generally contains less than 1 ppb of formaldehyde. In suburban areas, levels are typically in the range of 2 to 6 ppb. In urban areas, levels are generally 2 to 45 ppb. Examples of annual averages of urban formaldehyde levels monitored in 2004 include: Chicago area, averages ranging from 0.7 to 2.0 ppb (8.1 ppb maximum); St. Louis area, averages ranging from 1.7 to 4.2 ppb (35.6 ppb maximum); Houston area, averages ranging from 2.7 to 7.9 ppb (20.1 ppb maximum); and Los Angeles area, averages ranging from 2.8 to 7.2 ppb (15.5 ppb maximum) [1]. In the recent Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study, Weisel and associates measured indoor, outdoor, and personal exposures to numerous chemicals in three cities including Houston between 1999 and 2001. They observed similar mean levels of outdoor formaldehyde in Elizabeth, NJ (5.2 ppb), Houston, TX (5.1 ppb), and Los Angeles, CA (5.3 ppb). The median values were also similar: 5.8 ppb, 5.0 ppb, and 5.3 ppb, respectively [157].

Ambient 24-hr average formaldehyde concentrations monitored in the Houston area during 2005 were in the range of 2.8–7.9 ppb. Average 24-hr concentrations reached as high as 16.2 ppb in Deer Park and 18.8 ppb around the Ship Channel (Clinton Drive) [158].

Indoor Air. Indoor concentrations of formaldehyde tend to be higher than outdoor concentrations (Table 5). The size of the difference depends on the strength of indoor sources and the air exchange rate (AER) of the building. For the 306 homes investigated in the RIOPA study, the mean (and median) indoor and outdoor concentrations were 17.6 (16.3)

ppb and 5.2 (5.3) ppb, respectively [157]. The median contribution of outdoor formaldehyde to indoor levels was 19%.

Indoor sources of formaldehyde include indoor combustion sources (e.g., gas and wood stoves and cigarettes) and off-gassing (e.g., from pressed-wood products, carpets, and furnishings). The amount of formaldehyde released by off-gassing depends on the strength of the source as well as the temperature and humidity [159]. At higher temperatures and/or higher humidity, more formaldehyde is emitted. Many indoor sources, such as pressed-wood products containing urea-formaldehyde (UF) resin, urea-formaldehyde foam insulation (UFFI), and permanent-press fabrics, also release more formaldehyde when new. As they age, the amount of formaldehyde emitted decreases.

Off-gassing from pressed-wood products has gradually become less of a problem in the US since the early 1990s when the American National Standards Institute (ANSI) established voluntary formaldehyde emission limits for particle board, fiber board, and plywood. On average, pressed-wood products produced today emit about one-sixth as much formaldehyde as those produced in the early 1980s [160]. UFFI was banned in Canada in 1980 and is no longer widely used in the US today. A 1985 study of indoor air quality under warm weather conditions in a variety of Houston-area residences measured indoor formaldehyde concentrations ranging from less than 8 ppb to 290 ppb (mean 70 ppb) [161], whereas in the more recent RIOPA study investigators reported a mean formaldehyde concentration of 17.0 ppb (median 16.1 ppb) for Houston residences [157]. A 2005 Health Canada review of indoor air quality studies carried out in Canada since the early 1990s reports that formaldehyde concentrations in Canadian homes range between 2.5 and 88 $\mu g/m^3$ (2–71 ppb), with an average between 30 and 40 $\mu g/m^3$ (24–32 ppb) [162].

Studies from the 1980s report higher levels of formaldehyde in mobile homes (Table 5), which often contain more pressed-wood products than conventional homes [155, 163, 164]. Results from more recent studies, however, suggest that differences in indoor formaldehyde levels between mobile and conventional homes may be decreasing due to reductions in emissions from pressed-wood products over the past two decades as well as a tendency towards reducing the amount of air leakage in conventional homes [157, 165]. The RIOPA study actually measured slightly lower formaldehyde levels in the 31 mobile homes than in the 82 single-family houses studied in Houston (median 15.0 ppb and 17.3 ppb, respectively). In this study, the mobile homes in Houston and Los Angeles had a higher mean AER than the other types of homes studied (there were no mobile homes studied in Elizabeth) [157]. Still, despite considerable variability in housing types, AERs, and strength of outdoor sources, the mean and median levels of indoor formaldehyde measured in the non-smoking homes investigated in Elizabeth (18.2 and 17.2 ppb), Houston (17.0 and 16.1 ppb) and Los Angeles (17.5 and 15.4 ppb) were very similar.

Cigarette smoke can be a major source of formaldehyde exposure (Table 5). Health Canada, using standard testing conditions (35 ml/puff, 2-second puffs every 60 seconds, ventilation holes unobstructed), measured the formaldehyde content of mainstream smoke (smoke inhaled and exhaled by the smoker) of 20 brands of cigarettes. The formaldehyde concentrations ranged from 11 to 128 μg per cigarette, with a mean of 53 μg. The formaldehyde content of sidestream smoke (smoke released by the burning end of a cigarette) of the 5 brands tested in this study ranged from 327 to 440 μg per cigarette, with a mean of 367 μg per cigarette [162]. Assuming 50 μg formaldehyde per cigarette, a person

who smokes 20 cigarettes per day would inspire 1 mg/day of formaldehyde from the mainstream smoke alone [164]. Smokers or nonsmokers who live in the presence of second-hand smoke (40–280 ppb) typically inspire 0.4–3.5 mg/day of formaldehyde from the burning tip of the cigarette. Although exposed for shorter periods, persons exposed to cigarette smoke in the workplace, in vehicles, or in bars can also be exposed to significant levels of formaldehyde.

Formaldehyde levels within vehicles are often higher than either ambient or non-smoking indoor levels due to infiltration of on-road emissions and/or unusually high levels from the off-gassing of materials inside vehicles at high temperatures. For this reason, commuting can be an important source of exposure to formaldehyde. In the RIOPA study, 65 adults were monitored for exposure to selected air toxics while driving. The median in-vehicle formaldehyde level was highest in Los Angeles (20.8 ppb), compared with 10.5 ppb in Elizabeth and 8.3 ppb in Houston. However, the mean value was higher in Houston (41.4 ppb) than in Los Angeles (30.9 ppb) or Elizabeth (12.1 ppb). The significant difference between the median and mean values in Houston reflects the large variability (standard deviation of 153.7 ppb, vs. 29.7 ppb in Los Angeles and 7.6 ppb in Elizabeth) of the in-vehicle formaldehyde levels measured in Houston.

The authors of the RIOPA study offered no explanation regarding the extreme variability in the Houston in-vehicle levels. A study of in-vehicle pollution conducted for the California Air Resources Board reported that factors such as roadway type, freeway congestion level, and time-of-day influence the in-vehicle levels of VOCs [166]. In addition, variations in in-vehicle temperature may play a role in the variability observed in Houston. For example, Schupp and associates have estimated, based on an average in-vehicle formaldehyde concentration of 39 ppb at 73^{o}F, that formaldehyde levels may be as high as 1365 ppb at 149^{o}F [167]. Such in-vehicle temperatures are not uncommon in Houston in the summer after cars have been parked in the sun. Moreover, several studies have shown that formaldehyde levels rise indoors with the addition of ozone to mixtures of VOCs [168-170]. Whether the occasional high levels of in-vehicle formaldehyde measured in Houston in the RIOPA study are related to high ozone episodes is not known. Conditions under which unusually high levels of formaldehyde might be found in Houston cars (or homes, offices, or schools near freeways) warrant further investigation.

Occupational Exposure. Based on a survey conducted in the 1970s, the National Institute of Occupational Safety and Hygiene (NIOSH) estimated that 1.6 million workers were exposed to formaldehyde in their workplace. Of these, about one third were employed in medical and health services. Another third were employed in other businesses or industries that expose workers to formaldehyde including the chemical industry, printing and publishing, paper manufacturing, retail stores, automotive service stations, funeral services, and photographic studios [171]. Occupational exposure often contributes significantly to a person's total exposure to formaldehyde (Table 5) [164].

In a 1992 fact sheet, the Occupational Safety and Health Administration (OSHA) estimated that the total number of firms using formaldehyde was 112,066 with 2,156,801 employees exposed [172].

The estimated number of workers grouped according to exposure was:

- 83,818 employees exposed to between 750 and 1000 ppb, mainly in apparel (58,831), furniture (11,612), and foundries (6,085);
- 122,554 employees exposed to between 500 and 750 ppb, mainly in apparel (58,831), textile finishing (19,125), furniture (12,643), laboratories (12,220), and foundries (10,594); and
- 1,950,429 employees exposed to between 100 and 500 ppb, mainly in apparel (823,637), furniture (235,095), paper mills (100,100), and plastic molding (90,000).

2.2.3.3 Health Effects

2.2.3.3.1 Acute Effects

Adverse health effects due to inhalation of relatively high levels of formaldehyde have been extensively reviewed [154, 164, 173-178] and are summarized in Table 6.

Table 6: Acute Health Effects of Formaldehyde.

Concentration (ppb)	Symptoms
> 24	Odor detection threshold (single or repeated exposure)
> 80	Eye, throat or nose irritation threshold (single or repeated exposure)
400–1,600	Decreased nasal mucus flow rate (3–5 hour exposure)
3,000	Decreased pulmonary function (only with heavy exercise)
3,000–5,000	Tearing of the eyes
10,000–20,000	Difficulty breathing, nose and throat burning, cough, and heavy tearing of the eyes
20,000–48,000	Severe respiratory tract injury, danger to life
48,000–100,000	Death

2.2.3.3.2 Chronic Effects

For purposes of considering standards for formaldehyde in outdoor air, health effects associated with low-level chronic exposure are of particular concern.

Respiratory Effects. Chronic exposure to formaldehyde can lead to respiratory sensitization and lower airway and chronic pulmonary obstruction. Inhaled formaldehyde has been associated with asthma, although no clear evidence of a specific immunologic response has been reported [179-182]. Formaldehyde's ability to exacerbate asthma may be worsened by the presence of other irritants such as ozone in urban air [181]. Histopathologic effects in animals exposed to inhaled formaldehyde include squamous metaplasia and hyperplasia in the nasal cavity and respiratory tract. In the rat these changes occur at concentrations of 2000 ppb and above [183-187].

Reproductive and Developmental Effects. Experimental exposure of animals to formaldehyde does not appear to result in any significant teratogenic or reproductive effects [174].

Cancer. The association between formaldehyde and cancer in humans has been investigated in epidemiological studies of industrial workers, embalmers, and pathologists exposed to formaldehyde. Formaldehyde is classified by the United States Environmental Protection Agency (US EPA) as a Group B1 carcinogen (known animal carcinogen, probable human carcinogen), by OSHA as a carcinogen, by NIOSH as a carcinogen, and by the United States National Toxicological Program (US NTP) as reasonably anticipated as a carcinogen. Most recently, the International Agency for Research on Cancer (IARC) concluded that formaldehyde is carcinogenic to humans (group 1) based on sufficient evidence in humans and sufficient evidence in animals [173, 188].

Nasopharyngeal Cancer. The IARC working group cited a statistically significant excess of deaths from nasopharyngeal cancer in a large cohort (N = 25,619; 865,708 person-years) of industrial workers employed in 10 US formaldehyde-producing or formaldehyde-using facilities through 1994. The study found statistically significant exposure-response relationships for peak and cumulative exposures [189]. An excess of deaths from nasopharyngeal cancer was also observed in a proportionate mortality analysis of a US cohort of embalmers [190]. Excess cases of nasopharyngeal cancer were also observed in a Danish study of proportionate cancer incidence among workers at companies that manufactured or used formaldehyde [191]. Of seven case-control studies of nasopharyngeal cancer reviewed by the IARC working group [192-198], five found elevations of risk for exposure to formaldehyde. The group considered it "improbable that all of the positive findings for nasopharyngeal cancer that were reported from the epidemiologic studies, and particularly from the large study of industrial workers in the U.S., could be explained by bias or unrecognized confounding effects."

Sinonasal Cancer. Several case-control studies have investigated the relationship between formaldehyde exposure and sinonasal cancer. However, due to inconclusive findings and the potential for confounding by wood dust exposure, the IARC working group concluded that there is limited evidence that formaldehyde causes sinonasal cancer in humans.

Leukemia. Recent updates of two of three major industrial cohort studies suggest a possible association between formaldehyde exposure and leukemia. In a study of US industrial workers, a statistically significant exposure-response relationship (based on peak exposure and, to a lesser degree, on average intensity of exposure) was observed for leukemia and, particularly, for myeloid leukemia [199]. The study showed a positive association with its internal (relative risk) data but there was no excess mortality from leukemia when the industrial workers were compared with the general US population. The IARC working group accounted for this by noting that the comparison with the general population could be biased [188]. Excess mortality from leukemia among US garment workers was statistically significant among workers with a longer duration of exposure and follow-up [200]. Excess mortality from leukemia, particularly myeloid leukemia, has also been observed in six of seven studies of embalmers, funeral parlor workers, pathologists, and anatomists [190, 201-206]. A recently updated study of industrial workers in the United Kingdom, however, did not show excess mortality from leukemia. The IARC working group noted that peak exposures and the risk of myeloid leukemia were not specifically addressed in the study [207]. The IARC working group concluded that "there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde [188]."

2.2.3.4 Biologic Basis for Health Effects

2.2.3.4.1 Physiologic Pathway

Absorption. More than 90% of inhaled formaldehyde is absorbed in the upper respiratory tract [208]. In rodents, due to nose-breathing, absorption occurs in the nasal passages whereas in monkeys and humans, due to oral and nasal breathing, absorption occurs in the nasal passages, oral cavity, trachea, and bronchi [209].

Effective Dose. Formaldehyde occurs naturally in humans as an intermediate produced during the normal metabolism of amino acids. In humans, under normal physiologic conditions, concentrations are approximately 2.7 μg/g of venous blood [208]. The majority of inhaled formaldehyde is absorbed in the upper respiratory tract. Retention in the nasal passages of the rat was estimated at 93% of the inhaled amount, regardless of airborne concentrations. Because of deposition in the respiratory tract and rapid metabolism, inhalation of formaldehyde does not result in an increase in blood concentrations in animals, including humans [208, 210]. Formaldehyde has a half-life of about 1 minute in rat plasma. In a study by Heck and associates, exposing rats to 14,000 ppb and humans to 1,900 ppb of formaldehyde did not significantly increase the formaldehyde concentration of the blood [208]. Formaldehyde toxicity occurs locally when intracellular levels saturate the natural protective activity of formaldehyde dehydrogenase which converts formaldehyde to the less reactive metabolite formate [154].

Metabolism. The metabolism of endogenous and exogenous formaldehyde to formate takes place by multiple pathways in all tissues of the body. More than 90% of inhaled formaldehyde is absorbed in the upper respiratory tract where it is rapidly metabolized to formate. Formate is partially incorporated via normal metabolic pathways into the one-carbon pool of the body, for the biosynthesis of purines, thymidine, and certain amino acids which are incorporated into DNA, RNA, and proteins during macromolecular synthesis, or further oxidized to carbon dioxide (CO_2) [154].

Elimination. There are two pathways of final elimination: via exhalation and via the kidneys. Excess formate that does not enter the one-carbon biosynthesis pathway is removed from tissues by the blood and eliminated as CO_2 in expired air. A small percentage of excess formate is also eliminated directly in the urine. In rats exposed to [^{14}C]formaldehyde by inhalation, approximately 40% of the ^{14}C was exhaled as $^{14}CO_2$, 40% was incorporated into macromolecules, and the remainder was excreted in the urine and feces [211, 212].

2.2.3.5 Toxicity

Both genotoxic (direct or indirect DNA changes or damage) and cytotoxic (damage to cells) effects are involved in the changes observed in nasal tissues exposed to formaldehyde.

Genotoxicity. Workers who inhale formaldehyde typically exhibit DNA changes in their buccal or nasal mucosal cells [213-217]. The primary genotoxic effects of formaldehyde are clastogenic (chromosomal aberrations, deletions, and sister chromatid exchanges), as opposed to point mutations. These findings are consistent with a mechanism in which formaldehyde-induced DNA-protein cross-linking acts as a replication block which ultimately leads to a variety of deleterious effects including chromosomal aberrations, deletions, or cell death [211].

A few studies have shown genetic effects of formaldehyde exposure in peripheral lymphocytes whereas others have not. The potential physiologic substrate of formaldehyde-associated leukemia is poorly understood because formaldehyde is assumed to exhibit carcinogenicity at sites of contact and inhalation of high concentrations of formaldehyde has not been shown to raise blood levels [173].

Cytotoxicity. Studies in laboratory rats [218] and monkeys [219] have demonstrated increased cellular proliferation in nasal tissue at formaldehyde concentrations above 6,000 ppb. Histological evidence of damage to the nasal epithelial tissue (e.g., squamous metaplasia, loss of ciliated cells, and goblet cell hyperplasia) has been observed in chemical workers exposed to formaldehyde [220]. Increased cellular proliferation is postulated to play a role in carcinogenesis by fixing chemically-induced DNA alterations not repaired prior to cell division or by increasing the number of cells undergoing DNA replication and therefore available to undergo a mutation [221].

Although formaldehyde is clearly an irritant, inflammation does not appear to be a primary mechanism underlying cytotoxicity. However, one study suggested that low-level exposure may induce a non-specific proinflammatory response. In that study, adults were exposed to 400 ppb formaldehyde for 2 hours [222]. In another study, exposure to formaldehyde at levels typically found in homes was observed to be associated with increased levels of exhaled nitric oxide, a marker of inflammation, in healthy children [223].

2.2.3.6 Risk Assessment and Standards/Guidelines for Exposure

Different organizations, agencies, states, and countries use roughly the same health studies to derive different risk assessments and standards/guidelines for formaldehyde exposure (Table 7). Risk and standard/guideline values vary based on a number of factors including the population of concern, method of exposure, individual susceptibility, methodology used to determine uncertainty, who is responsible for safety, how current the assessment is, and the level of risk deemed acceptable. The following are some of the perspectives on formaldehyde risk that have been developed and the resultant standards or guidelines. In general, occupational and non-occupational risk assessments are handled separately although there is a growing appreciation of total exposure from different environments and via different pathways.

Table 7. Summary of Conclusions from Risk Assessments for Formaldehyde.

Agency	Non-cancer		Cancer	
	Outcome	Basis	Outcome	Basis
US EPA IRIS (currently undergoing review) [224]	N/A		Inhalation unit risk = 1.3×10^{-5} per $\mu g/m^3$ or 1.05×10^{-5} per ppb	Squamous cell carcinoma in the nasal cavity of rats [185]
CIIT (from US	N/A	DPX and	Inhalation unit	DPX and

Office of Air Quality Planning and Standards) [158]		CRCP dose response data in the rat	risk = 5.5 x 10^{-9} per $\mu g/m^3$ or 4.5 x 10^{-9} per ppb	CRCP dose response data in the rat [225]
ATSDR[154]	Acute inhalation MRL = 40 ppb or 49.6 $\mu g/m^3$ Chronic inhalation MRL= 8 ppb or 9.9 $\mu g/m^3$	Irritation and nasal alterations in humans	N/A	
California OEHHA	Acute REL = 75 ppb (93 $\mu g/m^3$) [178] Chronic REL = 2 ppb (2.5 $\mu g/m^3$) [226]	Eye irritation in humans	Inhalation unit risk = 7 x 10^{-6} per ppb or 8.68 x 10^{-6} per $\mu g/m^3$ [150]	Cancer in rat [150]
TCEQ [227]	Acute ESL = 15 $\mu g/m^3$ or 12 ppb Chronic ESL = 1.5 $\mu g/m^3$ or 1.2 ppb			
OSHA [228]	PEL = 750 ppb STEL = 2000 ppb			
NIOSH [171, 229]	REL (8–10 hr TWA) = 16 ppb or 19.8 $\mu g/m^3$ REL (15 min) = 100 ppb or 124 $\mu g/m^3$ IDLH = 20,000 ppb or 24,800 $\mu g/m^3$	Inhalation toxicity in humans		
ACGIH [230, 231]	TLV = 300 ppb or 372 $\mu g/m^3$	Irritation in workers		
AIHA [231,	EGRP1 = 1,000	Health effects		

232]	ppb or 1240 μg/m^3 EGRP2 = 10,000 ppb or 12,400 μg/m^3	in workers		

2.2.3.6.1 Non-Occupational Risk from Exposure to Formaldehyde: U.S. National Standards and/ or Guidelines

US EPA Integrated Risk Information System (IRIS)

Noncarcinogenic Risk. At this time, the US EPA has no reference concentration (RfC) for non-carcinogenic effects for chronic inhalation exposure to formaldehyde.

Carcinogenic Risk. The US EPA's weight-of-evidence classification for the carcinogenicity of formaldehyde categorizes it as a Group B1 (probable human) carcinogen based on "limited evidence in humans, and sufficient evidence in animals" [224]. The US EPA cites nine key epidemiological studies, out of 28 that were reviewed, that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products [194, 197, 233-241]. Among these, two cohort studies [234, 235, 240] and one case-control study [197, 241] were rated by the US EPA as particularly "well-conducted and specifically designed to detect small to moderate increases in formaldehyde-associated human risks." Although the 25 other studies were limited in their ability to detect small to moderate increases in formaldehyde risks, six of the studies reported significant associations between excess site-specific respiratory (lung, buccal cavity, and pharyngeal) cancers and exposure to formaldehyde [194, 233, 236-239]. The US EPA found indications in the remaining studies that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure, but noted that biological mechanisms for such associations have not yet been demonstrated. Although exposure to formaldehyde is a factor in all of these studies, the epidemiologic evidence is categorized by the US EPA as "limited," primarily because of possible exposures to other agents (e.g., wood dust) that could have contributed to excess cancer cases.

The US EPA's principal qualitative evidence of carcinogenicity comes from positive studies in both sexes of two strains of rats [185, 242, 243] and males of one strain of mice [185], all showing squamous cell carcinomas as a result of formaldehyde exposure. In vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes, such as acetaldehyde, are cited as additional qualitative support for the B1 carcinogenicity classification [224].

The US EPA's quantitative estimate of cancer risk was obtained by modeling rat nasal squamous cell carcinoma data from a two-year inhalation bioassay [185]. In this study, groups of male and female F344 rats were exposed to 0, 2,000, 5,600, or 14,300 ppb formaldehyde for 6 hours/day, 5 days/week, for up to 24 months followed by an observation period of 6 months. The investigators found that the incidence of squamous cell carcinoma in the nasal cavity was markedly increased in the high-concentration, but not in the low-concentration, groups compared with the unexposed controls. The incidence of tumors was

0/118, 0/118, 1/119 (1%) and 51/117 (44%) in males and 0/118, 0/118, 1/116 (1%), and 52/119 (44%) in females in the control, low-, mid-, and high-concentration groups, respectively.

Quantitative cancer risk estimates are presented in the US EPA IRIS as unit risk (UR). Chemical concentrations are presented in IRIS as the risk levels expected to cause a certain number of excess cases of cancer: 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The inhalation UR for formaldehyde is 1.3×10^{-5} per $\mu g/m^3$ (1.05×10^{-5} per ppb). This means that 13 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 individuals who are exposed daily for a lifetime to 1 $\mu g/m^3$ (0.8 ppb) of formaldehyde in the air. Air concentrations at the specified risk levels are 8 $\mu g/m^3$ (7 ppb) at 1 in 10,000, 0.8 $\mu g/m^3$ (0.7 ppb) at 1 in 100,000, and 0.08 $\mu g/m^3$ (0.07 ppb) at 1 in 1,000,000 [224]. In urban areas, outdoor formaldehyde levels commonly exceed the lifetime exposure guidelines currently developed for IRIS for all three carcinogenic risk categories; indoor levels are generally even higher.

The US EPA completed its last significant revision to its IRIS formaldehyde assessment in 1991. A recent model developed by the Chemical Industry Institute for Toxicology (CIIT) Centers for Health Research suggests that formaldehyde exposure may not be as hazardous to humans as indicated by earlier analyses. A new IRIS assessment is underway in light of the CIIT model that supports a UR on the order of 5.5×10^{-9} per $\mu g/m^3$ (4.5×10^{-9} per ppb) [158, 244]. This value is more than 2,000-fold lower than the current IRIS UR of 1.3×10^{-5} per $\mu g/m^3$. The new risk values from CIIT have been used in recent risk assessments of formaldehyde by the Office of Air Quality Planning and Standards [158] and in the development of regulations to control formaldehyde emissions from wood processing industries [244]. Using this new risk assessment for formaldehyde, approximately 50% more US wood-processing facilities have been exempted from emission-control improvements previously required under the maximum achievable control technology (MACT) rule for plywood and composite wood production [245].

Chemical Industry Institute for Toxicology (CIIT) Centers for Health Research. CIIT researchers have used mechanistic data to reduce uncertainty factors in predicting the human cancer response to inhaled formaldehyde [225, 246-250]. The CIIT model for assessing carcinogenicity of formaldehyde attempts to account for nonlinearity in the dose-response relationships for intermediate endpoints associated with formaldehyde-induced nasal cancer. The model also accounts for interspecies variations in dosimetry that result from differences in mode of inhalation (e.g., nasal vs. oral nasal breathing) and anatomical features of the nasal and respiratory passages. The CIIT approach utilizes (1) DNA–protein cross-links (DPX) and cytolethality/regenerative cellular proliferation (CRCP) dose-response data from the rat, (2) 3-D computational fluid dynamics modeling that predicts the site-specific flux of inhaled formaldehyde into tissue lining the human respiratory tract, and (3) a two-stage clonal growth model to link levels of DPX and CRCP with mutation accumulation and tumor formation. The model predicts additional risks of respiratory tract cancer to be negative up to 1,000 ppb for smokers and nonsmokers when the raw J-shaped dose-response CRCP data from the rat is used. The CIIT researchers' finding that the toxicity of inhaled formaldehyde in this range is concentration dependent, but not duration dependent, is consistent with published results [187, 247, 251-253]. However, it is a significant departure from the default assumption of a constant concentration and time (C x T) relationship assumed by the US

EPA in its 1991 IRIS formaldehyde assessment. When a hockey-stick-shaped curve was fit to the rat CRCP data and used in place of the raw data, the model estimated the additional risk for 80 years of continuous environmental exposure for nonsmokers to be 10^{-6} or less below 200 ppb [225]. For the occupational scenario, combining the environmental exposure (an 80-year lifetime with continuous environmental exposure of 4.0 ppb) with occupational exposures (8 hours/day, 5 days/week for 40 years beginning at age 18), the hockey-stick-shaped predictions of additional risk are 10^{-6} or less below 600 ppb for "light working" and below 200 ppb for "heavy working" [225]. The CIIT researchers conclude that current exposure standards primarily concerned with non-cancer effects of formaldehyde are sufficient for protection against potential carcinogenic effects [225].

The Agency for Toxic Substances and Disease Registry (ATSDR). ATSDR, based in Atlanta, Georgia, has produced toxicological profiles for more than 250 hazardous substances, including formaldehyde. ATSDR has determined an acute inhalation minimal risk level (MRL) of 40 ppb (0.04 ppm) for formaldehyde based on clinical symptoms (e.g. increased itching, sneezing, mucosal congestion, and transient burning sensation of the eyes and of the nasal passages) and nasal alterations (e.g. elevated eosinophil counts and a transient increase in albumin content of nasal lavage fluid) in a study of human volunteers [222, 254]. This MRL is based on a lowest observed adverse effects level (LOAEL) of 400 ppb and an uncertainty factor (UF) of nine (3 for use of the LOAEL and 3 for human variability).

ATSDR has also determined a chronic inhalation MRL of 8 ppb for formaldehyde on the basis of a LOAEL of 240 ppb for mild irritation of the eyes and upper respiratory tract and histological evidence of mild damage to the nasal epithelial tissue (e.g., squamous metaplasia, loss of ciliated cells, goblet cell hyperplasia, and mild dysplasia in biopsied tissue) in formaldehyde-exposed chemical workers [220]. To derive the chronic inhalation MRL, the LOAEL was divided by an UF of 30 (3 for the use of the LOAEL and 10 for human variability).

2.2.3.6.2 Non-Occupational Risk from Exposure to Formaldehyde: State Standards and/ or Guidelines

California Office of Environmental Health Hazard Assessment (OEHHA). CA EPA's OEHHA has developed reference exposure levels (RELs) for a number of pollutants including formaldehyde. The RELs have been developed for use with California's Hot Spots Program. They are health-based concentration levels that are typically derived through the use of no observed adverse effects levels (NOAELs) and LOAELs with various safety or UFs applied. In the case of formaldehyde, the benchmark concentration (BC) approach was also used.

Acute Reference Exposure Level (REL_A). The REL_A developed by OEHHA for formaldehyde is based on protection from eye irritation which is the most sensitive indicator of effect for the general population [178]. The key study used in the determination was that of Kulle and associates in which 19 non-asthmatic, non-smoking individuals were exposed to 0–3000 ppb of formaldehyde for 3 hours and asked to rate the severity of eye, nose, and throat irritation [255]. Compared with non-exposed controls, increased reported eye and nose/throat symptoms in the exposed group were statistically significant at 200 ppb and 2000 ppb, respectively.

The REL_A was calculated using a BC approach where 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 440 ppb formaldehyde. This value was adjusted to a 1-hour duration using the formula Cn x T = K, where n = 2, resulting in a value of 760 ppb. The REL_A was calculated to be 76 ppb using the formula REL = BC_{05}/UF. An UF of 10 was used to protect the most sensitive individuals in the general population. Ten was chosen by OEHHA for the UF rather than the customary UF of 3 because of evidence in the literature of an unusually wide variability in response to formaldehyde irritancy, including cellular changes and an immune response at levels below the one-hour extrapolated BC_{05}.

Chronic Reference Exposure Level (REL_C). A study by Wilhelmsson and Holmstrom [256] was chosen by OEHHA for the determination of the REL_C because it was an occupational study and because it contained both an LOAEL (170 ppb) and a NOAEL (60 ppb) [226]. In this study, occupational exposure (mean concentration = 170 ppb) of 70 workers to formaldehyde for 1 to 36 years (mean = 10 years) resulted in significantly increased symptoms of nasal and eye irritation and airway discomfort compared with the control group (mean concentration = 60 ppb). Adjusting the occupational NOAEL for daily exposure, the average worker's daily exposure would be 20 ppb. Applying an intraspecies variability UF of 10 results in a REL_C (NOAEL/UF = 20/10) of 2 ppb.

OEHHA cited a supporting occupational study by Edling and associates which found similar sensory irritation due to long-term formaldehyde exposure [257]. Nasal biopsies from exposed workers in this study exhibited nasal epithelial lesions similar to those found in subchronic and chronic animal studies.

Level Protective Against Severe Adverse Effects. Based on a study by Green et al. [258], OEHHA determined an acute LOAEL of 3000 ppb formaldehyde for a duration of 17 minutes in asthmatics, following moderate exercise for 15 minutes [178]. Under these conditions the researchers identified 5 out of 39 asthmatic and healthy subjects as having clinically significant (> 10%) decrements in forced expiratory volume (FEV_1). Three of these 5 subjects responded with a 20% or greater decrease in FEV_1 which is considered a severe adverse effect for acute toxicity exposure. Because the LOAEL actually represents a threshold for pulmonary effects in asthmatics and because exercise during exposure was required to observe pulmonary deficits, the LOAEL was considered by OEHHA to be a NOAEL and no uncertainty factor was applied. The 3000 ppb value was adjusted to a 1-hour exposure, using a modification of Haber's equation (Cn x T = K where n = 2) for extrapolation from a shorter duration to a 1-hour level. The resulting LOAEL is 1600 ppb for 1-hour exposure to formaldehyde [178].

Level Protective Against Life-threatening Effects. For the determination of a BC_{05}, OEHHA used the mortality data developed by Alarie [259], which showed a 10-minute LC_{50} in mice (concentration which kills 50% of the animals) for formaldehyde of 2,162,000 ppb. A BED_{05} (which represents an experimental threshold for lethality) of 778,000 ppb for a 130 minute exposure was estimated from the data [260] and adjusted for a 1-hour exposure using a modification of Haber's equation (Cn x T = K where n = 2) for extrapolation from the longer duration to one hour. The UFs applied were 3 for interspecies differences and 10 for increased susceptibility of sensitive human individuals. The resulting estimated level protective against life-threatening effects is 11,000 ppb for a 1-hour exposure to formaldehyde [178].

Cancer Unit Risk Factor. OEHHA cites the same tumor incidence study used by the US EPA [185, 261] in calculating a quantitative cancer risk assessment for formaldehyde [150]. The UR for lifetime exposure was calculated by OEHHA to be 0.000007 ppb^{-1} based on molecular dosimetry data in a three-stage model using the default surface-area scaling factor, 1.2. Epidemiologic data were used by OEHHA for quantitative comparisons [234]. Evaluating mortality in a cohort of more than 26,000 workers, Blair et al. observed risk of death by lung cancer in exposed workers to be 15×10^{-3} over a career. Based on extrapolation of rat cancer risk predictions to humans for a 40-hour work week for 20 years and an exposure level of 1,000 ppb, the prediction of 95% upper confidence limits on respiratory tract cancer was 32×10^{-3} for the three-stage tissue-dose model with a generic contact scaling factor. Thus, the upper range of human cancer risk predictions from the rat bioassay data [185] was consistent with the occupational exposure cancer risk data.

Table 8: Health Assessment Values for Formaldehyde Used by California Regulatory Programs

	Value	**Reference**
Acute reference exposure level (REL_A)	75 ppb	[178]
Chronic reference exposure level (REL_C)	2 ppb	[226]
Level Protective Against Severe Adverse Effects (LOAEL)	1,600 ppb (1-hr)	[178]
Level Protective Against Life-threatening Effects	11,000 ppb (1-hr)	[178]
Unit risk factor	0.000007 ppb^{-1}	[150]

Texas Commission on Environmental Quality (TCEQ). The TCEQ is mandated by the Texas Clean Air Act to conduct air permit reviews of all new and modified facilities to ensure that the operation will not cause or contribute to a condition of air pollution.

The current long-term and short-term Texas ESLs for formaldehyde are 1.5 $\mu g/m^3$ (1.2 ppb) and 15 $\mu g/m^3$ (12 ppb), respectively [227]. Although the Texas ESLs for formaldehyde are among the guidelines currently undergoing review by the TCEQ, communication with the TCEQ suggests that the ESLs for formaldehyde are not expected to change.

2.2.3.6.3 Non-Occupational Risk from Exposure to Formaldehyde: International Standards and/ or Guidelines

Environment Canada and Health Canada. Formaldehyde has been assessed as a priority substance under the Canadian Environmental Protection Act (CEPA) of 1999 [262]. In Canada's National Air Pollution Surveillance (NAPS) program, formaldehyde was detected in 99% of 3,842 24-hour samples collected at 16 rural, suburban, and urban sites in six provinces between August 1989 and August 1998 [263, 264]. Measured concentrations ranged from below the detection limit to a maximum of 8.0 ppb, 9.8 ppb, and 27.5 ppb for 6 rural, 2 suburban, and 8 urban sites, respectively. The median outdoor concentration of formaldehyde was 2.3 ppb [263, 264]. A 2005 Health Canada review of indoor air quality studies carried out in Canada since the early 1990s reports that formaldehyde concentrations in Canadian homes range between 2.5 and 88 $\mu g/m^3$ (2–71 ppb) with an average between 30

and 40 μg/m^3 (24–32 ppb) [162]. Probabilistic simulations indicate that 1 of every 2 individuals would be exposed to 24-hour average formaldehyde concentrations of 19–24 ppb or greater and 1 in every 20 individuals (i.e., 95th percentile) would be exposed to 24-hour average formaldehyde concentrations of 65–73 ppb.

The estimated median and mean 24-hour time-weighted average exposures to formaldehyde in the air in Canada are considered to be, at most, one third of the value at which humans experience ocular and upper respiratory tract sensory irritation (> 100 ppb) [264]. Although concentrations in some indoor locations approach the level of sensory irritation, these are below the time-weighted average exposure of 95% of the population. Health Canada considers the CIIT dose-response model "to provide the most defensible estimates of cancer risk, on the basis that it encompasses more of the available biological data, thereby offering considerable improvement over default" [263]. Using the CIIT model, the predicted risk of upper respiratory tract cancer associated with exposure to the median, mean, and 95th percentile concentrations of formaldehyde in air in Canada was < 2.7 x 10^{-8} [264]. Formaldehyde is determined by Health Canada to be "toxic" as defined in Paragraph 64(c) of the CEPA 1999 [262]. However, "the priority for investigation of options to reduce exposure on the basis of carcinogenicity is considered to be low." Given the more worrisome levels of formaldehyde found in Canadian homes, it was recommended that continued investigation of options to reduce exposure to formaldehyde in indoor air be considered under the authority of acts other than CEPA 1999.

2.2.3.6.4 Occupational Risk from Exposure to Formaldehyde

Occupational exposures to formaldehyde may be quite significant because of both the potentially high concentrations of chemicals in the work environment and the duration of the exposure, typically an 8-hour day, 5 days per week, over several years. Regulatory and guideline levels for formaldehyde have been set by a number of agencies in an attempt to protect the health of workers. Regulatory levels are values that have been incorporated into government regulations and are enforceable whereas guideline levels are those provided by the government or other groups as advice. Of the agencies listed below, only the levels developed by OSHA are enforceable; the others offer guidance.

The National Institute of Occupational Safety and Health (NIOSH). NIOSH develops and periodically revises recommended exposure limits (RELs) for hazardous substances or conditions in the workplace, which OSHA then promulgates and enforces. NIOSH's REL for formaldehyde for an 8- or 10-hour time-weighted average exposure is 16 ppb with a ceiling of 100 ppb for a 15-minute exposure. NIOSH's immediately dangerous to life or health (IDLH) limit is 20,000 ppb based on acute inhalation toxicity data in humans. NIOSH considers formaldehyde to be a potential occupational carcinogen and therefore recommends as part of its carcinogen policy that the "most protective" respirators be worn for formaldehyde at concentrations above 16 ppb. Note that 16 ppb is slightly below the range of formaldehyde concentration found in most homes and nearly 50 times lower than OSHA's permissible exposure limit discussed later in this section [229, 265].

The American Conference of Governmental Industrial Hygienists (ACGIH). The threshold limit values (TLV) developed by ACGIH to protect workers from adverse health effects of formaldehyde have decreased 30-fold over the last 50 years. TLVs have been used by a number of agencies as a basis for controlling occupational and community exposures.

However, the medical input and scientific rigor used in their development has been called into question by a number of investigators [266-268]. In 1995, the ACGIH set a ceiling TLV for formaldehyde of 300 ppb based on evidence of irritation from reports of occupational and other exposures to formaldehyde. ACGIH has designated formaldehyde as being a Group A2 (suspected human) carcinogen [230, 231].

The American Industrial Hygiene Association (AIHA). AIHA has developed emergency response planning guidelines (ERPGs) for chemicals in the workplace. ERPG 1 is defined by AIHA as the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild transient adverse health effects or perceiving an objectionable odor. The ERPG 1 for formaldehyde is 1,000 ppb. ERPG 2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed up to one hour without developing irreversible or other serious health effects that could impair their abilities to take protective action. The ERPG 2 for formaldehyde is 10,000 ppb [231, 232].

Occupational Safety and Health Administration (OSHA). Part of the US Department of Labor, OSHA has established enforceable permissible exposure limits (PELs) for a number of workplace-related chemicals. PELs, expressed as time-weighted averages (TWAs), are defined as the concentration of a substance to which most workers can be exposed without adverse effect averaged over a normal 8-hour work day or a 40-hour work week. In 1987, OSHA set the PEL for formaldehyde at 1000 ppb and established a 2000 ppb 15-minute short-term exposure limit (STEL). The standard also included an action level of 500 ppb measured as an 8-hour TWA. The action level is the level of a harmful substance that, although permitted, requires medical surveillance and monitoring. Action levels are usually set at one half the PEL. The formaldehyde PEL was challenged by four unions and a public interest group as being insufficiently protective and, in 1992, OSHA lowered the PEL for formaldehyde from 1000 to 750 ppb. The 15-min STEL of 2000 ppb and the action level of 500 ppb were not changed [228]. In addition, OSHA currently requires that workers use the "most protective" respirators in concentrations exceeding 75,000 ppb (i.e., 100 × the OSHA PEL of 750 ppb) [229]. OSHA has estimated that compliance with the 750 ppb PEL will result in the avoidance of up to three additional cases of formaldehyde-induced cancer annually. In addition, OSHA estimates that, of the 2.1 million workers exposed to formaldehyde, approximately 21,568 workers will avoid formaldehyde-induced respiratory distress if OSHA's exposure limits are followed [172]. As noted earlier, OSHA's 8-hour TWA PEL of 750 ppb is nearly 50 times higher than the 8-hour TWA recommended by NIOSH (16 ppb). Such discrepancies are common among governmental agencies, largely reflecting different underlying missions and philosophies, different emphasis on the research data and, in this instance, the difference between guidelines (NIOSH) and enforceable regulations.

2.2.3.7 Summary and Conclusion

Formaldehyde enters the Houston environment from direct sources such as automotive and other fuel combustion and industrial on-site uses. An even greater amount enters the environment secondarily as other organic compounds in the air (e.g., propene and ethene from petrochemical plants) that undergo photochemical oxidation. Formaldehyde does not persist in the environment, but continuous release and/or formation can result in chronic

exposure near direct and/or secondary sources. Additionally, because of its photoreactivity, formaldehyde plays a role in the photochemical formation of ground-level ozone.

Critical health effects associated with inhalation exposure to formaldehyde occur primarily at the site of first contact (i.e., the respiratory tract). Sensory irritation of the eyes and respiratory tract by formaldehyde has been observed consistently in clinical studies and epidemiological surveys in occupational and residential environments. Inhalation exposures of formaldehyde in laboratory animals cause degenerative non-neoplastic effects and nasal tumors in rats. DNA-cross-linking and increased cellular proliferation likely contribute to induction of these tumors. Similar conditions are believed to present a similar risk to humans.

Quantitative assessments of carcinogenic risk due to formaldehyde exposure vary from 1.05 $x10^{-5}$ per ppb by the EPA, to 7 $x10^{-6}$ per pbb by OEEHA, to 4.5 x 10^{-9} per pbb by CIIT, depending on the methodology. The CIIT biological computational model, which uses species-specific three-dimensional computer reconstruction of the respiratory tract and computational fluid dynamics modeling to predict the level of DNA cross-linking, estimates a human cancer risk for formaldehyde which is more than 2000 times lower than that derived by the US EPA using animal data and protective uncertainty factors.

Ambient 24-hour average formaldehyde concentrations monitored in the Houston area during 2005 were in the range of 2.8–7.9 ppb, but reached as high as 18.8 ppb around the Ship Channel [1]. The majority of the Houston population is exposed to ambient levels of formaldehyde that are less than those associated with sensory irritation; however, in some indoor, in-vehicle, and occupational environments formaldehyde concentrations may approach those associated with eye and respiratory tract sensory irritation. It is recommended that increased priority should be placed on investigating options to reduce indoor, in-vehicle, and occupational exposure to formaldehyde.

2.2.4 Diesel Particulate Matter

2.2.4.1 What is Diesel Particulate Matter (Diesel PM)?

Diesel PM is a mixture of solid and liquid phase particles in diesel exhaust which vary with respect to physical properties (mass, number, size, shape, and surface area), formation mode, and chemical composition, all of which are relevant to human health.

2.2.4.1.1 Physical Properties

The most common physical descriptor of PM is aerodynamic diameter. The "coarse" fraction contains particles ranging from 2.5–10 μm ($PM_{2.5–10}$) (Figure 9). The "fine" fraction contains particles that are smaller than 2.5 μm ($PM_{2.5}$). Diesel PM contains particles in the "ultrafine" (< 0.1 μm) and "nanoparticle" (< 0.05 μm) ranges. Approximately, 92% of diesel PM mass has an aerodynamic diameter < 1.0 μm; however, more than 99% of the diesel PM particle count has an aerodynamic diameter < 0.1 μm [269]. Particle size distributions, number concentrations, and mass concentrations are all very variable depending on engine type, operation conditions, fuel composition, and emission control treatments as well as meteorological conditions at the emission site. As a result, there is generally only a weak correlation between particle number concentrations and particle mass concentrations [270-273].

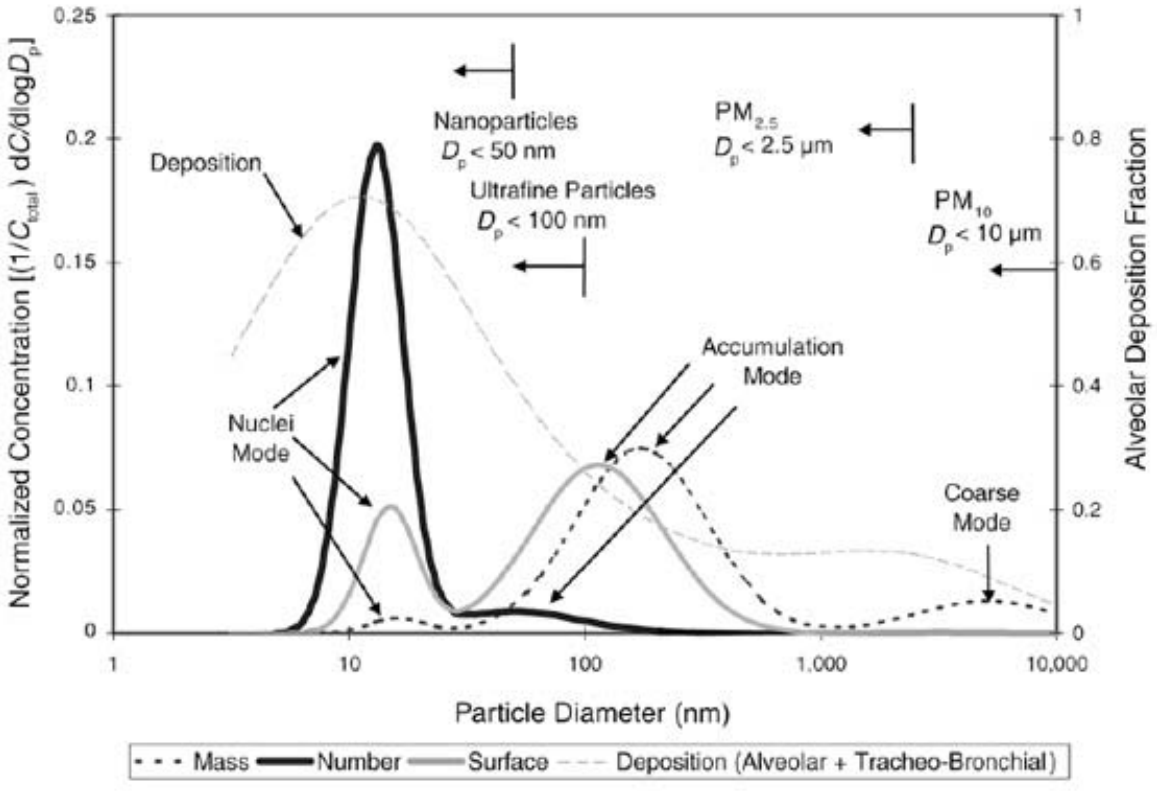

Figure 9. Normalized mass-weighted and number-weighted particle-size distribution curve from typical diesel exhaust. *C* denotes the number or mass concentration as indicated; *d* denotes differential; and D_p is the mean particle diameter [269].

The predominance of ultrafine and nanoparticles means that diesel PM has a tremendous amount of surface area for adherence of various chemical constituents and for interaction at biological interfaces. The relationship between particle mass, diameter, number, and surface area is shown in Table 9. The properties of small diameter and increased surface area contribute to the toxicity of particles in diesel exhaust.

Table 9. Particle number and surface area per 10 μg/m^3 airborne particles [274]

Particle diameter (nm)	Particle no. (cm^{-3})	Particle surface area (μm^2/cm^3)
5	153000000	12000
20	2400000	3016
250	1200	240
5000	0.15	12

2.2.4.1.2 Mode

Diesel exhaust particles have been classified according to three modes in the size distribution curve, namely nuclei, accumulation, and coarse, which correspond to their phase of formation [275]. In addition to size, the three modes also differ with respect to their chemical composition, physical state, and health effects (Figure 9).

Nuclei Mode. During the dilution and cooling of freshly emitted gaseous combustion exhaust, molecules of semi-volatile organic compounds (SVOCs) and sulfuric acid condense into liquid-phase nuclei with diameters ranging from 3 to 30 nm (0.003 to 0.03 μm) [271]. When formed, nuclei mode particles show large number concentrations in the area of emission, but have only a short lifetime. Although the nuclei mode typically contains only 0.1% to 10% of the total diesel PM mass, it often includes more than 90% of the total particle count [275]. The number concentration of the nanoparticles in the nuclei mode, as well as their chemical composition, can be dramatically affected by fuel composition and exhaust emission control measures.

Accumulation Mode. Accumulation mode particles are solid carbonaceous agglomerates with condensed SVOCs and sulfur species adsorbed onto them. Particles in the accumulation mode are frequently described as elemental carbon sponges which "soak up" the gaseous hydrocarbons and sulfuric acid molecules that would otherwise condense out as liquid nanoparticles in the nuclei mode [273, 276, 277]. Most of the particles in the accumulation mode have diameters around 100–200 nm (0.1–0.2 μm); however the mode extends from 30 nm (0.03 μm) at the upper end of the nanoparticle range through the ultrafine and fine particle range to 500 nm (0.5 μm). Accumulation mode particles make up approximately 10% of particle count and the majority (80% to 90%) of the diesel PM mass [275].

Coarse Mode. Diesel particles in the coarse mode have diameters above 1000 nm (1 μm). These particles are not generated in the diesel combustion process, but rather they are formed through deposition and subsequent re-entrainment of particle material from walls of the engine cylinder or exhaust system. The particles in the coarse mode contain 5–20% of the total diesel PM mass but contribute very little to particle numbers [275].

2.2.4.1.3 Chemical Composition

Diesel PM is generally thought of as consisting of elemental carbon "soot," organic hydrocarbon compounds, and small amounts of sulfate, nitrate, and trace metals. However, as described above, there is significant variation in the chemical composition of the particles depending on the mode of the particles (nuclei, accumulation, or coarse), properties of the engine source in which they were produced (heavy-duty vs. light-duty), operating conditions (idling, accelerating, or decelerating), fuel formulations (high vs. low sulfur fuel), lubricating oil, whether an emissions-control system is present, and the meteorological conditions and transformation processes that occur in the atmosphere after the particle is emitted [278].

Organic Carbon. The organic carbon fraction, composed of partially combusted lubricant and fuel, ranges from about 20% to 40% of the particle weight [278]. Many of the organic compounds in diesel exhaust are toxic or carcinogenic including aldehydes, 1,3-butadiene, monocyclic aromatic hydrocarbons such as benzene, and polycyclic aromatic hydrocarbons (PAHs) and their oxy- or nitro- derivatives. Some of these compounds are volatile organic compounds (VOCs) that, for the most part, remain in the gaseous phase. Others, like some PAHs and nitro-PAHs, are found in both the gaseous and particulate phase. As described above, these SVOCs are initially in the gaseous phase in the hot exhaust but then condense onto the particles as the exhaust is cooled and diluted in the ambient air. SVOCs may be extracted from the particles with organic solvents and analyzed. The species in this soluble organic fraction (SOF), to a large degree, determine the toxicological properties of diesel particles [278].

The sources of PAHs in diesel exhaust are unburnt PAHs from fuel, pyrosynthesis during combustion, and modification of one PAH into another. PAH emissions increase with increasing load and temperature and with the age of the engine [269]. In an analysis of eight diesel fuels, Westerholm and Li found that the fuel content of PAHs, aromatics, and sulfur have the strongest influence on PAH emissions [279]. The most abundant PAHs in the fuels studied were phenanthrene, 3-methylphenanthrene, 2-methylanthracen, 4&9-methylphenanthrene, and 1-methylanthracene. The most abundant PAHs in the SVOC phase and particulate fraction were phenanthrene, anthracene, and their methyl-derivatives. The particulate fraction also contained fluoranthene and pyrene. The PAH emission factors for the fuels varied in the range from 35 to 430 μg/km with the content of PAHs in the fuel having the strongest influence on PAH in emissions. The investigators found that by selecting diesel fuel with low total PAH content (< 4 mg/L), the PAH in exhaust emissions could be reduced by up to approximately 80% as compared with diesel fuels with PAH contents higher than 1 g/L (total PAHs).

Sulfur. Sulfur in diesel fuel has been identified as a major contributor to diesel PM emissions [280]. Reducing the sulfur content of diesel fuels reduces nucleation of SO_4 and allows the use of emissions control technologies such as diesel oxidation catalysts (DOCs) and diesel particle filters (DPFs). With many of these devices, low-sulfur fuel is necessary to limit the catalytic generation of sulfate nanoparticles (H_2SO_4 condensates) by oxidation of sulfur dioxide (SO_2) present in the exhaust gas. Since June 1, 2006, 80% of diesel fuel for on-road use produced by US refineries is required to have a sulfur content lower than 15 ppm.

2.2.4.2 Sources of Diesel PM

Diesel PM is emitted from on-road diesel engines (vehicles) or non-road diesel engines (locomotives, marine vessels, heavy-duty equipment, etc.) at a rate that can be as much as 20

times greater than gasoline-fueled engines [269, 281]. According to the United States Environmental Protection Agency (US EPA), from 1970 to 1998, PM_{10} emissions in the US decreased from slightly over 12,200,000 tons to just over 2,800,000 tons; however, PM_{10} emissions from on-road and non-road diesel engines increased from 320,000 tons to more than 521,000 tons during this same period. In other words, in 1970 diesel engine emissions were 3% of the PM_{10} inventory, whereas in 1998 diesel engine emissions were 18% of the PM_{10} inventory.

Marine vessels and port activities can significantly increase diesel PM levels in surrounding communities. A draft recently released by the California Air Resources Board (CARB) indicates that the combined diesel PM emissions from the ports of Long Beach and Los Angeles (1,760 tons per year in 2002) represented about 21% of the total South Coast Air Basin diesel PM emissions in 2002. These estimates do not include additional regional emissions from the trucks and locomotives transporting cargo outside the port boundaries.

Particulate emissions from diesel highway vehicles have decreased since 1988 due to the implementation of increasingly stringent US EPA emission standards for new model year heavy-duty diesel trucks. Diesel PM emissions from on-road sources are expected to decrease 37% from 1998 to 2007; however, since comparable standards do not exist for non-road sources, non-road diesel PM emissions are expected to increase 15% in the same period [278].

2.2.4.3 Where Does Exposure to Diesel PM Occur?

2.2.4.3.1 Outdoor Air

Unlike the other toxic air contaminants, no ambient monitoring data are available for diesel PM because no routine measurement method currently exists.

According to the US EPA, the annual average fraction of ambient $PM_{2.5}$ levels attributable to diesel PM is typically in the range of about 10% but may be as high as 35% in some urban environments [278]. A review by Lloyd et al. presents results from several studies that estimate 24-hour PM contributions from diesel exhaust (or a combination of diesel and gasoline exhaust) to be in the range of 1 to 20 $\mu g/m^3$ depending on location, sampling period, and method of estimating diesel source contributions [282]. Estimates for the early to mid-1990s derived by the US EPA place the national annual average diesel PM on the order of about 1.2 to 4.5 $\mu g/m^3$ for rural and urban areas, respectively [278].

Areas around roads will have higher levels of diesel PM (in the range of 8–42 $\mu g/m^3$) [283]. Study results reported by the CARB indicate that the 24-hour average diesel PM_{10} concentrations from the Long Beach freeway may be as high as 8 $\mu g/m^3$ above ambient concentrations [284].

Fraser et al. collected 24-hour integrated PM samples at four Houston area sites at regular intervals between March 1997 and February 1998. They used molecular speciation of ambient $PM_{2.5}$, source profiles detailing the compositional makeup of primary sources of fine particulate matter, and chemical mass balancing models to quantify the contribution from different emission categories to ambient fine particle burdens in Houston, TX [285, 286]. Their results showed diesel exhausts to be the most important primary source of ambient $PM_{2.5}$ in the Houston region, varying from 4% of the $PM_{2.5}$ mass at the Galveston site to 17%

of the $PM_{2.5}$ mass at the Clinton site. The contribution from diesel-powered vehicles was determined to range from 1.56 (± 0.27) μg/m^3 at the Bingle site, a suburban location, to 3.74 (± 2.61) μg/m^3 at the Clinton site, near the Ship Channel [285].

Monthly averages of elemental carbon concentrations measured at a monitor in Deer Park during 2005 ranged from 0.1–0.55 μg/m^3. Individual 24-hour averages reached higher than 5 μg/m^3 during the summer months. Using the conversion factor of 1.12 calculated by the Mayor's Task Force from the studies of Fraser et al., the average diesel PM concentration at this monitor was 0.11–0.62 μg/m^3 with 24-hour average levels reaching 6.45 μg/m^3.

Very high concentrations of diesel PM can accumulate in tunnels. Fraser et al. conducted sampling inside the Washburn tunnel in Houston during midday and afternoon over a period of 4 days between August 29, 2000 and September 1, 2000 [287]. On average, $PM_{2.5}$ levels were reported to be 35% higher inside the tunnel than on the outside. For the mid-day period when 1307 vehicles/hour (4.2% diesel) traveled through the tunnel, $PM_{2.5}$ levels were determined to be 99.1 (± 4.2) μg/m^3. In the afternoon with 2,550 vehicles/hr (2.1% diesel), $PM_{2.5}$ levels were 102.8 (± 4.5) μg/m^3. Source apportionment and chemical mass balance model calculations performed on the data revealed that the contribution from diesel vehicles was 64.3 (± 8.4) μg/m^3 and 67.3 (± 9.1) μg/m^3 for the mid-day and afternoon sampling periods, respectively.

A number of studies have reported increased personal diesel PM exposure associated with bus commutes, idling buses, and heavy bus traffic [288-292]. Average particulate levels inside diesel buses have generally been found to have particle mass concentrations which are 3 to 5 times higher than ambient levels. In Birmingham, AL, Hammond et al. observed average in-vehicle particle number concentrations in oxidation-catalyst diesel buses and compressed natural gas buses to be about 3-fold lower than in conventional diesel buses (9,954, 10,230, and 38,106 particles/cm^3, respectively) [290].

Measurements at a road edge in Birmingham (4 m from the curb) and downwind from it (more than 25 m from the curb) indicate that very small nanoparticles (< 10 nm diameter) accounted for approximately 36–44% of the total particle number concentrations emitted from traffic [293]. Nanoparticle concentrations at the edge of the road were in the range of 4.7×10^4 to 1.7×10^5 particles/cm^3 depending on the measuring technique employed. A study of on-road aerosol measurements completed in Minnesota showed particulate emissions ranging between 10^4 to 10^6, with the majority of the particles by number being less than 50 nm in diameter [294]. Higher speed was found to be associated with a greater nanoparticle concentration and smaller size.

Ultrafine particles (UFPs) and nanoparticles from freeways have been shown to rise and fall very dramatically depending on dispersion factors and distance from the freeway [272, 295-297]. The levels of these smaller particles in diesel emissions are of major interest because recent studies have indicated that they are more biologically toxic than $PM_{2.5}$ or PM_{10} in producing diesel PM-associated health effects [274, 298].

Particle counts measured 30 m downwind of Los Angeles Interstate 405 were in the range of $1.3–2.0 \times 10^5$/cm^3 [296]. Interstate 405 has a traffic volume of 13,900 vehicles/hour (93% gasoline-powered cars or light trucks). Interstate 710 in Los Angeles has a rate of 12,180 vehicles/hr and more than 25% of these vehicles are heavy-duty vehicles. Particle counts

obtained 17 m downwind of Interstate 710 were in the range of 1.8–3.5 x 10^5/cm^3 [297]. Particle concentrations on both freeways were observed to drop exponentially with distance downwind from the freeway [296, 297].

Freeways are a significant source of nano- and ultrafine particles; however, they contribute relatively little in terms of particulate mass. Dramatic changes in total particle number concentrations (dominated by UFPs) measured in the vicinity of Interstate 405 and 710 showed little correlation with total particle mass concentrations (dominated by $PM_{2.5}$ or PM_{10}) [272, 295-297]. Total particle mass concentration decreased by only a few percent throughout the entire measured range of 30 m to 300 m downwind of the freeway. Downwind PM_{10} mass concentrations were slightly higher than upwind concentrations and exhibited a small concentration gradient with distance from the freeway. $PM_{2.5}$ mass concentrations were about the same on the upwind and downwind sides of the freeway and exhibited almost no concentration gradient downwind [272].

Because fixed-site monitoring is not well suited for characterizing temporal gradients or spatial "hot spots" of UFPs in urban environments, recent studies have turned to mobile monitoring platforms using real-time instrument technologies [299]. Mobile monitoring of UFP number concentrations have been performed in Zurich, Switzerland [300], the Netherlands [301], Helsinki, Finland [302], New York City [303], Minneapolis [304], and Los Angeles [299]. The Los Angeles study found UFP number concentrations on the three freeway segments—110N, 10E, and 710S—to be up to 20 times higher than those measured on residential streets. The average daily traffic volumes for the three freeways were 209,000, 273,000, and 182,000 vehicles per day, respectively. Average diesel truck counts were 3,500, 10,000, and 25,000 per day which corresponds to 1.4%, 3.6%, and 14% of the total average daily traffic volumes. Particle counts on each of the freeway segments (47,000, 130,000, and 190,000 particles/cm^3, respectively) correlated well with the number of trucks per day on each. $PM_{2.5}$ mass concentration measurements did not correlate well with UFP counts or truck traffic (25, 110, and 54 μg/m^3 on each of the segments, respectively) [299].

2.2.4.3.2 Indoor Air

Unless a home or work place has an indoor diesel engine generating exhaust, it is generally assumed that the indoor concentration of diesel PM will be less than the outdoor concentration [282]. The 1990 average indoor diesel exhaust particle concentrations estimated by CARB using the California Population Indoor Exposure Model (CPIEM) ranged from 1.6 (± 0.7) μg/m^3 in office buildings to 3.0 (± 1.1) μg/m^3 in industrial plants and inside vehicles [284]. The model uses building air exchange rates, adult and children's activity pattern data, and population-weighted outdoor air concentrations of diesel exhaust particles as inputs to develop indoor concentration estimates and population exposure estimates across various environments. The 1990 population-weighted average outdoor concentration in California was estimated to be 3.0 μg/m^3. Inputting activity pattern data to the model, CARB estimated that Californians were exposed to average diesel exhaust particle concentrations of 2.0 (+ 0.7) μg/m^3 in enclosed environments in 1990. Using the 1995 estimated weighted average outdoor concentration of 2.2 μg/m^3 and the 1990 indoor:outdoor ratio (2.0:3.0), the 1995 average indoor concentration was estimated to be 1.5 μg/m^3.

The CPIEM results are in good agreement with the experimental results from the recent Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study of 100 homes and 100

adults in Los Angeles, CA, Elizabeth, NJ, and Houston, TX [157]. For the homes monitored in the RIOPA study, the average contribution of outdoor $PM_{2.5}$ to indoor $PM_{2.5}$ levels was determined to be 60%. Mean outdoor concentrations for total $PM_{2.5}$ for Los Angeles, Elizabeth, and Houston were 19.2 (± SD 13.3), 20.4 (± SD 10.7), and 14.7 (± SD 5.8) $\mu g/m^3$, respectively. Mean indoor $PM_{2.5}$ levels were 16.2 (± SD 9.4), 20.1 (± SD 15.5), and 17.1 (± SD 12.7) $\mu g/m^3$, respectively. Neither of the studies addressed concentrations of diesel nanoparticles or UFPs, or the contribution of outdoor levels of diesel UFPs to the $PM_{2.5}$ levels in the indoor environment.

2.2.4.3.3 Occupational Exposure

Workers who are likely to be exposed to elevated levels of diesel particle emissions include mine workers, bridge and tunnel workers, railroad workers, loading dock workers, truck and fork-lift drivers, farm workers, auto, truck, and bus maintenance garage workers, toll booth collectors, and people who work near areas where diesel-powered vehicles are used, stored, or maintained. In a 1997 review by the Health Effects Institute (HEI), the estimated ranges reported for 8-hour average workplace exposures to diesel PM varied from approximately 1–100 $\mu g/m^3$ in transportation occupations to 100–1,700 $\mu g/m^3$ for underground mining occupations where equipment powered by diesel engines is often used in enclosed spaces [305]. The US EPA estimates that the 70-year lifetime exposure equivalents for workers in these occupational groups range from 0.4–2 $\mu g/m^3$ on the low end to 2–269 $\mu g/m^3$ on the high end [278].

2.2.4.4 Acute Health Effects

2.2.4.4.1 Acute Health Effects Associated with PM

Epidemiologic studies have consistently shown that increases in daily average PM levels are associated with increases in daily mortality and hospitalizations for cardiovascular and respiratory disease [306-314].

Results of the time-series National Morbidity, Mortality, and Air Pollution Study (NMMAPS) found positive associations of PM_{10} with cardiopulmonary mortality and with hospital admissions for cardiovascular disease, chronic obstructive pulmonary disease (COPD), and pneumonia in patients 65 or more years of age living in varied environments across up to 90 cities in the US [308, 311]. Findings indicated an increase of about 0.3% in combined cardiorespiratory mortality for each 10 $\mu g/m^3$ of air increase in PM_{10} [312].

One of the most cited epidemiological studies is the Harvard Six Cities Study [315]. The group investigated the PM_{10} and $PM_{2.5}$ concentrations in six major US cities, comparing the measured values to excess daily mortality in the corresponding areas over eight years, and concluded that fine particulates showed a better correlation with mortality than did PM_{10} or other atmospheric pollutants. The study found that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ corresponded to a 1.5% increase in daily mortality.

Examples of several other studies that have found associations with PM and specific acute health effects are described below.

Respiratory Effects (Non-Asthma). Peel et al. found standard deviation increases of ozone, NO_2, CO, and PM_{10} in Atlanta were associated with 1–3% increase in hospital emergency

department visits for upper respiratory infections and a 2 μg/m^3 increase of $PM_{2.5}$ organic carbon was associated with a 3% increase in emergency department visits for pneumonia [316]. Delfino et al. similarly observed significant associations between PM_{10}, $PM_{2.5}$, and the sulfate fraction of $PM_{2.5}$ with respiratory emergency ward visits in Montreal [317]. Increases in PM_{10} concentration were associated with increases in cough, phlegm production, and sore throat in children with and without asthma in Port Alberni, British Columbia [318]. Tiittanen et al. reported associations between peak flow and cough and PM_{10}, $PM_{2.5}$, and $PM_{2.5–10}$ concentrations [319]. Pekkanen et al. found associations between peak flow and both PM_{10} mass concentration and number count of ultrafine particles [320]. A study in the Czech Republic reported associations between PM_{10} concentration and both peak flow and shortness of breath in children [321]. $PM_{2.5}$ was found to be more strongly associated with acute respiratory health effects in school children in the eastern US than coarse particles [322]. Mar et al. found children's self-reported symptoms of cough to be associated with PM_{10}, $PM_{2.5}$, $PM_{1.0}$, and $PM_{2.5–10}$ concentrations ($p < 0.05$). Sputum production and runny nose were associated with PM_{10} and $PM_{2.5–10}$ concentrations.

Asthma. Increases in PM concentrations have been found to be associated with increases in emergency room visits for asthma in Seattle, WA [323-325], Spokane, WA [324], Santa Clara County, CA [326], and London [327]. Elevated levels of PM have also been associated with increases in reported symptoms and/or use of medication for asthma [328, 329]. Pope et al. studied current-day and daily-lagged effects of PM fluctuations in healthy fourth- and fifth-grade elementary school students and in a group of asthmatics (8 to 72 yr of age) in Utah. They found that elevated PM_{10} pollution levels of 150 μg/m^3 were associated with an approximately 3% to 6% decline in lung function as measured by peak expiratory flow [330].

Cardiovascular Effects. $PM_{2.5}$ has been associated with effects on cardiac autonomic function as indicated by decreased heart rate variability [331]. PM has also been implicated in the triggering of myocardial infarction [332, 333], arrhythmias [334], acute decompensation in patients with congestive heart failure [309, 335, 336], and increased risk or severity of myocardial ischemia [337, 338].

2.2.4.4.2 Acute Health Effects Associated with Diesel PM

A number of studies have been performed trying to refine the original PM epidemiological studies by, for example, considering source specification. An association of $PM_{2.5}$ from mobile and coal combustion sources with daily mortality was probably first shown by Laden et al. in 2000 [339]. In this study, the original interpretation of the Harvard Six Cities Study [315] was extended by looking at the elemental composition of the measured $PM_{2.5}$ values, which was obtained by specific factor rotation analysis of 15 specified chemical elements. The source apportionment showed that a 10 μg/m^3 increase in $PM_{2.5}$ from mobile sources (i.e., traffic) corresponded to a 3.4% increase in daily mortality in the selected areas, whereas $PM_{2.5}$ from coal combustion accounted for a 1.1% increase. Increased levels of crustal $PM_{2.5}$ did not correlate with increases in daily mortality. In another study, researchers examined three years of daily mortality and pollution data (1995–1997) in Phoenix, AZ. They found that cardiovascular mortality was significantly associated with combustion-related pollutants and secondary aerosols (sulfates) [340].

In Europe, the correlation between particulate air pollution and adverse health effects was studied for several European cities in the APHEA (Air Pollution and Health: a European

Approach) time-series study [341-346]. A 10 μg/m^3 increase in daily PM_{10} was associated with a 0.5% increase in daily mortality [343, 346]. Katsouyanni et al. reported that an increase of 50 μg/m^3 in sulfur dioxide, black smoke, or PM_{10} was associated with an increase in daily mortality of 3%, 3%, and 2%, respectively, for the western European cities studied (London, Paris, Barcelona, and Athens) [342]. It was suggested that the stronger correlation of mortality with black smoke rather than PM_{10} may reflect the relatively greater toxicity of diesel-related pollution, which is the major source of black particles in many European cities [342].

Examples of several studies that have found associations with diesel particles (or diesel particle chemical components or physical properties) and specific acute health effects are described below.

Respiratory Effects (Non-Asthma). Diesel PM has been implicated in a number of studies that link acute respiratory symptoms and truck traffic [347]. In one study, 15 healthy volunteers who were exposed for 1-hour periods to diesel exhaust (300 μg/m^3 PM_{10} from an idling Volvo diesel engine and 1,600 ppb NO_2) developed elevated levels of neutrophils, macrophages, B-cells, mast cells, T-lymphocytes, histamine, endothelial adhesion molecules, and lactate dehydrogenase in their airways at 6 hours postexposure [348]. Diesel particles were considered to be the probable cause of the inflammatory effect because previous experiments, by the same authors using a similar protocol [349], showed that NO_2 alone at a higher concentration for a longer duration (2000 ppb NO_2 for 4 hours) did not show any cellular inflammatory response in the airway tissue at 6 hours postexposure. Nightingale et al. have also demonstrated that exposure to diesel particles at high ambient concentrations (200 μg/m^3 PM_{10} generated from an idling diesel engine) leads to an airway inflammatory response in normal volunteers [350].

Asthma. A case-control study of 417 children hospitalized for asthma and 461 age-matched controls hospitalized for non-respiratory diseases in Eric County, NY, revealed a relationship between pediatric hospitalization for asthma and living within 200 m of a road with heavy traffic, particularly truck and trailer traffic [351]. Components of diesel exhaust have been shown to worsen respiratory symptoms in individuals with preexisting asthma or allergies, and perhaps also to play a role in causing asthma [352-364].

Cardiovascular Effects. A few studies have monitored particle number as well as mass to investigate the role of UFPs versus $PM_{2.5}$ in PM-related acute cardiopulmonary events. A 3-year time-series study by Wichmann et al. revealed independent associations between daily ambient $PM_{2.5}$ concentration (represented by particle mass) and UFPs (represented by particle number) and mortality from cardiovascular and respiratory disease in Erfurt, Germany [365]. In another study, Pekkanen et al. conducted exercise tests on patients with stable coronary artery disease while monitoring ambient particle mass and number counts. They found significant independent effects for both $PM_{2.5}$ and UFPs on ST-segment depression on electrocardiograms during exercise [337].

Janssen et al. found that hospital admissions for cardiovascular disease increased significantly with increasing percentages of PM_{10} from highway vehicles, highway diesels, oil combustion, metal processing, population density, and vehicle miles traveled per square mile, and with a decreasing percentage of PM_{10} from fugitive dust [366]. All of these variables were significantly correlated with one another, except metal processing.

Nine healthy male North Carolina Highway Patrol troopers were studied from 3:00 pm to midnight on four consecutive days during their shift to determine cardiovascular effects as a result of in-vehicle $PM_{2.5}$ [367]. $PM_{2.5}$ levels inside the car (from engine emissions and brake wear) were found to be positively associated with mean heart cycle length (MCL, +7% per standard deviation increase in the factor score), heart rate variability (HRV, +16%), and supraventricular ectopic beats (+39%).

Salvi et al. have shown acute exposure to diesel exhaust to be associated with thrombocytosis [348] and Peters and colleagues have demonstrated increased plasma viscosity during increased levels of PM in a large sample of the population [321]. It has been suggested that an increase in platelet numbers during a PM pollution episode, especially in elderly people with compromised cardiovascular function, may increase the risk of developing strokes and coronary vessel thrombosis, thereby increasing cardiovascular mortality and morbidity [348].

Chan et al. [368] investigated whether the number of UFPs, with a size range of 0.02–1 μm measured by number concentrations ($NC_{0.02–1}$), is associated with increased HRV. Nine young healthy adults and 10 elderly patients with lung function impairment were monitored over a 10-hour day for personal exposure to UFPs and to assess HRV. Using mixed-effects linear models, they found that decreases in both time- and frequency-domain HRV indices were associated with exposure to 1- to 4-hour moving averages of $NC_{0.02–1}$ before the 5-minute HRV measurements after adjusting for age, sex, body mass index, environmental tobacco smoke exposure, and temperature. Associations were stronger for the elderly patients with the strongest effects associated with increased 2-hour averages of $NC_{0.02–1}$.

Von Klot et al. evaluated the short-term effects of urban air pollution on cardiac hospital re-admissions in survivors of myocardial infarction in a European cohort study of 22,006 survivors of a first myocardial infarction recruited from Augsburg, Germany, Barcelona, Spain, Helsinki, Finland, Rome, Italy, and Stockholm, Sweden from 1992 to 2000. Cardiac re-admissions (N = 6,655) were found to increase in association with same-day estimated particle number increases of 10,000 particles/cm^3 (relative risk (RR) 1.026, 95% CI 1.005–1.048) as well as with increases of 10 μg/m^3 in the concentrations of PM_{10} (RR 1.021, 95% CI 1.004–1.039) [369].

2.2.4.5 Chronic Health Effects

2.2.4.5.1 Chronic Health Effects Associated with PM

Non-Cancer. Chronic inhalation exposure to PM has been correlated with an increase in the frequency of respiratory diseases [307, 370-375]. There is a wide body of evidence indicating that diesel particles act as an adjuvant for allergic sensitization to common environmental allergens [376] and chronic PM exposure has been linked to allergic airway diseases such as asthma [377-380].

A frequently cited closed-cohort study on the association between mortality and $PM_{2.5}$ is the American Cancer Society (ACS) study which focused on the relationship between long-term exposure to fine particulate air pollution and all-cause, lung cancer, and cardiopulmonary mortality in US adults [381]. After adjustments for numerous potential confounders including cigarette smoking, and using 16 years of data from more than 500,000 adults in 151 US cities, Pope et al. found that a 10 μg/m^3 elevation in $PM_{2.5}$ was associated with an 8–18%

increases in mortality due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest [382].

Cancer. Using the same ACS cohort, and adjusting for significant confounders, researchers estimated that for each 10 $\mu g/m^3$ increase in annual average exposure to $PM_{2.5}$ mortality from lung cancer was increased by approximately 8% [381].

2.2.4.5.2 Chronic Health Effects Associated with Diesel PM

Non-Cancer. Diesel PM has been specifically implicated in the adverse respiratory effects associated with living near busy roadways. In a study of six areas near roadways in the Netherlands, children living near busy diesel trucking routes were found to have decreased lung function in comparison with children living near roads with mostly automobile traffic [383].

A population-based survey conducted in 10 areas of northern and central Italy (from autumn 1994 to winter 1995) of more than 39,000 children found that children living on streets with heavy truck traffic were 60–90% more likely to report acute and chronic symptoms such as wheeze, phlegm, and diagnoses such as bronchitis, bronchiolitis, and pneumonia than children who did not live near heavily traveled roadways [384].

A 12-month self-report study of over 3,700 adolescent students in Munster, Germany in 1994–1995 found that those living on streets with "constant" truck traffic were 71% more likely to report symptoms of allergic rhinitis and more than twice as likely to report wheezing than those who lived on streets with a lower volume of traffic [385].

Utilizing traffic counts within 50 m of a residence as a measure of PM exposure, a study of German school children found strong associations between traffic counts and increased respiratory symptoms such as asthma, wheezing, and coughing [386].

Künzli et al., using results from several epidemiologic studies as inputs, estimated the impact of total and traffic-related particulate air pollution on public health in Switzerland, France, and Austria [387]. In this modeling study, PM_{10} population exposures were estimated and the traffic-related (primary plus secondary particulates) fraction of PM_{10} estimate was extracted from emission inventories. Disease and mortality cases attributable to air pollution were estimated from epidemiology-based exposure-response functions. The study estimates that, in the selected countries, air pollution was responsible for 6% of the total mortality or more than 40,000 attributable cases per year. About half of the mortality caused by air pollution was attributed to traffic. Traffic was also found to be responsible for more than 25,000 new cases of chronic bronchitis (adults), 290,000 episodes of bronchitis (children), 0.5 million asthma attacks, and 16 million person-days of restricted activities.

Hoek et al. evaluated effects of traffic exposures near the home in a cohort study of 5,000 adults followed for 8 years in the Netherlands [388]. Living near a major road was more strongly associated with cardiopulmonary mortality than was the level of ambient background air pollution.

Cancer. Various constituents of diesel PM, such as PAHs and their derivatives, are known to be mutagenic and/or carcinogenic. Extracts of diesel PM are carcinogenic as measured in the Salmonella typhimurium (Ames) assay [389, 390]. There is also evidence of carcinogenicity for diesel PM (and associated diesel PM organic compound extracts) in rodents by non-

inhalation routes of exposure such as when painted on the skin or applied subcutaneously to mice or when administered by intrapulmonary implantation to rats [391]. Particles or their extracts have also been shown to induce gene mutations and sister chromatid exchanges in rodents in vivo and in cultured human cells [391].

Effects of inhaled diesel PM on lung cancer have been studied in rats, mice, and hamsters with significant findings observed only in rats at high levels (> 3500 $\mu g/m^3$) [392, 393]. Rats exposed to elemental carbon particles (i.e., carbon particles without the adsorbed organic compounds found on diesel particles) developed the same kinds of tumors as diesel PM exposed rats [394]. It is now understood that exposures to concentrations greater than 3500 $\mu g/m^3$ result in lung-particle overload characterized by slowed particle clearance, lung tissue inflammation, lung pathology, and eventually a tumorigenic response [392, 393, 395]. A meta-analysis by Valberg and Crouch of rat studies conducted at low exposures indicated a threshold of rat tumorigenic response in the range of 160–600 $\mu g/m^3$ continuous lifetime exposure [396]. The authors concluded that the animal data support a lack of diesel PM carcinogenicity in humans below lifetime exposure threshold concentrations at least as high as 230 $\mu g/m^3$ (or a plausible range of 7–300 $\mu g/m^3$) [396].

Some studies have found associations between proximity to traffic and higher rates of childhood cancer [397-400], whereas others have failed to show any association [401, 402].

An association of risk for lung cancer with diesel PM exposure has been observed in many occupational epidemiologic studies [278]. Brüske-Hohlfeld et al. [403] conducted a case-control analysis of male workers in Germany that found an association between lung cancer and occupational exposure to diesel engine emissions. In this study, lung cancer cases and controls, matched for sex, age, and region of residence, were selected randomly from compulsory municipal registries. Demographic information and detailed smoking and occupational history data was collected for 3,498 cases and 3,541 controls. All odds ratios were adjusted for smoking and asbestos exposure. The study found increased risk for all diesel exhaust-exposed job categories. The evaluation of lung cancer risk for all jobs with diesel exhaust-exposure combined showed an odds ratio (OR) of 1.43. For professional drivers (of trucks, buses, and taxis), the ORs ranged from 1.25 to 2.53. For other traffic-related jobs (switchmen, diesel locomotive drivers, diesel forklift truck drivers), the ORs ranged from 1.53 to 2.88. Most pronounced was the increase in lung cancer risk in heavy equipment operators (OR 2.31). The risk of lung cancer in tractor drivers increased with length of employment and reached statistical significance for exposures longer than 30 years (OR 6.81, $CI_{95\%}$ 1.17, 39.51) [403].

Garshick et al. [404], using US Railroad Retirement Board records to identify 1,319 lung cancer deaths and 2,385 matched controls, found an increased risk of lung cancer associated with increasing cumulative exposure to diesel engine exhaust. An analysis using number of years in a diesel-exposed job as a continuous variable, with adjustment for exposure to asbestos and smoking, yielded an OR of 1.41 ($CI_{95\%}$ 1.06, 1.88) for 20 years or more of diesel exhaust exposure in the younger than 64 years of age group. When diesel exhaust exposure was categorized as 0 to 4, 5 to 19, or 20 or more diesel years, the risk of lung cancer in the longest exposure group was significantly increased compared with the group with the shortest exposure (OR 1.64; $CI_{95\%}$ 1.18, 2.29).

Steenland et al. [405], using death certificates from pension files to identify 1,058 cases and

1,160 controls, observed an increased, but not statistically significant, risk of lung cancer with increasing years of exposure in Teamsters Union truck drivers and support personnel. Information on work history and potential confounders were collected from next-of-kin interviews. For truck drivers who primarily drove diesel trucks and worked for a minimum of 35 years, the OR was 1.89 ($CI_{95\%}$ 0.81, 2.22).

Garshick et al. [406] investigated the risk of lung cancer from exposure to diesel exhaust from railroad locomotives in a cohort of 55,407 white male railroad workers between 40 and 64 years of age in 1959 who had started railroad service 10 to 20 years earlier. After the exclusion of workers exposed to asbestos, a RR of 1.57 ($CI_{95\%}$ 1.19, 2.06) and 1.34 ($CI_{95\%}$ 1.02, 1.76) was found for ages 40 to 44 and 45 to 49, respectively. The investigators reported that the risk of lung cancer increased with increasing duration of employment (10 to 20 yrs).

The results of the Garshick et al. 1988 study are controversial. The study has been reanalyzed by several groups [393, 407, 408] with varying results. Depending on how age was controlled, the RR is positively or negatively related to duration of occupational exposure. An HEI special panel [409] conducted their own analyses of the data and found a consistently elevated risk of lung cancer for train workers compared with clerks for all durations of employment and an intermediate risk of lung cancer for shop workers; however, they found decreasing risk of lung cancer with increasing duration of employment. The panel offered possible explanations for the negative dose response including unmeasured confounding by smoking, exposure to other sources of pollution, previous occupational exposures, exposure misclassification, use of duration of employment as a surrogate measure for exposure, healthy worker effect, and differential or incomplete ascertainment of lung cancer deaths [409].

Three aggregate analyses of studies concerned with the relationship of diesel exhaust exposure and lung cancer risk (23 to 35 eligible studies each) [283, 410, 411] concluded that the data support a causal association between lung cancer and diesel exhaust exposure. On the other hand, three other analyses [412-414] argue that because methodological problems are prevalent among the occupational studies, especially with respect to evaluating diesel exhaust exposure and controlling for cigarette smoking, the observed associations are likely due to bias.

In 1988, the National Institute of Occupational Safety and Health (NIOSH) recommended that diesel exhaust be regarded as a potential carcinogen based on animal and human evidence [415] and in 1989, the International Agency for Research on Cancer (IARC) concluded that diesel engine exhaust was probably carcinogenic to humans (Group 2A) [391]. California has identified diesel exhaust as a chemical “known to the State to cause cancer” [416]. The World Health Organization (WHO) has found the epidemiologic data to be consistent in showing associations between exposure to diesel exhaust and lung cancer [164]. The US EPA has identified diesel exhaust as a probable human carcinogen by inhalation [393].

2.2.4.6 Biological Basis for Health Effects

Research efforts have been geared towards defining the toxic pathways and identifying the components and characteristics of diesel PM that mediate their adverse health effects. The wide spectrum of diesel PM-associated disease outcomes (from cardiovascular death to

asthma attack) suggests that there are likely multiple toxic pathways and components driving the health effects. Critical determinants of diesel PM toxicity are believed to include particle size (e.g., larger surface area to volume ratio and greater capacity to penetrate into the airways), chemical properties (e.g., redox potential), and bioavailability.

2.2.4.6.1 Physiologic Pathways

Dosimetry separates the respiratory tract into three regions: extrathoracic, tracheobronchial, and alveolar, based on anatomical features and particle deposition and clearance phenomena within each region [393]. The processes that aerosols undergo when they enter the airways include inhalation, deposition, and clearance. Comprehensive reviews of these processes as they relate to particulate toxicity have been prepared by WHO and others [277, 417, 418].

Inhalation. The nasopharyngeal region filters particles larger than 10 μm. The remaining particles enter the pharyngeal and the tracheobronchial region. The air is then transported to the pulmonary zone where gas exchange between the alveoli and the blood occurs.

Deposition. Particles in the accumulation mode size range (0.1 to 1.0 μm) have the lowest deposition. Coarse and ultrafine particles have higher fractional deposition [393]. Large-size particles mainly deposit in the upper part of the respiratory tract. Additionally, more than 50% of inhaled UFPs can be deposited in the nasopharyngeal region during nasal breathing [419]. UFPs have greater surface area and pulmonary deposition efficiency than larger particles [420-422] and also are much more likely to deposit in deeper parts of the respiratory tract due to their high diffusivities. About 10–15% of inhaled diesel soot particles are deposited in the alveolar region of the lungs of rats and guinea pigs; in humans, about 10% of diesel particles are deposited in the alveolar region [269].

Clearance. Particles depositing on airway surfaces may be completely cleared from the respiratory tract or translocated to other sites by regionally specific clearance mechanisms. Clearance is either absorptive (dissolution) or non-absorptive (transport of intact particles). Deposited particles may be dissolved in body fluids, taken up by phagocytic cells, or transported by the mucociliary system [393]. In the upper respiratory tract, deposited particles are removed by mucociliary clearance either to the outside of the body (by coughing) or to the gastrointestinal tract. This process is most relevant for large particles.

Smaller particles are taken up by the epithelium tissue or by macrophage phagocytosis [423]. Smaller particles that have entered the lower respiratory tract, where no mucus or cilia are present, are believed to be removed mainly by alveolar macrophage phagocytosis. Clearance in this region is much slower [423]. Studies with ^{3}H-benzo[a]pyrene and ^{14}C-nitropyrene show that when PAHs are associated with particulate matter, their clearance from the lungs is significantly delayed in comparison with the clearance of inhaled PAHs not associated with particulate matter [269].

Translocation. The toxicity of diesel particles is believed to be due, in part, to their propensity to escape the normal clearance mechanisms. As reviewed by Donaldson et al. [298], the large number of UFPs in diesel exhaust have the potential to overload the macrophage phagocytic mechanisms in the lung leaving a large number of particles in direct contact with epithelial cells. Rat studies have shown that UFPs can penetrate the epithelium and translocate to interstitial sites in the respiratory tract as well as to extrapulmonary organs such as the liver within 4 to 24 hours postexposure [424]. UFPs have the potential to enter

the blood and lymph circulation and reach sensitive target sites such as bone marrow, lymph nodes, and the spleen, heart, and brain [424-427]. Intravenously injected UFPs have been found to cross the blood-brain barrier [428]. From animal studies, it is reported that nanoparticles and UFPs may find their way out of the respiratory tract via neurons by transsynaptic transport and/or that the central nervous system is another target organ for UFPs [274, 429, 430].

2.2.4.6.2 Inflammation

Diesel particles and their components induce pro-inflammatory cytokines in macrophage and bronchial epithelial cell lines as well as in primary cultures of bronchial epithelial cells [431-441]. Humans exposed to diesel PM in chamber studies exhibit symptoms of airway inflammation (increased neutrophils and myeloperoxidase in the sputum in parallel with increased NO in exhaled air) [350].

Abe et al. found that human bronchial epithelial cells exposed to unfiltered diesel exhaust in vitro release inflammatory cytokines, whereas filtered diesel exhaust (i.e., diesel exhaust that contains gaseous components but no particles) did not have this effect [442]. The hydrocarbon and/or the trace metal components of diesel PM (as opposed to the carbonaceous core) are believed to be responsible for the inflammatory effects of diesel exhaust [358, 362, 443]. This is consistent with the finding that carbon UFPs, in isolation, do not cause significant lung inflammation in healthy humans and animals. Toxic co-factors and/or a susceptible host are required to induce inflammatory pulmonary responses to UFP inhalation [362, 444, 445].

The lining of the normal healthy lung consists of secretions from underlying lung and resident immune cells as well as plasma-derived exudate. To protect against oxidation of the pulmonary epithelial cells, this fluid contains a range of antioxidant defenses similar to that found in blood plasma [376, 446]. Examples of important antioxidants in the body include those that are ingested such as ascorbic acid (vitamin C) and α-tocopherol (vitamin E) and others that are synthesized. The latter include various low molecular weight scavengers, as well as metal-binding proteins and enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, thiol-specific antioxidants, metallothionein, caeruloplasmin, transferrin, ferritin, heme oxygenase-1, urate, GSH, and ubiquinol) [376, 446]. The relative concentrations of different antioxidants vary along the respiratory tract [446].

It has been demonstrated that free radicals and strong oxidant pollutants will deplete antioxidants from the human respiratory tract lining fluids [447]. This “oxidative stress” within the lung causes an influx of activated inflammatory cells to the lung. This influx leads to a second wave of oxidative damage since activated inflammatory cells also generate and release large quantities of free radicals [446].

Many of the adverse health affects associated with diesel exhaust appear to be related to the ability of diesel PM components to overwhelm natural antioxidant defenses and, thereby, initiate pulmonary and systemic oxidative stress and inflammation. In this scenario, redox-sensitive transcription factors promoting the transcription of pro-inflammatory cytokines are activated by oxidants (or oxidant-generating components on the particle surface) [433]. It is hypothesized that trace transition metals and/or PAHs, including oxyderivatives such as

quinones, on diesel particles exert proinflammatory and tissue-damaging effects by generating reactive oxygen species (ROS) such as superoxide ion, hydrogen peroxide, and hydroxyl radical [358, 362, 376, 434, 448, 449].

Diesel PM-induced ROS would, in turn, initiate intracellular signaling and transcriptional activation of cytokine and chemokine genes, resulting in a heightened inflammatory response. It has been shown that redox-cycling quinones [434, 450], PAHs [434, 450], and transition metals [451, 452] on diesel particles are capable of catalyzing oxidation reactions in cells and/or in cell extracts, leading to the production of ROS. Additional support for this mechanism comes from the detection of ROS in mice lungs [453] and in human airway epithelial cells exposed to diesel exhaust particles or their extracts [434].

Redox-active metals, such as iron, copper, and chromium, undergo redox cycling whereas redox-inactive metals, such as lead, cadmium, and mercury, can deplete cellular antioxidants such as glutathione, resulting in the production of ROS which in turn results in the upregulation of oxidative stress-sensitive signaling pathways [454]. Costa et al. have shown that the iron content of ambient particles collected from different urban settings correlates with oxidative stress in exposed phagocytic cells. It has been suggested that the dose of bioavailable metal, rather than particulate mass, may be the primary determinant of the acute inflammatory response [455].

Organic extracts of diesel PM have been further fractionated by silica gel chromatography into aliphatic, aromatic, and polar compounds, enriched for N-alkanes, PAHs, and quinones, respectively. Among these, the polar compounds are the most potent in redox-cycling reactions as determined by a thiol derivative, dithiothreitol (DTT), assay [456, 457]. Li et al. have previously shown that there is good correlation between results of the DTT assay and the ability of diesel PM components to induce oxidative stress in tissue culture macrophages and epithelial cells [449, 456, 457].

PAHs are converted to quinones via biotransformation involving cytochrome P450 1A1, epoxide hydrolase, and digydrodiol dehydrogenase leading to redox-cycling and production of ROS [376, 434]. Cell studies by Xia et al. indicate that the quinone-enriched polar fraction of diesel particulate extracts is more potent than the PAH-enriched aromatic fraction in perturbing mitochondrial function (as indicated by O_2 generation, decrease in membrane potential, loss of mitochondrial membrane mass, and induction of apoptosis). The aromatic fraction has been found to increase the Ca^{2+} retention capacity at low doses and to induce mitochondrial swelling and a decrease in membrane potential at high doses. These chemical effects on isolated mitochondria can be reproduced by intact diesel particles as well as by ambient UFPs. In contrast, commercial polystyrene nanoparticles fail to exert mitochondrial effects. These results suggest that diesel and ambient particle effects on mitochondria are mediated by adsorbed chemicals [450]. Hiyoshi et al. have shown that a single intratracheal exposure to phenanthraquine, a relatively abundant quinone in diesel PM, enhances the lung expression of IL-5 and eotaxin and causes the recruitment of inflammatory cells such as neutrophils and eosinophils to mouse airways [458].

There is some evidence that diesel particles themselves, even without their adhering organic compounds and trace metals, are capable of eliciting toxicity. Pan et al. have demonstrated that diesel particles, whose easily extractable components have been removed by organic solvent or acid washes, maintain the ability to catalyze the generation of ROS [459].

Paramagnetic properties may play a role in the ability of diesel PM to catalyze the formation of ROS [459]. Using electron paramagnetic spectrometry, Pan et al. demonstrated that the particles had paramagnetic properties that were resistant to organic solvent and aqueous acid extraction and thus appeared to be associated with the particle itself [459]. The prevailing view is that both the particles and the adsorbed chemicals are important because the particles act a carrier for the chemicals and may also provide a reaction surface on which redox cycling chemistry can take place [449].

The addition of diesel PM to bronchial epithelial cell cultures induces pro-inflammatory cytokine production through the activation of the redox-sensitive transcription factors nuclear factor κB (NF-κB) and activator protein-1 (AP-1) and their associated upstream mitogen-activated protein kinases (JNK and p38 MAPK) [431-439]. Activation of NF-κB and AP-1 by diesel PM leads to increased expression of a range of proinflammatory chemokines and cytokines, immunoglobulins, and oxidants in the upper and lower airways. These mediators, in turn, initiate a cascade that can culminate in symptoms of airway inflammation, mucus secretion, serum leakage into the airways, and bronchial smooth muscle contraction [361]. Treatment of epithelial cells and macrophages with antioxidants has been shown to reduce diesel PM-induced cytokine production by down-regulating the activation of these signaling pathways [432, 435-437, 439]. Recent results from humans exposed to diesel PM are consistent with those obtained using cell lines. Pourazar et al. have demonstrated that NF-κB and AP-1 are strongly activated in bronchial cells from healthy human subjects exposed to diesel PM compared with subjects exposed to filtered air [460]. Results from in vitro studies show that epithelial and macrophage cell lines challenged with increasing concentration of diesel particles, or particle extract, elicit a hierarchical response with protective antioxidant responses predominating at low particle concentrations and inflammation and injury occurring at high particle concentrations [437, 451, 461].

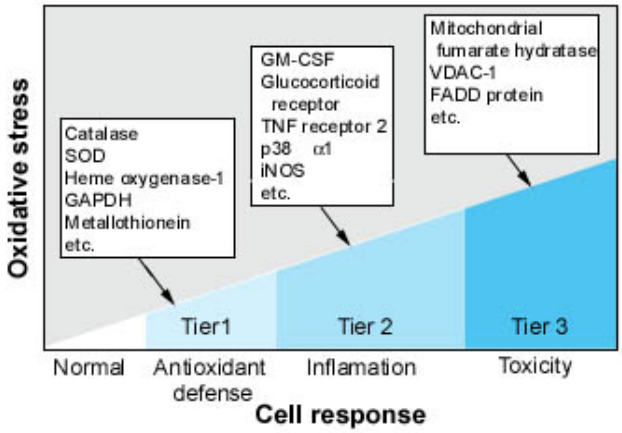

Figure 10. Hierarchical Oxidative Stress Model [449, 462]

Behndig et al. examined whether similar hierarchical responses occurred in vivo, specifically whether antioxidants were upregulated following a low-dose diesel exhaust challenge and how these responses might relate to the development of airway inflammation at different levels of the respiratory tract where particle dose varies markedly [448]. In this study, bronchial mucosa from human volunteers exposed to diesel exhaust (100 $\mu g/m^3$ PM_{10} for 2 hours) showed an increase in bronchial mucosa neutrophil and mast cell numbers. Increased neutrophil numbers, as well as elevated concentrations of interleukin-8 and myeloperoxidase, were observed in bronchial lavage. No inflammatory responses were seen in the lower alveolar compartment following diesel exposure, but both reduced glutathione and urate concentrations were increased in the airway lumen [448].

Behndig et al. argue that the differences in responses of the alveolar and bronchial regions reflect differences in the balance between antioxidant and inflammatory processes and that these differences occur largely due to differences in upper and lower respiratory area tissue doses. The small median mass diameter of the diesel particles allows similar deposition of diesel PM in the bronchial and alveoli regions, but the much greater surface area of the alveoli would result in a lower dose per unit surface area in the alveoli than the bronchial region. Mobilized antioxidant defenses, such as GSH and urate, are thereby overwhelmed in the bronchial region (with the greater dose of diesel PM/surface area) but not in the aveoli region (with the smaller dose of diesel PM/surface area).

A three-tiered hierarchical oxidative stress model has been proposed which posits a transition from protective to injurious effects as the level of oxidative stress increases [449, 462] (Figure 10). In Tier 1 of the model, at a low level of oxidative stress, antioxidants and antioxidant enzymes are induced to restore cellular redox homeostasis. In Tier 2, at an intermediate level of oxidative stress, intracellular signaling cascades, including three MAP kinase cascades, are activated which lead to expression of tumor necrosis factor-a, interleukin (IL)-8, IL-6, and vascular endothelial growth factor. In Tier 3, at a high level of oxidative stress, perturbation of the mitochondrial permeability transition pore and disruption of electron transfer occur resulting in cellular apoptosis ("suicide" or "programmed" cell death) or necrosis ("unprogrammed" death).

2.2.4.6.3 Asthma

Atopic (or allergic) asthma is characterized by reversible airway obstruction, elevated serum levels of immunoglobulin E (IgE), chronic eosinophilic airway inflammation, airway remodelling, mucus hypersecretion, and airway hyperresponsiveness to bronchospasmogenic stimuli [462, 463].

The early asthmatic phase is considered to be predominantly IgE mediated, whereas the late phase involves complex networks of inflammatory mediators including eosinophils, T cells, cytokines, chemokines, and immunoglobulins [464]. There is evidence that diesel PM may be associated with both the early and late phases of the inflammatory response in asthma [361]. Direct effects of diesel PM include stimulation of IgE production, eosinophilic degranulation, augmentation of cytokine and chemokine production and release, free radical formation, and effects on the production of NO in the airways. The potential pathways by which diesel PM may promote asthma have been reviewed [361, 376].

Numerous studies have demonstrated that diesel PM can act as an adjuvant in mice or humans when combined with inhaled or instilled experimental allergens [465-472]. In combination with common airborne allergens, diesel particles appear to enhance the differentiation of CD4+ T lymphocytes into the TH2 phenotype and enhance allergen-specific IgE and IgG production [361]. TH2-type cells produce signaling molecules that have been most strongly linked to asthmatic responses (IL-4, IL-5, IL-6, IL-10, and IL-13). Stimulation of the TH2-type pathway and increase in IgE production are considered two of the most important and likely mechanisms by which diesel PM may generate and sustain an asthmatic response [361].

A weakened antioxidant defense is believed to play a role in determining susceptibility to diesel PM-induced or diesel PM-exacerbated asthma [376]. In healthy humans, the

deleterious effects of ROS are controlled by an antioxidant defense system that operates intracellularly in bronchial lining fluid and in the blood. Asthmatics have been shown to have diminished antioxidant protection at one or more of these levels. Evidence for this mechanism, reviewed extensively by Li et al. [376], includes the following symptoms which have been detected in asthmatics: decreased ascorbate and α-tocopherol levels in the lung lining fluid, generally decreased superoxide dismutase activity (in erythrocytes, bronchial epithelial cells, and/or lung lining fluid) possibly due to oxidative inactivation, decreased levels of glutathione (in adults and children with asthma), and decreased red blood cell glutathione peroxidase (in children with asthma). Additionally, it appears that genes involved in pollutant detoxification and antioxidant defense may have a role in determining susceptibility to asthma. Individuals who are homozygous for the GST M1 (null) genotype are totally lacking the glutathione-S-transferase activity needed for the detoxification of environmental chemicals, including redox-cycling components in tobacco smoke and diesel PM. These individuals have been shown to have an increased risk for asthma development. In contrast, homozygous expression of the GST P1 (Val) genotype confers a protective effect on individuals with respect to developing asthma and has also been shown in particular to protect against toluene di-isocyanate-induced occupational asthma (see references in Li et al. [376]).

2.2.4.6.4 Cardiovascular Events

Diesel PM-induced oxidative stress and inflammation are believed to instigate cardiovascular events including thrombosis, cardiac dysrhythmias, acute vascular dysfunction, plaque instability, and the long-term development of atherosclerosis [371]. As reviewed by Brook et al., the cardiovascular response may also involve additional pathways such as changes in autonomic balance via lung neural reflex arcs and/or PM (or certain components) reaching the circulation system [371].

Particulate-induced changes in autonomic nervous system activity, as assessed by heart rate variability, have been observed in both animal studies [473] and human panel studies [474-478]. It has been suggested that sympathetic activation or vagal suppression after PM exposure may cause alterations in autonomic tone which, under appropriate circumstances, might contribute to the instability of a vascular plaque or initiate cardiac arrhythmias [371, 479].

Seaton et al. have postulated that inflammation in the peripheral airways caused by air pollutants might increase the coagulability of the blood and thereby lead to an increased number of deaths [480]. Increases in plasma viscosity [321] and C-reactive protein (a sensitive marker of inflammation, tissue damage, and/or infection) [481, 482] have been observed in healthy adults after exposure to particulate air pollution. Short-term exposure of healthy adults to concentrated ambient particles has been shown to increase plasma fibrinogen [483, 484] as well as other blood markers (e.g., hemoglobin, platelets, and white cells) [482]. There are also indications that particulate matter may accelerate the development of atherosclerosis in genetically susceptible mice [485] and humans [486]. Persons with diabetes, a disease associated with accelerated atherosclerosis, exhibit increased susceptibility to the effects of particulate pollution [487, 488].

2.2.4.6.5 Genotoxicity

A number of constituents of diesel PM are known to be mutagenic and/or carcinogenic as measured in the Salmonella typhimurium (Ames) assay [389, 390, 489]. The most mutagenic compounds among these are PAHs and their nitrated and oxygenated derivatives. Extracts of diesel PM are carcinogenic as measured in the Salmonella typhimurium (Ames) assay [389, 390]. Results from animal experimental models, cell-culture experiments, and cell-free systems show that exposure to diesel PM causes oxidative DNA damage [490, 491]. PM-induced DNA damage includes increased frequency of mutations, single-strand breaks, and the formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine and PAH-DNA adducts [391, 490, 492, 493].

2.2.4.6.6 Cytotoxicity

Using electron microscopy and assays for ROS, it has been shown that UFPs, and to a lesser extent fine particles, localize in mitochondria where they induce oxidative structural damage [459]. ATP production in the mitochondria requires stepwise acceptance of four-electrons by O_2 to form H_2O. The addition of one, two, or three electrons results in the formation of superoxide ($O2\cdot^-$) radicals, hydrogen peroxide (H_2O_2), or hydroxyl radicals ($OH\cdot$), respectively (reviewed by Li et al. [449]). As described in section 2.2.4.6.2, at sufficiently high levels, ROS will react with proteins, lipids, and DNA leading to cellular damage. However, under normal conditions, ROS are generated at only a low frequency and potentially injurious effects are neutralized by a variety of cellular antioxidants. Under high levels of ROS production, such as may occur during asthma and diesel PM exposure, the antioxidant defenses may be overwhelmed, leading to a state of cellular oxidative stress.

According to the hierarchical oxidative stress model [449, 462] described in section 2.2.4.6.2, perturbation of the mitochondrial permeability transition pore and disruption of electron transfer may result in premature cellular apoptosis or necrosis.

2.2.4.7 Risk Assessment & Standards/Guidelines for Exposure

The following are some perspectives on diesel PM or diesel exhaust "risk" that have been developed and the resultant standards or guidelines. Guideline values are summarized in Tables 10 and 11.

2.2.4.7.1 US National Standards and/or Guidelines

US EPA Integrated Risk Information System (IRIS). The first IRIS assessment for diesel exhaust went online in 1993; the latest revision was released in 2003.

Non-Carcinogenic Risk. The RfC for diesel PM is an "estimate (with uncertainty spanning perhaps an order of magnitude) of the daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" [393]. The US EPA considered chronic respiratory effects to be the principal non-cancer hazard in humans from long-term environmental exposure to diesel PM. Other effects (e.g., neurological, growth and survival, neurobehavioral, lowered resistance to respiratory infection, and liver effects) are observed in animal studies at higher exposures than those producing the respiratory effects [278]. At the time of the assessment, the US EPA considered human and animal data for the immunological effects of diesel PM exposure (i.e., exacerbation of allergenicity and asthma symptomology) to be inadequate for dose-response

evaluation. It was noted that no teratogenic, embryotoxic, fetotoxic, or female reproductive effects have been observed in mice, rats, or rabbits at inhalation exposure levels lower than those associated with respiratory effects. Therefore, respiratory effects were used as the "critical effect" for the derivation of the chronic RfC for diesel exhaust. In 1993, the US EPA determined an inhalation RfC of 5 $\mu g/m^3$ of diesel PM from dose-response data on inflammatory and histopathological changes in the lung from rat inhalation studies. The RfC was reassessed in 2003 using studies of Ishinishi et al. [494] on lung deposition and a mathematical model of diesel PM deposition and clearance by Yu and Yoon [495]; however, the value was not changed. A brief description of the study of Ishinishi et al. and the procedure used by US EPA to determine RfC is described below.

In the study of Ishinishi et al., rats (120 males and 95 females per exposure level) were exposed for 16 hours per day, 6 days a week, for 30 months to 0.11, 0.41, 1.18, or 2.32 mg/m^3 diesel exhaust from a light-duty (LD) engine or to 0.46, 0.96, 1.84, or 3.72 mg/m^3 diesel exhaust from a heavy-duty (HD) engine. (Equivalent duration-adjusted concentrations were 0.063, 0.23, 0.67, or 1.3 mg/m^3 LD engine exhaust and 0.26, 0.55, 1.05, or 2.13 mg/m^3 HD engine exhaust.) Hematology, clinical chemistry, urinalysis, and light and electron microscopic examinations of histopathology were performed. Findings included minor body weight changes and equivocal alterations in liver and kidney function. The body weight of female rats exposed to 3.72 mg/m^3 was 15–20% less than controls throughout the study. A dose-dependent decrease in body weight of the other groups was also observed. Impaired liver and kidney function were indicated (increased liver enzyme activities and urea nitrogen, altered electrolyte levels and gamma globulin concentration, and reduced total blood proteins), although neither was confirmed histopathologically.

No histopathological changes were observed in the lungs of rats exposed to 0.46 mg/m^3 diesel PM or less; however, at higher concentrations, severe morphological changes were observed including shortened and absent cilia in the tracheal and bronchial epithelium, marked hyperplasia of the bronchiolar epithelium, and swelling of the Type II cellular epithelium. The lowest observed adverse effects levels (LOAELs) reported for chronically exposed rats were 1.18 and 0.96 mg/m^3 (actual exposure) for the LD and HD exposure series, respectively. The no observed adverse effects levels (NOAELs) were 0.41 and 0.46 mg/m^3 (actual exposure) for the LD and HD exposure series, respectively.

Human equivalent concentrations corresponding to the animal NOAEL and LOAEL values were computed using the dosimetry model developed by Yu and Yoon [495], which accounts for species differences (rat to human) in respiratory exchange rates, particle deposition efficiency, differences in particle clearance rates at high and low doses, and transport of particles to lymph nodes [495]. In performing the modeling, rats were assumed to weigh 300 g with a total pulmonary surface area of 4,090 cm^2. Human equivalent concentrations (HECs) were derived using respiratory parameters for a 25-year-old male having a total pulmonary surface area of 627,000 cm^2, tidal volume of 0.926 L, respiratory frequency of 15 breaths per min, and total daily pulmonary volume of 20 m^3; exposure was assumed to last 70 years [278]. The resulting LOAEL HECs for the LD and HD series were computed to be 1.25 and 0.883 mg/m^3, respectively. The NOAEL HECs for the LD and HD series were computed to be 0.128 and 0.144 mg/m^3 (128 and 144 $\mu g/m^3$), respectively [393]. To obtain the RfC, the NOAEL HEC was divided by two types of uncertainty factors (UFs): a factor of 3 for interspecies (i.e., rat to human) extrapolation uncertainties, and a factor of 10 for

interindividual human variation in sensitivity. This resulted in the published RfC value of 5 μg/m³.

The US EPA's confidence level in the resultant RfC is in the medium range [393]. The animal data used to characterize the critical effects, chronic inflammation and pathologic changes, are considered relevant to humans; however, the rat lung is known to be more sensitive than human lungs to insoluble elemental carbon particles (i.e., clearance effects). It is not known whether this is true for the inflammatory effects of diesel PM caused by organic carbon constituents. Evidence for diesel PM's ability to exacerbate allergenic effects to known sensitizers, while also evoking production of biochemical markers typically associated with asthma, was noted by the US EPA but exposure-response data was considered to be insufficient at the time of the assessment.

Carcinogenic Risk. The US EPA found that diesel exhaust is likely to be carcinogenic to humans based on the following lines of evidence [393]:

- strong but less than sufficient evidence for a causal association between diesel exhaust exposure and increased lung cancer risk among workers in various occupations where exposure to diesel exhaust occurs;
- extensive supporting data including the demonstrated mutagenic and/or chromosomal effects of diesel exhaust and its organic constituents, and knowledge of the known mutagenic and/or carcinogenic activity of a number of individual organic compounds that adhere to the particles and are present in diesel exhaust gases;
- evidence of carcinogenicity of diesel PM and associated organic compounds in rats and mice by other routes of exposure (dermal, intratracheal, subcutaneous, and intraperitoneal); and
- suggestive evidence for the bioavailability of organic compounds from diesel exhaust in humans and animals.

Given a carcinogenicity hazard, the US EPA typically performs a dose-response assessment of the human or animal data to develop a cancer unit risk estimate. However, in the case of diesel PM, the US EPA has not developed a quantitative estimate of cancer unit risk. Indeed, the US EPA considers the human epidemiological exposure-response data to be too uncertain to derive an estimate of cancer unit risk at this time. Moreover, although rodent studies demonstrate mutagenic and chromosomal effects, it is the US EPA's view that these studies do not reflect normal human exposure.

California Environmental Protection Agency (CA EPA). CA EPA's Office of Environmental Health Hazard Assessment (OEHHA) completed an assessment in 1998 that formed the basis to formally identify diesel PM as a "toxic air contaminant that may pose a threat to human health" [408].

Non-Cancer. OEHHA concurred with the US EPA that the chronic rat study by Ishinishi et al. [494] is the most appropriate study for the determination of a chronic inhalation reference exposure level (REL). OEHHA adopted the US EPA's concentration of 5 $\mu g/m^3$ of diesel PM, citing a high confidence from a database of studies from the WHO that had consistent results and were in agreement [408].

Cancer. OEHHA used the carcinogenicity data from two human studies to calculate a

quantitative risk assessment for exposure to diesel exhaust. A quantitative risk assessment (QRA) was also prepared for rat data but was not used in the final range of risks. Cited problems with extrapolating human risk from rat studies included the scaling of clearance rates, the presence or absence of a threshold for onset of carcinogenic effects, and the possible presence of multiple carcinogenic mechanisms. The relevance of induction of rat lung tumors by particles such as carbon black and titanium dioxide to human cancer risk was also questioned since these tumors are generally understood to be caused by an overwhelming of the rat's ability to clear the particles from the lungs [408].

The two human studies used by OEHHA for the cancer QRA were the Garshick et al. case-control study [404] and the Garshick et al. cohort study of US railroad workers [406]. According to their calculations, the UR ranges between 1.3 cancers per 10,000 to 2.4 per 1,000 (based on a lifetime exposure of 1 $\mu g/m^3$). They have recommended using a mid-range UR value for diesel PM of 3×10^{-4} per 1 $\mu g/m^3$. This means that if a million people are exposed chronically to 1 $\mu g/m^3$ of diesel PM, 300 individuals may get lung cancer from that exposure [408].

The California Air Resource Board (CARB) estimated that the average annual ambient concentration of diesel PM to which Californians are exposed is 1.54 $\mu g/m^3$; this includes both indoor and outdoor exposure. The upper limit potential of additional cancer cases over a lifetime in California was estimated to range from 200 to 3,600 additional cancer cases for every one million Californians over a 70-year lifetime [408].

Based on the human and experimental animal evidence, the CARB formally identified diesel PM as a "toxic air contaminant," which set in motion additional strategies to reduce diesel emissions [280].

2.2.4.7.2 International Standards and/or Guidelines

Many international agencies and countries other than the US have established guidelines or standards for diesel exhaust. A few are briefly discussed below.

International Agency for Research on Cancer (IARC). Based on epidemiologic and animal studies, the IARC has classified diesel exhaust as a probable human carcinogen (class 2A) [391].

International Programme on Chemical Safety (IPCS)

Chronic Non-Cancer Effects. Two general approaches were used for risk characterization of non-neoplastic effects: (1) a NOAEL divided by an uncertainty factor; and (2) use of a benchmark concentration (BC) (Table 10) [269].

The NOAEL used in the first approach was 0.41 mg/m^3 from the Ishinishi et al. study [494] of rats exposed by inhalation to light-duty engine exhaust [393]; this study was also used by the US EPA. The NOAEL was converted to an equivalent continuous exposure of 0.23 mg/m^3 in rats and then, using the dosimetric model of Yu and Yoon [495], to an equivalent continuous exposure of 0.139 mg/m^3, assumed to be the NOAEL in humans.

Application of the dosimetric model decreased the uncertainty in interspecies extrapolation from 10 to $10^{0.4}$ (2.5). Application of the usual uncertainty factor of 10 for intraspecies differences results in a total uncertainty factor of $10 \times 10^{0.4} = 25$. The guidance value derived from this approach was 5.6 $\mu g/m^3$.

Uncertainties in the dosimetric model relate to the following assumptions: (1) clearance in humans is inhibited at the same lung burden (mass per alveolar surface area) as in rats; and (2) the correct dose measure for lung damage is mass of particle core per alveolar surface area. It was noted that, since the damage is localized to specific areas, another dose measure may be more appropriate.

For this reason, the guidance value was also calculated without using the dosimetry model and applying the full default value of 10 for interspecies uncertainty as well as the uncertainty factor of 10 for intraspecies differences. The more conservative guidance value obtained with this approach is 2.3 $\mu g/m^3$.

As an alternative to using the NOAEL approach, IPCS derived a BMC for diesel exhaust as described by Crump [496]. The BMC is defined as the statistical lower limit on the concentration of a substance that produces a pre-determined change in response rate of an adverse effect (benchmark response or BMR) compared with background. The BMR change in response rate over background is usually in the range of five to ten percent. The BMCs chosen by IPCS correspond to a 10% response (the lower 95% confidence limit on the exposure concentration for hyperplastic lung injury and impaired lung clearance) or a 3% response (the lower 95% confidence limit on the exposure concentration for excess of polymorphonuclear neutrophils in lung lavage fluid as indicators of chronic alveolar inflammation). The dose-response datasets used by IPCS were those from the rat studies Ishinishi et al. [494] and Creutzenberg et al. [497]. The dosimetric model of Yu and Yoon [495] was used or appropriate uncertainty factors were applied, as previously described, to convert the rat BMCs to human BMCs. The human guidance values and BMCs calculated by IPCS, with and without the dosimetry model, are shown in Table 10.

Table 10. Summary of IPCS non-cancer guidance values and BMCs [269]

Analytical Approach	Guidance/BMC ($\mu g/m^3$)
NOAEL with dosimetric conversion from rats to humans	5.6
NOAEL without dosimetric conversion from rats to humans	2.3
Benchmark concentration with dosimetric conversion from rats to humans	
Chronic alveolar inflammation	2
Impaired lung clearance	3
Hyperplastic lesions	14
Benchmark concentration without dosimetric conversion from rats to humans	
Chronic alveolar inflammation	0.9
Impaired lung clearance	1.2
Hyperplastic lesions	6.3

Cancer. IPCS considered the results of the available epidemiological studies not adequate for a quantitative estimate of unit risk. They used data from several studies of long-term inhalation in rats in which carcinogenesis occurred at concentrations higher than 2 mg/m^3. A geometric mean of four risk estimates (ranging from 1.6 to 7.1×10^{-5} $\mu g/m^3$) resulted in a cancer unit risk of 3.4×10^{-5} per $\mu g/m^3$ diesel exhaust particles. An alternative biologically based model, which assumed that diesel particles affect cell initiation and/or proliferation at low concentrations, yielded a similar unit risk [269].

World Health Organization (WHO). The WHO found that "the weight of evidence from numerous epidemiological studies on short-term responses points clearly and consistently to

associations between concentrations of particulate matter and adverse effects on human health at low levels of exposure commonly encountered in developed countries" [164]. However, because "the available information does not allow a judgment to be made of concentrations below which no effects would be expected," the WHO has no guideline values for PM. For guidance in decision-making regarding standards to be set for PM, the WHO has prepared a summary of relative risk estimates for effects from long-term exposure to PM [164].

The WHO recognizes that the latest studies are showing that $PM_{2.5}$ is generally a better predictor of health effects than PM_{10} and that constituents of $PM_{2.5}$ such as sulfates are sometimes even better predictors of health effects than $PM_{2.5}$ per se; however, it has not prepared risks for diesel PM.

Table 11. Summary of conclusions from risk assessments for diesel PM

Agency	Non-cancer		Cancer	
	Outcome	Basis	Outcome	Basis
US EPA IRIS [393]	Chronic inhalation RfC = 5 $\mu g/m^3$	Lung deposition in rats [494]	N/A	
California OEHHA [408]	Chronic inhalation REL = 5 $\mu g/m^3$	Lung deposition in rats [494]	Inhalation UR = 3 x 10^{-4} per $\mu g/m^3$ diesel PM	Human epidemiological studies [404] and Garshick et al. [406]
IPCS[269]	Chronic inhalation guidance values with or without dosimetric model = 5.6 or 2.3 $\mu g/m^3$, respectively	Lung deposition in rats [494]	3.4×10^{-5} per $\mu g/m^3$	Cancer in rats [269]

2.2.4.7.3 Occupational Risk from Exposure to Diesel PM

National Institute of Occupational Safety and Health (NIOSH). In 1988, NIOSH recommended that whole diesel exhaust be regarded as a potential occupational carcinogen in conformance with the OSHA Cancer Policy (29 CFR 1990) [415]. NIOSH typically develops and periodically revises recommended exposure limits (RELs) for hazardous substances or conditions in the workplace which OSHA then promulgates and enforces. At the time of the recommendation it was NIOSH's view that the excess cancer risk for workers exposed to diesel exhaust had not yet been quantified. NIOSH noted that although "a substantial amount of information suggests that some component (or combination of components) of the

particulate fraction of diesel exhaust is associated with tumor initiation, the relative roles of the particulate and gaseous phases of emissions need further characterization" [415]. NIOSH advises that the probability of developing cancer should be decreased by minimizing exposure, noting that "as prudent public health policy, employers should assess the conditions under which workers may be exposed to diesel exhaust and reduce exposures to the lowest feasible limits" [415].

2.2.4.8 Mitigation

The US EPA and CARB have signed heavy-duty engine standards for model year 2007 and later, which include emission standards and diesel fuel regulation [498]. The emissions standards include 0.01 g/bhp-hr for PM, 0.20 g/bhp-hr for NO_x, and 0.14 g/bhp-hr for non-methane hydrocarbons (NMHC). The PM emission standard will take full effect in the 2007 heavy-duty engine model year. The NO_x and NMHC standards will be phased in for diesel engines between 2007 and 2010.

US EPA regulations currently prohibit the sale or supply of diesel fuel having a sulfur content greater than 500 ppm by weight for use in on-road motor vehicles. Since June 1, 2006, 80% of diesel fuel for on-road use produced by US refineries is required to meet a limit of 15 ppm sulfur. This ultra-low sulfur fuel must be available at distribution terminals by September 1, 2006 and for retail sale by October 15, 2006 (extended 6 weeks beyond original implementation deadlines of July 15, 2006 and September 1, 2006). The US EPA will cap non-road, locomotive, and marine fuel at 500 ppm on June 1, 2007. On June 1, 2010, all non-road diesel fuel will need to meet a limit of 15 ppm sulfur and on June 1, 2012, locomotive and marine diesel fuel will also be capped at 15 ppm [499]. The new sulfur standard will enable the use of more advanced emission control technologies required to ensure compliance with the new emission standards adopted by the US EPA for 2007 and subsequent model-year heavy-duty engines and vehicles.

The CARB is following the US EPA's implementation schedule for sulfur limits (keeping the original deadlines of July 15, 2006 and September 1, 2006 for terminals and retail, respectively). However, the CARB's proposed diesel fuel sulfur limit would apply to both on-road and off-road engines. California diesel fuel regulations, adopted in 1988, additionally set limits on aromatic hydrocarbon content (10 percent by volume). The new sulfur standard will enable the use of the emissions control technologies required to ensure compliance with the new emissions standards adopted by the US EPA for 2007 and subsequent model-year heavy-duty engines and vehicles. The proposed low sulfur requirement is anticipated to reduce emitted SO_2 by 88% and PM by 4% [499]. Several other regulations adopted by the CARB to reduce diesel PM emissions are listed in section 3.2.1.4 of this report.

The strengthening of national and/or state standards for $PM_{2.5}$ will help protect against the hazards of diesel PM to the extent that they force appropriate changes in diesel fuel, engines, after-treatment technologies, and operation. However, compliance with $PM_{2.5}$ standards as determined by ambient PM monitors at distances from major diesel emission sources such as freeways is no assurance that those spending time on or near such sources are protected against the hazards of diesel ultrafine and nanoparticles for two primary reasons. First, the fine particles in diesel PM tend to form steep concentration gradients around emission sources that are very variable depending on meterological conditions. Second, ambient $PM_{2.5}$ monitors measure particle mass concentrations and quantification of UFPs and nanoparticles

requires measurements of particle number concentrations (note: the correlation between particle number and mass is poor).

Short of tracking diesel particle number concentrations around major emission sources, better protection of human health would be derived from sensible limits on the proximity of schools, work places, hospitals, and residential areas to major freeways, truck routes, and port operations. California, for example, has passed legislation (SB 352 Escutia) to prohibit siting new schools within 500 feet (168 m) of a busy road [500]. Similarly, consideration should be given to the health of occupants of established neighborhoods and schools in the citing or expanding of nearby freeways, truck routes, and port operations.

2.2.4.9 Conclusions

Diesel PM is a mixture of solid and liquid phase particles in diesel exhaust. Approximately, 92% of diesel PM mass has an aerodynamic diameter smaller than 1.0 μm; however, more than 99% of the diesel PM particle count has an aerodynamic diameter smaller tha 0.1 μm. The greatest number (and the smallest amount of mass) concentration of diesel PM is in the nucleation mode. Particles in the nucleation mode are most sensitive to fuel and engine variables and can change widely with respect to size, numbers, and chemical composition depending on engine type, operation conditions, fuel composition, and emission controls as well as meteorological conditions at the emission site.

Exposure to diesel PM is associated with acute pulmonary and cardiovascular events and chronic diseases. The mechanisms of diesel PM-induced health effects are believed to involve pulmonary inflammation and oxidative stress. The oxidative stress mediated by diesel PM may arise from direct generation of reactive oxygen species (ROS) from the surface of particles, soluble compounds such as transition metals or organic compounds, altered function of mitochondria or NADPH-oxidase, and/or activation of inflammatory cells capable of generating ROS and reactive nitrogen species. Translocation of particles from the lungs into the circulation system allows more of a direct effect on cardiovascular endpoints than by other pathways. Changes in autonomic nervous system activity (sympathetic activation or vagal suppression) after exposure to diesel PM circulating in the blood may cause alterations in autonomic tone which, under appropriate circumstances, may contribute to the instability of a vascular plaque or initiate cardiac arrhythmias.

Compared with fine or coarse particles, diesel particles—primarily in the ultrafine (aerodynamic diameter less than 0.1 μm) and nanoparticle (diameter smaller than 0.05 μm) range—are especially hazardous to health and challenging in terms of exposure and risk assessment for the following reasons:

- Their small radii and large surface-to-volume ratios allows enhanced oxidant and/or mutagenic capacity, greater pulmonary deposition efficiency and potential to deposit in deeper parts of the respiratory tract, increased propensity to escape the normal clearance mechanisms, and increased potential to penetrate the epithelium and enter the blood and lymph circulation and reach sensitive target sites such as bone marrow, lymph nodes, spleen, heart, and brain.
- The proportion of PM that is diesel PM varies widely (e.g., from city to city, from location to location within cities, from summer to winter, and from day to night).

- Diesel PM has a tendency to form steep spatial and temporally dynamic concentration gradients at emission source sites thereby escaping characterization, or even detection, by ambient monitors at fixed sites.
- There is only poor correlation between particle size and mass. Small particles require quantification by number, as opposed to mass, and most exposure and epidemiological studies to date have only measured particle mass (and only a few of these have included source apportionment data).

The US EPA used respiratory effects as the "critical effect" for deriving a chronic RfC of 5 $\mu g/m^3$ for diesel PM. The US EPA found diesel exhaust to be a likely carcinogen based on (1) evidence for a causal association between diesel exhaust exposure and increased lung cancer risk among workers where exposure occurs, (2) demonstrated mutagenic and/or carcinogenic activity of a number of individual organic compounds in diesel PM, (3) evidence of carcinogenicity of diesel PM and the associated organic compounds in rats and mice by several routes of exposure, and (4) suggestive evidence for the bioavailability of organic compounds from diesel exhaust in humans and animals. However, the US EPA has not developed a quantitative estimate of cancer unit risk because the agency considers human epidemiological exposure-response data to be too uncertain and because they feel that the rodent data do not adequately reflect normal human exposure.

California concurred with the US EPA and adopted the same value (5 $\mu g/m^3$ diesel PM) for its chronic inhalation reference exposure level. Two human studies, the Garshick et al. case-control study [404] and the Garshick et al. cohort study of US railroad workers [406] were used by OEHHA in their calculation of a mid-range unit risk for cancer of 3.0×10^{-4} per $\mu g/m^3$ diesel PM. This unit risk translates to an estimated three excess cancers per 10,000 individuals, based on a lifetime exposure of 1 $\mu g/m^3$.

The IPCS used two alternative approaches, a NOAEL without application of a dosimetry model and a NOAEL with application of a dosimetry model, to derive guidance values of 2.3 $\mu g/m^3$ and 5.6 $\mu g/m^3$, respectively for non-cancer effects. BMCs for specific responses were also derived with and without application of the dosimetry model. The IPCS considered the results of the available epidemiological studies inadequate for a quantitative estimate of unit cancer risk and instead used data from several studies of long-term inhalation in rats and estimated a cancer unit risk of 3.4×10^{-5} per $\mu g/m^3$ diesel PM.

National and/or state standards for $PM_{2.5}$ will provide only limited protection against the hazards of diesel ultrafine and nano-particles because these regulations address particle mass concentrations and quantification of ultrafine particles and nanoparticles requires measurements of particle number concentrations, which are not commonly performed. National and state diesel heavy-duty engine emission standards and diesel fuel regulations currently in effect will reduce DPM emissions and exposures per on-road diesel engine; however, a significant but relatively unquantified health risk remains for those who live, work or go to school near off-road sources or in the vicinity of major roadways. Improved protection of human health would be derived by restricting the proximity of schools, work places, hospitals, and residences from areas which are likely to be major sources of diesel particulates.

2.3 Vulnerable Populations and Air Toxics: Modified Health Risks

2.3.1 Introduction

The overall goal of this report is to present an academic investigation into the regulations of air toxics in several states and internationally and the toxicological motivation for these regulations. The toxicological motivation for regulation becomes more persuasive at the juncture of demographic and socioeconomic variation and public health. From a population health perspective, socioeconomic inequities, racial and demographic differences, and disparities in health and access to health care [501-503] may compound the health effects of air pollution in vulnerable populations. In this context, we define vulnerable populations as groups of people for whom the risk of poor physical health has, or is quite likely to become, a reality [504]. In particular, high risk mothers and children, the frail and the ageing, certain racial and ethnic groups, and people in lower socioeconomic positions have certain characteristics that make them particularly susceptible to the health impacts of air pollution. This section reviews literature in the field of environmental epidemiology to detail the potential impacts of air pollution exposure when the risk is modified by variables such as race, ethnicity, income, and age.

The review highlights the following three propositions:

- Certain demographic and socioeconomic groups may systematically be exposed to higher levels of air pollution.
- Low health status of these groups makes them especially vulnerable to the health effects of air pollution
- These groups are likely to suffer more severe health effects from air pollution due to their vulnerability and greater exposure.

These propositions are framed by the following beliefs about the relationship between socioeconomic variables and health [505]:

- The negative relationship between socioeconomic position (SEP) and health is not solely a function of poverty. Even as the greatest risks of premature mortality and morbidity are concentrated among the poor, studies demonstrate the presence of a graded relationship between SEP and health.
- Neighborhood, or area-level, SEP exerts an independent influence on an individual's health status. Individuals with the same level of income or educational attainment could experience differing health status depending on their neighborhood patterns. Neighborhood characteristics may differ in terms of access to services (e.g. access to health and civic services), physical conditions (e.g. traffic congestion and clean air), and social environment (e.g. social capital and crime).
- The history of socioeconomic change influences the SEP effects on health. For example, childhood socioeconomic circumstances are believed to exert an effect on adult health independently of SEP attained in adulthood.
- Change in geographic location affects health status profiles and behaviors potentially due to accumulated exposures of local population groups.

- Racial variances and socioeconomic disparities are observed to have independent effects on health. Social epidemiologists differentiate between SEP from race, even as racial minorities may be overrepresented among lower-SEP groups.

A review by Pollock and Vittas highlights the fact that, although occupational and housing patterns explain much of the variation in proximity to pollution, there is persistent inequity in potential exposure across population groups [506]. The review indicates that the socioeconomic and demographic determinants of health confound and further exacerbate the health impacts of air pollution.

While the overall study evaluates available toxicology and risk assessments in order to provide in-depth data for four pollutants of concern: benzene, 1,3-butadiene, formaldehyde, and diesel particulate matter (PM), the review in this section is not necessarily restricted to just these four toxic agents. For example, a study cited below examines the linkage between environmental equity, socioeconomic status, and respiratory health and assesses air quality in terms of four air pollutants that include benzene, SO_2, PM_{10}, and NO_2 [507]. Likewise, a study that explores childhood cancer incidence rates and hazardous air pollutants in California considered exposure scores of 25 potentially carcinogenic HAPs including benzene, 1,3-butadiene, and formaldehyde [508]. Similarly, Lopez [509] examines non-criteria air pollutants which include 148 chemicals such as benzene and formaldehyde to note variability in concentrations across racially grouped census tracts to highlight the impact of racial differences in exposure to air toxics. The intent of this section is to highlight the presence of risk factors in certain population subgroups that makes them particularly vulnerable to the health impacts of air pollution. The additional vulnerability makes the case for environmental regulation more compelling and urgent. It also implies that the standards being recommended may be rather conservative as they are largely based on assuming a healthy populace.

The modification of the health impacts of air pollution by socioeconomic and demographic variables has policy implications for environmental regulation. The related discussion draws attention to socioeconomic and demographic variables in pollution affected areas in Houston. In this context, the United States Environmental Protection Agency's (US EPA's) National Air Toxics Assessment (NATA) concentration maps are presented to show countywide distribution of HAPs. Although, additional study may be needed to comprehensively illustrate racial and demographic overlaps, median household income (a surrogate socioeconomic variable) is used to illustrate the higher exposure risk among vulnerable populations in the Houston area.

2.3.2 Health Effects of Socioeconomic Position and Air Pollution

The effect of both ambient air pollution and SEP on health is documented in numerous epidemiologic studies [505, 510-513]. Research shows that groups with greater susceptibility to air pollution-induced illness are also likely to receive the highest exposure. Therefore, poor air quality exerts larger effects on their health than it does on the average or reference population. The increased likelihood arises from certain predisposing health conditions, behaviors, or traits that seem to be associated with lower SEP, race, ethnicity, and age. For example, diabetes can be associated with race and ethnicity, lower SEP, as well as with more

advanced age, which combine to contribute to greater vulnerability to the health effects of air pollution [505].

This section organizes the health effects of air pollution according to certain predisposing health conditions (risk factors) associated with lower SEP.

2.3.2.1 Diabetes

A review article notes that, in the United States, diabetes is more common among the elderly, non-hispanic blacks, Mexican Americans, and among people living in or near a central city [505]. The review also states that US residents with non-insulin dependent diabetes mellitus, or type-2 diabetes, (after adjusting for age) tend to have less education, lower income, and higher unemployment rates than do non-diabetics. Another complementary risk factor noted among diabetics is obesity, which is a condition that increases with age and is associated with increased systemic inflammation, including markers of cardiovascular risk. The vulnerability of diabetics to air pollution arises from these and various other reasons including lower heart rate variability and higher levels of inflammatory markers in blood. Internationally, in Mexico, incidence of type-2 diabetes was higher among low income individuals, while in the United Kingdom early childhood deprivation is a risk factor.

2.3.2.2 Asthma

Another medical condition reported to be unevenly distributed across population groups is asthma [505]. Like diabetes, it is noted to be differentially distributed by socioeconomic level. Similarly, studies indicate that the prevalence of asthma and diabetes was higher in European countries with lower gross national product. Likewise, it has been observed that there is much higher asthma prevalence in the more industrialized countries, although prevalence is increasing overall [505].

2.3.2.3 Genetic Traits

In addition to diabetes and asthma, some genetic traits that may affect response to air pollution exposure are differentially distributed by race and/or ethnicity [505]. These traits include fast versus slow acetylation, which affects the ability to remove toxins; deficiency in glucose 6-phosphate dehydogenase, an enzyme that affects the red blood cell membrane; and sickle cell trait (more common in those of West African descent), which can cause health problems even in heterozygous individuals when exposure to pollutants such as carbon monoxide happens [505].

2.3.2.4 Smoking

Smoking behavior, yet another health status modifier linked to SEP, is unequally distributed across socioeconomic levels. In the US, smoking has become concentrated among individuals in lower socioeconomics strata, as measured by income and educational attainment [505]. This contrasts to Mexico, where a national survey showed that higher income households consumed more tobacco in the form of cigarettes.

Smoking-related lung conditions can affect uptake and response to exposure to environmental air pollutants. Deposition of particles is relatively higher among persons who have chronic obstructive pulmonary disease, especially in the part of the lung that is

functional [505]. Lung function can decrease among smokers, resulting in increased ventilation-perfusion inhomogeneity, which can in turn affect delivered dose of particles.

2.3.2.5 Social Class and Residential Air Quality

Wheeler and Ben-Shlomo [507] examined relations between socioeconomic status and local air quality, and combined effects on respiratory health from a linkage analysis of routine data from a health survey for England. The main results of their study indicate that lower social class households were more likely to be located in areas of poor air quality and that low social class and poor air quality were independently associated with decreased lung function. The study highlights that the adverse effects of air pollution seem to be greater in lower social classes, and particularly among men. In this context, the coincidence between the high exposures modeled by NATA for the four pollutants and the areas of lower median family income is presented below as a specific Houston area example.

2.3.2.6 Cardiovascular

Another study examined whether socioeconomic status, as measured by an ecological measure of income level is a potential modifier of the effects of airborne pollution on all-cause, respiratory, and cardiovascular mortality [514]. Their estimates of risk are based on population-based linked data of residents of the greater Vancouver area in British Columbia, Canada. The study found increased risk of all-cause and cardiovascular mortality at lower levels of socioeconomic status (SES). While the relationship between SES and cardiovascular disease may be a complex web of causal factors, air quality is one among them [515]. Several studies have established the relationship between cardiovascular diseases and PM and PM exposure to SES [515-517].

2.3.2.7 Cancer

A study that linked risk estimates from the US EPA's NATA to racial and socioeconomic characteristics of census tracts in Maryland observed disparities in estimated cancer risk from exposure to air toxics by emission category [511]. In Maryland, the average cancer risk across census tracts was highest from on-road sources (50% of total risk from non-background sources), followed by non-road sources (25%), area (23%), and major sources (< 1%). Census tracts in the highest quartile defined by the fraction of African American residents were three times more likely to be high risk than those in the lowest quartile. Conversely, risk decreased as the proportion of Whites increased. Census tracts in the lowest quartile of socioeconomic position, as measured by various indicators, were 10–100 times more likely to be high risk than those in the highest quartile. The study observed substantial risk disparities for on-road, area, and non-road sources by socioeconomic measure and on-road and area sources by race. There was considerably less evidence of risk disparities from major source emissions. The study found a statistically significant interaction between race and income, suggesting a stronger relationship between race and risk at lower incomes.

2.3.3 Health Effects of Age and Air Pollution

2.3.3.1 Child Health

While environmental justice research has been mostly directed toward examining the inequities in the burden of environmental hazards on minority communities, demographic

inequities in health risks among children are also persistent [508, 517-529]. Children differ from adults in terms of their physiology, metabolism, and absorption and exposure patterns and are therefore more susceptible to the effects of environmental pollutants [530]. In this regard, research indicates that maternal and child health disparities are linked with the "double jeopardy" of exposure to environmental hazards combined with place-based stressors [531].

Childhood leukemia is the most common cause of malignancy under the age of 15, representing an annual incidence rate of 43 cases per million in the US [518]. Parental occupational exposures, ambient air pollution, other chemical exposures, such as household solvents and pesticides, radiation, dietary factors, immunological factors, socioeconomic, and genetic factors all contribute together and independently toward childhood cancers. In particular, in a study conducted in California, HAPs were shown to cause cancer or other adverse health effects in children [508].

Likewise, a population-based case-control study presented evidence to find an association between ozone exposure and pulmonary artery valve defects, and other select birth defects among livebirths and fetal deaths in a population of women from seven counties in Texas [520].

Acute exacerbations of asthma in children as measured by hospital use, symptoms, or lung function deficits have been found to be associated with exposure to criteria air pollutants and hazardous air pollutants [527]. In particular, the study examined asthma symptoms in Hispanic children and daily ambient exposures to hazardous and criteria air pollutants. It noted that hazardous air pollutants in the pollutant mix from traffic and industrial sources may have adverse effects on asthma in children.

2.3.3.2 Senior Health

As susceptibility to the health effects of air pollution may derive from prior health status and conditions, the aging of the US population is also a reason for concern. Although malignant tumors occur at all ages, the disease disproportionately strikes older individuals [532]. More than half of all newly diagnosed cancer patients and 71% of cancer deaths are in the 65 years and older age group. Barring any cancer prevention breakthroughs, the expansion of the aged population alone will increase the absolute number of individuals diagnosed and treated for cancer in the coming months. Environmental health risk abatement measures will potentially contribute to alleviate any related health burdens associated with vulnerable populations. For example, air pollution is cited as a risk factor (along with low socioeconomic status, inadequate nutrition, exposure to tobacco smoke, insufficient immunization) that predisposes older people to community-acquired pneumonia [533, 534]. Likewise, frail individuals diagnosed with myocardial infarction or diabetes were at greatest risk of death associated with high concentrations of particulate air pollution [535].

2.3.3 Health Effects of Race, Ethnicity and Air Pollution

Although asthma is the most common chronic disease of childhood in the US, it disproportionately burdens socially and economically disadvantaged urban communities [536]. In the US, asthma prevalence, hospitalization, and mortality are higher for African

American compared to Caucasian (White) children and adults. Studies reviewed indicate that childhood asthma in an integrated middle class population was twice as high for African American compared with non Hispanic White children; this finding suggests that even in middle class communities unmeasured socioeconomic factors (e.g., racial discrimination, differential access to medical care, differential access to housing, differential patterns of medical care use), and perhaps biologic factors (e.g., genetic variation in vulnerability to effects of exposures) may contribute to these disparities. In this context, it may be noted that disparity in asthma morbidity is observed to be greater than the disparity in asthma prevalence, suggesting that once asthma is established, many factors converge to make asthma worse for children and adults who are African American.

The role of environmental hazardous air pollutants in asthma occurrence has been reported extensively [537, 538]. Studies, conducted in New York City and Boston, indicate asthma hospitalizations and death rates among Blacks and Hispanics were 3–5 times those of Whites. Socioeconomic and biologic factors increase vulnerability to adverse effects of air pollution on asthma morbidity. The study noted that direct exposure to traffic and industrial pollutants is often high in socioeconomically disadvantaged urban neighborhoods.

Lopez [509] examines non-Hispanic Black and non-Hispanic White differences in exposure to non-criteria air pollutants in 44 US Census Bureau-defined metropolitan areas with populations greater than one million. The examination used data on air toxics concentrations prepared for the US EPA as part of its Cumulative Exposure Project combined with US census data. The study finds that in every metropolitan area, non-Hispanic Blacks are more likely than non-Hispanic Whites to be living in tracts with higher total modeled air toxics concentrations. The study cites various factors that may contribute towards the wide variation in exposure differences and concludes that increased minority residential clustering is associated with increased disparity in potential exposure to air pollution.

Likewise, Shaikh and Loomis [539] find a statistically significant correlation between minorities (particularly Hispanics and Native Americans) and the location of new stationary sources of air pollution in the Denver Metropolitan area. The study suggests that correlation between minority status and pollution may be due to the fact that there exists a correlation between race and socioeconomic factors such as high unemployment rates, high percentage of housing being rental units and low incomes.

The race, SEP, and minority status interplay is nonlinear and complex. For example, racial gradients of ambient air pollution exposure are not confined to any particular race but to minority-status communities in particular, even after controlling for SEP [540]. In this context, it may be noted that micro-area studies conclude that race is not a significant predictor for the location of facilities but that income may play a role. On the other hand, “meso-area” studies expand the area of interest to include blocks adjacent to facilities often conclude that race is an important predictor for facility location but income is not. Furthermore, results from macro-level studies that compare counties with other counties or states with other states have correlated industrial facility location with large percentages of minorities and persons in poverty [541].

2.3.4 Health Effects of Traffic and Air Pollution

Residential proximity to busy roads has been associated with adverse health outcomes, and school location may also be an important determinant of children's exposure to traffic-related pollutants. A number of studies have shown differences in health impacts as a function of proximity to a roadway [505, 542]. If proximity to traffic depresses property values, as indicated by hedonic pricing literature, then it is likely that the lower dwelling values will attract residents of lower SEP. Thus the higher ambient exposure is experienced by relatively disadvantaged groups living near roadways [543].

In this context, a study found that traffic exposure was related to race/ethnicity [522]. Examination of proximity of California schools to busy roads reveals that as the traffic exposure of schools increased, the percentage of both non-Hispanic black and Hispanic students attending schools increased substantially. Exposure to hazardous air pollutants was also related to school based and census-tract-based socioeconomic indicators.

Similarly, Gunier et al. [528] found that low-income children of color were more likely than white children and higher income children to live in block group with high traffic density. Since traffic density is related to vehicle emissions and was found to be moderately correlated with the ambient concentrations of several vehicle-related pollutants, children living in these neighborhoods have a higher potential for exposure.

Another study examined variations in traffic-related pollution exposure in Los Angeles neighborhoods [521]. The study found that traffic-related air pollution exposure disproportionately affected low SES neighborhoods in the winter. Further, in these poorer neighborhoods, the winter season evidenced increased susceptibility among women for preterm births.

Again, in the context of traffic studies too, socioeconomic status as reflected in housing characteristics is a confounder and a potential source of bias [544]. A related study reports that multifamily residences were 1.7 times more likely that single family residences to be within 100 meters of a busy road, residential apartment buildings were 2.0 times more likely, and apartment units above commercial storefronts 3.7 times more likely. Living in apartments is associated with increased exposure to allergens from cockroaches, rodents, and mold, all of which are considered risk factors for asthma.

2.3.5 Health Effects of Residential Characteristics and Air Pollution

The health effects of separate, unequal residential characteristics and hazardous air pollutants are linked to wide-ranging and complex political and socioeconomic forces, coupled with patterns of industrialization and development. These forces and patterns have isolated people of color, particularly African Americans, into neighborhoods with some of the highest indices of urban poverty and deprivation. Race-based residential separation may lead to a disproportionate burden of cumulative exposures of potential environmental hazards among certain communities while enhancing their vulnerability or susceptibility to the toxic effects of exposures due to individual and area-level stressors, and lack of neighborhood resources. Lopez [509] examines the relationship between residential isolation and community environmental health jointly to analyze the relationship between outdoor air pollution

exposure and residential isolation. The study's results shows that race-based residential clustering is associated with elevated risks of adult and infant mortality and tuberculosis.

Another study examines links between racial residential separation and estimated cancer risk associated with modeled ambient air toxics exposures [545]. The study modeled ambient air toxics concentration estimates for the U.S. EPA's NATA and combined these data with cancer potency information. Next, the study integrates the cancer risk estimates with socioeconomic and demographic information derived from the 1990 US Census for all tracts within 309 metropolitan areas in the continental US. The analysis encompassed 45, 710 tracts and more than 79% of the population of the US, including 76% non-Hispanic whites, 85% of non-Hispanic blacks; 91% of Hispanics; 87% of Asian/Pacific Islanders; and 53% of American Indians/Native Alaskans. The average individual lifetime cancer risks estimates for each metropolitan statistical area ranged across several orders of magnitude, with some of the highest risk estimates found in southern California and in the industrial Midwest. Cancer risk estimates exceeded the regulatory goal of one in a million by several orders of magnitude. Among source contributions, mobile sources make the most significant contribution to estimated cancer risk, followed by area sources and then major point sources.

The study points out that the northeastern, southern, and Midwestern regions have some of the highest levels of multiethnic/racial clustering and isolation, whereas the western, mountain, and plain states tend to have lower levels of minority clustering. In this context, the study reports two patterns: the cancer risks across all metropolitan areas increase with increasing separation levels for all racial/ethnic groups. And that overall, Hispanics and Asians, followed by African Americans, have some of the highest cancer risk burdens in metropolitan areas with higher separation levels compared with the average risk across all groups and compared with Whites and Native Americans.

2.3.6 Socioeconomic and Demographic Risk Factors and Air Pollution in Houston

The literature identifies several locations in Houston's industrial complex as sources that create toxic "hot spots" in the area [546-549]. In particular, the Houston Ship Channel is a heavily industrialized area with several petroleum refineries and chemical manufacturing facilities and is also a large volatile organic compound (VOC) sources. For example, various studies have examined that presence of non-methane VOC sources in the Deer Park, Haden Road, and Clinton Drive neighborhoods, and nonpolar organic fine particulate matter in areas of Aldine, Houston Ship Channel, and La Porte. Furthermore, the atmosphere of areas downwind from emission sources were found to be directly affected by toxic air pollutants from industrial processes, but not at the levels seen in areas closer to the Houston Ship Channel. A study collected urban air samples at five locations in Harris County to measure VOCs in residential areas in close proximity to industrial facilities [550]. Three of the locations were along the Houston Ship Channel while two others were located several miles away from the ship channel and any industrial facilities that are required to report toxic air emissions. The study notes that total VOC concentrations were highest at two of the industrial sites and lowest at the site farthest away from the ship channel and any industrial facilities. The study concluded that the atmosphere near Harris County's industrial complex had higher concentrations of VOCs than the atmosphere in areas farther away from the

Houston Ship Channel. Likewise, ambient measurements of hydrocarbon emissions from industrial release events in the area have shown that ozone formation in the Houston-Galveston region is frequently much more rapid than in other urban areas [551]. The Houston-Galveston area is one of the most severe ozone non-attainment regions in the US [552].

While it is important to find the location of a nearby source to identify the causes of local toxic "hot spots" to reconcile emission inventories observed concentrations, it is also important to recognize that the distribution of environmental burdens is spatially uneven. For example, TCEQ air pollution surveillance in the Houston area indicates that the Clinton Drive/Galena Park monitoring sites reported average benzene levels that exceeded the annual ESL of 1 ppb for benzene [39]. In addition, the report indicates that in Texas City, Galena Park, and at the Lynchburg Ferry lifetime exposure to monitored concentrations of benzene would probably cause cancer cases in the range of 1 in 100,000 to 4 in 100,000 people. Figure 11 illustrates data from the US EPA's 1999 NATA showing the estimated concentrations across Harris County census tracts for benzene.

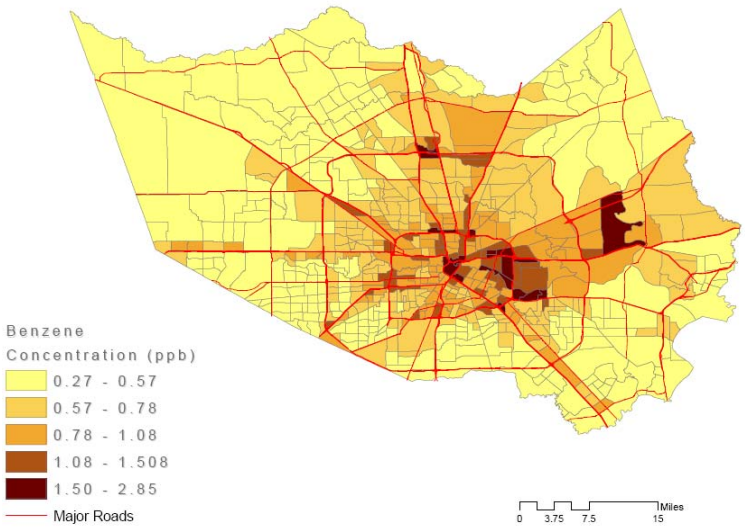

Figure 11. Modeled annual averaged benzene concentrations in Harris County in 1999. From the US EPA's National-scale Air Toxics Assessment (NATA) [553].

It is also reported that air monitoring at Milby Park, Chavez High School, and Clinton Drive recorded elevated emissions of 1,3-butadiene. In Houston's East End, in a public park, it is reported that levels of 1,3-butadiene in 2003 may be considered high enough (with lifetime exposure) to potentially impact more than 1 in 10,000 people with cancer. Milby Park, off the La Porte Freeway, is also identified for its proximity to one of the largest emitters of 1,3-butadiene in the state. TCEQ concludes that reductions are needed in ambient 1,3-butadiene, benzene, and several VOCs in the several areas around Houston's ship channel and the TCEQ Region 12 [39]. Figure 12 illustrates data from the US EPA's 1999 NATA showing the estimated concentrations across Harris County census tracts for 1,3-butadiene.

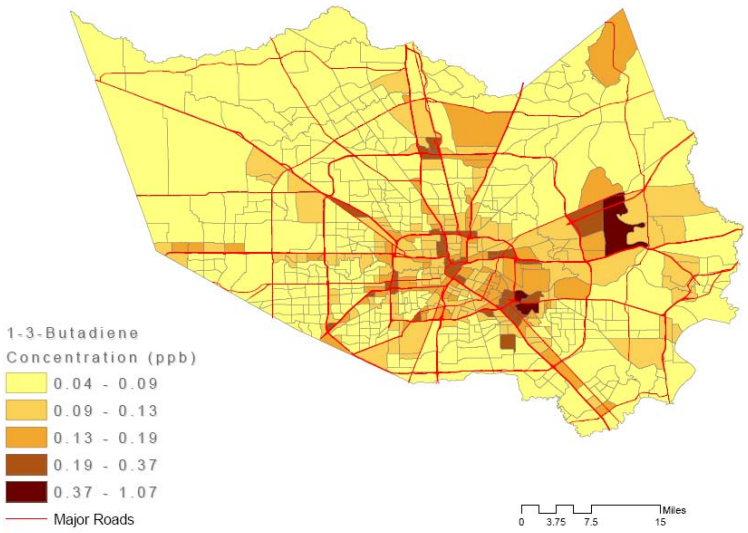

Figure 12. Modeled annual averaged 1,3-butadiene concentrations in Harris County in 1999. From the US EPA's National-scale Air Toxics Assessment (NATA) [553].

At Clinton Drive, Channelview, and Deer Park, formaldehyde was recorded in concentrations that could, with lifelong exposure, result in an excessive number of people getting cancer. Figure 13 illustrates data from the US EPA's 1999 NATA showing the estimated concentrations across Harris County census tracts for formaldehyde.

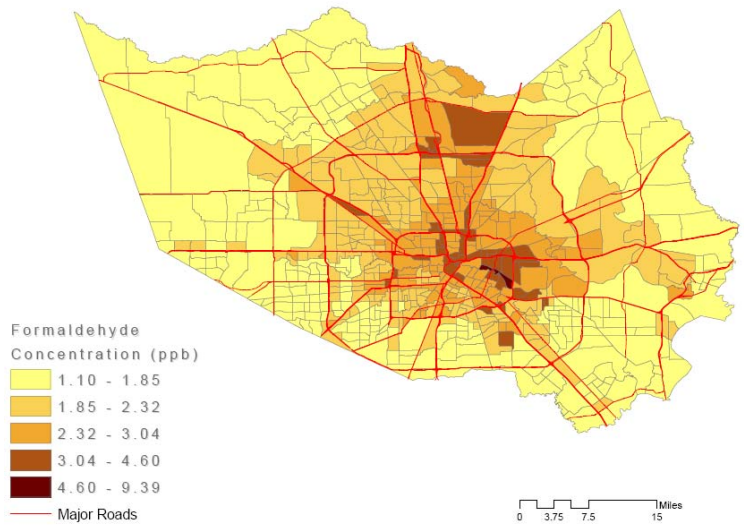

Figure 13. Modeled annual averaged formaldehyde concentrations in Harris County in 1999. From the US EPA's National-scale Air Toxics Assessment (NATA) [553].

Figure 14 illustrates data from the US EPA's 1999 NATA showing the estimated concentrations across Harris County census tracts for diesel PM.

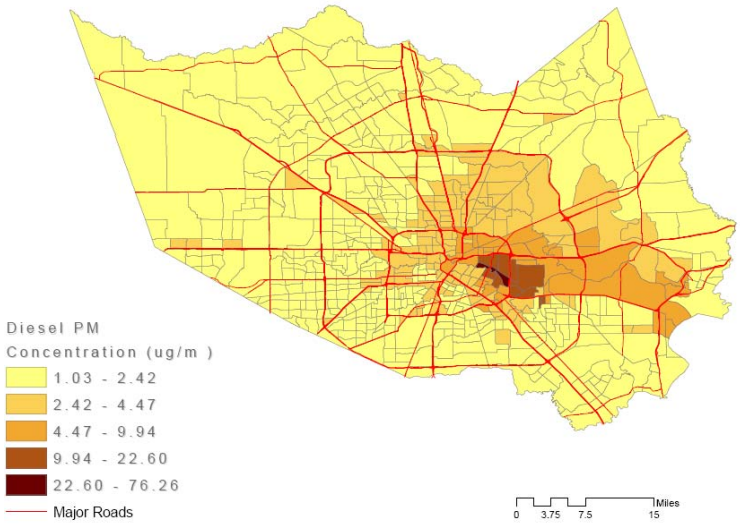

Figure 14. Modeled annual averaged diesel PM concentrations in Harris County in 1999. From the US EPA's National-scale Air Toxics Assessment (NATA) [553].

Figures 11 to 14 illustrate data from the US EPA's 1999 NATA showing the estimated concentrations across Harris County census tracts for benzene, 1,3-butadiene, formaldehyde, and diesel PM respectively. These maps contain data from the US EPA's National Scale Air Toxics Assessment (NATA) [553] and are modeling calculations made using emission estimates from point and mobile sources. Various factors such as emission rate, locations of emission sources, and weather patterns affect the predicted concentrations. While each of these factors can introduce uncertainty into the model results, the NATA concentrations are useful to show the countywide distribution of HAPs, since monitoring is conducted at only a limited number of locations, many of them in eastern Harris County. The maximum 2004 annual average concentrations listed in Table 12 are in general agreement with the maximum annual average concentrations predicted by NATA.

Table 12: A comparison of the 2004 annual average concentration of three hazardous air pollutants at the single highest monitoring location in four US cities [1].

	Benzene	1,3-Butadiene	Formaldehyde
Chicago	0.5 ppb	0.08 ppb	2.0 ppb
Los Angeles	0.9 ppb	0.2 ppb	7.2 ppb
St. Louis	0.5 ppb	0.07 ppb	4.2 ppb
Houston	1.7 ppb	4.0 ppb	7.9 ppb

What adds to the problem is that the various localities monitored for air pollution acuity contain communities that are mostly populated with minority and people with low socioeconomic status. Figure 15 displays the distribution of median family incomes across the Harris County census tracts. Median family income is used as surrogate for socioeconomic position.

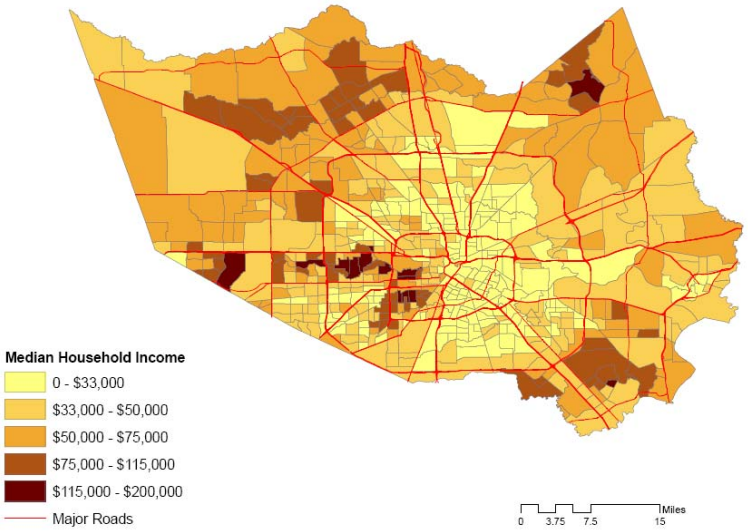

Figure 15. Median household income in Harris County census tracts.

A comparison of Figure of 15 with Figures 11-14 highlights the coincidence of higher exposure levels with lower median family income in eastern Harris County. For example, Galena Park is among the neighborhoods adversely affected by air pollution in the Houston area. It has a population of about 10,000 and is located in east Harris County. It is about 3.2 miles from Pasadena and about 8 miles from Houston. Galena Park has a significant Hispanic population (69%) with Non-Hispanic Whites amounting to only about 22% of the population. The median household income in Galena Park is reported to be around thirty one thousand dollars, while about a quarter of the population is below the poverty line. Likewise, Clinton Park, another high risk neighborhood, has almost 35% of its children living below the poverty level and over 40% of the adults in this aging community do not have a high school diploma. The median per capita income in Clinton Park is about a third of the US per capita income. Over 90% of the population is African American, while the next largest population group is Hispanic (about 7%). From its inception Clinton Park is an almost entirely African American community economically dependent on the Ship Channel industries. Similarly, Channelview, another community that is dependent on the petrochemical industry, is located 6.2 miles from Pasadena and 15 miles from Houston. It has a population of over twenty-nine thousand comprising mostly of Hispanics (37%) and Blacks (13%) with White non-Hispanics in the minority (about 46%). The Channelview air pollution monitoring site is located a mile northeast of Alice B. Johnson Junior High School. It is a highly populated area with the land use being primarily single-family residences. The Channelview school district serves a student population that is about 16% African-American, 39% Hispanic, and about 44% non-Hispanic White. A petrochemical company and several other companies operate

north of the site. In short, the spatial unevenness of air pollution in Houston is complicated by health impact susceptibilities related to socioeconomic and demographic inequities.

2.3.7 Policy Relevance of Socioeconomic, Demographic and Air Pollution Health Impacts

The approach for setting standards for hazardous air pollutants was changed from health-based to a technology-based approach with the Clean Air Amendments of 1990 [554]. The MACT approach provides the US EPA with considerable leeway in establishing categories of emissions sources, as well as in designating a particular emission level as achievable for each category (after taking into consideration the costs of compliance). Initially, MACT was expected to reduce public health risks from many sources of air toxics. However, as the regulatory system exchanged regulatory depth for regulatory breadth by covering large numbers of substances with moderate stringency, potential for significant residual risks became apparent. There is no guarantee that the ambient concentration of air toxics will not impact human health due to the cumulative cancer risk and other health effects from exposure to low levels of many substances.

In order to make the most of MACT, a coordinated use of both technology-based and health-based standards promises long-term improvements in environmental quality and public health. The coordination may take the form of local and state initiatives to complement regulation at the federal level. Federalism points to a regulatory structure in which decentralized levels of governments take responsibility for those dimensions of environmental quality that are contained within their jurisdictional boundaries. Accordingly, the US EPA sets uniform national standards and MACT may provide the operational framework at the national level. Also, with MACT, the US EPA avoids, to some extent, the task of overly implementing legislative mandates and takes on the relatively more practical task of defining emission categories and available control technologies. The residual management of environmental concerns and related regulatory control then becomes the responsibility of state and local governments. In this regard, local governments may be better suited to realize more specific advantages as they may have a better understanding of the economic development, environmental and other concerns of its constituents.

As the review indicated, the differences in environmental burdens along demographic and socioeconomic position result in increased adverse public health outcomes (such as premature deaths, infant mortality, childhood asthma and decreased lung function and development). Consequently, it is observed that the poor and low income communities tend to benefit most from air quality improvements [505]. This suggests that alleviation of the health burdens from environmental pollution exposure on the economically disadvantaged will potentially reduce related public health insurance and health safety net costs. There is considerable literature that attempts to quantify the illness costs of air pollution [336, 555-564]. The studies range from estimating increased asthma medication use, costs and morbidity caused by allergic rhinitis to estimating the economic burden of lung cancer or estimating the direct and indirect costs of asthma in school-age children or assessing hospital admissions associated with particulate air pollution and congestive heart failure. Interestingly, when insurance status is used as an indicator of socioeconomic/health coverage

status, higher relative risks were indicated for the poor/working poor (i.e., those on Medicaid and the uninsured) than for those who were economically better off (i.e., privately insured).

2.3.8 Conclusion

The implication that people of lower SES are more susceptible to the adverse effects of air pollution has far reaching policy relevance. Health risks from ambient air pollution are not the results of personal decisions (unlike that from smoking) and have no direct benefit to an individual. Arguably, poverty is also not the direct result of an individual's personal decision. Thus, a large subset of the state and local population may be at increased health risk from exposure to environmental agents over which they have little control, merely because of their social status. This aspect clearly identifies a role for state and local jurisdictions in adopting environmental measures that will enhance the health and quality of life of its constituents. To the extent that physical and economic burdens of pollution are unevenly distributed across society they will raise concerns about environmental equity. This issue is particularly important for Texas given its large and ethnically diverse population and the potential for exposure.

3.0: Regulations

3.1 Texas Effects Screening Levels

3.1.1 Definition of Effects Screening Level (ESL)

The Texas Commission on Environmental Quality (TCEQ) has developed effects screening levels (ESLs) for toxic air contaminants. ESLs are chemical-specific air concentrations the TCEQ has established to protect human health and welfare. ESLs are used in the air permitting process to evaluate the potential for adverse effects to occur as a result of exposure to predicted concentrations of air contaminants. However, they are screening levels, not ambient air standards. ESLs do not regulate the ambient concentration of air toxics and are only used in permitting decisions. If the predicted airborne level of a contaminant released from a source applying for a permit exceeds the ESL, the TCEQ could conduct a more in-depth review instead of assuming adverse health or welfare effects would occur.

There are two types of ESLs, short-term and long-term. Short-term ESLs represent the air contaminant exposure level safe for 1-hour duration while the long-term ESLs represent air concentrations to which a lifetime of exposure is expected to be free of adverse health effects for the general public.

ESLs have been developed for all substances determined by the Toxicology Section of the TCEQ to be airborne toxicants. The Toxicology Section exempts certain substances if the scientific evidence or prior regulatory experience indicates that the substance should not be classified as an airborne toxicant. In addition, ESLs are not developed for constituents that must meet National Ambient Air Quality Standards (NAAQS).

3.1.2 Procedures for Developing ESLs

Short-term ESLs are based on data concerning acute health effects, odor potential, and vegetative effects. Long-term ESLs are generally based on data concerning chronic non-carcinogenic and/or carcinogenic health effects. The exposure concentrations for the short-term ESLs and the long-term ESLs are calculated using a reference toxicity factor[8]. The reference toxicity factors employed by the TCEQ in determining ESLs have been developed by the US EPA's Integrated Risk Information System (IRIS) as well as by other federal and state agencies.

3.1.2.1 Non-Carcinogens

For non-carcinogens, the hazard quotient (HQ) is defined as the ratio of the exposure concentration (E) to the reference toxicity factor (ReV). For non-carcinogens, the ReV is an estimation of an inhalation exposure concentration of a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse effects [227].

Accordingly:

$$HQ = E / ReV \quad \text{(Eqn. 1)}$$

$$\Rightarrow E = HQ * ReV$$

[8] For carcinogenic air toxics the reference toxicity factor is the ReV and for non-carcinogenic air toxics it is known as the URF.

For non-carcinogens, the TCEQ Toxicology Section has determined the screening level of a chemical that corresponds to a target HQ of 0.1 for an acute exposure period (1-hour) ($_{Acute}ESL_{Noncarc}$) or a chronic exposure period (lifetime) ($_{Chronic}ESL_{Noncarc}$) and is calculated as follows:

$$_{Acute}ESL_{Noncarc} = HQ \times \text{acute ReV} = 0.1 \times \text{acute ReV} \quad \text{(Eqn. 2)}$$

$$_{Chronic}ESL_{Noncarc} = HQ \times \text{chronic ReV} = 0.1 \times \text{chronic ReV} \quad \text{(Eqn. 3)}$$

3.1.2.2 Carcinogens

For carcinogens, the risk level is defined as the product of exposure concentration (E) and the unit risk factor (URF). For carcinogens determined to exhibit a linear dose-response relationship, the URF is calculated using extrapolation from an inhalation dose-response curve. As a result, this represents the upper-bound excess cancer risk estimated to result from continuous lifetime exposure to an agent at a concentration of 1 $\mu g/m^3$ in air. For carcinogens that exhibit a nonlinear dose-response relationship, a chronic ReV is developed using either chronic human epidemiology studies, chronic animal studies, or well-conducted subchronic animal studies [227].

Accordingly:

$$\text{Risk Level} = E * URF \quad \text{(Eqn. 4)}$$
$$\Rightarrow E = \text{Risk Level} / URF$$

For carcinogens, the TCEQ Toxicology Section calculates the screening level of a chemical that corresponds to a target risk level of 1×10^{-5} (or one excess cancer death in 100,000) for a lifetime exposure period ($_{Chronic}ESL_{Carc}$) as follows [227]:

$$_{Chronic}ESL_{Carc} = (1 \times 10^{-5}) / URF \quad \text{(Eqn. 5)}$$

3.1.2.3 Odor-based ESLs

The TCEQ has set odor-based ESLs (ESL_{Odor}) based on the chemical's odor threshold. The Toxicology Section at the TCEQ conducted a comprehensive literature search of published odor thresholds for a variety of air contaminants to identify and interpret the odor threshold values of odorous chemicals. The TCEQ set an appropriate ESL_{Odor} for odorous air contaminants using the odor threshold values for chemicals that had been critiqued and accepted by American Industrial Hygiene Association (AIHA) and the US EPA [227].

3.1.2.4 Vegetation Effects

If a chemical's adverse effect level in plants is found to be substantially higher than its odor threshold or adverse effect level in humans, the TCEQ would review the available plant toxicity information. However, the Toxicology Section has not developed any vegetation-based ESL ($_{Acute}ESL_{Veg}$) as of the writing of this report.

3.1.2.5 Determination of ESLs

The lowest value of the following health and welfare based ESLs is selected as the governing short-term ESL:

$_{Acute}ESL_{Noncarc}$; $_{Acute}ESL_{Odor}$; $_{Acute}ESL_{Veg}$.

The lowest value of the following health-based ESLs is selected as the governing long-term ESL:

$_{Chronic}ESL_{Noncarc}$; $_{Chronic}ESL_{Carc}$.

3.1.3 Peer Review of the Development of Texas ESLs

A recent peer review of the TCEQ methodology on setting ESLs was organized by Toxicology Excellence for Risk Assessment (TERA). TERA is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. The panel consisted of experts in the fields of acute and chronic inhalation toxicology, air pollution exposure, and cancer and non-cancer risk assessment methods.

The panel suggested that the Texas ESLs distinguish between cumulative risk and aggregate risk. Although using a hazard quotient of 0.1 as a screening tool has been done by some federal and state programs, the review panel suggested that this approach does not follow accepted risk assessment methods. If the sole purpose of the ESL program is determining suitability of air permits, then using an HQ of 0.1 is likely adequate. The review panel recommended risk management objectives that require a more "detailed" risk value. The panel suggested that an approach be developed to accumulate risk according to target organ, mode of action, or chemical class. The panel determined this would be more appropriate and recommended that the TCEQ develop HQs for the non-cancer properties of carcinogens and consider them in developing a cumulative risk assessment approach [565].

The panel suggested that criteria for describing chemicals that are exempt from ESL development should be clarified. In addition, if chemicals are on the exempt list because they are regulated by another program, then the panel suggested that the Texas ESLs state this and describe which program regulates these chemicals.

The panel also suggested that the choice of a 50% odor threshold for setting the odor ESL should be better justified in the Texas ESL guidance document because the ability to perceive odor does not necessarily correlate with concentrations associated with toxicity and odor detection also involves cognitive issues not related to chemical concentration. The panel suggested that the potential for sensory irritation, as measured by the concentration that results in a 50% reduction in respiratory rate in rodents (the RD_{50}), would be a better basis for an ESL than odor [565].

Finally, the panel members suggested that the TCEQ consider applying the following analytical approach as the foundation of the ESL guidance document [565]. This analysis would apply to both evaluation of "ready made" ESL values for which the supporting risk assessment is strong as well as data sets for which no risk assessment values are available. This type of analysis would place emphasis on the availability of data, rather than the availability of a risk value. One panel member noted that the issue of peer review became

more pressing as TCEQ deviated from existing assessments and created independent assessments.

- Review the underlying data.
- Describe expectations for chemical toxicity based on physical and chemical characteristics e.g., does this chemical have properties that indicate it is likely to be reactive in the portal of entry.
- Conduct a mode of action analysis that describes in detail the potential for toxicity and the nature of the dose response curve.
- Choose an appropriate dose metric.
- Conduct appropriate dosimetric modeling.
- Select critical effect and point of departure.
- Apply appropriate uncertainty

3.1.4 Conclusion

Currently, the only effort to address HAPs in Texas beyond the requirements of federal regulation has been in the establishment by the Texas Commission on Environmental Quality (TCEQ) of Effects Screening Levels (ESLs). ESLs are non-binding target concentrations used in issuing permits for new facilities. When a permit application for a new emission source is reviewed, the permitted emissions of pollutants are calculated without consideration of other existing sources or of background pollutant levels. If the expected ambient contribution from the new facility exceeds the established ESLs, additional emissions controls may or may not be required before an operating permit is issued. It is important to note that the Texas ESLs are established at a screening level equivalent to a health impact of one excess cancer death in 100,000 people Also, ESLs do not govern the surrounding ambient air concentrations and do not take into account the residual or pre-existing risks due to the ambient concentration of HAPs. The ESLs for the compounds studied in this investigation are summarized in Table 13.

Table 13: Summary of Texas ESLs for the four HAPs discussed in this report [227].

Compound	***Short-Term ESL***	***Long-Term ESL***
Benzene	25 ppb	1 ppb
1,3-Butadiene	50 ppb	5 ppb
Formaldehyde	12 ppb	1.2 ppb
Diesel Fuel Combustion Products	1.5 $\mu g/m^3$	0.15 $\mu g/m^3$

3.2 Review of Air Toxic Regulations in Other States

This section highlights what other states were doing about managing residual risks from air toxics. The following sections summarize the results from twelve states (California, Connecticut, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, North Carolina, Oregon, Rhode Island, and Wisconsin) selected by the study authors as potentially having programs or strategies of interest to Texas.

In each case, the focus was on the legal justification for the state regulation of residual air toxics risk, what the standard or guideline is, and what evidence they used to set that standard or guideline. The information for each state is stated in a narrative format and is also summarized in a summary table. The narrative sections give some background on the regulating entity and enabling legislation for each state as well as a summary of some programs being utilized in the state to reduce air toxics emissions. The table summarizes the standards adopted and also describes the risk assessment(s) consulted in setting the standard level. Figures in each section show a general trend in air toxics emissions from point sources over the last decade using data obtained from the toxics release inventory (TRI) Although this data includes some compounds not denoted as HAPs by the US EPA, trends are the key message.

In particular, the state regulations of the four toxic compounds addressed in this report (benzene, 1,3-butadiene, formaldehyde, and diesel PM) as well five other compounds thought to be of particular interest to the Houston area (acrolein, H2S, styrene, vinyl chloride, and toluene) were examined. Data for state standard for diesel PM is missing from the summary tables as these states have not adopted standards for diesel PM in particular. Instead, programs affecting diesel PM emissions are discussed as such in the narrative section.

3.2.1 California

The California Air Resources Board's (CARB) statewide comprehensive air toxics program was established in the early 1980s [566]. It remains one of the most progressive and comprehensive programs in the country. Many other states reference the independent risk assessments conducted by the California Office of Environmental Health Hazard Assessment (CA OEHHA) in setting standards, and the OEHHA assessments of benzene, 1,3-butadiene, formaldehyde, and diesel PM are discussed in detail elsewhere in this report. Currently, the CARB regulates a total of 748 pollutants.

The Toxic Air Contaminant Identification and Control Act (AB 1807) created California's program to reduce exposure to air toxics [567]. Under AB 1807, the CARB is required to use certain criteria in the prioritization for the identification and control of air toxics [568]. In selecting substances for review, the CARB must consider criteria relating to “the risk of harm to public health, amount or potential amount of emissions, manner of, and exposure to, usage

of the substance in California, persistence in the atmosphere, and ambient concentrations in the community" [569].
The 1987 Air Toxics "Hot Spots" Information and Assessment Act (AB 2588) supplements the AB 1807 program, by requiring a statewide air toxics inventory, notification of people exposed to a significant health risk, and facility plans to reduce these risks [570]. Furthermore, AB 1807 was amended to require the CARB to use available information gathered from the AB 2588 program in the prioritization of compounds [571].

3.2.1.1 AB 1807 Program

In 1983, the California Legislature established a two-step process of risk identification and risk management to address the potential health effects from air toxic substances and protect the public health of Californians [572]. During the first step (identification), the CARB and the OEHHA determines if a substance should be formally identified as a toxic air contaminant (TAC) in California [573]. During this process, the CARB and the OEHHA staff draft a report that serves as the basis for this determination [574]. The CARB staff assesses the potential for human exposure to a substance and the OEHHA staff evaluates the health effects. The statute allows for any person to provide information and requires that the CARB hold a public hearing to allow public input [575, 576]. Public workshops are intended to allow for direct exchange of information with interested constituencies. The draft risk assessments themselves are published and widely distributed with a public notice requesting comment to further assure involvement. The final risk assessment (identification) report includes a record of the public comments and how they were addressed. After the CARB and the OEHHA staff hold several comment periods and workshops, the report is then submitted to an independent, nine-member Scientific Review Panel (SRP), who review the report for its scientific accuracy [577]. If the SRP approves the report, they develop specific scientific findings which are officially submitted to the CARB [577]. The CARB staff subsequently prepares a hearing notice and draft regulation to formally identify the substance as a TAC [578]. Based on the input from the public and the information gathered from the report, the CARB will decide whether to identify a substance as a TAC [579]. Any person may petition the Board to review a previous determination by providing new evidence [580].

If the CARB lists a TAC, it must also attempt to identify a threshold level of exposure below which there are "no significant adverse effects" with "an ample margin of safety" [581]. The acceptable exposure level is expressed as a reference exposure level (REL), which is an exposure level at or below which no non-cancer adverse health effect is anticipated to occur in a human population exposed for a specific duration [582]. RELs are used to evaluate toxicity endpoints other than cancer [583] and the specific duration of an acute exposure is specified by chemical [584].

In the second step (risk management), the CARB must produce a report reviewing the emission sources of an identified TAC to determine if any regulatory action is necessary to reduce the risk [585]. The analysis includes a review of controls already in place, the available technologies and associated costs for reducing emissions, and the associated risk [586]. The CARB must hold public hearings before deciding on the control technologies for types or categories of sources [568].

In 1993, the California Legislature amended the AB 1807 program for the identification and control of TACs (AB 2728). Specifically, AB 2728 required the CARB to identify the 189 federal hazardous air pollutants as TACs [585, 587].

3.2.1.2 AB 2588 "Hot Spots" Program

In September 1987, the California Legislature established the AB 2588 air toxics "Hot Spots" program [588]. It requires facilities to report their air toxics emissions to the CARB [589, 590] and this information is made public [591, 592]. Based on their emissions, certain high priority facilities must ascertain health risks and notify nearby residents of significant risks [593]. In September 1992, the "Hot Spots" Act was amended by Senate Bill 1731 which required facilities that pose a significant health risk to the community to reduce their risk through a risk management plan [594].

3.2.1.3 Regulations

California is split into 35 local air districts [595]. Each district must adopt rules and regulations to achieve state and federal ambient air quality standards [596], with the oversight from the CARB [597]. Local districts also are required to adopt control measures to meet the CARB's standards for airborne toxics [598]. Local districts may also adopt air toxics standards for pollutants CARB has not yet listed [599].

The CARB has adopted a large number of air toxic control measures (ATCMs) which can be found in Titles 13 and 17 of the California Code of Regulations [600]. Many of the CARB's adopted control measures use pollution prevention techniques as the foundation of the regulation. Such measures can include product reformulation or elimination. Other measures include bans the use of perchloroethylene, methylene chloride, and trichloroethylene from automotive consumer products such as brake cleaners [601]; restricted usage of asbestos-containing material for surfacing applications [602]; and bans on toxic metals like hexavalent chromium and cadmium from auto refinishing paints [603]. Reduced usage is another pollution prevention technique currently being promoted by the CARB.

The CARB controls have concentrated on several particular chemical due to their proven risk. Hexavalent chromium was one of the most toxic substances identified by the CARB and several sources are subject to ATCMs [603-605]. The CARB requires that perchlorethylene be removed from certain automotive consumer products [601] and that controls and training be used to reduce emissions from dry cleaning operations [606]. In addition to an ATCM controlling dioxin emissions from medical waste incinerators [607], the CARB is developing a comprehensive air quality monitoring and testing program to collect ambient data on dioxins, furans, and dioxin-like polychlorinated biphenyls in California [608]. Under this program, the CARB will evaluate potential health impacts, assess the need for additional control strategies, and identify areas where additional study may be required.

The CARB has also established programs to reduce toxic air pollutants from motor vehicles and fuels. The potential cancer risk from gasoline-powered vehicle emissions has been reduced because the benzene emissions have been cut in half and 1,3-butadiene has been reduced in cleaner burning gasoline [609]. The 2003 amendments to the California

Reformulated Gasoline Regulations also phased out MTBE [610]. Other programs specifically targeting diesel exhaust will be discussed in the next section.

3.2.1.4 Diesel PMs

In 1998, the CARB identified diesel exhaust as a toxic air contaminant based on its potential to cause cancer and other adverse health effects [611, 612]. The CARB estimates that diesel PM contributes over 70% of the known risk from air toxics [613].

In September 2000, the CARB approved a comprehensive diesel risk reduction plan to reduce diesel emissions from both new and existing diesel-fueled engines and vehicles [614]. The goal of the plan is to reduce diesel PM emissions by 75% by 2010 and 85% by 2020 [615]. Diesel PM is one of the air toxics identified as making children more susceptible to illness [616]. This reduction will also lower the associated health risk. One of the first measures to be adopted was targeted at reducing emissions from the garbage waste haulers that operate in residential area.

In 2003, the CARB adopted a new regulation lowering the sulfur content of diesel fuel to enable the use of advanced emission control technologies for diesel engines [614].

Other diesel emission reduction measures have targeted sources that impact schools. The Carl Moyer [617] and School Bus Programs [618] provide funds to replace some of the dirtiest diesel engines, including those in school buses. Idling limits at schools require buses and commercial vehicles to switch off their engines upon arrival, and only restart them 30 seconds before departure [619]. In 2005, idling controls were expanded to all commercial diesel vehicles in California [620].

The CARB has adopted several regulations that will reduce diesel emissions from in-use vehicles and engines throughout California. These regulations will apply to transit agencies [621], stationary engines in generators [622], transport refrigeration units [623], and portable engines [624]. In some cases, the diesel PM reduction strategies also reduce smog-forming emissions such as NO_x

The CARB is also currently evaluating methods of controlling and reducing emissions from the Ports of Los Angeles and Long Beach [625].

The CARB has an active enforcement program. Heavy-duty vehicle smoke inspections for diesel trucks and buses ensure that these vehicles are not in violation of motor vehicle standards that would allow excessive pollution to be emitted [626]. The CARB conducts reviews of the individual districts' control programs which includes their air toxics programs [627]. Multi-media enforcement cases address not only toxic air pollutants, but also toxic pollutants of water and soil, and the disposal of toxic wastes [628]. These cases call upon investigative resources from local air districts other agencies within the California environmental protection agency, and the US EPA.

3.2.1.5 Results

Between 1990 and 2002, the CARB claims to have reduced cancer risk from toxic air pollutants by 45%, measured statewide [613]. They point out that this is in the face of California's significant growth in the number of motor vehicles and other industry in the

same period. They list reductions of 65% in benzene (95% drop in benzene emissions from gas stations), 45% in 1,3-butadiene, and 40% in diesel PM over the same period.

CARB's emissions inventory contains a publicly available list of over 30,000 facilities which must report their emissions of any of over 700 toxic substances [629, 630]. An CARB survey found 21 companies which voluntarily reduced air toxics emissions by almost 2 million pounds in recent years [631].

Figure 16 below illustrates the decrease in total amount of reported emission releases of compounds identified as air toxics by the Toxics Release Inventory [632].

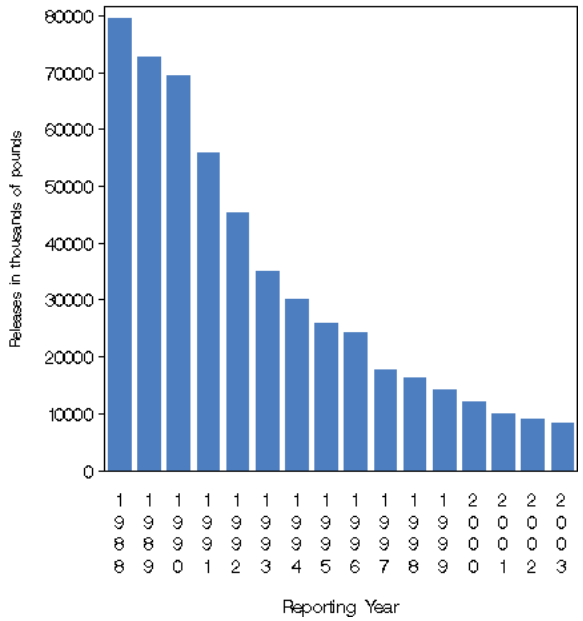

Figure 16: California's total reported release of air toxics (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 14: California's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Inhalation Reference Exposure Level (REL)			Inhalation cancer risk value	Primary Evidentiary Support	Regulated Sources
		Acute		Chronic ($\mu g/m^3$)	($\mu g/m^3$)$^{-1}$		
		($\mu g/m^3$)	Avg. time (hr)				
Benzene	Recognized Carcinogen, Developmental and Reproductive Toxin; Suspected Respiratory and Organ Toxin	1,300	6	60	2.9E-05	OEHHA	New & existing sources
1,3-Butadiene	Recognized Carcinogen, Developmental and Reproductive Toxin; Suspected Respiratory and Organ Toxin			20	1.7E-04	OEHHA	
Formaldehyde	Recognized Carcinogen; Suspected Respiratory, Reproductive and Organ Toxin	94		3	6.0E-06	OEHHA	
Toluene	Recognized Developmental Toxin; Suspected Acute & Chronic Respiratory Toxin, Reproductive and Organ Toxin	37,000	1	300		OEHHA	
Acrolein	Suspected Carcinogen, Reproductive, Respiratory and Organ Toxin	0.19	1	0.06		OEHHA	
H_2S	Acute & Chronic Respiratory Toxin, Suspected Reproductive Toxin	42	1	10		OEHHA	
Styrene	Suspected Carcinogen, Reproductive and Organ Toxin	21,000	1	900		OEHHA	
Vinyl Chloride	Recognized Carcinogen; Suspected Reproductive and Organ Toxin	180,000	1		7.8E-05	OEHHA	

Acute Exposure: One or a series of short-term exposures generally lasting less than 24 hours.
Chronic Exposure: Long-term exposure, usually lasting one year to a lifetime.
Inhalation Unit Risk Factor: The theoretical upper bound probability of extra cancer cases occurring in the exposed population assuming a lifetime exposure to the chemical when the air concentration is expressed in exposure units of per microgram/cubic meter ($\mu g/m^3$)$^{-1}$.

3.2.2 Connecticut

In 1986, Connecticut adopted and began implementing the law controlling toxic air emissions. Statutory authority for the Commissioner of Environmental Protection to formulate, adopt, amend, and repeal regulations for the abatement of air pollution are found in sections 22a-6 and 22a-174 of the Connecticut General Statutes [633]. The Commissioner's powers and duties are to be exercised in accordance with the environmental policy of the State [634]. Controls of mobile sources are authorized under 22a-174g of the Connecticut General Statutes.

In 1986, Section 22a-174-29 established emission limits known as hazard limiting values (HLVs) for 850 chemicals based on national occupational health standards [635]. These substances are regulated or addressed by the Occupational Safety and Health Administration, American Congress of Government Industrial Hygienists, and the National Institute of Occupational Safety and Health. The occupational standards are used to establish both 30-minute and 8-hour emission limits for exposure. The law does not specify how the occupational exposure levels are to be transformed into the HLVs but they are defined as the highest acceptable concentration of a hazardous air pollutant in the ambient air. The primary use of this term is in the derivation of the maximum allowable stack concentration (MASC) for a source [636].

Stationary sources must comply with the emission limitations in the regulation. The MASC sets the allowable emission concentration at the stack based on calculations worked back from the acceptable ambient level derived from the HLV [635]. It is based on a formula incorporating the HLV and the stack's discharge flow rate, height, and distance to the closest property line [635]. Periodic testing and inspections conducted by the Connecticut Department of Environmental Protection (CT DEP) enforcement staff [635] ensures compliance with these limitations. The Commissioner may require sampling to determine actual concentrations of listed air toxics at discharge points triggered by an observed exceedance, or other air enforcement action [635]. The Commissioner may require a stationary source to seek a permit if they fail to comply with the MASC [635].

Following the passage of the 1990 Clean Air Act Amendments with its maximum achievable control technology (MACT) requirements, the CT DEP decided to retain the existing state regulation for control of air toxics as well as to implement the required federal MACT program. Connecticut viewed its existing regulation as being more protective since it is health-based, covers 850 chemicals, is flexible enough to address urban hot spots, and applies to all sources [637].

The CT DEP has the ability to monitor approximately 100 chemicals including metals, volatile organic compounds, and aldehydes. In addition to monitoring programs mandated by the US EPA, the CT DEP also conducts additional monitoring programs for air toxics at various locations throughout the state to assess air quality. Additionally, the CT DEP conducts special monitoring projects (e.g., in response to odor complaints), photochemical assessment monitoring (collecting data on 70 air toxics, in addition to ozone precursors), dioxin and mercury monitoring, and monitoring of municipal waste combustion stacks [638].

Mobile source programs have been developed to combat both ozone and air toxics including the adoption of the National Low Emission Vehicle Program, vapor recover program, enhanced reformulated gasoline, enhanced vehicle inspections, and diesel truck inspections. The CT DEP has passed a regulation adopting the second phase of California's Low Emission Vehicle Program for motor vehicles from 2008 onwards with its tighter controls on toxic air pollutant emissions [639, 640]. Since 1994, the CT DEP has operated a small business assistance program to facilitate their compliance with all air quality regulations, including air toxics [641].

3.2.2.1 Diesel PMs

The CT DEP states that the reduction of diesel emissions is a priority and lists a multi-faceted reduction strategy that includes stationary and mobile source applications [642]. Measures implemented and considered include emission reduction technology, cleaner fuels, education and outreach, and voluntary partnerships. These strategies are targeted at school buses, off-road construction equipment, stationary diesel engines, electric generating units, and transit buses and trucks. Future sectors include barges, ferries, and locomotives.

The CT DEP passed legislation prohibiting idling of school buses in 2002 [643] and CT DEP's anti-idling regulations apply to every vehicle in Connecticut, including diesels [644]. The CT DEP provided signage for school areas and actively enforced this regulation at schools resulting in numerous violation notices and increased compliance.

CT DEP's initial diesel retrofit efforts prioritized school bus retrofits based on the health risks posed to children and included the use of Supplemental Enforcement Project (SEP) money to fund it. Any heavy-duty diesel truck engine sold in, or transferred to, the State from 2006 onwards must also be approved for sale in California [645].

3.2.2.2 Results

Connecticut has reduced toxic air emissions from over 25.3M lbs in 1988 to 1.8M lbs in 2003 according to data reported to the Toxics Release Inventory, as shown in Figure 17 [632]. This represents a reduction of 92.9% from 1988 levels. These reductions are primarily from manufacturing facilities.

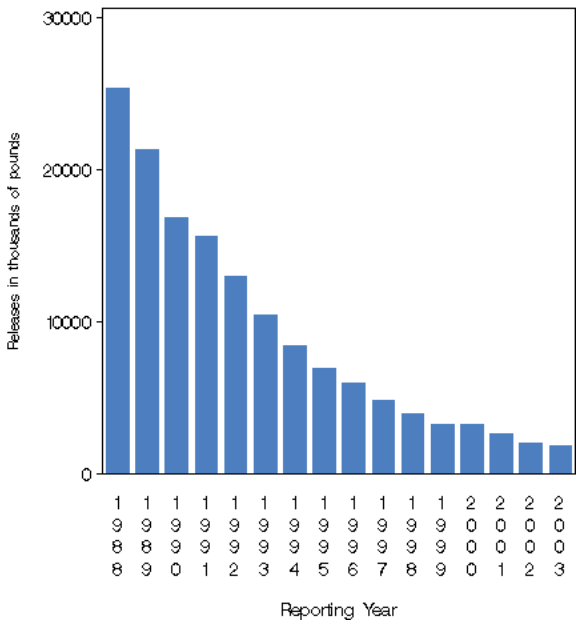

Figure 17: Connecticut's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 15: Connecticut's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Hazard Limiting Value		Primary Evidentiary Support	How Measured	Regulated Sources
		($\mu g/m^3$) (30 min avg)	($\mu g/m^3$) (8 Hr avg)			
Benzene	Known or Probable Carcinogen	750	150	Occupational Exposure Limits with various safety factors applied	Maximum Allowable Stack Concentration calculation or sampling (with the application of modeling, etc. to determine what the exposure at the fenceline will be.)	New & existing stationary sources
1,3-Butadiene	Suspected Carcinogen & Reproductive Toxin	110,000	22,000			
Formaldehyde	Known or Probable Carcinogen	30	12			
Toluene	Acute & Chronic Effects	37,500	7,500			
Acrolein	Suspected Carcinogen & Reproductive Toxin	25	5			
H_2S	Acute & Chronic Effects	1,400	280			
Styrene	Suspected Carcinogen & Reproductive Toxin	21,500	4,300			
Vinyl Chloride	Known or Probable Carcinogen	250	50			

3.2.3 Louisiana

Louisiana has regulated air toxics for over a decade at the time of this writing. According to the Louisiana Department of Environmental Quality (LDEQ), the State began to regulate air toxics in response to increasing public concern about air quality [646]. The LDEQ notes that Louisiana is heavily industrialized because of its deep-water port for shipping along the Lower Mississippi River Corridor. In 1987, the Toxic Release Inventory Report ranked Louisiana among the top five states in total amount of toxic air emissions. According to the LDEQ, public concern in the wake of this report prompted the State Legislature to enact the Louisiana Comprehensive Toxic Air Pollutant Emission Control Act in 1989 [647].

Among other mandates, the law called for (1) the establishment of a "toxic air pollutant emission control program," (2) the development of a 1987 baseline for toxic air pollutant (TAP) emissions, and (3) the reduction of statewide TAP emissions by 50 percent from 1987 levels by December 31, 1996.

The statute mandated that the Secretary of LDEQ develop and publish a list of one hundred toxic air pollutants (TAPs) [647]. The legislature defined TAP to mean an air pollutant which, “based on scientifically accepted data, is known to cause or can reasonably be anticipated to cause either directly or indirectly through ambient concentrations, exposure levels, bioaccumulation levels, or deposition levels, adverse effects in humans [648].” The statute specified that the negative health effects included but were not to be limited to cancer, mutagenic, teratogenic, or neurotoxic effects, reproductive dysfunction, acute health effects, and chronic health effects [648].

In addition to the air pollutants defined by the Secretary, the statute required that the list of TAPs also include substances listed as hazardous air pollutants in Section 112 of the Federal Clean Air Act. Pollutants for which National Ambient Air Quality Standards have been established under Section 108 of the Federal Clean Air Act were excluded with the exception of lead compounds. Still, the statute specifically excluded elemental lead and those pollutants chosen solely for their contribution to the formation of pollutants regulated under the National Ambient Air Quality Standards.

As mandated by the law, the LDEQ developed and promulgated the Comprehensive Toxic Air Pollutant Emission Control regulation [649]. The state regulation surpasses the federal regulation. In addition to incorporating the federal maximum achievable control technology (MACT) standards, the state rule establishes emission reporting requirements for major sources of TAPs and sets an emission air standard for each pollutant. The LDEQ bases the eight-hour standard on one forty-second of the selected occupational exposure level or other data it finds to be superior. The annual standard is based on a unit risk factor and a residual risk of one in ten thousand or other data determined to be superior by the administrative authority.

According to LDEQ, Louisiana's current toxic air pollutant control program covers over 200 pollutants and tracks toxic air emissions from over 250 industrial facilities [646]. Facilities are required to report annual emission totals to the LDEQ's Toxic Emission Data Inventory.

LDEQ claims that the State has already reduced statewide air toxic emissions by 50 percent from 1987 levels. At the end of 1997, emissions of TAPs from all sources in the state were down by 60 percent (166,439,000 pounds) from 1987 levels. Toxic emissions are down across a broad spectrum of sources. For example, benzene emissions have decreased statewide by 58 percent, while hydrogen sulfide emissions are 83 percent lower than in 1987. The LDEQ expects the downward trend to continue [632].

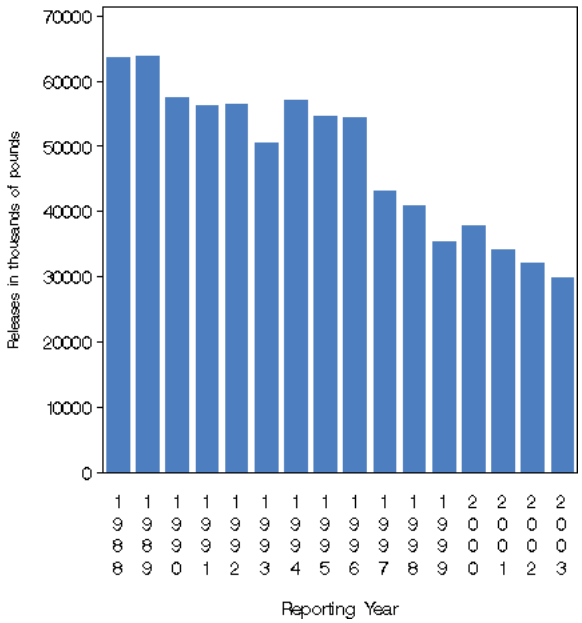

Figure 18: Louisiana's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 16: Louisiana's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Emission Air Standard		Regulated Sources
		($\mu g/m^3$) (8 Hr)*	($\mu g/m^3$) (Ann. Avg.)**	
Benzene	Known or Probable Carcinogen	NA	2.00	New & existing major sources
1,3-Butadiene	Suspected Carcinogen & Reproductive Toxin	NA	0.92	
Formaldehyde	Known or Probable Carcinogen	NA	7.69	
Toluene	Acute & Chronic Effects	8,900	NA	
Acrolein	Suspected Carcinogen & Reproductive Toxin	5.40	NA	
H_2S	Acute & Chronic Effects	330	NA	
Styrene	Suspected Carcinogen & Reproductive Toxin	5,070	NA	
Vinyl Chloride	Known or Probable Carcinogen	NA	1.19	

NA – Not applicable

* Based on one forty-second of the selected occupational exposure level or other data determined to be superior by the administrative authority.

** Based on unit risk factors and a residual risk of one in ten thousand or other data determined to be superior by the administrative authority.

3.2.4 Maryland

The State of Maryland has regulated toxic air pollutants (TAPs) since September 1988 in order to protect the public from TAP emissions from stationary sources of air pollution [650]. According to the Maryland Department of the Environment (MDE), Maryland's air toxics regulations are noteworthy due to the number of pollutants considered and the number of sources considered [650]. There are over 750 pollutants, or classes of pollutants, listed in Maryland's air toxics regulations [651].

The Maryland legislature has charged the MDE with jurisdiction over emissions into the air and ambient air quality in the state [652]. The MDE is responsible for monitoring ambient air quality in the state and coordinating all State agency programs on ambient air quality control [652]. Specifically, Maryland's ambient air quality control statute mandates that the MDE shall set identical ambient air quality standards for pollutants for which national primary or secondary ambient air quality standards have been set by the federal government, unless a political subdivision requests a more restrictive standard [653]. The statute also authorizes the MDE to set ambient air quality standards for substances for which national ambient air quality standards have not been set [653].

Maryland's air toxics emissions regulations have three basic requirements [653]: (1) the owner or operator of an emission source must quantify the emissions of TAPs from the premises, (2) the owner or operator of all new sources of air pollution (and certain existing sources) must apply the best available control technology for toxics (T-BACT)[9], and (3) each TAP must not adversely affect public health. In order to not adversely affect public health, premises-wide emissions must not exceed established benchmarks called screening levels. According to the MDE, public health is protected when the emissions of a facility are less than the maximum allowable emissions or when the off-site impact of each TAP is less than the screening level for the TAP as determined by dispersion modeling.

Owners or operators of emissions sources constructed, or reconstructed, on or after July 1, 1988 that discharges TAPs, and were required to obtain an air quality permit to construct, must comply with the air toxics regulations. Owners or operators of sources constructed before July 1, 1988 that discharge TAPs, and are of the type of source that was required to obtain a state permit to operate on or before March 1, 1993, are required to comply with air toxics regulations as well.

Maryland has reduced toxic air emissions from 15.8M lbs in 1988 to 4.7M lbs in 2003 according to data reported to the Toxics Release Inventory as shown in Figure 19 [632]. This represents a reduction of 70.1% from 1988 levels.

[9] T-BACT is a control strategy that reduces the most toxic air pollution while still being cost effective.

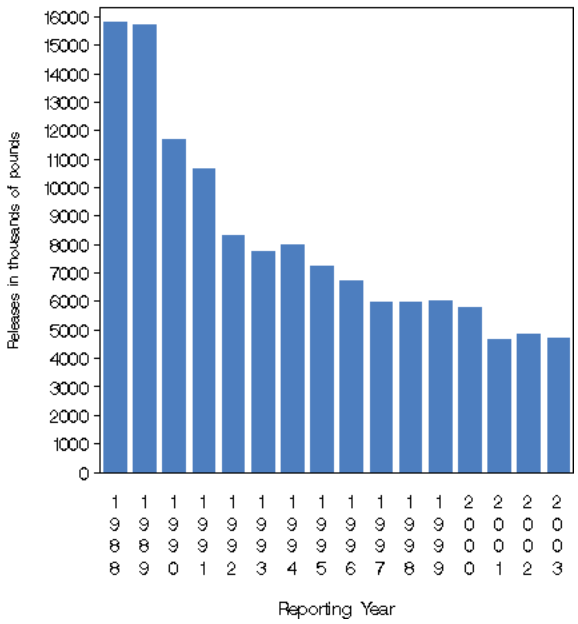

Figure 19: Maryland's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 17: Maryland's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Screening Level* ($\mu g/m^3$) (8 hr)	Primary Evidentiary Support	Regulated Sources
Benzene	Known Carcinogen	15.9734151329	IRIS	New & Existing Sources
1,3-Butadiene	Probable Human Carcinogen	44.2454	California Hot Spots Program	
Formaldehyde	Probable Human Carcinogen	6.3000	IRIS	
Toluene		1884.0491		
Acrolein		0.5600		
H_2S		139.386503067		
Styrene		852.024539877		
Vinyl Chloride		25.5623721881	IRIS	

* Screening level at point of contact with public as determined through dispersion modeling. Accuracy included in the listed screening level values is an illusion due to the application of modeling.

3.2.5 Massachusetts

In order to protect the health of Massachusetts residents and preserve the environment, the policy of the Massachusetts Department of Environmental Protection (MDEP), working with the US EPA, is to reduce emissions of a number of toxic air pollutants, used by business, industry, and individuals in the State, to the ambient (outdoor) air.

Statutory authority for the control of air toxics comes from Chapter 111 of the Massachusetts General Laws on Public Health [654]. The Massachusetts Toxics Use Reduction Act (TURA) was enacted in 1989 to promote pollution prevention while increasing the economic competitiveness of Massachusetts industry [655]. Emission standards for vehicles were established in 1990 [656]. The State passed an anti-idling law in 1972 [657].

Massachusetts has a number of measures that control the emissions of toxic air pollutants within the Commonwealth. These state and national programs include the following:

- TURA requires Massachusetts companies that use large quantities of specific toxic chemicals to evaluate pollution prevention opportunities, implement them if practical, and measure and report their results on an annual basis. They must also evaluate their efforts and update their toxics use reduction plans every other year. TURA set a goal of reducing toxic byproduct generation by 50 percent, which was met in 1998. Progress toward this goal is measured by using data normalized for changes in production reported by a core group of industries that have been subject to reporting since 1990. MDEP has promulgated regulations for implementing TURA [658]. MDEP monitors nearly 60 pollutants as part of the photochemical assessment monitoring system programs, many of which are air toxics.
- TURA requires certain facilities that manufacture, process, or otherwise use a quantity of listed toxic materials in their operations above specific thresholds to file annual reports detailing their management of toxics and to undergo a planning process to identify opportunities for toxics use reduction [659]. The specific threshold is determined in accordance with 310 CMR 50.20. When more than one threshold applies to a facility's manufacturing, processing, or other use of a toxic substance, the toxics user is a large quantity toxics user if the facility exceeds any applicable threshold [658].

- MDEP's ozone control programs have a direct effect on air toxics since many volatile organic compounds (VOCs) are toxic and some can cause cancer. Benzene is an example of a VOC that is also an air toxic. MDEP's programs to reduce VOC emissions include controls on large industrial sources, gasoline vapor recovery systems, federal reformulated gasoline, automobile inspection and maintenance, low emission vehicle performance standards, and reformulated consumer products and architectural coatings.

In the late 1980's MDEP developed 115 health-based air toxics guidelines to determine Allowable Ambient Limits (AALs). These guidelines have been used in permitting certain stationary sources [660]. The AALs are based on potential known or suspected

carcinogenic and toxic health properties of individual compounds, established reference concentrations or occupational exposure levels with adjustments to account for exposures from pathways other than air, and exposures to children and sensitive individuals. For cancer risk, AALs denote the concentration of a carcinogen associated with a one in a million excess cancer risk over a lifetime of exposure. For non-cancer effects, the concentration represents the value likely to present no appreciable risk of adverse non-cancer effects with long-term continuous inhalation. AALs are reviewed and updated periodically to reflect current toxicity information [661].

Massachusetts has implemented several national and local programs to reduce emissions of air toxics from mobile sources. Massachusetts has adopted gasoline vapor recovery programs that capture the vapors released when gasoline is stored and transferred to and from bulk storage plants and vapors that would otherwise be vented during individual vehicle refueling at gas stations. In addition, all gasoline tank trucks operating in Massachusetts must be equipped with gasoline vapor control equipment. Since the 1998 model year, federal rules required fueling vapor emission control systems on new cars and light-duty trucks.

Reformulated gasoline (RFG) is blended to reduce volatility and significantly reduces air toxics emissions over conventional gasoline. Massachusetts chose to participate in the RFG program in order to reduce emissions of VOCs that contribute to unhealthy ozone concentrations, but has also benefited from a reduction in toxic emissions [660]. Phase I of the national RFG program began in 1995 and resulted in a 17% reduction in toxic emissions from cars and trucks. Phase II of the program began on January 1, 2000 and resulted in a 22% reduction in air toxic emissions from conventional gasoline [660]. The Massachusetts enhanced emissions & safety test checks vehicle emissions once every two years [662].

3.2.5.1 Diesel PMs

In Massachusetts, testing of heavy-duty diesel vehicles began in 2001 [663] using a snap acceleration test. During this test, the vehicle remains stationary while the operator quickly moves the throttle to the fully open position and the inspector uses a smoke opacity meter to measure the opacity of the exhaust. Effective with model year 2004, the MDEP has adopted the California low emission vehicle (LEV) standards for light-duty diesel powered passenger vehicles and trucks [664, 665]. All vehicles sold or registered in the State must be certified as meeting this standard.

In Massachusetts, the state anti-idling law and MDEP regulations have limited vehicle idling to no more than five minutes in most cases [657, 666]. A vehicle may idle longer only if absolutely necessary. There are exceptions for vehicles being serviced, vehicles making deliveries that need to keep their engines running (to power refrigerators for example), and vehicles that need to run their engines to operate accessories (such as power lifts). Local boards of health, local police, and state and federal officials are authorized to enforce the state anti-idling law. MDEP offers training and enforces its own regulations.

3.2.5.2 Results

Massachusetts has reduced toxic air emissions from 25.9M lbs in 1988 to 1.9M lbs in 2003 according to data reported to the Toxics Release Inventory as shown in Figure 20 [632]. This represents a reduction of 92.7% from 1988 levels.

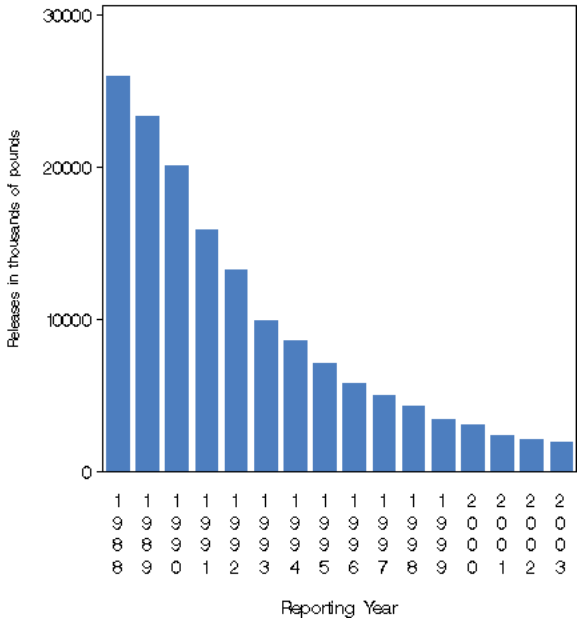

Figure 20: Massachusetts' total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 18: Massachusetts' Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Threshold Effects Exposure Limit (TEL)* ($\mu g/m^3$) (24 Hr)	Allowable Ambient Limit (AAL) ($\mu g/m^3$) (Annual Avg)	Primary Evidentiary Support	Regulated Sources
Benzene	Known or Probable Carcinogen	1.74	0.12	Federal MACT and the State's 115 health-based guidelines for cancer and/or non-cancer effects. Carcinogen-based limits are set at the 10^{-6} risk level, Non-cancer effects use reference concentrations or occupational levels with adjustments.	Utilized for limited categories of sources
1,3-Butadiene	Suspected Carcinogen & Reproductive Toxin	1.20	0.003		
Formaldehyde	Known or Probable Carcinogen	0.33	0.08		
Toluene	Acute & Chronic Effects	80	20		
Acrolein	Suspected Carcinogen & Reproductive Toxin				
H_2S	Acute & Chronic Effects	0.9	0.9		
Styrene	Suspected Carcinogen & Reproductive Toxin	200	2		
Vinyl Chloride	Known or Probable Carcinogen	3.47	0.38		

3.2.6 Michigan

Michigan's Department of Environmental Quality (MDEQ) first promulgated air toxic rules on April 17, 1992 [667]. Over time, the rules were revised under the authority granted under part 55 of the state Natural Resources and Environmental Protection Act of 1994. The revised rules became effective November 10, 1998 [667].

Michigan regulates air contaminants not included under the National Ambient Air Quality Standards for criteria pollutants. It regulates those contaminants that may become harmful to public health or the environment when present in the outdoor atmosphere in sufficient quantities and duration [667]. There is not a list of all toxic air contaminants, but forty substances are specifically exempt from the definition of toxic air contaminant. These exempt substances include inert gases, nuisance particulates, and substances that have relatively low toxicity [668]. The Michigan air toxic rules apply to any new or modified emission unit that requires a permit to install and emits a toxic air contaminant. This would, therefore, apply to sources subject to MACT regulation under the federal HAP regulations. The air toxic rules do not apply to existing sources [668].

There are two basic requirements of the rules. First, each source must apply the best available control technology for toxics (T-BACT). After the application of T-BACT, the emissions of the toxic air contaminant cannot result in a maximum ambient concentration contribution that exceeds the applicable health-based screening level.

The health-based screening level for non-carcinogenic effects of a toxic air contaminant is called the initial threshold screening level (ITSL). It is determined by a number of different methods depending upon the available toxicological data [667]. For the toxics of particular interest to Texas, the screening levels used in Michigan are all based on the US EPA's IRIS work[10].

There are two health-based screening levels for carcinogenic effects. The initial risk screening level (IRSL) is set at a concentration associated with an increased cancer risk of one in one million and the secondary risk screening level (SRSL) is set at a concentration associated with an increased cancer risk of one in one hundred thousand. The IRSL applies only to the new or modified source subject to the permit application. If the applicant cannot demonstrate that the emissions of the toxic air contaminant meet the IRSL, they may choose to demonstrate compliance with the SRSL. However, in this case they must include all sources of that toxic air contaminant emitted from the plant not just the emission unit being permitted.

The air toxic rules allow the MDEQ to require a lower emission rate than that specified by T-BACT or the health-based screening level on a case-by-case basis. These more strict requirements are allowed if the MDEQ finds that the existing requirements may not provide adequate protection of human health or the environment [668]. In making this

[10] Michigan's ITSL standards can be found at http://www.deq.state.mi.us/itslirsl/. Screening levels can be looked up based on chemical name or CAS number. For each chemical, information is provided about the basic methodology for determining the screening level. All standards however, rely on information available on the US EPA's Integrated Risk Information System (IRIS) website which is available at http://www.epa.gov/iris/.

case-by-case determination, the MDEQ considers all relevant scientific information including exposure from routes of exposure other than direct inhalation, synergistic or additive effects of toxic air contaminants, and effects on the environment [667]. According to this research, there has not yet been a case in which a lower emission rate has been required.

Michigan has reduced toxic air emissions from 84.6M lbs in 1988 to 18.1M lbs in 2003 according to data reported to the Toxics Release Inventory as shown in Figure 21 [632]. This represents a reduction of 78.6% from 1988 levels.

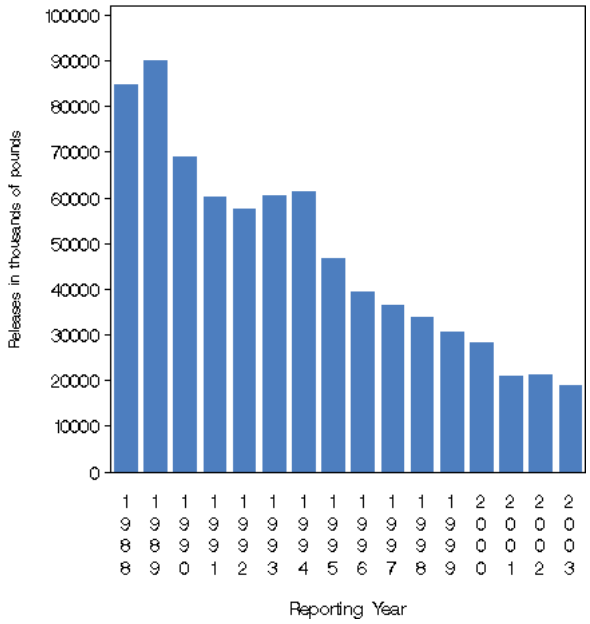

Figure 21: Michigan's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 19: Michigan's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Standards		Regulated Sources
	Non-cancer ITSL ($\mu g/m^3$) (24 Hr)	Cancer IRSL ($\mu g/m^3$) (Ann. Avg)	
Benzene	30	0.1	New or modified emission unit(s) requiring permit
1,3-Butadiene	2	0.03	
Formaldehyde	NA	0.08	
Toluene	400	NA	
Acrolein	0.02	NA	
H_2S	2	NA	
Styrene	1000	1.7	
Vinyl Chloride	100	0.11	

NA – not applicable

3.2.7 New Jersey

The New Jersey Department of Environmental Protection (NJDEP) has regulated air toxics since 1979, well before most states [669]. At that time, NJDEP adopted a rule titled Control and Prohibition of Air Pollution by Toxic Substances [670]. The rule regulated 11 toxic volatile organic substances (TVOSs) including benzene, carbon tetrachloride, chloroform, dioxane, ethylenimine, ethylene dibromide, ethylene dichloride, 1,1,2,2-tetrachloroethane, tetrachloroethylene, vinyl trichloride, and trichloroethylene. This initial rule required that sources emitting any of these eleven TVOSs register with the NJDEP and demonstrate that they were using state-of-the-art (SOTA) controls to limit their emissions. Additionally, New Jersey passed right-to-know laws to encourage voluntary disclosure to citizens [669].

New Jersey employs a combination of control technology and risk assessment requirements in the permitting process. When a company applies for an air pollution control permit for a new or modified source of air emissions, they are required to use SOTA control techniques. The NJDEP developed a SOTA workgroup to assist in producing technical manuals for applicants [671]. SOTA techniques generally include performance limits that are based on air pollution control technology, pollution prevention methods, and process modifications or substitutions that will provide the greatest emission reductions that are technologically and economically feasible [669].

In the early 1980s, the NJDEP "recognized that one shortcoming of the control technology approach was that it does not guarantee that the emissions from a source with state-of-the-art controls are sufficiently low to protect public health" [669]. NJDEP began to require most large sources of air toxic emissions to submit a risk assessment along with their permit application. Large sources include municipal waste and hazardous waste incinerators, coal-fired power generating facilities, cogeneration units, and other sources as determined by the NJDEP on a case-by-case basis.

NJDEP provides permit applicants with a worksheet that estimates risk by using information about the source's stack height and distance to the property line, in addition to the emission rate and toxicity of each chemical [672]. The worksheet includes a risk estimate of one in a million for carcinogens, so proposed permit projects that would result in an excess cancer risk less than one in a million are considered safe for that chemical. When a risk assessment shows an excess cancer risk greater than one in a million, the NJDEP conducts a more extensive evaluation to determine whether the permit should be approved on a case-by-case basis. Generally, NJDEP denies permit applications for a specific process if the excess risk is greater than one in ten thousand. If the risk is above one in a million but less than one in ten thousand after second-level risk screening, NJDEP's permit evaluator would have a discussion with the applicant about ways to bring the risk down. If the risk can't be decreased to a reasonable level, the permit application would be reviewed by NJDEP's air program Risk Management Committee which usually includes the permit evaluator in addition to a risk assessor, inspector who is familiar with the facility, and bureau chiefs. When NJDEP evaluates an entire facility instead of a specific operation the "negligible" risk level is an order of magnitude less stringent.

Additionally, NJDEP works to determine whether additional pollution prevention and control measures could be implemented to reduce emissions. Reference concentrations are used for non-carcinogens and are based on a combination of research conducted by the US EPA and California OEHHA.

NJDEP relies on its permit evaluators to screen for risk at smaller facilities. On January 23, 2003, NJDEP adopted revisions to the emissions statements rule which resulted in additional facility-wide information on 36 toxic air pollutants [673]. NJDEP's plans for smaller facilities include the development of general permits for dry cleaners and halogenated solvent cleaners and compliance plans for area sources.

New Jersey has reduced toxic air emissions from 32.4M lbs in 1988 to 3.3M lbs in 2003 according to data reported to the Toxics Release Inventory as shown in Figure 22 [632]. This represents a reduction of 89.8% from 1988 levels.

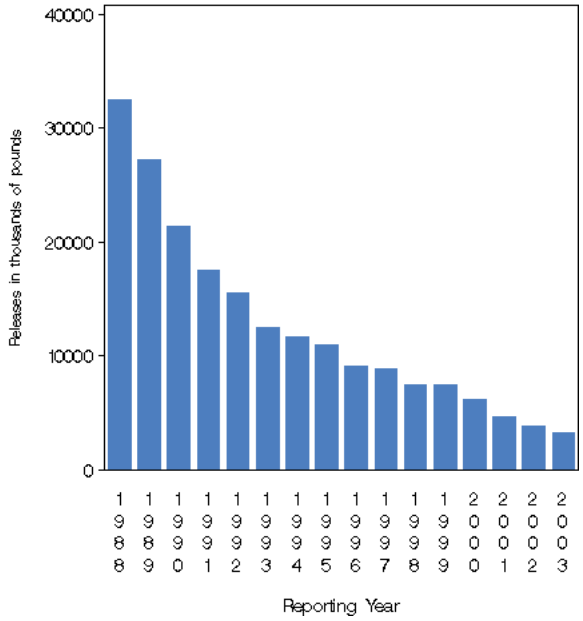

Figure 22: New Jersey's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

New Jersey's Regulation of Air Toxics that are of Primary Concern in Texas

New Jersey does not currently have any ambient air quality standards used in its permitting process. Instead, the state relies on mandatory risk assessments from permit applicants. If the risk exceeds one in one million, the applicant is to "work with" the state to try and reduce it to below one in ten thousand. There is no record of any applicant having to reduce the risk below one in one million as long as it is below one in ten thousand.

3.2.8 New York

The New York State Department of Environmental Conservation (NYSDEC) has been responsible for the implementation of the State's comprehensive air toxics control program for over twenty years [674] at the time of this writing. The State of New York recognizes the federal list of HAPs [675]. The regulatory requirements of the air toxics control program are principally contained in 6 NYCRR Part 212 [674]. Compliance with air pollution permitting and regulation is mandatory, unless specifically exempted pursuant to 6 NYCCR § 201-3 [676]. The State of New York regulates air toxics through the permitting process as specified in Part 212. Prior to issuing a source permit pursuant to 6 NYCRR Part 212, applicants must comply with applicable federal and state ambient standards [677].

The NYSDEC may adopt rules or regulations that are more restrictive than those required by the Federal Clean Air Act [678]. However, the NYSDEC must provide a regulatory impact statement which includes a detailed justification as to why the state regulation must be more restrictive than the federal minimum for a particular air toxic, an evaluation of the cost-effectiveness of the proposed state regulation in comparison with the cost effectiveness of reasonably available alternatives, a review of reasonably available alternative measures considered by the NYSDEC, and an explanation of the reasons for rejecting such alternatives [678].

The State of New York utilizes ambient air guidelines instead of standards when determining the air quality impact of certain air toxics. The reasons for this are very practical. According to the New York State DAR-1 Guidelines For the Control of Toxic Ambient Air Contaminants report [677], released by the Division of Air Resources, the use of guidelines, as opposed to standards, is to ensure flexibility in applying standards to allow for the consideration of the most current toxicological information and to avoid the inefficient administrative effort that is required to adopt these guidelines as standards [677]. To adopt these guidelines as standards would make it difficult to modify as new toxicological data became available. These guidelines are known as annual guideline concentrations (AGCs).

New York has an environmental rating system for air toxics that ranges from an "A" to "D" rating. The criteria for the various rating levels are as follows [679]: **"*A*"** = An air contaminant whose discharge results, or may result, in serious adverse effects on receptors or the environment. These effects may be of a health, economic, or aesthetic nature or any combination of these. **"*B*"** = An air contaminant whose discharge results, or may result, in only moderate and essentially localized effects; or where the multiplicity of sources of the contaminant in any given area require an overall reduction of atmospheric burden of that contaminant. **"*C*"** = An air contaminant whose discharge may result in localized adverse effects of an aesthetic or nuisance nature. **"*D*"** = An air contaminant whose discharge will not result in measurable or observable effects on receptors nor add to an existing or predictable atmospheric burden of that contaminant which may cause adverse effects considering properties and concentrations of the emissions, isolated conditions, stack height, and other factors.

All emissions sources that emit "A" rated (e.g. high toxicity) contaminants require 99% or greater pollution control or the application of best available control technology (BACT) [677]. Where a source owner can demonstrate that he will apply BACT, the NYSDEC may specify a less restrictive permissible emission rate, emission standard, or degree of air cleaning [680]. For emission sources not equipped with BACT, the annual impact must be less than the AGC specified for a particular air toxic [677]. In other words, though New York examines toxicity, the response is primarily technological in nature. However, it still allows New York to regulate existing sources with BACT ahead of the federal response on area sources.

The Division of Air Resources has implemented a compliance monitoring and enforcement program as authorized by the statute [681]. The goal of the compliance monitoring program is to maintain a regulatory presence in order to deter non-compliance with air quality regulations [682]. The program consists of on-site inspections, review of periodic monitoring reports and performance tests, compliance evaluations, and tracking of compliance related activities [682]. When violations are detected, an enforcement response may involve the assessment of penalties [682].

New York has reduced toxic air emissions from 83.3M lbs in 1988 to 8.3M lbs in 2003 according to data reported to the Toxics Release Inventory [632]. This represents a reduction of 90.1% from 1988 levels.

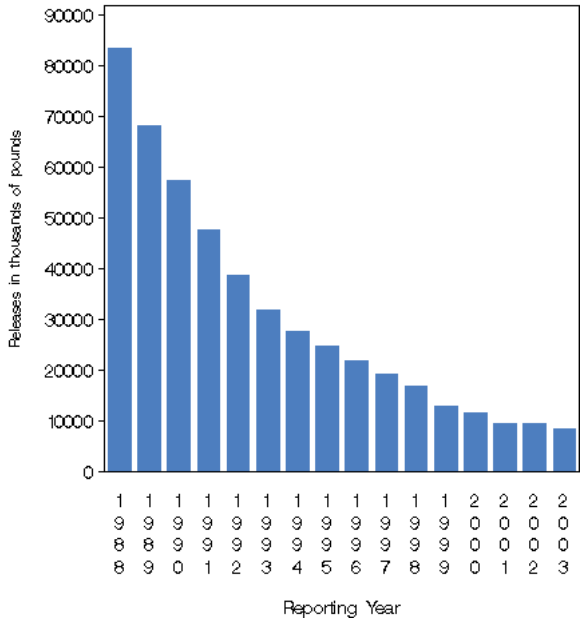

Figure 23: New York's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 20: New York's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Annual Guideline Concentration (AGC) (µg/m^3)*	Toxicity Level	Primary Evidentiary Support	NYSDEC Environmental Rating	Regulated Sources
Benzene	Carcinogen	0.13	High	US EPA IRIS Data	A	New & Existing Sources
1,3-Butadiene	Suspected Carcinogen	0.028	High	US EPA IRIS Data	A	
Formaldehyde		0.060	High	NY State Dept of Health; more conservative than US EPA values.	A	
Toluene		400.	Low	US EPAIRIS Data	C	
Acrolein		0.020	High	US EPA IRIS Data	A	
H_2S		14/hr†	Moderate	US EPA IRIS Data	B	
Styrene		1000.0	Moderate	US EPA IRIS Data	B	
Vinyl Chloride		0.11	High	US EPA IRIS Data	A	

N/A – not applicable
*Annual Average
† NY has adopted a one hour "standard" for hydrogen sulfide as opposed to a "guideline".

3.2.9 North Carolina

In 1998, North Carolina Department of Environmental and Natural Resources (NCDENR) implemented toxic air pollution procedures that are used in pollution permitting to insure that toxic air pollutants from new or modified facilities do not make toxic air pollutant levels worse [683]. North Carolina's risk-based program is designed around a set of acceptable ambient level (AAL) guidelines for toxic air pollutants (TAPs).

AALs are set "below the concentration that would produce adverse health effects in sensitive subgroups of the general population" [683]. For health effects other than cancer, AALs were determined by taking occupational exposure standards and lowering exposure guidelines to acceptable concentration levels by safety factors of 10 to 160. Safety factors were used "because the state recognized that chemical compounds differed in the nature and severity of the toxic effects and how much was known about the health effects of a chemical."[684]. In general, larger safety factors are used when less is known about a chemical.

For substances known to cause cancer in humans, AALs are set at levels calculated to represent an increment of one in a million excess cancer risk. For "probable" and "possible" human carcinogens, the risk levels increase to one in one hundred thousand and one in ten thousand, respectively. To keep up with current research on the health effects of various pollutants, the air toxics program maintains a Scientific Advisory Board (SAB) of toxicology experts that periodically suggest changes to AAL guidelines.

Regulated pollution sources are asked to reduce their emissions below those levels that are predicted to exceed the AAL beyond their fenceline. Computer-based dispersion models compare the impact of pollution from a smokestack to the appropriate AAL. The model is used to predict the downwind concentrations of a given pollutant from a particular source. The models attempt to simulate the real world by accounting for wind, temperature, and terrain. According to NCDENR, AALs are not, therefore, directly comparable to air concentrations measured during ambient monitoring because AALs are applicable only to the portion of the air concentration emitted from a specific industrial source [684]. Some North Carolina environmental groups believe that the distinctions that NCDENR attempts to draw between AALs and air concentrations measured during ambient monitoring are improper. The Blue Ridge Environmental Defense League disputes the department's claim that the AALs are different from an ambient standard based on the language of the statute and the legislative intent to protect public health [685].

The statute being disputed states, "A facility shall not emit any of the following toxic air pollutants in such quantities that may cause or contribute beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health. In determining these significant ambient air concentrations, the Division shall be guided by the following list of acceptable ambient levels" [686].

North Carolina's regulations do, however, allow for consideration of multiple pollutant risk from the same facility if there is "evidence that two or more toxic air pollutants being emitted from a facility or combination of facilities act in the same way to affect human health" [687].

North Carolina has reduced toxic air emissions from 105.6M lbs in 1988 to 27.3M lbs in 2003 according to data reported to the Toxics Release Inventory [632]. This represents a reduction of 74.2% from 1988 levels.

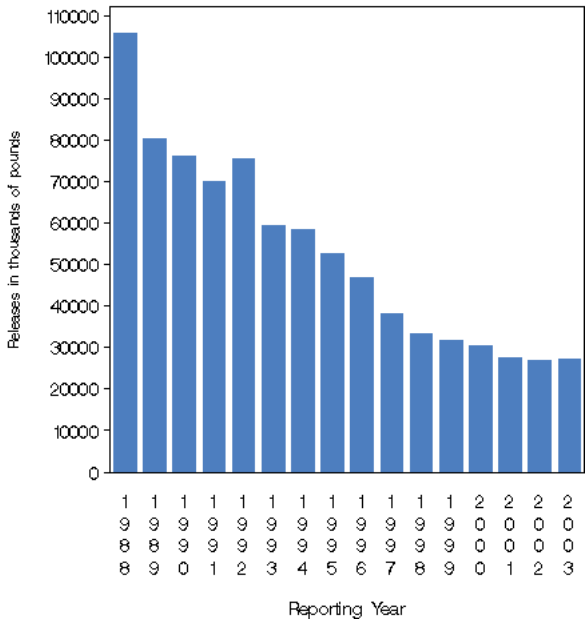

Figure 24: North Carolina's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 21: North Carolina's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Acceptable Ambient Levels*			Regulated Sources
	Acute Irritant (mg/m^3) (1 hr)	Chronic Toxicant ($\mu g/m^3$) (24 Hr)	Carcinogen (mg/m^3) (Ann Avg)	
Benzene	NA	NA	1.2×10^{-4}	New or modified emission unit(s) requiring permit
1,3-Butadiene	NA	NA	1.7×10^{-4}	
Formaldehyde	0.15	NA	NA	
Toluene	56	4.7	NA	
Acrolein	0.08	NA	NA	
H_2S	NA	0.12	NA	
Styrene	10.6	NA	NA	
Vinyl Chloride	NA	NA	3.8×10^{-4}	

NA – not applicable

N.C. Admin. Code tit. 15A, r 2D. 1104 (2005) lists AALs for all 105 TAPs.

* LEVEL at the fenceline which is expected to yield a one in a million excess cancer risk, but note that no direct measurements occurs at the fenceline and the ambient level is estimated based on modeling.

3.2.10 Oregon

After five years of extensive collaboration between the Oregon Department of Environmental Quality (ODEQ) and the Hazardous Air Pollutant Consensus Group, the Oregon Environmental Quality Commission (OEQC) adopted rules which implemented Oregon's air toxics program in October 2003 [688]. The pertinent elements of Oregon's air toxics program are the formation of an Air Toxics Science Advisory Committee (ATSAC), formulation of ambient benchmark values, implementation of a geographic program, formulation of a source category strategy and rules, and a safety net program [689].

The ODEQ, Air Quality Division, created the Air Toxics Science Advisory Committee for the purpose of providing the ODEQ with scientifically and technically sound advice on the state air toxics program [690]. The ATSAC[11] is solely intended to be a neutral technical advisory body and not a committee designed to reflect stakeholder views [690]. The ATSAC prioritized air toxics based on 5 criteria [689]: (1) effects (toxicity, potency), (2) exposure and number of people at risk, (3) impact on sensitive human populations, (4) number and degree of ambient benchmark exceedances, and (5) potential to cause harm through persistence or bioaccumulation. The ATSAC is then charged with reviewing ambient benchmarks for these toxics and these benchmarks serve as goals for the Oregon air toxics program.

The geographic program is intended to focus on specific geographic areas (e.g., Portland metropolitan area) and resolve air toxics concerns related to those areas in particular [691]. The safety net program is intended to be used in the rare situation where a source lying outside of a selected geographic area is the sole cause of ambient air benchmark exceedances of one or more air toxics [691]. The source category program authorizes ODEQ to promulgate statewide categorical rules based on standards developed as part of the geographic program and/or the safety net program [691].

The OEQC is charged with establishing air purity standards, establishing areas of the state, and prescribing the degree of air pollution or air contamination that may be permitted in those areas [692]. The current ambient benchmark concentration for carcinogenic air toxics is an excess lifetime cancer risk level of one in a million [691].

When determining air purity standards, the OEQC shall consider factors [693] such as: 1) the quality or characteristic of air contaminants or the duration of their presence in the atmosphere which may cause air pollution in the particular area of the state 2) existing physical conditions and topography 3) possible chemical reactions between air contaminants 4) availability of air-cleaning devices 5) economic feasibility of air cleaning devices 6) effect on normal human health of particular air contaminants 7) effect on efficiency of industrial operation resulting from use of air-cleaning devices.

[11] Per ORS §340-246-0070(2), the ATSAC must have at least 5, but no more than 7, members with relevant air toxics experience in the following six disciplines: (1) toxicology, (2) environmental science or engineering, (3) risk assessment, (4) epidemiology & biostatistics, (5) public health medicine (physician), and (6) air pollution modeling, monitoring, meteorology, or engineering.

All sampling and testing of air toxics shall be conducted in accordance with methods used by the Department [694]. The ODEQ uses a combination of modeling and/or monitoring to measure the concentration of an air toxic. The Oregon air quality statute mandates that the ODEQ establish a program for measurement and testing of contamination sources and may perform such sampling or testing or may require any person in control of the contamination source to perform the sampling or testing [694].

The OEQC may grant specific variances, which may be limited in time from the particular requirements of any rule or standard, to specific persons or a specific contamination source that it may consider necessary to protect the public health and welfare if it finds that strict compliance with the rule or standard is inappropriate or economically impracticable [695].

The Oregon legislature authorized the formation of regional air quality control authorities in contiguous territories having a population of at least 130,000 and consisting of two or more counties or parts of counties, two or more cities, or any combination thereof [696]. Areas of the state that are not covered by a regional air quality control authority are regulated by the ODEQ. The cities or counties proposing to form the regional authority shall adopt ordinances or resolutions specifying the name and boundaries of the proposed regional authority and file a certified copy of the ordinances or resolutions with the Secretary of State and the Director of Environmental Quality [696]. The Environmental Quality Commission shall order the regional authority formed if it finds that the participating governments plan adequate financing [696]. Joining and forming the air pollution authority is voluntary. Each regional authority shall exercise the functions relating to air pollution control vested in the commission and the Department of Environmental Quality [697]. Regional authorities are required to comply with state air quality standards [698] and are not authorized to adopt any rule or standard that is less strict than any rule or standard promulgated by the commission and must submit all air quality standards adopted by the authority for approval by the commission [697]. The penalty for non-compliance with any rule or standard adopted, or any order issued by a regional authority relating to air pollution, is a Class A misdemeanor [699].

Oregon has reduced toxic air emissions from 16.9M lbs in 1988 to 10.8M lbs in 2003 according to data reported to the Toxics Release Inventory [632]. This represents a reduction of 36.2% from 1988 levels.

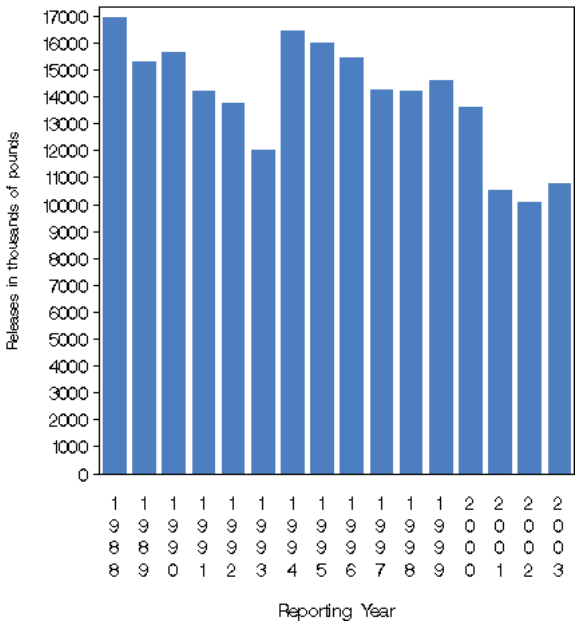

Figure 25: Oregon's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 22: Oregon's Regulation of Air Toxics that are of Primary Concern in Texas

Compound*	Basis of Regulation	Ambient Benchmark Concentrations** (µg/m^3) (Annual avg)	Primary Evidentiary Support (as implemented by ATSAC)	Regulated Sources
Benzene (1)	Known Carcinogen	0.13	Committee considered both cancer and non-cancer studies. In the end, they focused on cancer studies related to this air toxic.	New & Existing Sources
1,3-Butadiene (6)	Carcinogen	0.033	IRIS unit risk estimate since it was derived from a recent human study.	
Formaldehyde (3)	Carcinogen	3.0	California OEHHA non-cancer RfC.	
Toluene (59)		400.0		
Acrolein (25)	Suspected Carcinogen & Reproductive Toxin; Suspected in increasing susceptibility in infants and children.	0.020	Current IRIS value	
H_2S (78)		TBD		
Styrene (22)		TBD		
Vinyl Chloride (9)	Carcinogen	0.11	USEPA IRIS URF	

* The number in parentheses indicates the prioritization rank number as assigned by the ATSAC according to the 5 criteria ranking system.
** All values listed represent the Interim Ambient Benchmark Concentration as determined by the ATSAC.
TBD – To be determined

3.2.11 Rhode Island

Rhode Island has regulated air toxics since 1988 when it listed ambient air levels (AALs) for forty substances in Air Pollution Regulation No. 22, Air Toxics [700, 701]. Upon notification from the Rhode Island Department of Environmental Management (RIDEM), the rule requires that stationary sources that emit more than the minimum quantity of a listed pollutant must apply for air toxics operating permits (ATOPs) [702, 703]. ATOPs are only issued if the stationary source is in compliance with Regulation No. 22. That is, if the emissions from that source do not contribute to ground level impacts above the AALs beyond the facility's property line [702]. The ATOP may impose reasonable conditions or limitations on operations, monitoring, and testing [704]. RIDEM states that since 1988, it has evaluated most of the major stationary sources of the forty pollutants and has required compliance for these sources.

After the listing of the federal HAPs and in light of the work of California and the Federal Agency for Toxic Substances and Disease Registry (ATSDR), Rhode Island amended Regulation No. 22 to expand the list of air toxics to include all HAPs and other pollutants that have significant air pollution related health impacts. The final regulation added 188 federally recognized HAPs, 47 other substances that have derived inhalation health benchmarks, and included 17 substances that RIDEM evaluated in past air permit reviews [705]. AALs were also updated to reflect the current data from the US EPA, California, and ATSDR [705].

The purpose of the air resources program is to carry out the policy of the State as declared in R.I.G.L. 23-23-2, [706] that is, to preserve, protect, and improve the air resources of the State so as to promote public health, plant and animal life, and physical property in order to foster the comfort and convenience of the State's inhabitants [707]. The Office of Air Resources (OAR) states that the program goals are to protect the public from toxic air emissions, identify air toxics emission sources that may have public health impacts, require those sources to reduce impacts to acceptable levels, and to screen proposed sources to determine appropriate emissions limitations [707].

The AALs are ground level impact limits, taking into account only inhalation exposures from single sources. Rhode Island used the inhalation benchmarks developed by the US EPA, ATSDR, and California as the basis for the amended AALs. Criteria used include inhalation reference concentrations (RfC), reference doses (RfD), or cancer potency factor from the US EPA's IRIS database, minimal risk levels (MRL) from ATSDR, and reference exposure level (REL) from California [707]. When available benchmarks are contradictory, the more stringent standard was usually adopted.

Regulation No. 22 includes AALs for three averaging times: one-hour for acute effects, 24-hours for effects associated with intermediate length exposures, and annual for chronic effects [707]. These AALs are listed for each pollutant and each averaging time in the table, the main value listed is the simple AALs and value given in parenthesis is the AALs that result from the lowest achievable emissions rate (LAER) [708]. The OAR must reevaluate Regulation No. 22 once every two years to determine whether further amendments are necessary.

The regulation applies to any stationary source that emits a listed air toxic, except certain specified facilities (*e.g.* gas stations) or a specific air toxic emission for particular facilities (*e.g.* perchloroethylene from dry cleaners) [709]. No source with the potential to emit more than the specified minimum quantity will be issued a construction, modification, or installation permit unless it can be demonstrated to be in compliance with the AALs, or AALs with LAER, in accordance with RIDEM guidelines [710]. The RIDEM Director has some discretion to alter the modeling analysis requirements [711].

Rhode Island has reduced toxic air emissions from 6.2M lbs in 1988 to 0.4M lbs in 2003 according to data reported to the Toxics Release Inventory [632]. This represents a reduction of 92.7% from 1988 levels.

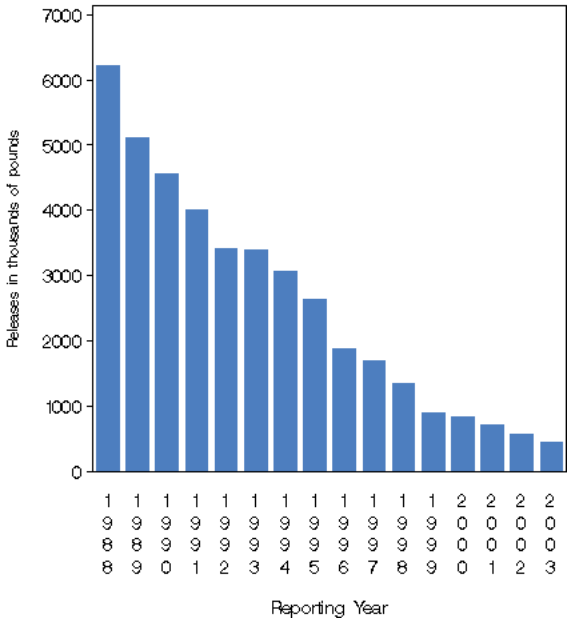

Figure 26: Rhode Island's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 23: Rhode Island's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Minimum Quantities	Ambient Air Level (with LAER if different)			Primary Evid. Support	Regulated Sources
		(lbs/yr)	Acute ($\mu g/m^3$) 1 Hr	Intermediate ($\mu g/m^3$) 24 Hr	Chronic ($\mu g/m^3$) Annual		
Benzene	Known or Probable Carcinogen, HAP	10	200	30	0.1 (1.0)	ATDSR (1hr), RfC (24hr), IRIS (ann.)	Any stationary source that emits a listed toxic air contaminant (if they are over a minimum threshold) *certain exceptions to this are particular sources, like dry cleaners, etc.
1,3-Butadiene	Suspected Carcinogen & Reproductive Toxin, HAP	3			0.9 (0.3)	IRIS (ann.)	
Formaldehyde	Known or Probable Carcinogen, HAP	9	50	40	0.08 (0.8)	ATDSR (1hr), ATDSR (24hr), IRIS (ann.)	
Toluene	Acute & Chronic Effects, HAP	1,000	4,000	400	300	ATDSR (1hr), RfC (24hr), IRIS (ann.)	
Acrolein	Suspected Carcinogen & Reproductive Toxin, HAP	0.04	0.1	0.02		ATDSR (1hr), RfC (24hr)	
H_2S	Acute & Chronic Effects, CAL	10	40		10	CAL (1hr), CAL (ann.)	
Styrene	Suspected Carcinogen & Reproductive Toxin, HAP	3,000	20,000	1,000	100	CAL (1hr), RfC (24hr), RfC/10 (ann.)	
Vinyl Chloride	Known or Probable Carcinogen, HAP	20	1,000	100	0.2		

3.2.12 Wisconsin

The State of Wisconsin has been concerned with the development of hazardous air pollutant rules since the early 1980's [712]. At that time, there was concern in Wisconsin about the health effects of toxic air releases and a concern about the lack of policy and regulations of hazardous air pollutants at the federal level [712]. As a result of this concern, the Hazardous Emissions Task Force was formed in May 1983 and was charged with defining toxic and/or hazardous air emissions, recommending a methodology for establishing emission limits that would adequately protect public health, and recommending which sources should be exempt from regulation. In July 1985, the Hazardous Emissions Task Force made its report of recommendations to the Wisconsin Department of Natural Resources (WDNR). After much debate and public comment, Wisconsin adopted hazardous air pollutant requirements in October 1988 [713].

The WDNR has the authority to establish emissions limitations on Wisconsin sources. Among other mandates, the Wisconsin air pollution legislation requires that the WDNR prepare and develop one or more comprehensive plan for the prevention, abatement, and control of air pollution and to specify the best available control technology on a case-by-case basis considering energy, economic, and environmental impacts and other costs related to the source [714]. Ambient air quality standards apply to the entire State without exception [715]. The WDNR defines hazardous air pollutants as any air contaminant for which no ambient air quality standard is set in Ch. NR 404 and which the department determines may cause, or significantly contribute to, an increase in mortality, serious irreversible illness, incapacitating reversible illness, or may pose any significant threat to human health or the environment.[12]

The WDNR is required to classify, by rule, air contaminant sources which may cause or contribute to air pollution according to levels and types of emissions and other characteristics which relate to air pollution [716]. Further, the WDNR may, by rule or in an operation permit, require the owner or operator of an air contaminant source to monitor the emissions of the air contaminant source, or to monitor the ambient air in the vicinity of the air contaminant source, and report those results to the Department [716]. Of those owners or operators who are required to monitor emissions, the WDNR shall require them to furnish a report of their findings not less than every six months [716]. Any duly authorized officer, employee, or representative of the WDNR may enter and inspect any property or place where an air contaminant source is located, is being constructed, or at any reasonable time for the purpose of ascertaining compliance with air quality regulations [717].

Wisconsin air quality legislation mandates that the WDNR promulgate, by rule, ambient air quality standards similar to those promulgated under section 109 of the Federal Clean Air Act. However, this standard may not be more restrictive than the federal standard [718]. The WDNR is authorized, for the purpose of protecting the public health or welfare, to promulgate an ambient air quality standard for any air contaminant for which

[12] The term hazardous air contaminant includes the substances listed in Tables 1 to 5 in s. NR445.04 and Tables A, B, and C in s. NR 445.07.

an ambient standard has not been set by the Federal Clean Air Act [718]. However, the WDNR may not make this determination unless the finding is supported by written documentation that includes, among other things [718], (1) a public health risk assessment that characterizes the types of stationary sources in the state that are known to emit the air contaminant and the population groups that are at risk, (2) an analysis showing that members of population groups are subjected to levels of the air contaminant that are above recognized environmental health standards, (3) an evaluation of options for managing the risks caused by the air contaminant considering risks, costs, economic impacts, feasibility, energy, safety, and (4) a finding that the proposed ambient air quality standard reduces risks in the most cost-effective manner.

Any person who violates the provisions of the Wisconsin air quality laws, any rule promulgated thereof, or any permit issued under the air quality laws shall forfeit not less than 10 or more than 25,000 dollars for each violation [719]. Any person who intentionally violates or fails to perform an act required by these laws shall be fined not more than $25,000 per day of violation, imprisonment for not more than 6 months, or both [719].

Wisconsin hazardous pollutant control regulations apply to all stationary air contaminant sources which may emit hazardous contaminant and their owners and operators [713].

Wisconsin has reduced toxic air emissions from 42.2M lbs in 1988 to 12.6M lbs in 2003 according to data reported to the Toxics Release Inventory [632]. This represents a reduction of 70.2% from 1988 levels.

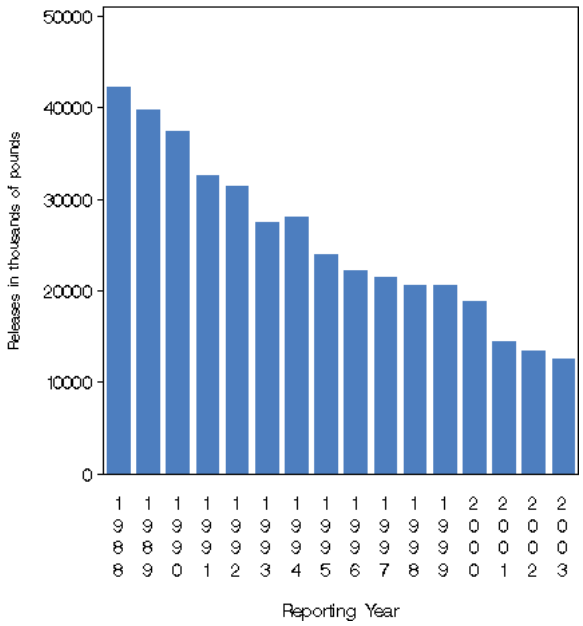

Figure 27: Wisconsin's total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Table 24: Wisconsin's Regulation of Air Toxics that are of Primary Concern in Texas

Compound	Basis of Regulation	Allowable Ambient Limits ($\mu g/m^3$) (*)	Emission Thresholds (emissions from stacks ≥ 75 ft.) (+)	Primary Evidentiary Support	Control Requirement	Regulated Sources
Benzene	Carcinogen	N/A	7854 lbs/yr	IRIS	LAER	New & existing sources
1,3-Butadiene	Carcinogen	N/A	219 lbs/yr	IRIS	BACT	
Formaldehyde	Carcinogen	N/A	4712 lbs/yr	IRIS	BACT	
Toluene	Acute Non-Carcinogen	4522/24 hr avg		IRIS	N/A	
Acrolein	Acute Non-Carcinogen	22.9/24 hr avg		IRIS	N/A	
H_2S	Acute Non-Carcinogen	335/24 hr avg		IRIS	N/A	
Styrene	Acute Non-Carcinogen	2,045/24 hr avg		IRIS		
Vinyl Chloride	Carcinogen	N/A	2961 lbs/yr	IRIS	LAER	

Values derived from combined chemical table for Air Toxics Rule Revisions, available at: http://www.dnr.state.wi.us/org/aw/air/health/airtoxics/toxics_nr445_list.htm.

*The AALs (Allowable Ambient Limits) are ground level impact limits, taking into account only inhalation exposures from single sources.

+ For compounds of most concern in Houston, the limit is set in absolute amounts per source, like a technology standard; not as an ambient standard

3.2.13 Toxic Reduction in Texas for Comparison: Total Reductions and Percentage Reductions

Texas has reduced toxic air emissions from 187.4M lbs in 1988 to 66.1M lbs in 2003 according to data reported to the Toxics Release Inventory [632]. This represents a reduction of 64.7% from 1988 levels.

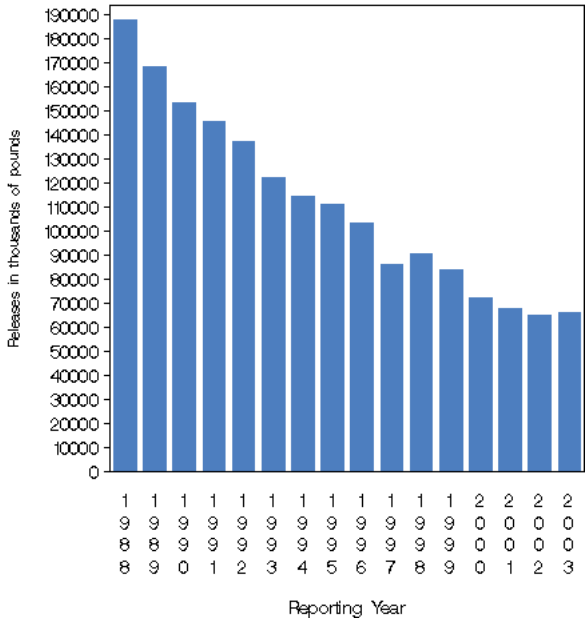

Figure 28: Texas' total reported air toxics releases (as defined by the TRI) from 1988-2003, in thousands of pounds. Data from the Toxics Release Inventory [632].

Figures 29 and 30 compare the air toxics release information for all of the states highlighted in this report. It is important to note the downward trend that appears to be present in the data from each of the states studied. This general trend could be a result of implementation of federal MACT standards, effective state regulations and enforcement, improvements in industrial processes and control technologies, voluntary reductions in emission due to an increased awareness of pollution and the associated health effects, or a combination of the afore mentioned factors. A definite cause and effect relationship cannot be clearly established from this data. Figure 29 also shows that in terms of total amount of air toxic releases, Texas is by far a leader among the states discussed.

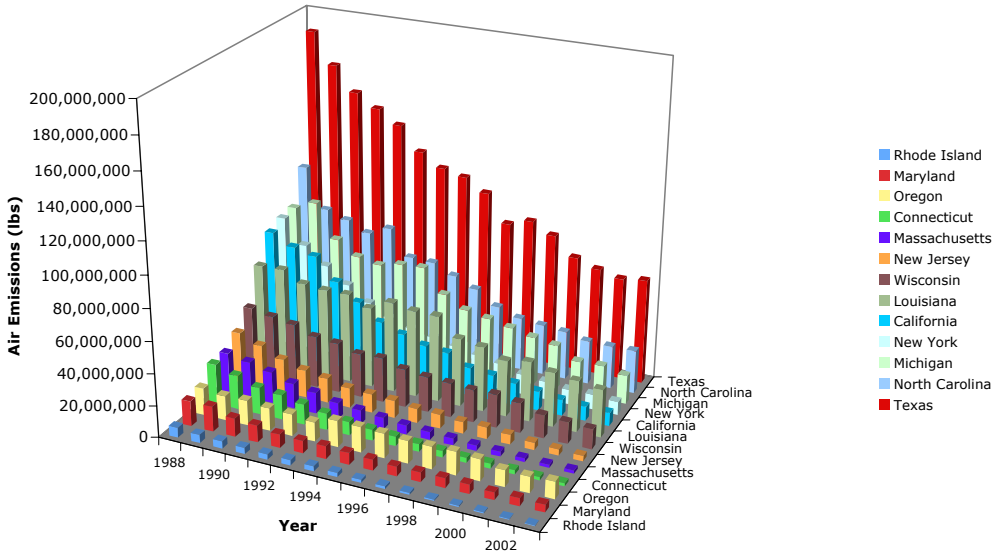

Figure 29: Total reported air toxics (as defined by the TRI) emissions between 1988-2003 as reported in the Toxic Release Inventory [632].

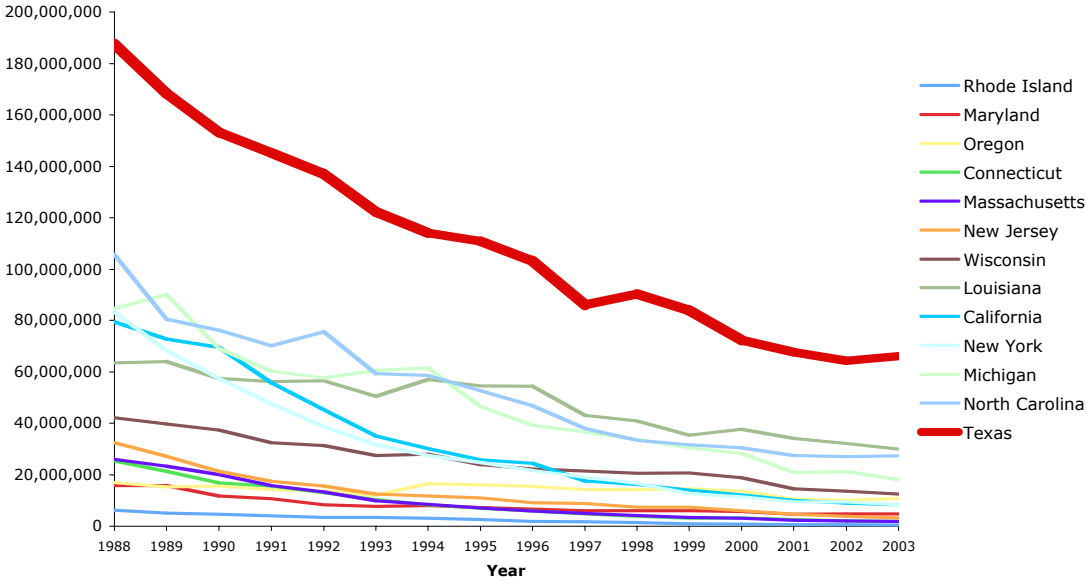

Figure 30: Total reported air toxics (as defined by the TRI) emissions between 1988-2003 as reported in the Toxic Release Inventory [632].

Figure 31 illustrates the percent reductions achieved by each state from a 1988 benchmark. It is interesting to note that some states have made more progress than others. This could potentially be due to the method of state regulation, the effectiveness of enforcement strategies adopted, ineffective control of specific sources or industries, or a combination of these, and other, factors.

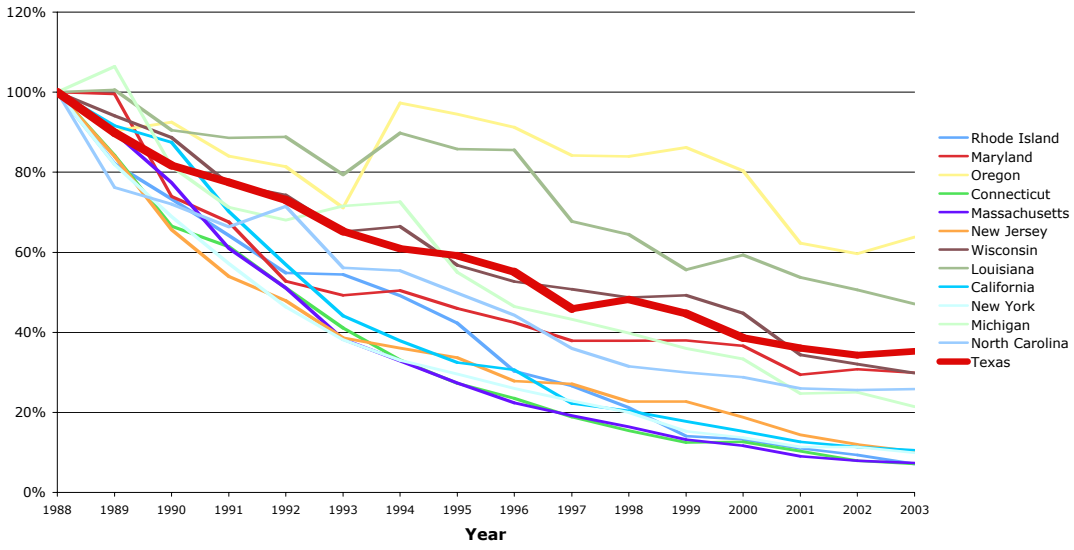

Figure 31: A graph of the percentage change in total reported emissions using a 1988 baseline as reported in the Toxic Release Inventory [632].

3.3 Relevance of Other State Risk Guidelines to the State of Texas

From an examination of the legal regime governing air toxics and the standards from other states, certain conclusions and recommendations have been drawn.

The State of Texas releases a considerable amount of air toxics. Although efforts have reduced the released concentrations over the last decade and a half, data reported here and in other studies indicate that the ambient concentration of air toxics in Houston are high and that additional progress is needed to be made to reduce the ambient concentrations to levels more protective of human health.

The federal government and other states have decided that regulations or guideline governing the use of control technologies, the amount allowable emissions from a permitted process, or acceptable ambient concentrations are the most effective way of reducing air toxics concentration and the associated health risks.

The US EPA has set its goal for the management of residual risk remaining after the implementation of MACT at one excess cancer death out of a million. With respect to

emission standards, many states, including Massachusetts, Michigan, New Jersey, North Carolina, and Oregon, have utilized this same residual health risk goal in setting their standards. However, some states regulate at a less stringent health risk level (e.g. Louisiana uses one in ten thousand), use a variable residual health risk level (e.g., California's standard for 1,3 butadiene appears to be set at a risk level higher than the other California standards), or do not regulate based on a residual health risk level but instead consult other safe exposure determinations like occupational exposure limits and then adopt some variation thereof.

In order to determine either a suitable exposure level or to determine what risk exists at a particular level, the states investigated in this study use either the US EPA's IRIS risk assessment, the California Office of Environmental Health Hazard Assessment risk assessment, the federal Agency for Toxic Substances Registry (ATSDR) risk assessment, or occupational safety standards (such as those set by OSHA). The states may then apply a safety factor to the data based on an assumption about relative exposure of their citizens or particularly susceptible populations before setting their final exposure level. These standards will also appear to be different based on where they are to be measured, what assumptions and models will be applied, and when the risk assessments were consulted. Therefore, it becomes somewhat difficult to directly compare the states to each other with respect to what each state calls it ambient standards.

This means that it is important in proposing standards that the proposal clearly state the residual risk that is targeted and what health effect exposure models will be used. In terms of Texas, it might be defensible to utilize a residual risk standard to protect health at a excess cancer risk equivalent to one excess death in one million or adopt the exposure levels set out in any of aforementioned risk assessments.

There is also some leeway in how a state will identify which air toxics are to be regulated. Some states have chosen to set out particular substances directly in the statute. Others have asked their regulatory agency to make determinations when necessary. While this latter approach does allow for more flexibility it also requires more time and an agency that is responsive to getting this work done. For Texas, a hybrid of statutory establishment of particular compounds that must be regulated, and authority to the TCEQ to adopt others as necessary, is recommended.

The states vary in their methods, and thus presumably strength of, enforcement. While all of the laws of the states that were examined are legally valid, how well they actually work is related to the enforcement approach which they adopt. In this way, the states have some wide variation. For instance, the states of Rhode Island, Connecticut, and Maryland, have clearly defined reporting standards, measurement or modeling standards, and specific requirements with which to compare them to. Other states have more problematic enforcement schemes.

Finally, California's controls are not directly on the sources themselves in the statute but require the state agency to take further action on sources to force reductions when there are findings that the ambient levels exceed those that they have established as safe levels. Unfortunately, with this method the sources cannot be deemed non-compliant until such time as further action is taken by the state agency which may choose not to proceed against that industry or source particularly. However, this ability to address hot spots is

unique and recommended as a hybrid strategy with general regulation and emission source reporting for the State of Texas.

In general, theories of enforcement would suggest that the better enforcement schemes are the ones which put the responsibility of compliance directly on the regulated entities, and has a state scheme to ensure that they are meeting these requirements. In cases in which the state agency has limited resources some compliance can be achieved without strong enforcement if the laws directly penalize exceedances of standards.

3.4 Feasibility of Local Government Regulations

It is a general truism that unless they are pre-empted by the state from doing so, local governments are able to enact laws that further health and welfare under their general police powers granted them by the state. Environmental laws do fit under this rubric. Without undertaking an analysis of Texas law (outside the scope of the assignment and qualifications of the project team), in general, since Texas has not directly regulated air toxics, it is feasible that local regulation of air toxics has not been pre-empted. An argument could be made that the area of air toxics control is pre-empted because there is some air pollution regulation. However, since there is no evidence that the state thought about and/or rejected restrictions on toxics, it is arguable they did not enact legislation designed to pre-empt such laws.

From a practical perspective, enacting regulations regarding air toxics on a local level would probably force the state's hand in one way or another. They would either have to let it proceed, wait for a private party to sue, regulate themselves, or go on record as not being in favor of regulation of air toxics.

Suggested legislation might also include pollution prevention as a goal (as has been done in some states). Particularly if this is coupled with state assistance, it might go a long way toward actual reductions. It would also fit with the goals of TCEQ, which has made assistance to the regulated community a high priority.

In summary, if the legislation being proposed in Texas would regulate specific hazardous air toxics by the establishment of ambient standards, it should reduce the risk of cancer (the driving risk determiner) to one in one million, using any of the appropriate data in other states.

4.0: International Policy

4.1 International Initiatives on Toxic Substances

4.1.1 Purpose of Comparison

International ongoing and emerging strategies to manage health risk due to toxic chemicals in the environment are relevant to our own efforts in the US and the Houston-Galveston region. This section will examine several international organizations as well as selected national and regional governments, in particular Canada, Australia, and the European Union, and will briefly describe their efforts to provide information regarding chemical hazards and to assess and manage chemical risks. The emphasis of our report is on selected hazardous air pollutants (HAPs), as defined by US law, for which there are no national ambient standards. However, since other governments may categorize air pollutants differently, this section also necessarily includes some of the underlying principles and strategies used internationally to reduce exposure to other pollutants including the six criteria air pollutants (CAPs) for which there are US National Ambient Air Quality Standards (NAAQSs). For the sake of brevity, the following discussion focuses on just a few countries and international organizations that have well-developed processes, guidelines, and regulations to address air pollutants.

4.1.2 International Organizations

A number of cooperative international efforts have formed to provide scientific consensus for assessment of chemical risks and to promote the development of measures to protect populations from excess risk from chemical exposure.

The United Nations Environment Programme (UNEP): Established in 1972, UNEP is the designated authority of the United Nations regarding environmental issues at the global and regional level. Its mandate is to coordinate the development of environmental policy consensus by governments and the international community. UNEP is based in Africa with major offices in Geneva and Paris. The Programme hosts several environmental convention secretariats, such as the Ozone Secretariat and the Montreal Protocol's Multilateral Fund, and several chemical-related agreements, such as the Basel Convention on the Transboundary Movement of Hazardous Wastes and the recently negotiated Stockholm Convention on Persistent Organic Pollutants [720].

World Health Organization (WHO): The WHO was established in 1948 as a specialized agency of the United Nations to direct matters related to public health. In 1989 the WHO Regional Office for Europe published guidelines to provide a basis for protecting public health from the adverse effects of air pollutants and to guide national and local authorities in their risk management decisions [721]. New developments in the fields of air pollution toxicology, epidemiology, and risk assessment have led to revised guidelines developed by the WHO European Centre for Environment and Health in cooperation with the WHO headquarters and the European Commission [156]. Guidelines have been established for the US-designated CAPs as well as selected HAPs such as benzene (Table 25).

The International Agency for Research on Cancer (IARC): As part of the WHO,

IARC was established in 1965 to promote international collaboration in cancer research [722]. The IARC Monographs series publishes independent assessments by international experts on the carcinogenic risk to humans posed by a variety of agents, mixtures, and exposures. Since its inception in 1972, the series has reviewed approximately 900 agents. The IARC rating system for carcinogens, although slightly different from that established by the United States Environmental Protection Agency (US EPA), is used extensively in the US by governmental entities and academia.

International Programme on Chemical Safety (IPCS): The IPCS was organized in 1980 as a cooperative effort of the WHO, International Labor Organization, and UNEP to define environmental health criteria that member states may use to establish their own workplace exposure limits for chemicals [723].

Organization for Economic Cooperation and Development (OECD): The OECD is an intergovernmental organization of 30 industrialized countries and the European Commission [724]. It was established to provide a forum for member countries to coordinate and harmonize national policies. The OECD Screening Information Data Set (SIDS) project, started in 1989, is a multinational effort to develop data on approximately 600 high production volume (HPV) chemicals. The US is responsible for developing data on approximately 25% of the 300 or so HPV chemicals that are now active in the OECD SIDS testing program [725]. Data on the other chemicals are being developed by the other OECD member countries.

4.1.3 National and Regional Strategies

4.1.3.1 Canada

Canada has two primary national regulatory agencies involved in protecting the environment and human health from chemical hazards: Environment Canada, which focuses on environmental quality, and Health Canada, which focuses on human health. Toxic substances, including those in the air, are regulated under the Canadian Environmental Protection Act (CEPA) of 1988 and the amended version, CEPA 1999 [726].

As defined under CEPA 1999, a "substance" includes any distinguishable kind of organic or inorganic matter, whether animate or inanimate, that is capable of being released as a single substance, an effluent, emission, waste, or a mixture into the Canadian environment. Substances are regulated differently depending on whether they are domestic (i.e., existing) or new.

Domestic Substances. Currently, about 23,000 substances are included on the domestic substances list (DSL). These are existing substances that can be manufactured in, imported into, or used in Canada on a commercial scale that have not been assessed for the risks they pose to the environment or human health. There are three key processes, which are discussed in the next subsections, for assessing substances on the DSL [262].

Categorization. Under CEPA 1999, all substances on the DSL must be categorized by September 13, 2006. Categorization is essentially an initial priority setting mechanism which involves the systematic identification of substances on the DSL that meet the

following criteria:

- are inherently toxic (cause toxic effects) to humans or non-human organisms,
- display either the characteristics of persistence or bioaccumulation, and
- may present to individuals in Canada the greatest potential for exposure.

Screening Assessment. Substances that meet the above criteria undergo a screening level risk assessment to determine whether the substance is toxic or capable of becoming toxic as defined in CEPA 1999. Section 64 of CEPA 1999 defines a substance as toxic "if it is entering or may enter the environment in a quantity or concentration or under conditions that:

- have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
- constitute or may constitute a danger to the environment on which life depends; or
- constitute or may constitute a danger in Canada to human life or health" [726].

Priority Substance List. Substances believed to require investigation on a priority and in-depth basis to determine if they are toxic are placed on the priority substance list (PSL). Substances can also be added to the PSL when a more comprehensive assessment is required following a screening assessment or review of another jurisdiction's decision. Additionally, any person may ask the minister to add a substance to the PSL. CEPA 1999 requires that the substance be assessed within five years from the date the substance is added to the list. Historically, Canadian regulatory bodies have relied on exposure standards and limits generated by other countries and organizations, such as the US EPA and the WHO.

The CEPA of 1988 created a mandate for carrying out risk assessments and the 44 chemicals placed on the first PSL were assessed for toxicity in 1989. Of the 44 substances first listed, 25 were declared to be toxic. The second PSL of 25 more substances was published in 1995. Of the 23 assessments subsequently published, 18 substances were deemed to be toxic. In general, quantitative risk assessments in Canada are performed on a case-by-case basis and different assessment methodologies may be used depending on the nature of the substance [727].

Review of Decisions of Other Jurisdictions. The 1999 CEPA calls for cooperation and developing procedures for exchanging information on substances with other jurisdictions. When the ministers learn that another government has prohibited, or substantially restricted, a substance for environmental or health reasons they are obliged to review the decision. The review determines whether the substance is toxic or capable of becoming toxic in the Canadian environment. The intent is that Canada will benefit from the sharing of scientific data and the capacity and efforts of others to develop risk management measures.

Once the ministers have conducted a screening level risk assessment, a review of a decision by another jurisdiction, or a risk assessment of an existing substance on the PSL,

they must propose one of three measures [262]:

- add the substance to the PSL, if the substance is not already on it and they believe that there is a need for a more comprehensive risk assessment;
- recommend that the substance be added to the List of Toxic Substances (Schedule 1) and, if applicable, to the Virtual Elimination List; or
- recommend that no further action under CEPA 1999 be taken if the substance is found not toxic or if actions being taken, or about to be taken, under other federal acts or by provincial, territorial, or aboriginal governments are sufficient to manage the risks in a timely manner.

Once a substance is on Schedule 1 [728], CEPA 1999 provides the authority for various risk assessment and management measures developed through the Toxics Management Process (TMP) [729]. The TMP, administered by Environment Canada in conjunction with Health Canada, is the strategy for addressing risks to human health and the environment posed by the use and/or release of each toxic substance. A variety of management tools, including "instruments" developed under CEPA 1999, may be used to reduce risk associated with any aspect of the substance's life cycle. Examples of preventive or control instruments include the following [729].

- *Regulations:* restrictions imposed on an activity related to a substance, or limits set on the concentrations of a substance that can be used, released to the environment, or present in a product.
- *Pollution Prevention Plans:* preparation and implementation of a plan outlining actions to prevent or minimize the creation or release of pollutants and waste.
- *Environmental Emergency Plans:* preparation and documentation of information regarding the prevention of, preparedness for, response to, or recovery from an environmental emergency.
- *Environmental Codes of Practice:* recommendation of procedures, practices, or release limits for environmental control relating to works, undertakings, and activities during any phase of their development and operation, and any subsequent monitoring activities.
- *Environmental Release Guidelines:* development of limits expressed as concentrations or quantities, for the release of substances into the environment from works, undertakings, or activities.

When substances are inherently toxic, persistent, bioaccumulative, or present in the environment primarily as a result of human activity, but are not naturally occurring radionuclides or naturally occurring inorganic substances, they may be added to the Virtual Elimination List, which requires reduction of the release of a substance to the environment to a level below which its release cannot be accurately measured.

Non-Domestic (new) Substances. The Non-Domestic Substances List is an inventory of substances that are not on the DSL but are accepted as being in commercial use

internationally. The list is based on the US EPA's Toxic Substances Control Act Chemical Substances Inventory and contains more than 58,000 entries. Importers or manufacturers of a new substance, or an old substance for a new purpose, must provide specific information to regulating agencies for risk assessment purposes. Environment Canada and Health Canada then conduct a new substance assessment with the data which results in one of the three following outcomes:

- If the substance is not suspected to be toxic, the notifier may import or manufacture the substance after the assessment period has expired.
- If the substance is suspected of being toxic or becoming toxic, the government may take risk management measures.
- If the substance is not suspected of being toxic but a significant new activity could result in the substance becoming toxic, the substance can be subject to re-notification under certain conditions.

Possible risk management measures for new substances that are toxic or suspected to be toxic include:

- Permit the manufacture or import of the substance subject to specified conditions.
- Prohibit the manufacture or import of the substance for a period not exceeding two years unless replaced by a regulation.
- Prohibit the manufacture or import of the substance until additional information or test results have been submitted and assessed.

Canada utilizes a wide variety of risk management instruments to control toxic air emissions. These include setting National Ambient Air Quality Objectives, Canada-wide standards and regulations, and participating in international agreements, primarily with the US and the United Nations.

National Ambient Air Quality Objectives (NAAQOs). Canada's NAAQOs prescribe targets for air quality to protect human health and the environment, while also considering technologic and economic limits. The Maximum Desirable Level is the long-term air quality goal and the basis for continuing development of pollution control technologies. The Maximum Acceptable Level is an interim goal intended to provide "adequate" protection against effects on the environment and personal comfort and well-being (Table 25) [730].

Canada-wide Standards (CWSs). The CWSs are standards, guidelines, objectives, and/or criteria developed by the Canadian Council of Ministers of the Environment and approved by federal and provincial governments which protect the environment and reduce human health risks. Since 2000, the Government of Canada has been working with the provinces, with the exception of Quebec, and territories to develop and implement CWSs that reduce levels of specific air pollutants including benzene, mercury, particulate matter (PM), and ground-level ozone (Table 25) [731].

CWS for $PM_{2.5}$. The recommended standard for $PM_{2.5}$ is 30 $\mu g/m^3$ averaged over a 24-hour period, to be achieved by 2010. Achievement is to be based on the 98th percentile ambient measurement annually, averaged over three consecutive years.

CWSs for Benzene. Benzene has been classified as carcinogenic to humans, and is considered a substance posing some probability of harm at any level of exposure. The CWSs for benzene target the following sectors for reductions in benzene emissions: oil and gas, transportation, petroleum refining, chemical manufacturing, and steel manufacturing. Other actions include national application of best management practices and of best available pollution prevention and control techniques for new and expanding facilities [732].

On-Road Vehicle and Engine Emission Regulations. New on-road vehicle and engine emission regulations, passed in 2003, introduce more stringent emission standards for 2004 and later model year on-road vehicles and engines. The new standards, now being phased in, will reduce allowable emission levels from new on-road vehicles by up to 95 percent. By 2009, the regulations will subject all cars and light-duty trucks to the same set of emission standards [733].

Canada-United States Air Quality Agreement. This 1991 agreement addresses transboundary air pollution leading to acid rain [734]. Both countries agreed to reduce emissions of sulfur dioxide (SO_2) and nitrogen oxides (NO_x), the primary precursors to acid rain, and to work together on acid rain-related scientific and technical issues. The Ozone Annex was added to the agreement in 2000 with the long-term goal of attaining ozone air quality standards in both countries. The Ozone Annex commits both countries to reduce their emissions of ozone precursor pollutants, i.e., NO_x and volatile organic compounds, in areas where there are transboundary flows [735].

4.1.3.2 Australia

Criteria Air Pollutants. In 1998, through the National Environment Protection Council (NEPC), the Australian state and territory governments agreed to the National Environment Protection Measure for Ambient Air Quality. The measure sets air quality standards for six criteria air pollutants, carbon monoxide (CO), nitrogen dioxide (NO_2), photochemical oxidants, SO_2, lead (Pb), and PM that are legally binding on each level of government (Table 25). The standards were set on the basis of scientific studies of air quality and human health from other countries as well as the standards set by other organizations such as the WHO [736].

The NEPC of Australia also identified a list of 29 priority air toxics of which five—benzene, toluene, formaldehyde, xylenes, and polycyclic aromatic hydrocarbons (PAHs)—were selected to become the subject of a National Environment Protection Measure (NEPM) for Air Toxics [737]. A summary of key findings from the Impact Statement for the Air Toxics NEPM is included here because of its relevance to the air toxics issue in Houston [737].

The three options that were considered by the NEPC as types of standards for the Air Toxics NEPM were: (1) standard with compliance goal and specified monitoring and reporting protocol, (2) advisory reporting standard, and (3) investigation levels.

It was the conclusion of the NEPC that, given the limited data and information on sources of air toxics available in Australia, the setting of full compliance standards or advisory reporting standards (options 1 & 2) could not be justified and the most viable option at the time was to set investigation levels (option 3).

As defined by NEPC, option 3 would set numerical values that are protective of human health and would trigger an investigation if exceeded. This investigation could involve further monitoring and assessment of circumstances that may have led to the levels being exceeded. Measurements would be made at locations where significantly elevated ambient levels of the pollutant might be expected and where significant numbers of people may be exposed.

Where monitoring indicates ambient levels of the pollutant exceed the investigation level, management actions of a localized rather than regional nature may be required. The proposed NEPM requires the collection of data that reflect the distribution of air toxics in urban airsheds and facilitates an assessment of the health risks posed by air toxics in the Australian air environment.

In selecting overseas standards or guidelines for use as investigation levels for the air toxics under consideration in the Air Toxics NEPM, a range of criteria, including similarity of purpose were applied. For each standard or guideline, the approach to setting the standard or guideline had to be identified and assessed for its suitability for Australia. The criteria used by the NEPC in the assessment include:

- evaluation of studies used in the identification of health endpoints and dose-response relationships (unit risk factors, NOAELs, LOAELs, etc.);
- assessment of the quality of the information, especially the quality of the exposure data;
- assessment of the relevance of the health endpoints for Australia;
- determination of risk levels associated with the standards for carcinogens and acceptability for Australia;
- assessment of uncertainty factors used;
- assessment of the unit risk factors and dose-response data used;
- comparison of data with those derived from any Australian studies;
- evaluation of the purpose of the standards and "fit" with the intent of the NEPM; and
- assessment of the appropriateness of the exposure route (i.e., was the inhalation route assessed?).

The health endpoints selected by the NEPC as being appropriate as the basis of air toxics standards in Australia are:

- Cancer: benzene
- Respiratory irritation: formaldehyde

It was noted that these health endpoints are also consistent with the health endpoints used in the derivation of overseas standards and guidelines for ambient air quality.

For benzene, the NEPC considered that the European Commission's (EC) maximum tolerance level of 3 ppb should be adopted as an investigation level in the proposed Air Toxics NEPM. It is noted that the EC annual standard for benzene, which applies everywhere including at peak sites is 1.5 ppb. In the opinion of the NEPC, the EC has the

most transparent and extensive health review of any of the agencies that have developed standards for benzene and, therefore, the level of protection offered by the EC maximum tolerance level is reasonable for the purpose of this NEPM.

The NEPC noted that, with the accumulation of adequate data over the life of the benzene NEPM, judgments could be made on the adoption of an investigation level of 1.5 ppb, consistent with the approach adopted by the European community, the United Kingdom, and New Zealand, or some other level if warranted.

For formaldehyde, the NEPC considered the science behind California's Office of Environmental Health Hazard Assessment (OEHHA) Reference Exposure Levels (RELs) and the process of scientific peer review undertaken to be the most sound of those assessed. However, since monitoring was to be conducted over a 24-hour period, it was proposed that Haber's Law would be applied to obtain a consistent 24-hour averaging time as opposed to a one-hour period.

4.1.3.3 The European Union

The European Commission (EC) has initiated a series of directives aimed at monitoring and controlling levels of certain pollutants in the air. In 1996, the Environment Council adopted a Framework Directive for ambient air quality assessment and management [738] that revised existing legislation and introduced new air quality standards for previously unregulated air pollutants. It also set the timetable for the development of future Daughter Directives for a range of pollutants. The list of atmospheric pollutants considered in the directive includes SO_2, NO_2, PM, Pb, and ozone, pollutants governed by already existing ambient air quality objectives, and benzene, CO, poly-aromatic hydrocarbons, cadmium, arsenic, nickel, and mercury. A procedure for the exchange of information and data on ambient air quality in the European community was established [739], amended [740], and currently exists in a guidance report for member states [741].

The Daughter Directives were developed to set the limit or target values for each pollutant of concern. They also lay out monitoring strategies, and measurment, calibration, and quality assessment methods to arrive at comparable measurements. Working groups developing the Daughter Directives consist of technical experts from the commission, including the Community's Joint Research Centre in Ispra, member states, industry, and environmental non-governmental organizations with support from the European Environment Agency, the WHO, the United Nations Economic Commission for Europe, and consultants involved in cost-benefit analysis studies among others.

The first Daughter Directive, adopted in 1999, related to setting limit values for NO_x, SO_2, Pb, and PM_{10} in ambient air [742]. The findings of the EC working groups have been summarized for NO_2 [743], Pb [744], SO_2 [745], and PM [746]. Member states have until 2001 to meet the vegetation protection limit values for NO_x, until 2005 to meet the health limit values for SO_2 and PM_{10}, and until 2010 to meet the health limit values for NO_2 and Pb. Member states are required to submit attainment plans for meeting limit values for each of the pollutants as dictated in the directive. Methods and results of the preliminary assessment of air quality under the first Daughter Directive have been summarized [747]. More current information is given in a review report adopted by the

commission in 2005 [748] and an accompanying, more detailed, commision staff working document [749].

The second Daughter Directive established limit values for concentrations of benzene and CO in ambient air which must be met by 2005 and 2010, respectively [750]. Draft versions of position papers from the commission working groups are available for CO [751] and benzene [752].

The third Daughter Directive set long-term objectives for ozone, equivalent to the WHO's new guideline values and target values, which must be attained where possible by 2010 [753]. These targets follow Directive 2001/81/EC on national emission ceilings [754]. Non-compliance requires member states to work out reduction plans to be reported to the commission and made available to the public. The directive also sets alert thresholds and requires authorities of the member states to take short-term action if exceeded. A position paper, developed by the commission's ozone working group [755], and a guidance manual for implementation [756] have been made available.

The fourth Daughter Directive of 2004 relates to arsenic, cadmium, mercury, nickel, and PAHs in ambient air [636]. The position paper and annexes of the working group on ambient arsenic, cadmium, and nickel compounds [757], PAHs [758] and mercury [759] have been made available.

A "Thematic Strategy on Air Pollution" was recently developed under the technical analysis and policy development program Clean Air for Europe (CAFE) [760]. The strategy, which updates, merges, simplifies, and streamlines the Framework Directive and the four Daughter Directives into a single directive, was adopted by the EC in September 2005. Relevant CAPs and HAPs limit values defined in the Strategy are listed in Table 25.

To provide information about the amount of pollution that different installations release, a European Pollutant Emission Register (EPER) was established by Commission Decision [761]. Member states are required to produce a triennial report on the emissions of industrial facilities into the air and waters for activities listed in Annex A3 of the EPER Decision. The report covers 50 pollutants that must be included if the threshold values indicated in the EPER Decision are exceeded. The threshold values have been chosen in order to include about 90% of the emissions of the industrial facilities considered. The EPER currently provides information on the annual emissions of approximately 10,000 industrial facilities in the 15 member states of the EU, as well as in Norway and Hungary.

Currently in Europe, as in the US, there are different rules for new and existing chemicals that may make their way into the air. In Europe, chemicals introduced to the market after 1981 (about 3,000) are termed new chemicals. New chemicals with volumes greater than 10 kg per year must be tested before they are placed on the market. All chemicals that were put on the market before 1981 (about 100,106) are called existing chemicals. No testing is currently required for existing chemicals.

The commission's criticisms of its current system are as follows [762].

- *Lack of information about existing chemicals.* The assessment of environmental and health risks of substances has been resource intensive and slow. Since 1993, only 141

high-volume chemicals have been identified for risk assessment and only 27 of these have completed the process.

- *The burden of responsibility not appropriate.* Public authorities are responsible for undertaking risk assessments of substances rather than those who manufacture, import, or use the substances. Furthermore, since only manufacturers and importers of chemicals are required to provide information about chemical use (industrial users and formulators are exempt), exposure arising from downstream uses has been difficult to assess.
- *Current system hampers research and innovation.* More stringent requirements for new chemicals, as compared with existing chemicals, have encouraged the use of existing substances over the development of new ones.

Proposed Management of Toxic Chemicals in the EU: REACH. In the White Paper on the Strategy for a Future Chemicals Policy, published in February 2001, the commission outlined the problems of the current system and proposed a new strategy for ensuring chemical safety and a competitive chemicals industry through registration, evaluation, and authorization of chemicals (REACH) [762]. The key elements of REACH (registration, evaluation, and authorization) are described below [763, 764].

Registration. Manufacturers and importers of articles must register constituent chemicals in a central database if they meet the criteria for classification as dangerous, are intended to be released during normal and reasonably foreseeable conditions of use, and at least one ton per year of the chemical is released as a constituent of the article type. Each "dossier" must include information on properties, use, and intrinsic hazards (such as physicochemical, toxicologic, and eco-toxicologic properties). Based upon these assessments, if a manufacturer or importer concludes that the substance is dangerous, then the manufacturer or importer must perform an exposure assessment and a risk characterization and apply the appropriate measures to control risk adequately.

Evaluation. A new European Chemicals Agency (ECA) will manage the central database of chemical dossiers and provide information to the public. A "dossier evaluation" for each will confirm that the registration was in compliance with the registration requirements, determine whether sufficient test data are available, and if not, the quantity and nature of additional testing needed. Required tests must minimize animal testing by sharing data using alternative sources of information. REACH does not define the standard of review for the scientific and risk-based decision making required by its program. The ECA may conduct a substance evaluation on any substance it suspects is a risk to human health or the environment. Rolling schedules prepared by competent authorities in the EU member states, covering a period of three years and updated annually, will specify the substances each member state plans to evaluate each year.

Authorization. The commission is responsible for granting or refusing authorization to manufacture, import, or use chemicals categorized to be "of very high concern," including those that are carcinogenic, mutagenic, or toxic to reproduction (CMRs); persistent, bioaccumulative, and toxic (PBTs); or very persistent and very bioaccumulative (vPvBs). Authorization is not required for PBT or vPvB substances present in concentrations of less than 0.1 percent or for substances being used solely for

scientific research.

Once an application is received, the ECA will prepare two opinions, one addressing the risk posed to human health and the environment and another addressing socioeconomic factors. Following a public comment period, final opinions are to be made available to the commission, member states, the applicant, and the public. Restricted substances cannot be manufactured, placed on the market, or used unless they comply with the conditions of the restriction.

Enforcement. The REACH program relies upon the ECA or member states to enforce provisions and correct violations. Penalties for violations of REACH provisions are left to the member states and, conceivably, could vary widely depending on the member state. REACH specifies the legal venue to challenge regulatory decisions from the ECA. The first appeal is heard by the agency's Board of Appeal. Subsequent appeals are heard by the Court of Justice of the European Communities. REACH contains no provisions for citizen suits.

In November 2005, the European Parliament approved an amended version of REACH [765]. To address industry's concerns of over-regulation, the amended proposal requires fewer of the estimated 17,000 chemicals used in volumes of less than 10 tons/year to undergo safety tests. Substances would still have to be registered but less data would be required and some would not need any testing. The European Council voted to adopt REACH in December 2005. The parliament and the council will come together in early 2006 to agree on the final version of the proposal. Formal approval of the legislation is scheduled for May 2006 with introduction of the legislation slated for spring 2007 [766].

Table 25: Guidelines, standards, or risk values of the World Health Organization (WHO), Canada, Australia, and the European Union for the US-designated criteria air pollutants (carbon monoxide, nitrogen dioxide, ozone, particulate matter, and sulfur) and selected HAPs.

WORLD HEALTH ORGANIZATION [156]		
Pollutant	**Averaging Period**	**Guideline / Risk Value**
Benzene[a]	--	6×10^{-6} (unit risk)
1,3-Butadiene	--	Reviewed without conclusion
Carbon monoxide	15 minutes 30 minutes 1 hour 8 hours	100,000 $\mu g/m^3$ (86,200 ppb) 60,000 $\mu g/m^3$ (34,480 ppb) 30,000 $\mu g/m^3$ (17,240 ppb) 10,000 $\mu g/m^3$ (8,620 ppb)
Formaldehyde	30 minutes	0.1mg/m^3 (80 ppb)
Lead	1 year	0.5 $\mu g/m^3$
Nitrogen dioxide	1 hour 1 year	200 $\mu g/m^3$ (105 ppb) 40 $\mu g/m^3$ (21 ppb)
Ozone	8 hours	120 $\mu g/m^3$ (60 ppb)
Particulate matter < 2.5 μm[b]	--	1.015 (Relative Risk)
Particulate matter < 10 μm[b]	--	1.0074 (Relative Risk)
Sulfur dioxide	10 minutes 24 hours 1 year	500 $\mu g/m^3$ (188 ppb) 125 $\mu g/m^3$ (47 ppb) 50 $\mu g/m^3$ (18.8 ppb)

CANADA [730]		
Pollutant	**Averaging Period**	**Guideline**
Benzene[c]	--	None
1,3-Butadiene[d]	--	None
Carbon monoxide[e]	1 hour 8 hours	31,000 ppb (13,000 ppb) 13,000 ppb (5,000 ppb)
Formaldehyde[f]	--	None
Lead[g]	--	None
Nitrogen dioxide[e]	1 hour 24 hours 1 year	213 ppb 106 ppb 53 ppb (32 ppb)
Ozone[h]	8 hours	65 ppb
Particulate matter < 2.5 μm[i]	24 hours	30 $\mu g/m^3$
Particulate matter, total[e]	24 hours 1 year	120 $\mu g/m^3$ 70 $\mu g/m^3$ (60 $\mu g/m^3$)
Sulfur dioxide[e]	1 hour 24 hours 1 year	334 ppb 172 ppb) 115 ppb (57 ppb) 23 ppb (11 ppb)
AUSTRALIA [736, 767]		
Pollutant	**Averaging Period**	**Monitor Investigation Level**[j]
Benzene[k]	1 year	3 ppb
1,3-Butadiene	--	None
Carbon monoxide	8 hours	9,000 ppb
Formaldehyde[m]	24 hours	40 ppb
Lead	1 year	0.5 $\mu g/m^3$
Nitrogen dioxide	1 hour 1 year	120 ppb 30 ppb
Ozone	1 hour 4 hours	100 ppb 80 ppb
Particulate matter < 2.5 μm	24 hours 1 year	25 $\mu g/m^3$ 8 $\mu g/m^3$
Particulate matter < 10 μm	24 hours	50 $\mu g/m^3$
Sulfur dioxide	1 hour	200 ppb

	24 hours 1 year	80 ppb 20 ppb
EUROPEAN UNION [768]		
Pollutant	**Averaging Period**	**Limit Value** [n]
Benzene[o]	1 year	5 μg/m^3 (1.5 ppb)
1,3-Butadiene	--	None
Carbon monoxide	8 hours	10,000 μg/m^3 (8,620 ppb)
Formaldehyde	--	None
Lead	1 year	0.5 μg/m^3
Nitrogen dioxide[o]	1 hour 1 year	200 μg/m^3 (105 ppb) 40 μg/m^3 (21 ppb)
Ozone[o]	8 hours	120 μg/m^3 (60 ppb)
Particulate matter < 2.5 μm[o]	1 year	25 μg/m^3
Particulate matter < 10 μm	24 hours 1 year	50 μg/m^3 40 μg/m^3
Sulfur dioxide	1 hour 24 hours	350 μg/m^3 (131.6 ppb) 125 μg/m^3 (47 ppb)

[a] Cancer risk estimates for lifetime exposure to a concentration of 1 μg/m^3.

[b] Relative increase in daily mortality associated with a 10 μg/m^3 increase in PM.

[c] A phased approach to benzene reduction calls for a 30% reduction in total benzene emissions from 1995 emission inventory levels by the end of 2000 (Phase I) and a further 6-kilotonne reduction in benzene emissions by the end of 2010 (Phase II). New and expanded facilities are required to minimize benzene emissions by applying sector-specific best management practices [732].

[d] Based on estimates of tumorigenic potency and exposure for the general population, the priority to investigate options to reduce exposure to 1,3-butadiene in ambient air is considered to be high [769].

[e] Maximum acceptable level; maximum desirable level is in parenthesis.

[f] Most of the Canadian population is exposed to airborne concentrations of formaldehyde less than those associated with sensory irritation. Priority for investigation of options to reduce exposure on the basis of carcinogenicity is considered to be low [263].

[g] Regulations exist to limit lead release from smelters [770] and lead concentration in gasoline [771].

[h] Target to be attained by 2010. Achievement is to be based on the fourth-highest measurement annually, averaged over three consecutive years.

[I] Target to be attained by 2010. Achievement is to be based on the 98th percentile ambient measurement annually, averaged over three consecutive years.

[j] Monitoring investigation level values are levels below which lifetime exposure, or exposure for a given averaging time, does not constitute a significant health risk. If there are regular exceedances at the same site, jurisdictions may wish to consider management actions [767].

[k] Eight-year goal is to gather sufficient data nationally to facilitate development of a standard.

[n] Limit values are from the Clean Air for Europe (CAFE) "Thematic Strategy on Air Pollution" adopted by the European Commission in September 2005. The number of days per year in which the limit value may be

exceeded (0-35 days per year) varies depending on the pollutant and averaging time [768].

[o] Limit value is to be attained by 2010 [768].

4.2 Relevance of Canadian and European Policies to the Policies of the US

Tens of thousands of chemicals are currently in commercial use in the US and, on average, over 700 new chemicals are placed on the market each year. The US EPA's review of new chemicals provides only limited assurance that health and environmental risks have been adequately identified before chemicals are released on the market [772]. This is primarily because the US EPA lacks sufficient data to ensure that potential health and environmental risks of new chemicals are identified.

Companies are required to submit pre-manufacture notice information on the anticipated production levels and uses of a chemical. However, they are not required by the Toxic Substances Control Act (TSCA) to test new chemicals before they are submitted for the US EPA's review. As a result, companies generally do not voluntarily perform such testing. The US EPA has the authority to request that chemical companies develop test data, but only if the US EPA has first proved (1) a chemical may present an "unreasonable" risk of injury to health or the environment and (2) the chemical is or will be produced in substantial quantity and there is or may be significant, or substantial, human exposure to the chemical or it enters, or may reasonably be anticipated to enter, the environment in substantial quantities [772].

A growing international trend that could affect chemical regulation in the US involves increased responsibility on the part of chemical companies for providing information and test data on chemicals. Under CEPA 1999 and the proposed EU regulation, US chemical companies may be required to provide information on some chemicals that are manufactured or processed in, or exported to, Canada and the EU. As it currently stands, the US chemical companies would not be required to submit this same information to the US EPA. This could change, however, because TSCA provides authority to the US EPA to promulgate rules requiring chemical companies to submit existing information of chemicals manufactured in or imported into the US [772]. Under this circumstance, with little additional work on the part of chemical companies, the US EPA's ability to assess and manage chemical risk to human health and the environment could be greatly improved.

Another international influence that might change how chemicals are regulated in the US is the growing awareness that existing chemicals pose risks to human health and the environment that can not simply be grandfathered away. Under TSCA, the US EPA is not required to systematically prioritize existing chemicals for purposes of determining their risks. Chemicals on the market prior to December 1979, which still make up 99% by volume of all chemicals used in the US today, have undergone little or no testing [772]. Both CEPA and REACH contain requirements for systematically prioritizing and reviewing existing chemicals. REACH, in fact, largely eliminates the distinction between existing and new chemicals.

In closing, it should be noted that the US, the World Health Organization, Canada, Australia and the European Union, along with other countries and organizations not discussed in this section, have developed standards, guidelines, and methodologies for addressing the undesirable effects of air pollutants that, for the most part, are all based on a common body of scientific research, health effects studies, and risk assessment methodologies. Differences between governments with regard to the guidelines and regulations enacted, as well as the commitment to supporting and/or enforcing these decisions, largely reflect differing philosophies regarding the importance of environmental and human health, especially when weighed against economic considerations, especially in the short-term. In examining the usefulness of developing health-driven guidelines and/or standards for selected air toxics alone, and in combination with other exposures, we can benefit significantly by examining what other governments and international organizations are doing. The underlying issues are fundamentally the same.

5.0 Summary & Recommendations

Current federal regulation of hazardous air pollutants (HAPs) has aimed at controlling the emission of these air toxics through the use of technology. Currently, maximum achievable control technology (MACT) standards have been set for a number of different emission sources. The use of this technology alone, however, does not ensure that ambient concentrations of HAPs do not rise to levels of concern with regard to the health effects of the various pollutants. Congress has charged the United States Environmental Protection Agency (US EPA) with creating regulations to address this residual risk, but these regulations have yet to be established.

In the interim, individual states have taken the initiative to try to address the residual risk posed by HAPs by developing regulations beyond the MACT standards set by federal regulation. The method of regulating stationary sources varies. For example, states may:

- offer guidelines or set standards;
- recommend or mandate control technologies and/or measure ambient concentrations;
- create a state infrastructure for regulation and compliance or reqire the emission sources to monitor and report compliance; or
- establish a list of regulated compounds or add individual compounds as regulation is deemed necessary.

Regulation of mobile sources can be somewhat trickier and may require different methods such as regulation of vehicle and fuel manufacturers or regulations concerning the manner of vehicle operation.

No matter what methods a state decides to use in regulating air toxics, the fundamental question involved is common to all regulating bodies: What is an acceptable ambient concentration of these HAPs? The US EPA has chosen a benchmark of reducing the excess cancer risk to below one in a million. As any future federal legislation is likely to also use this benchmark, many states have chosen it as their goal. The benchmark goal is less clear for non-carcinogens.

Because each hazardous air pollutant has a unique dose-response relationship in the human population (due to differences in metabolic pathways, the toxicity of metabolites, and individual sensitivity), detailed toxicology data is needed on each compound. Years of scientific investigation has provided much of the needed information on the toxicology of HAPs and organizations including the US EPA, the California Environmental Protection Agency, and the Agency for Toxic Substances and Disease Registry have reviewed this data in their risk assessments. Most states refer to these risk assessments or occupational standards when setting safe exposure levels and sometimes include a multiplier to account for any modifying factors associated with the exposure of their citizens. However, the need for re-evaluation of risk assessments should not be underestimated as ongoing research, aimed at providing more data on effects in human populations, using more relevant exposure concentration levels and sophisticated research tools becomes available.

Internationally, the story is the same. Foreign regulating bodies ask similar questions, peruse the same scientific literature, and gather information from risk assessments conducted by other entities. A growing trend internationally is requiring producers of

new chemicals to conduct scientific studies regarding their chemicals toxicity. This information makes regulations easier to establish as chemicals come to the market and alleviates some of the burden on regulating bodies. The US EPA, as well as the states, could capitalize on this information in the future.

Based on the compiled information documenting health impacts from toxic air pollutants, it is the recommendation of the study authors that:

- All persons should be protected from negative health impacts resulting from toxic air pollutants.
- In the state of Texas, additional measures are required to protect our population from toxic air pollutants.
- In this effort, the state of Texas can look to other states and jurisdictions for guidance on measures that can effectively protect our population.
- The population should not be subject to health risks from individual air toxics greater than one in 1 million excess cancer deaths over a lifetime exposure or occurrence of other measurable health impacts.
- To provide this protection, general regulation of toxic air pollutants through ambient standards and pollution reduction measures are warranted.

Mounting evidence demonstrates that the population of Southeast Texas is exposed to disproportionate levels of toxic air pollutants considered to be a health risk to this population. In Southeast Texas, benzene, 1,3 butadiene, formaldehyde, and diesel particulate matter (diesel PM) have been identified as particularly pernicious pollutants requiring priority regulation. Based on the toxicological information and the concentrations seen in the Houston area for the selected four air pollutants, it is clear that large portions of the city have ambient air concentrations posing a risk higher than one excess cancer death in every 100,000 people. Observed concentrations of 1,3-butadiene and diesel PM approach a level indicating risk greater than one excess cancer death per 10,000 people. With respect to these compounds, the evidence summarized in this report is strong enough to specify enforceable ambient standards.

The project team recommends an ultimate goal that the one in one million excess cancer risk be utilized as a basis for ambient air quality standards. In Table 26, the ambient levels associated with a one in a million risk level for the four air toxics studied are listed.

Table 26: Proposed Ambient Standard Goals

	Benzene	1,3-Butadiene	Formaldehyde	Diesel PM
Proposed Ambient Standard Goal	0.14 ppb	0.013 ppb	10 ppb *	0.03 $\mu g/m^3$

* 24-hour average standard based on acute irritation.
Other standards are proposed as annual averages.

We recommend that these levels be attained throughout the state of Texas. However, recognizing that there are areas in Houston region where the current ambient air quality is associated with an excess cancer risk significantly greater than 1 in 100,000, the project team recommends urgent action to achieve a 1 in 100,000 excess cancer risk as an interim goal. In Table 27, interim ambient standards for a risk of 1 in 100,000 are set out.

Table 27: Proposed Interim Ambient Standard

	Benzene	1,3-Butadiene	Formaldehyde	Diesel PM
Proposed Interim Ambient Standard	1.4 ppb	0.13 ppb	10 ppb *	0.29 $\mu g/m^3$

* 24-hour average standard based on acute irritation.
Other standards are proposed as annual averages.

In review of ambient data relative to these standards, certain "hot spots" can be identified where benzene levels will have to be reduced by up to 40%, formaldehyde levels by up to 50%, and 1,3 butadiene levels by up to 95% from measured 2004 levels and diesel particulates will have to be reduced by up to 90% from the measured 1998 levels. Adoption of these interim standards is essential to make immediate progress in protecting public health.

We recommend state legislation as the most effective approach for comprehensive protection of the populace. Legislation from other jurisdictions and the relative effectiveness of these laws suggest a model statute for the state of Texas. Absent legislation at the state level, local government may be able to accomplish some of these protections.

There are unresolved implementation issues associated with attaining a one in a million cancer risk ambient air quality standard. The study authors recommend further study into these issues. For guidance, the authors offer the following comments:

- The effects screening levels (ESL) approach utilized by the Texas Commission on Environmental Quality (TCEQ) is not adequate to address this problem. The ESL approach is deficient because it is permit-specific rather than comprehensive and, as practiced, not enforceable. The project team is of the opinion that relying solely on ESLs applied to individual permit actions will never lead to attainment of the one in a million health based risk level throughout the community.
- To the extent that the ESL approach is maintained by the TCEQ, the project team strongly urges that the screening levels for air toxics be based on a risk of one in one million excess cancer risk, rather than the current levels which are no higher than 1 in 100,000 excess cancer risk.
- Reporting requirements should be placed on emission sources to aid in enforcement.
- Regulations provide for a mechanism for addressing hot spots.

In determining an appropriate implementation plan, attention should be drawn to strategies that other states and countries are using. One strategy to reduce ambient concentrations of HAPs is anti-idling regulations which have been adopted in California, Connecticut, and Massachusetts. Such a strategy, and others like it, can be recommended for rapid implemenation and can make an immediate difference to ambient air quality, but they are only part of an overall solution.

From a community health perspective, the effects of air pollution on vulnerable populations may be compounded by socioeconomic inequities, racial and demographic

differences, and disparities in access to health care and use of health services. Although occupational and housing patterns explain much of the variation in proximity to pollution, there is persistent inequity in potential exposure across population groups. Modifiers of the health effects of air pollution include income, race, ethnicity, age, proximity to traffic, and residential patterns. These factors need to be considered in determining an implementation strategy to ensure that everyone shares a similar risk. These factors underscore that for immediate improvements in health, initial implementation steps should focus on the most heavily impacted populations.

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7.0 Glossary

7.1 Agency Acronyms:

ACGIH – American Conference of Governmental Industrial Hygienists

AIHA – American Industrial Hygiene Association

ANSI – American National Standards Institute

API – American Petroleum Institute

ATSAC – Air Toxics Science Advisory Committee – State of Oregon

ATSDR – Agency for Toxic Substances and Disease Registry

CA EPA – California Environmental Protection Agency

CARB – California Air Resource Board

CDHS – California Department of Health Services

CIIT – Chemical Industry Institute for Toxicology

CT DEP – Connecticut Department of Environmental Protection

EC – European Commission

ECA - European Chemicals Agency

HEI – Health Effects Institute

IARC – International Agency for Research on Cancer

IISRP – International Institute of Synthetic Rubber Producers

IPCS – International Programme on Chemical Safety

LDEQ – Louisiana Department of Environmental Quality

MDE – Maryland Department of the Environment

MDEP – Massachusetts Department of Environmental Protection

MDEQ – Michigan Department of Environmental Quality

NCDENR – North Carolina Department of Environmental and Natural Resources

NCI – National Cancer Institute

NEPC – National Environment Protection Council – Australia

NJDEP – New Jersey Department of Environmental Protection

NMMAPS – National Morbidity, Mortality, and Air Pollution Study

NPRA – National Petroleum Refiners Association

NYSDEC – New York State Department of Environmental Conservation

OAR – Office of Air Resources

ODEQ – Oregon Department of Environmental Quality

OECD – Organization for Economic Cooperation and Development

OEHHA – Office of Environmental Health Hazard Assessment – State of California

OEQC – Oregon Environmental Quality Commission

OSHA – Occupational Safety and Health Administration

RIDEM – Rhode Island Department of Environmental Management

TECQ – Texas Council on Environmental Quality

TRI – Toxics Release Inventory

UNEP – United Nations Environment Programme

US EPA – United States Environmental Protection Agency

US NTP – United States National Toxicology Program

WDNR – Wisconsin Department of Natural Resources

WHO – World Health Organization

7.2 Other Acronyms:

AER – Air Exchange Rate

ALC – Absolute Lymphocyte Count

AML – Acute Myelogenous Leukemia

APHEA – Air Pollution and Health: a European Approach

ATOPs – Air Toxics Operating Permits

autoGC – Automated gas chromatography

BACT – Best Available Control Technology

BDO – Butadiene Monoepoxide

BDO_2 – Butadiene Diepoxide

BDO diol – Butadiene Diolepoxide

CAA – Clean Air Act

CAFÉ – Clean Air for Europe

CEPA – Canadian Environmental Protection Act

CI_{95} – 95% Confidence Interval

CMRs – Chemicals that are Carcinogenic, Mutagenic, or toxic to Reproduction

COPD – Chronic Obstructive Pulmonary Disease

CPIEM – California Population Indoor Exposure Model

CRCP - cytolethality/regenerative cellular proliferation

CWS – Canada-wide Standards

CYP2E1 – Cytochrome P450 2E1

DEB – Butadiene Diepoxide

Diesel PM – Diesel Particulate Matter

DOC – Diesel Oxidation Catalyst

DPF – Diesel Fine Particles

DPX – DNA–protein cross-links

DSL - Domestic Substances List

EB – Butadiene Monoepoxide

EB diol – Butadiene Diolepoxide

EPER – European Pollutant Emission Register

ERPG – Emergency Response Planning Guideline

GSH – glutathione

GST – glutathione S-transferase

GSTM1 – glutathione-S-transferase M1

HAP – Hazardous Air Pollutant – also known as a Toxic Air Pollutant

HD – Heavy Duty

HEC – Human Equivalent Concentration

HLV – Hazard Limiting Value – an emission limit set by the State of Connecticut

HPV – High Production Volume Chemical

HQ – Hazard Quotient

HRV – Heart Rate Variability

IRIS – US EPA Integrated Risk Information System

LAER – Lowest Achievable Emissions Rate

LD – Light Duty

LEC – Least Effective Concentration

LEV – Low Emission Vehicle Standards

M1 – 1,2-dihydroxy-4-(N-acetylcysteinyl)-butane

M2 – 1-hydroxy-2-(N-acetylcysteinyl)-3-butene

MA – Trans,trans-muconaldehyde

MACT – Maximum Achievable Control Technology

MASC – Maximum Allowable Stack Concentration

mEH – microsomal epoxide hydrolase

MIR – Maximum Individual Risk

NAAQO – National Ambient Air Quality Objectives – Canada

NAPS – National Air Pollution Surveillance program – Canada

NEPM – National Environment Protection Measures – Australia

NHL – Non-Hodgkin's Lymphoma

NIOSH – National Institute of Occupational Safety and Health

NQO1 – NAD(P)H:quinone oxidoreductases

NRDC – Natural Resources Defense Council

OELs – Occupational Exposure Levels

PAH - Polycyclic Aromatic Hydrocarbon

PBTs – Persistent Bioaccumulative Toxic chemicals

PEL – Permitted Exposure Limit

POD – Point of Departure

PSL – Priority Substance List

QRA – Quantitative Risk Assessment

REL_A – Acute Reference Exposure Level

REL_C – Chronic Reference Exposure Level

PM – Particulate Matter

REL – Reference Exposure Level

ReV – Inhalation Reference Value

RFG – Reformulated Gasoline

RIOPA – Relationships of Indoor, Outdoor, and Personal Air study

ROS – Reactive Oxygen Species

SBR – Styrene-Butadiene Rubber

SEP – Socioeconomic Position

SEP – Supplemental Enforcement Project

SES – Socioeconomic Status

SD – Standard Deviation

SIDS – Screening Information Data Set Project

SOF – Soluble Organic Fraction

SOTA – State-Of-The-Art

SVOC – Semi-Volatile Organic Compound

T-BACT – Best Available Control Technology for Toxics

TAP – Toxic Air Pollutant – also known as a Hazardous Air Pollutant

TEL – Threshold Effects Exposure Limit

TERA – Toxicology Excellence for Risk Assessment

TMP – Toxics Management Process

TURA – Toxics Use Reduction Act – Massachusetts

TVOS – Toxic Volatile Organic Substance

TWA – Time-Weighted Average

UF – Uncertainty Factor

UF – Urea-Formaldehyde

UFFI – Urea-Formaldehyde Foam Insulation

UFPs – Ultrafine Particles

URF – Unit Risk Factor

VOC – Volatile Organic Compound

vPvBs – very Persistent and very Bioaccumulative chemicals

7.3 Definitions

AAL – Acceptable Ambient Level – emission concentration cap set by the State of North Carolina and associated with an excess cancer risk of one in a million at the fenceline.

AALs – Allowable Ambient Limits – permitting guidelines established by the State of Massachusetts.

AGCs – Annual Guideline Concentrations – annual impact guidelines for emission sources in the State of New York that are no equipped with BACT.

Air toxics – hazardous air pollutants

BMC – Benchmark Concentration – an inhalation concentration that produces a predetermined change in the response rate of an adverse effect (called the benchmark response) compared to background.

BMCL – Benchmark Concentration Level – a statistical lower confidence limit on the concentration at the benchmark concentration (BMC).

BMR – Benchmark Response – a predetermined change in an adverse effect response rate over background (typically 5-10%) – used to define a benchmark dose.

CAPs – Criteria Air Pollutants – pollutants for which US NAAQS standards exist. The current CAPs include ozone, carbon monoxide, lead, sulfur dioxide, nitrogen dioxide, and particulate matter.

ESL – Effects Screening Level – a permissible emission guideline set by the Texas Commission on Environmental Quality used in permitting new facilities.

FEV_1 – Forced Expiratory Volume - the volume of air that can be forcibly exhaled during the first second of expiration following a maximal inspiration.

IDHL – concentration level defined by NIOSH as Immediately Dangerous to Life or Health

IRSL – Initial Risk Screening Level – a health-based screening level set by the State of Michigan for carcinogenic effects of a toxic air contaminant associated with an increased cancer risk of one in one million.

ITSL – Initial Threshold Screening Level – a health-based screening level for non-carcinogenic effects of a toxic air contaminant defined and used by the State of Michigan.

LOAEL – Lowest Observed Adverse Effects Level – the lowest exposure level at which there is a statistically significant increases in the frequency or severity of an adverse effect.

MLE – Maximum Likelihood Estimate – a statistical method for estimating a population parameter most likely to have produced the sample observations.

MRL – Minimal Risk Level – an estimate of daily human exposure to a dose of a chemical that is likely to be without appreciable risk of adverse non-cancerous effects over a specified duration of exposure.

NAAQS – National Ambient Air Quality Standards – the acceptable ambient concentrations of criteria air pollutants (CAPs).

NOAEL – No Observable Adverse Effects Level – the highest exposure level at which there is no statistically significant increase in the frequency or severity of an adverse effect.

OR – Odds Ratio – ratio of the odds of an event occurring in one group to the odds of it occurring in another group.

PEL – Permissible Exposure Limit – an 8-hour time-weighted average permissible exposure concentration established by OSHA.

$PM_{2.5}$ – Particulate matter having an aerodynamic diameter less than 2.5 microns.

REACH – The EU's strategy for ensuring chemical safety and a competitive chemicals industry through Registration, Evaluation, and Authorization of Chemicals published in February 2001.

REL – Recommended Exposure Limit – NIOSH – 8-hour time-weighted average.

RfC – Reference Concentration – used in the US EPA IRIS to denote a daily averaged inhalation exposure estimate that is likely to be without an appreciable risk of adverse non-cancer effects over the course of a lifetime.

RfD – Reference Dose – used in the US EPA IRIS to denote a daily averaged oral exposure estimate that is likely to be without an appreciable risk of adverse non-cancer effects over the course of a lifetime.

RR - Residual Risk – the rate of disease among the exposed divided by the rate of the disease among the unexposed.

SMR – Standardized Mortality Ratio – relative measure of the difference in risk between the exposed and unexposed populations in a cohort study.

SRSL – Secondary Risk Screening Level – a health-based screening level set by the State of Michigan for carcinogenic effects of a toxic air contaminant associated with an increased cancer risk of one in one hundred thousand.

STEL – Short Term Exposure Limit – an exposure concentration defined by the ACGIH as the concentration to which a worker may be exposed to for no more than 15 minutes without suffering an adverse effect.

TLV – Threshold Limit Value – ACGIH occupational guideline for average concentration in mg/m^3 for an 8-hour workday and a 40-hour work week to which nearly all workers may be repeatedly exposed without adverse effects.

UR – Unit Risk – the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air of 1 $\mu g/L$ in water.