Regulatory Impact Analysis

Control of Hazardous Air Pollutants from Mobile Sources

Chapter 1
Mobile Source Air Toxics Health Information

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Chapter 1: Mobile Source Air Toxics Health Information

1.1. What Are MSATs?

Section 202(l) refers to "hazardous air pollutants from motor vehicles and motor vehicle fuels." We use the term "mobile source air toxics (MSATs)" to refer to compounds that are emitted by mobile sources and have the potential for serious adverse health effects. There are a variety of ways in which to identify compounds that have the potential for serious adverse health effects. For example, EPA's Integrated Risk Information System (IRIS) is EPA's database containing information on human health effects that may result from exposure to various chemicals in the environment. In addition, Clean Air Act section 112(b) contains a list of hazardous air pollutants that EPA is required to control through regulatory standards; other agencies or programs such as the Agency for Toxic Substances and Disease Registry and the California EPA have developed health benchmark values for various compounds; and the International Agency for Research on Cancer and the National Toxicology Program have assembled evidence of substances that cause cancer in humans and issue judgments on the strength of the evidence. Each source of information has its own strengths and limitations. For example, there are inherent limitations on the number of compounds that have been investigated sufficiently for EPA to conduct an IRIS assessment. There are some compounds that are not listed or not quantitatively assessed in IRIS but are considered to be hazardous air pollutants under Clean Air Act section 112(b) and are regulated by the Agency (e.g., propionaldehyde, 2,2,4-trimethylpentane).

1.1.1. Compounds Emitted by Mobile Sources and Identified in IRIS

In its 2001 MSAT rule, EPA identified a list of 21 MSATs. We listed a compound as an MSAT if it was emitted from mobile sources, and if the Agency had concluded in IRIS that the compound posed a potential cancer hazard and/or if IRIS contained an inhalation reference concentration or ingestion reference dose for the compound. Since 2001, EPA has conducted an extensive review of the literature to produce a list of the compounds identified in the exhaust or evaporative emissions from onroad and nonroad equipment, using baseline as well as alternative fuels (e.g., biodiesel, compressed natural gas).[1] This list, the Master List of Compounds Emitted by Mobile Sources ("Master List"), currently includes approximately 1,000 compounds. It is available in the public docket for this rule and on the web (http://www.epa.gov/otaq/toxics.htm). Table 1.1.-1 lists those compounds from the Master List that currently meet those 2001 MSAT criteria, based on the current IRIS.

Table 1.1.-1 identifies all of the compounds from the Master List that are present in IRIS with (a) a cancer hazard identification of known, probable, or possible human carcinogens (under the 1986 EPA cancer guidelines) or carcinogenic to humans, likely to be carcinogenic to humans, or suggestive evidence of carcinogenic potential (under the 2005 EPA cancer guidelines); and/or (b) an inhalation reference concentration or an ingestion reference dose. Although all these compounds have been detected in emissions from mobile sources, many are emitted in trace amounts and data are not adequate to develop an inventory. Those compounds for which we have developed an emissions inventory are summarized in Chapter 2 Table 2.2.-1. There are

several compounds for which IRIS assessments are underway and therefore are not included in Table 1.1.-1. These compounds are: cerium, copper, ethanol, ethyl tertiary butyl ether (ETBE), platinum, propionaldehyde, and 2,2,4-trimethylpentane.

The fact that a compound is listed in Table 1.1.-1 does not imply a risk to public health or welfare at current levels, or that it is appropriate to adopt controls to limit the emissions of such a compound from motor vehicles or their fuels. In conducting any such further evaluation, pursuant to sections 202(a) or 211(c) of the Act, EPA would consider whether emissions of the compound from motor vehicles cause or contribute to air pollution which may reasonably be anticipated to endanger public health or welfare.

Table 1.1.-1. Compounds Emitted by Mobile Sources That Are Listed in IRIS*

1,1,1,2-Tetrafluoroethane	Cadmium	Manganese
1,1,1-Trichloroethane	Carbon disulfide	Mercury, elemental
1,1-Biphenyl	Carbon tetrachloride	Methanol
1,2-Dibromoethane	Chlorine	Methyl chloride
1,2-Dichlorobenzene	Chlorobenzene	Methyl ethyl ketone (MEK)
1,3-Butadiene	Chloroform	Methyl isobutyl ketone (MIBK)
2,4-Dinitrophenol	Chromium III	Methyl tert-butyl ether (MTBE)
2-Methylnaphthalene	Chromium VI	Molybdenum
2-Methylphenol	Chrysene	Naphthalene
4-Methylphenol	Crotonaldehyde	Nickel
Acenaphthene	Cumene (isopropyl benzene)	Nitrate
Acetaldehyde	Cyclohexane	N-Nitrosodiethylamine
Acetone	Cyclohexanone	N-Nitrosodimethylamine
Acetophenone	Di(2-ethylhexyl)phthalate	N-Nitroso-di-n-butylamine
Acrolein (2-propenal)	Dibenz[a,h]anthracene	N-Nitrosodi-N-propylamine
Ammonia	Dibutyl phthalate	N-Nitrosopyrrolidine
Anthracene	Dichloromethane	Pentachlorophenol
Antimony	Diesel PM and Diesel exhaust organic gases	Phenol
Arsenic, inorganic	Diethyl phthalate	Phosphorus
Barium and compounds	Ethylbenzene	Phthalic anhydride
Benz[a]anthracene	Ethylene glycol monobutyl ether	Pyrene
Benzaldehyde	Fluoranthene	Selenium and compounds
Benzene	Fluorene	Silver

Benzo[a]pyrene (BaP)	Formaldehyde	Strontium
Benzo[b]fluoranthene	Furfural	Styrene
Benzo[k]fluoranthene	Hexachlorodibenzo-p-dioxin, mixture (dioxin/furans)	Tetrachloroethylene
Benzoic acid	n-Hexane	Toluene
Beryllium and compounds	Hydrogen cyanide	Trichlorofluoromethane
Boron (Boron and Borates only)	Hydrogen sulfide	Vanadium
Bromomethane	Indeno[1,2,3-cd]pyrene	Xylenes
Butyl benzyl phthalate	Lead and compounds (inorganic)	Zinc and compounds

*Compounds listed in IRIS as known, probable, or possible human carcinogens and/or pollutants for which the Agency has calculated a reference concentration or reference dose.

1.1.2. Compounds Emitted by Mobile Sources and Included on Section 112(b) List of Hazardous Air Pollutants

Clean Air Act section 112(b) contains a list of hazardous air pollutants that EPA is required to control through regulatory standards. As discussed above, there are some compounds emitted by mobile sources that are not listed in IRIS but are considered to be hazardous air pollutants under Clean Air Act section 112(b) and are regulated by the Agency such as propionaldehyde and 2,2,4-trimethylpentane. Compounds emitted by mobile sources that are Clean Air Act section 112(b) hazardous air pollutants are listed in Table 1.1.-2. Although all these compounds have been detected in emissions from mobile sources, many are emitted in trace amounts and data are not adequate to develop an inventory. Those compounds for which we have developed an emissions inventory are summarized in Table 2.2.-1.

Table 1.1.-2. Compounds Emitted by Mobile Sources That Are Listed in CAA Section 112(b)

1,1,2-Trichloroethane	Carbon disulfide	Methyl ethyl ketone
1,2-Dibromoethane	Carbon tetrachloride	Methyl tert-butyl ether
1,3-Butadiene	Chlorine	Methylchloride
2,2,4-Trimethylpentane	Chlorobenzene	Naphthalene
2,3,7,8-Tetrachlorodibenzo-p-dioxin	Chloroform	Nickel compounds
2,4-Dinitrophenol	Chromium (III and VI)	N-Nitrosodimethylamine

2-Methylphenol (o-cresol)	Cumene	Pentachlorophenol
4-Methylphenol (p-cresol)	Di(2-ethylhexyl)phthalate (DEHP)	Phenol
Acetaldehyde	Dibutylphthalate	Phosphorus
Acetophenone	Dichloromethane	Phthalic anhydride
Acrolein	Ethyl benzene	Polycyclic organic matter*
Antimony compounds	Formaldehyde	Propionaldehyde
Arsenic compounds	Hexane	Selenium compounds
Benzene	Hydrogen cyanide ("Cyanide compounds in Section 112(b))	Styrene
Beryllium	Lead compounds	Tetrachloroethylene
Biphenyl	Manganese	Toluene
Bromomethane	Mercury compounds	Xylenes (isomers and mixture)
Cadmium compounds	Methanol	

*Includes organic compounds with more than one benzene ring, and which have a boiling point greater than or equal to 100.5 C.

1.1.3. Other Sources of Information on Compounds with Potential Serious Adverse Health Effects

Additional sources of information are available to characterize the potential for cancer or noncancer health effects from toxic air pollutants. These include the Agency for Toxic Substances and Disease Registry list of minimal risk levels (http://www.atsdr.cdc.gov/mrls.html), California EPA list of Reference Exposure Levels (http://www.oehha.ca.gov/risk/ChemicalDB/index.asp), International Agency for Research on Cancer lists of carcinogenic compounds (http://www.iarc.fr/ENG/Databases/index.php), the National Toxicology Program list of carcinogenic compounds (http://ntp-server.niehs.nih.gov/), and the U.S. EPA Emergency Planning and Community Right-to-Know Act list of extremely hazardous substances (http://yosemite.epa.gov/oswer/ceppoehs.nsf/content/BackGround). EPA relies on these sources of information, as appropriate, for certain types of analyses.[2]

1.1.4. Which Mobile Source Emissions Pose the Greatest Health Risk at Current Levels?

The 1999 National-Scale Air Toxics Assessment (NATA) provides some perspective on which mobile source emissions pose the greatest risk at current estimated ambient levels.[A] We also conducted a national-scale assessment for future years, which is discussed more fully in Chapters 2 and 3 of the RIA. The limitations and uncertainties associated with NATA are discussed in Section 3.2.1.3 of the RIA. Our understanding of what emissions pose the greatest risk will evolve over time, based on our understanding of the ambient levels and health effects associated with the compounds.[B]

1.1.4.1. Risk Drivers in 1999 National-Scale Air Toxics Assessment

The 1999 NATA evaluates 177 hazardous air pollutants currently listed under CAA section 112(b), as well as diesel PM. NATA is described in greater detail in Chapters 2 and 3 of this RIA. Additional information can also be obtained from the NATA website (http://www.epa.gov/ttn/atw/nata1999). Based on the assessment of inhalation exposures associated with outdoor sources of these hazardous air pollutants, NATA has identified cancer and noncancer risk drivers on a national and regional scale (Table 1.1.-3). A cancer risk driver on a national scale is a hazardous air pollutant for which at least 25 million people are exposed to risk greater than ten in one million. Benzene is the only compound identified in the 1999 NATA as a national cancer risk driver.[C] A cancer risk driver on a regional scale is a hazardous air pollutant for which at least one million people are exposed to risk greater than ten in one million or at least 10,000 people are exposed to risk greater than 100 in one million. Twelve compounds (or groups of compounds in the case of POM) were identified as regional cancer risk drivers. The 1999 NATA concludes that diesel particulate matter is among the substances that pose the greatest relative risk, although the cancer risk cannot be quantified.

A noncancer risk driver at the national scale is a hazardous air pollutant for which at least 25 million people are exposed at a concentration greater than the inhalation reference concentration. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. Acrolein is the only compound identified in the 1999 NATA as a national noncancer risk driver.[D] A noncancer risk driver on a regional scale is defined as a hazardous air pollutant for which at least 10,000 people are exposed to an ambient concentration greater than the inhalation reference concentration.

[A] It is, of course, not necessary for EPA to show that a compound is a national or regional risk driver to show that its emission from motor vehicles may reasonably cause or contribute to endangerment of public health or welfare. A showing that motor vehicles contribute some non-trivial percentage of the inventory of a compound known to be associated with adverse health effects would normally be sufficient. Cf. Bluewater Network v. EPA, 370 F. 3d 1, 15 (D.C. Cir. 2004).

[B] The discussion here considers risks other than those attributed to ambient levels of criteria pollutants.

[C] Benzene was assigned an overall confidence level of "higher" based on consideration of the combined uncertainties from the modeling estimates.

[D] Acrolein was assigned an overall confidence level of "lower" based on consideration of the combined uncertainties from the modeling estimates.

Sixteen regional-scale noncancer risk drivers were identified in the 1999 NATA (see Table 1.1.-3.).

Table 1.1.-3. National and Regional Cancer and Noncancer Risk Drivers in 1999 NATA

Cancer [1]	Noncancer
National drivers [2]	**National drivers** [4]
Benzene[H]	Acrolein[L]
Regional drivers [3]	**Regional drivers** [5]
Arsenic compounds[L]	Antimony[H]
Benzidine[L]	Arsenic compounds[L]
1,3-Butadiene[L]	1,3-Butadiene[L]
Cadmium compounds[L]	Cadmium compounds[L]
Carbon tetrachloride[H]	Chlorine[L]
Chromium VI[L]	Chromium VI[L]
Coke oven[M]	Diesel PM[M]
Ethylene oxide[H]	Formaldehyde[M]
Hydrazine[M]	Hexamethylene 1-6-diisocyanate[M]
Naphthalene[M]	Hydrazine[H]
Perchloroethylene[M]	Hydrochloric acid[L]
Polycyclic organic matter[M]	Maleic anhydride[L]
	Manganese compounds[L]
	Nickel compounds[L]
	2,4-Toluene diisocyanate[L]
	Triethylamine[L]

[1]The list of cancer risk drivers does not include diesel particulate matter. However, the 1999 NATA concluded that it was one of the pollutants that posed the greatest relative cancer risk.
[2] At least 25 million people exposed to risk >10 in 1 million
[3] At least 1 million people exposed to risk >10 in 1 million or at least 10,000 people exposed to risk >100 in 1 million
[4] At least 25 million people exposed to a hazard quotient > 1.0
[5] At least 10,000 people exposed to a hazard quotient > 1
EPA has assigned an overall confidence level for each pollutant in NATA based on consideration of the combined uncertainties from emissions estimation, ambient concentration modeling, and exposure modeling. These judgments refer to the relative confidence between two air toxics compounds. A judgment of "Higher" (H) means the confidence is higher for this compound than for compounds assigned a "Medium" (M) or "Lower" (L).

It should be noted that varying levels of confidence are associated with risk estimates for individual pollutants, based on the quality of the data used to estimate emissions, ambient concentrations and exposure. For the pollutants included in NATA, EPA rated its confidence inrisk estimates, based on the quality of the data used for emissions, air quality, and exposure modeling, as high, medium, or lower. EPA has a high level of confidence in the data for benzene, medium confidence in the data for formaldehyde, but lower confidence in data for 1,3-butadiene and acrolein.

1.1.4.2. 1999 NATA Risk Drivers with Significant Mobile Source Contribution

Among the national and regional-scale cancer and noncancer risk drivers identified in the 1999 NATA, seven compounds have significant contributions from mobile sources: benzene, 1,3-butadiene, formaldehyde, acrolein, polycyclic organic matter (POM), naphthalene, and diesel particulate matter and diesel exhaust organic gases (Table 1.1.-4.). For example, mobile sources contribute 68% of the national benzene inventory, with 49% from on-road sources and 19% from nonroad sources based on 1999 NATA data.

Table 1.1.-4. Mobile Source Contribution to 1999 NATA Risk Drivers

1999 NATA Risk Drivers	Percent Contribution from All Mobile Sources	Percent Contribution from On-road Mobile Sources
Benzene[H]	68%	49%
1,3-Butadiene[L]	58%	41%
Formaldehyde[M]	47%	27%
Acrolein[L]	25%	14%
Polycyclic organic matter*[M]	6%	3%
Naphthalene[M]	27%	21%
Diesel PM and Diesel exhaust organic gases[M]	100%	38%

*This POM inventory includes the 15 POM compounds: benzo[b]fluoranthene, benz[a]anthracene, indeno(1,2,3-c,d)pyrene, benzo[k]fluoranthene, chrysene, benzo[a]pyrene, dibenz(a,h)anthracene, anthracene, pyrene, benzo(g,h,i)perylene, fluoranthene, acenaphthylene, phenanthrene, fluorene, and acenaphthene.

EPA has assigned an overall confidence level for each pollutant in NATA based on consideration of the combined uncertainties from emissions estimation, ambient concentration modeling, and exposure modeling. These judgments refer to the relative confidence between two air toxics compounds. A judgment of "Higher" (H) means the confidence is higher for this compound than for compounds assigned a "Medium" (M) or "Lower" (L).

1.2. Dose-Response and Agency Risk Assessment Practice

This section describes EPA's formal process for conducting risk assessment. The EPA framework for assessing and managing risks reflects the risk assessment and risk management paradigm set forth by the National Academy of Sciences in 1983[3] which was incorporated into the 1986 EPA risk guidance[4] and revised in 2005 in the EPA Guidelines for Carcinogen Risk Assessment and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens.[5] The paradigm divides the risk assessment and management process into four general phases. The first three phases (exposure assessment, dose-response assessment, and risk characterization) comprise risk assessment. The fourth phase, risk management, involves evaluation of information provided by the risk assessment to the environmental manager who makes a risk management decision.

An exposure assessment is the quantitative or qualitative evaluation of contact to a specific pollutant and includes such characteristics as intensity, frequency, and duration of contact. The numerical output of an exposure assessment may be either exposure or dose, depending on the purpose of the evaluation and available data.

The dose-response assessment produces two sequential analyses. The first analysis is the hazard identification, which identifies contaminants that are suspected to pose health hazards, describes the specific forms of toxicity (e.g., neurotoxicity, carcinogenicity, etc.) that they may cause, and evaluates the conditions under which these forms of toxicity might be expressed in exposed humans. The types of effects that are relevant to a particular chemical (e.g., cancer, noncancer) are determined as part of the hazard identification.

The second analysis is the human health dose-response assessment, which generally describes the characterization of the relationship between the concentration, exposure, or dose of a pollutant and the resultant health effects. Dose-response assessment methods generally consist of two parts. First is the evaluation of the experimentally observed relationship between health effects and the concentration, exposure and/or dose of a particular compound, and second is the extrapolation from the observed range to lower doses and risks.

1.2.1. Cancer

The term 'cancer' is used to describe a group of related diseases that affect a variety of organs and tissues. Cancer results from a combination of genetic damage and nongenetic factors that favor the growth of damaged cells. The EPA document, *Guidelines for Carcinogen Risk Assessment*[6] (2005) provides guidance on hazard identification for carcinogens. The approach recognizes three broad categories of data: (1) human data (primarily, epidemiological); (2) results of long-term experimental animal bioassays; and (3) supporting data, including a variety of short-term tests for genotoxicity and other relevant properties. The 2005 Guidelines for hazard identification recommend that an agent's human carcinogenic potential be described in a weight-of-evidence

narrative. The narrative summarizes the full range of available evidence and describes any conditions associated with conclusions about an agent's hazard potential (e.g., carcinogenic by some routes of exposure and not others). To provide additional clarity and consistency in weight-of-evidence narratives, the Guidelines suggest a set of weight-of-evidence descriptors to accompany the narratives. The five descriptors are: Carcinogenic to Humans, Likely to be Carcinogenic to Humans, Suggestive Evidence of Carcinogenic Potential, Inadequate Information to Assess Carcinogenic Potential, and Not Likely to be Carcinogenic to Humans. These descriptors replace those based on the EPA 1986 Risk Assessment Guidelines which classified a compound as Group A: Carcinogenic to Humans, Group B: Probably Carcinogenic to Humans, Group C: Possibly Carcinogenic to Humans, Group D: Not Classifiable as to Human Carcinogenicity, or Group E: Evidence of Noncarcinogenicity for Humans.

A quantitative assessment is performed depending on the weight-of-evidence and the suitability of the available information regarding a relationship between the dose of a compound and the effect it causes (dose-response data). Dose-response models are used to calculate unit risk estimates (URE). Inhalation cancer risks are quantified by EPA using the unit risk, which represent the excess lifetime cancer risk estimated to result from continuous lifetime exposure to an agent at a concentration of 1 $\mu g/m^3$ in air. These unit risks are typically upper-bound estimates, although where there are adequate epidemiological data, the unit risk may be based on a maximum likelihood estimate (MLE). Except for benzene and chromium, where risks are based on maximum likelihood dose-response values, risks from mobile source air toxics should all be considered upper-bound values. This means they are plausible upper limits to risks. True risks could be greater, but are likely to be lower, and could be zero. A discussion of the confidence in a quantitative cancer risk estimate is provided in the IRIS file for each compound. The discussion of the confidence in the cancer risk estimate includes an assessment of the source of the data (human or animal), uncertainties in dose estimates, choice of the model used to fit the exposure and response data and how uncertainties and potential confounders are handled.

The 2005 Guidelines include Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens.[7] The Supplemental Guidance is part of EPA's response to the recommendation of the National Research Council (1994) that "EPA should assess risks to infants and children whenever it appears that their risks might be greater than those of adults." For several potential carcinogens, there is some evidence of higher cancer risks following early-life exposure. Accordingly, the Supplemental Guidance describes the approaches that EPA could use in assessing cancer risks following early-life exposures. The 1999 NATA does not include default adjustments for early life exposures recently recommended in the Supplemental Guidance. Incorporation of such adjustments, if needed, would lead to higher estimates of lifetime risk.

1.2.2. Chronic Exposure and Noncancer Health Effects

Noncancer effects resulting from chronic exposures include a wide range of effects in many organ systems, e.g., respiratory, cardiovascular, immune, kidney. Hazard identification procedures for chronic noncancer effects are described in EPA guidelines. The EPA has published guidelines for assessing several specific types of noncancer effects, including mutagenicity,[8] developmental toxicity,[9] neurotoxicity[10]; and reproductive toxicity.[11] For identification of hazards resulting from long-term (chronic) exposures, EPA reviews available data on different health endpoints and target organs and describes the range of effects observed and the related dose/exposure levels. EPA focuses particular attention to effects that occur at relatively low doses or that may have particular relevance to human populations. The inhalation reference concentration (RfC) and oral reference dose (RfD) are the Agency consensus quantitative toxicity values for use in chronic noncancer risk assessment. The RfC or RfD is defined as an estimate, with uncertainty spanning perhaps an order of magnitude, of an inhalation exposure/oral dose to the human population (including sensitive subgroups) that is likely to be without appreciable risks of deleterious effects during a lifetime. The RfC or RfD is derived using 1) a thorough review of the health effects database for an individual chemical and 2) the most sensitive and relevant endpoint and the principal study(ies) demonstrating that endpoint. RfCs for inhalation are derived according to the Agency's 1994 guidance.[12] A statement regarding the confidence in the RfC and/or RfD is developed to reflect the confidence in the principal study or studies on which the RfC or RfD are based and the confidence in the underlying database. Factors that affect the confidence in the principal study include how well the study was designed, conducted and reported. Factors that affect the confidence in the database include an assessment of the availability of information regarding identification of the critical effect, potentially susceptible populations and exposure scenarios relevant to assessment of risk. In 2002 an EPA RfC/RfD Technical Panel prepared several recommendations for preparation of noncancer reference values.[13]

1.2.3. Acute Exposure and Noncancer Health Effects

Noncancer health impacts resulting from acute (short-term) exposures have been assessed for many compounds in the occupational setting. EPA currently does not have acute exposures reference values in IRIS comparable to the RfC described above. EPA's Office of Research and Development proposed an Acute Reference Exposure (ARE) approach for evaluating short term exposure effects in 1998.[14] In 2002 EPA completed a review document which summarizes recommendations of the EPA RfC/RfD Technical Panel for preparation of noncancer reference values including acute exposure values.[15] In response to the EPA Science Advisory Board review of the Acute Reference Exposure methodology and recommendations from EPA's RfC/RfD Technical Panel, ORD is currently developing an advanced acute inhalation reference concentration (acute RfC) methodology. As part of this new methodology, acute inhalation assessments are being developed for a few selected compounds including acrolein and hydrogen sulfide.

1.3. Summary of Air Toxic Health Effects

From a public health perspective, it is important to assess the emission contributions to atmospheric levels of various air toxics (including diesel PM and exhaust organic gases) emitted by motor vehicle engines, including their physical properties, sources of potential exposure, and health hazards. In this section, we describe the cancer and noncancer health effects attributed to chronic exposure to various mobile source air toxics as well as any acute exposure health effects, where data are available. We focus here on the air toxics that are identified in the NATA as risk drivers (see Section 1.1) and that account for a significant share of mobile sources emissions. We also consider compounds for which we expect emission reductions from today's proposed rule. We are also including diesel particulate matter and diesel exhaust organic gases in this discussion. EPA has concluded that diesel exhaust ranks with the other substances that the national-scale assessment suggests pose the greatest relative risk.

1.3.1. Benzene

Benzene is an aromatic hydrocarbon that is present as a gas in both exhaust and evaporative emissions from mobile sources. Inhalation is the major source of human exposure to benzene in the occupational and non-occupational setting.

The EPA's IRIS database lists benzene as a known human carcinogen (causing leukemia) by all routes of exposure.[16] A number of adverse noncancer health effects including blood disorders and immunotoxicity, have also been associated with long-term occupational exposure to benzene.

Long-term occupational inhalation exposure to benzene has been shown to cause cancers of the hematopoetic (blood cell) system in adults. Among these are acute nonlymphocytic leukemia,[E] and chronic lymphocytic leukemia.[17,18] A doubling of risk for acute nonlymphocytic leukemia and myelodysplastic syndrome was found at average exposure levels under 10 ppm (32 mg/m^3).[19] EPA has not formally evaluated this study as part of the IRIS review process. Leukemias, lymphomas, and other tumor types have been observed in experimental animals exposed to benzene by inhalation or oral administration. Exposure to benzene and/or its metabolites has also been linked with

[E] Leukemia is a blood disease in which the white blood cells are abnormal in type or number. Leukemia may be divided into nonlymphocytic (granulocytic) leukemias and lymphocytic leukemias. Nonlymphocytic leukemia generally involves the types of white blood cells (leukocytes) that are involved in engulfing, killing, and digesting bacteria and other parasites (phagocytosis) as well as releasing chemicals involved in allergic and immune responses. This type of leukemia may also involve erythroblastic cell types (immature red blood cells). Lymphocytic leukemia involves the lymphocyte type of white blood cell that is responsible for antibody and cell-mediated immune responses. Both nonlymphocytic and lymphocytic leukemia may, in turn, be separated into acute (rapid and fatal) and chronic (lingering, lasting) forms. For example; in acute myeloid leukemia there is diminished production of normal red blood cells (erythrocytes), granulocytes, and platelets (control clotting), which leads to death by anemia, infection, or hemorrhage. These events can be rapid. In chronic myeloid leukemia (CML) the leukemic cells retain the ability to differentiate (i.e., be responsive to stimulatory factors) and perform function; later there is a loss of the ability to respond.

chromosomal changes in humans and animals[20, 21] and increased proliferation of mouse bone marrow cells.[22, 23]

The latest assessment by EPA estimates the excess risk of developing leukemia from inhalation exposure to benzene at 2.2×10^{-6} to 7.8×10^{-6} per $\mu g/m^3$. In other words, there is an estimated risk of about two to eight excess leukemia cases in one million people exposed to 1 $\mu g/m^3$ of benzene over a lifetime.[24] This range of unit risks reflects the MLEs calculated from different exposure assumptions and dose-response models that are linear at low doses. At present, the true cancer risk from exposure to benzene cannot be ascertained, even though dose-response data are used in the quantitative cancer risk analysis, because of uncertainties in the low-dose exposure scenarios and lack of clear understanding of the mode of action. A range of estimates of risk is recommended, each having equal scientific plausibility. There are confidence intervals associated with the MLE range that reflect random variation of the observed data. For the upper end of the MLE range, the 5th and 95th percentile values are about a factor of 5 lower and higher than the best fit value. The upper end of the MLE range (7.8×10^{-6} per $\mu g/m^3$) was used in the 1999 NATA.

It should be noted that not enough information is known to determine the slope of the dose-response curve at environmental levels of exposure and to provide a sound scientific basis to choose any particular extrapolation/exposure model to estimate human cancer risk at low doses. EPA risk assessment guidelines suggest using an assumption of linearity of dose response when (1) there is an absence of sufficient information on modes of action or (2) the mode of action information indicates that the dose-response curve at low dose is or is expected to be linear.[25] Data that were considered by EPA in its carcinogenic update suggested that the dose-response relationship at doses below those examined in the studies reviewed in EPA's most recent benzene assessment may be supralinear. This relationship could support the inference that cancer risks are as high, or higher than the estimates provided in the existing EPA assessment.[26] However, since the mode of action for benzene carcinogenicity is unknown, the current cancer unit risk estimate assumes linearity of the low-dose response. Data discussed in the EPA IRIS assessment suggest that genetic abnormalities occur at low exposure in humans, and the formation of toxic metabolites plateaus above 25 ppm (80,000 $\mu g/m^3$).[27] More recent data on benzene adducts in humans, published after the most recent IRIS assessment, suggest that the enzymes involved in benzene metabolism start to saturate at exposure levels as low as 1 ppm.[28,29,30] These data highlight the importance of ambient exposure levels and their contribution to benzene-related adducts. Because there is a transition from linear to saturable metabolism below 1 ppm, the assumption of low-dose linearity extrapolated from much higher exposures could lead to substantial underestimation of leukemia risks. This is consistent with recent epidemiological data which also suggest a supralinear exposure-response relationship and which "[extend] evidence for hematopoietic cancer risks to levels substantially lower than had previously been established".[31,32,33] These data are from the largest cohort study done to date with individual worker exposure estimates. However, these data have not yet been formally evaluated by EPA as part of the IRIS review process, and it is not clear how they might influence low-dose risk estimates. A better understanding of the

biological mechanism of benzene-induced leukemia is needed.

Children may represent a subpopulation at increased risk from benzene exposure, due to factors that could increase their susceptibility. Children may have a higher unit body weight exposure because of their heightened activity patterns which can increase their exposures, as well as different ventilation tidal volumes and frequencies, factors that influence uptake. This could entail a greater risk of leukemia and other toxic effects to children if they are exposed to benzene at similar levels as adults. There is limited information from two studies regarding an increased risk to children whose parents have been occupationally exposed to benzene.[34,35] Data from animal studies have shown benzene exposures result in damage to the hematopoietic (blood cell formation) system during development.[36, 37, 38] Also, key changes related to the development of childhood leukemia occur in the developing fetus.[39] Several studies have reported that genetic changes related to eventual leukemia development occur before birth. For example, there is one study of genetic changes in twins who developed T cell leukemia at 9 years of age.[40] An association between traffic volume, residential proximity to busy roads and occurrence of childhood leukemia has also been identified in some studies, although some studies show no association. These studies are discussed later in Chapter 3.

A number of adverse noncancer health effects, including blood disorders such as preleukemia and aplastic anemia, have also been associated with long-term exposure to benzene.[41,42] People with long-term occupational exposure to benzene have experienced harmful effects on the blood-forming tissues, especially in the bone marrow. These effects can disrupt normal blood production and suppress the production of important blood components, such as red and white blood cells and blood platelets, leading to anemia (a reduction in the number of red blood cells), leukopenia (a reduction in the number of white blood cells), or thrombocytopenia (a reduction in the number of blood platelets, thus reducing the ability of blood to clot). Chronic inhalation exposure to benzene in humans and animals results in pancytopenia,[F] a condition characterized by decreased numbers of circulating erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (blood platelets).[43, 44] Individuals that develop pancytopenia and have continued exposure to benzene may develop aplastic anemia, whereas others exhibit both pancytopenia and bone marrow hyperplasia (excessive cell formation), a condition that may indicate a preleukemic state.[45, 46] The most sensitive noncancer effect observed in humans, based on current data, is the depression of the absolute lymphocyte count in blood.[47, 48]

EPA's inhalation reference concentration (RfC) for benzene is 30 $\mu g/m^3$. The overall confidence in this RfC is medium. The RfC is based on suppressed absolute lymphocyte counts seen in humans under occupational exposure conditions. Since

[F] Pancytopenia is the reduction in the number of all three major types of blood cells (erythrocytes, or red blood cells, thrombocytes, or platelets, and leukocytes, or white blood cells). In adults, all three major types of blood cells are produced in the bone marrow of the skeletal system. The bone marrow contains immature cells, known as multipotent myeloid stem cells, that later differentiate into the various mature blood cells. Pancytopenia results from a reduction in the ability of the red bone marrow to produce adequate numbers of these mature blood cells.

development of this RfC, there have appeared reports in the medical literature of benzene's hematotoxic effects in humans that provide data suggesting a wide range of hematological endpoints that are triggered at occupational exposures of less than 5 ppm (about 16 mg/m^3)[49] and, more significantly, at air levels of 1 ppm (about 3 mg/m^3) or less among genetically susceptible populations.[50] These studies had large sample sizes and extensive individual exposure monitoring. One recent study found benzene metabolites in mouse liver and bone marrow at environmental doses, indicating that even concentrations in urban air may elicit a biochemical response in rodents that indicates toxicity.[51] EPA has not formally evaluated these recent studies as part of the IRIS review process to determine whether or not they will lead to a change in the current RfC. EPA does not currently have an acute reference concentration for benzene. The Agency for Toxic Substances and Disease Registry Minimal Risk Level for acute exposure to benzene is 160 µg/m^3 for 1-14 days exposure.

1.3.2. 1,3-Butadiene

1,3-butadiene is formed in engine exhaust by the incomplete combustion of fuel. It is not present in engine evaporative emissions because it is not generally present in an appreciable amount in vehicle fuels.

EPA has characterized 1,3-butadiene as a leukemogen, carcinogenic to humans by inhalation. [52, 53] The specific mechanisms of 1,3-butadiene-induced carcinogenesis are unknown however, it is virtually certain that the carcinogenic effects are mediated by genotoxic metabolites of 1,3-butadiene. Animal data suggest that females may be more sensitive than males for cancer effects; nevertheless, there are insufficient data from which to draw any conclusions on potentially sensitive subpopulations. The upper bound cancer unit risk estimate is 0.08 per ppm or $3x10^{-5}$ per µg/m^3 (based primarily on linear modeling and extrapolation of human data). In other words, it is estimated that approximately 30 persons in one million exposed to 1 µg/m^3 of 1,3-butadiene continuously for their lifetime would develop cancer as a result of this exposure. The human incremental lifetime unit cancer risk estimate is based on extrapolation from leukemias observed in an occupational epidemiologic study.[54, 55, 56] This estimate includes a two-fold adjustment to the epidemiologic-based unit cancer risk applied to reflect evidence from the rodent bioassays suggesting that the epidemiologic-based estimate (from males) may underestimate total cancer risk from 1,3-butadiene exposure in the general population, particularly for breast cancer in females.[57]

A recent study extended the investigation of 1,3-butadiene exposure and leukemia among synthetic rubber industry workers.[58] The results of this study strengthen the evidence for the relationship between 1,3-butadiene exposure and lymphohematopoietic cancer. This relationship was found to persist after controlling for exposure to other toxics in this work environment.

1,3-Butadiene also causes a variety of reproductive and developmental effects in mice; no human data on these effects are available. The most sensitive effect was ovarian atrophy observed in a lifetime bioassay of female mice.[59] Based on this critical effect

and the benchmark concentration methodology, an RfC for chronic health effects was calculated at 0.9 ppb (approximately 2 $\mu g/m^3$). Confidence in the inhalation RfC is medium.

1.3.3. Formaldehyde

Formaldehyde is the most prevalent aldehyde in engine exhaust. It is formed as a result of incomplete fuel combustion in both gasoline and diesel engines, although formaldehyde accounts for a smaller quantity of total exhaust hydrocarbons from gasoline engines. Formaldehyde emissions can vary substantially by engine duty cycle, emission control system and composition of fuel. Formaldehyde is not a component of evaporative emissions but it can be formed photochemically in the atmosphere.

Since 1987, EPA has classified formaldehyde as a probable human carcinogen based on evidence in humans and in rats, mice, hamsters, and monkeys.[60] EPA's current IRIS summary provides an upper bound cancer unit risk estimate of $1.3x10^{-5}$ per $\mu g/m^3$.[G] In other words, there is an estimated risk of about thirteen excess leukemia cases in one million people exposed to 1 $\mu g/m^3$ of formaldehyde over a lifetime. EPA is currently reviewing recently published epidemiological data. For instance, research conducted by the National Cancer Institute (NCI) found an increased risk of nasopharyngeal cancer and lymphohematopoietic malignancies such as leukemia among workers exposed to formaldehyde.[61, 62] NCI is currently performing an update of these studies. A recent National Institute of Occupational Safety and Health (NIOSH) study of garment workers also found increased risk of death due to leukemia among workers exposed to formaldehyde.[63] Extended follow-up of a cohort of British chemical workers did not find evidence of an increase in nasopharyngeal or lymphohematopoeitic cancers, but a continuing statistically significant excess in lung cancers was reported.[64]

Based on the developments of the last decade, in 2004, the working group of the International Agency for Research on Cancer concluded that formaldehyde is carcinogenic to humans (Group 1 classification), on the basis of sufficient evidence in humans and sufficient evidence in experimental animals—a higher classification than previous IARC evaluations. In addition, the National Institute of Environmental Health Sciences recently nominated formaldehyde for reconsideration as a known human carcinogen under the National Toxicology Program. Since 1981 it has been listed as a "reasonably anticipated human carcinogen." Recently the German Federal Institute for Risk Assessment determined that formaldehyde is a known human carcinogen.[65]

In the past 15 years there has been substantial research on the inhalation dosimetry for formaldehyde in rodents and primates by the CIIT Centers for Health Research (formerly the Chemical Industry Institute of Toxicology), with a focus on use of rodent data for refinement of the quantitative cancer dose-response assessment.[66,67,68] CIIT's risk assessment of formaldehyde incorporated mechanistic and dosimetric information on formaldehyde. The risk assessment analyzed carcinogenic risk from

[G] U.S. EPA (1989). Integrated Risk Information System File for Formaldehyde. This material is available electronically at http://www.epa.gov/iris/subst/0419.htm.

inhaled formaldehyde using approaches that are consistent with EPA's draft guidelines for carcinogenic risk assessment. In 2001, Environment Canada relied on this cancer dose-response assessment in their assessment of formaldehyde.[69] In 2004, EPA also relied on this cancer unit risk estimate during the development of the plywood and composite wood products national emissions standards for hazardous air pollutants (NESHAPs).[70] In these rules, EPA concluded that the CIIT work represented the best available application of the available mechanistic and dosimetric science on the dose-response for portal of entry cancers due to formaldehyde exposures. EPA is reviewing the recent work cited above from the NCI and NIOSH, as well as the analysis by the CIIT Centers for Health Research and other studies, as part of a reassessment of the human hazard and dose-response associated with formaldehyde.

Noncancer effects of formaldehyde have been observed in humans and several animal species and include irritation to eye, nose and throat tissues in conjunction with increased mucous secretions.[71]

1.3.4. Acetaldehyde

Acetaldehyde is formed as a result of incomplete fuel combustion in both gasoline and diesel engines, although acetaldehyde accounts for a smaller quantity of total exhaust hydrocarbons from gasoline engines. Acetaldehyde emissions can vary substantially by engine duty cycle, emission control system and composition of fuel. Acetaldehyde is not a component of evaporative emissions but it can be formed photochemically in the atmosphere.

Acetaldehyde is classified in EPA's IRIS database as a probable human carcinogen and is considered toxic by inhalation.[72] Based on nasal tumors in rodents, the upper confidence limit estimate of a lifetime extra cancer risk from continuous acetaldehyde exposure is about 2.2×10^{-6} per $\mu g/m^3$. In other words, it is estimated that about 2 persons in one million exposed to 1 $\mu g/m^3$ acetaldehyde continuously for their lifetime (70 years) would develop cancer as a result of their exposure although the risk could be as low as zero.

In short-term (4 week) rat studies, compound-related histopathological changes were observed only in the respiratory system at various concentration levels of exposure.[73, 74] Data from these studies showing degeneration of the olfactory epithelium were found to be sufficient for EPA to develop an RfC for acetaldehyde of 9 $\mu g/m^3$. Confidence in the principal study is medium and confidence in the database is low, due to the lack of chronic data establishing a no observed adverse effect level and due to the lack of reproductive and developmental toxicity data. Therefore, there is low confidence in the RfC.[75] The Agency is currently conducting a reassessment of risk from inhalation exposure to acetaldehyde.

The primary acute effect of exposure to acetaldehyde vapors is irritation of the eyes, skin, and respiratory tract.[76] Some asthmatics have been shown to be a sensitive

subpopulation to decrements in functional expiratory volume (FEV1 test) and broncho-constriction upon acetaldehyde inhalation.[77]

1.3.5. Acrolein

Acrolein is found in vehicle exhaust and is formed as a result of incomplete combustion of both gasoline and diesel fuel. It is not a component of evaporative emissions but it can be formed photochemically from 1,3-butadiene in the atmosphere.

EPA determined in 2003 using the 1999 draft cancer guidelines that the human carcinogenic potential of acrolein could not be determined because the available data were inadequate. No information was available on the carcinogenic effects of acrolein in humans and the animal data provided inadequate evidence of carcinogenicity.

Acrolein is an extremely volatile organic compound which possesses considerable water solubility.[78] As such, it readily absorbs into airway fluids in the respiratory tract when inhaled. The toxicological data base demonstrating the highly irritating nature of this vapor has been consistent, regardless of test species. Acrolein is intensely irritating to humans when inhaled, with acute exposure resulting in upper respiratory tract irritation, mucus hypersecretion and congestion.

Lesions to the lungs and upper respiratory tract of rats, rabbits, and hamsters exposed to acrolein formed the basis of the reference concentrations for inhalation (RfC) developed in 2003.[79] The Agency has developed an RfC for acrolein of 0.02 $\mu g/m^3$ and an RfD of 0.5 ug/kg-day.[80] The overall confidence in the RfC assessment is judged to be medium and the confidence in the RfD is medium to high.

The Agency is currently in the process of conducting an assessment of acute exposure effects for acrolein. The intense irritancy of this carbonyl has been demonstrated during controlled tests in human subjects who suffer intolerable eye and nasal mucosal sensory reactions within minutes of exposure.[81]

1.3.6. Naphthalene

Naphthalene is found in small quantities in gasoline and diesel fuels. Naphthalene emissions have been measured in larger quantities in both gasoline and diesel exhaust and evaporative emissions from mobile sources.

In 2004, EPA released an external review draft of a reassessment of the inhalation carcinogenicity of naphthalene.[82] The draft reassessment (External Review Draft, IRIS Reassessment of the Inhalation Carcinogenicity of Naphthalene) completed external peer review in 2004 by Oak Ridge Institute for Science and Education.[83] Based on external comments, additional analyses are being considered. California EPA has released a new risk assessment for naphthalene with a cancer unit risk estimate of $3x10^{-5}$ per $\mu g/m^3$.[84] The California EPA value was used in the 1999 NATA and in the analyses done for this rule. In addition, IARC has reevaluated naphthalene and re-classified it as Group 2B:

possibly carcinogenic to humans.[85] Current risk estimates for naphthalene are based on extrapolations from rodent studies conducted at higher doses. At present, human data are inadequate for developing estimates.

The current EPA IRIS assessment includes noncancer data on hyperplasia and metaplasia in nasal tissue that form the basis of the inhalation RfC of 3 $\mu g/m^3$.[86] The principal study was given medium confidence because adequate numbers of animals were used, and the severity of nasal effects increased at the higher exposure concentration. However, the study produced high mortality and hematological evaluation was not conducted beyond 14 days. The database was given a low-to-medium confidence rating because there are no chronic or subchronic inhalation studies in other animal species, and there are no reproductive or developmental studies for inhalation exposure. In the absence of human or primate toxicity data, the assumption is made that nasal responses in mice to inhaled naphthalene are relevant to humans; however, it cannot be said with certainty that this RfC for naphthalene based on nasal effects will be protective for hemolytic anemia and cataracts, the more well-known human effects from naphthalene exposure. As a result, we have medium confidence in the RfC.

1.3.7. 2,2,4-Trimethylpentane

2,2,4-Trimethylpentane is a colorless liquid hydrocarbon also known as isooctane, isobutyltrimethylmethane, and TMP. Automotive exhaust and automotive evaporative emissions are important sources of 2,2,4-trimethylpentane in the atmosphere.

EPA is in the process of assembling a review draft of a reassessment of its 1991 2,2,4-TMP health effects assessment in EPA's IRIS database. The earlier document found little conclusive evidence of specific health effects associated with 2,2,4-TMP exposures in humans.[87] Overall, there was "inadequate information to assess carcinogenic potential," in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986), for 2,2,4-trimethylpentane. No chronic bioassay studies were available that assessed the carcinogenic effects of 2,2,4-trimethylpentane in humans.

Oral studies existed linking 2,2,4-TMP with male rat kidney toxicity and an increase in $alpha_{2u}$-globulin protein and hyaline droplet accumulation in the proximal tubules of the kidneys.[88] These effects were not seen in the female rat test subjects. These renal effects, specific to the male rat, are not thought to be relevant to humans. Inhalation studies in animals had been performed but none were adequate to calculate an inhalation RfC for the compound.

1.3.8. Ethylbenzene

Ethylbenzene is present as in both gasoline and diesel exhaust and in evaporative emissions from gasoline-powered vehicles.[89] Limited information is available on the carcinogenic effects of ethylbenzene in humans and animals. Under the 1987 Cancer Guidelines, EPA has classified ethylbenzene as a Group D carcinogen, meaning it is not classifiable as to human carcinogenicity. This classification is the result of inadequate

data from animal bioassays and human studies.[90]

Chronic (long-term) exposure to ethylbenzene by inhalation in humans may result in effects on the blood, kidney and liver. No information is available on the developmental or reproductive effects of ethylbenzene in humans, although animal studies have reported developmental effects via inhalation. The data from these studies were found to be sufficient for EPA to develop an RfC of $1x10^3$ ug/m^3 for ethylbenzene exposure. Confidence in the RfC is considered low because higher study exposure levels might have been more informative and no chronic studies or multi-generational developmental studies were available at the time. Animal studies have reported effects on the blood, liver, and kidneys from ingestion exposure to ethylbenzene. The data from these studies were found to be sufficient for EPA to develop an RfD for ethylbenzene exposure of 100 ug/kg-day. Confidence in this RfD is considered low because rats of only one sex were tested, no chronic studies were then available, and no other oral toxicity data were found. Ethylbenzene is currently undergoing an IRIS update for both cancer and noncancer effects, based on new data.

Acute (short-term) exposure to ethylbenzene in humans results in noncancer respiratory effects, such as throat irritation and chest constriction, irritation of the eyes, and neurological effects such as dizziness.[91]

1.3.9. n-Hexane

n-Hexane is a component of gasoline and is also found in exhaust and evaporative emissions from motor vehicles. Monitoring data indicate that n-hexane occurs widely in the atmosphere.[92]

Under the 2005 Guidelines for Carcinogen Risk Assessment, there is inadequate information to assess the carcinogenic potential of n-hexane.[93] Chronic exposure to n-hexane in air is associated with polyneuropathy in humans, with numbness in the extremities, muscular weakness, blurred vision, headache, and fatigue observed. Neurotoxic effects have also been exhibited in rats. Mild inflammatory and degenerative lesions in the nasal cavity have been observed in rodents chronically exposed by inhalation. Limited information is available on the reproductive or developmental effects of n-hexane; one study reported testicular damage in rats exposed to n-hexane through inhalation. Birth defects have not been observed in the offspring of rats chronically exposed via inhalation in several studies. The data from a study of peripheral neuropathy was used to develop an RfC of 700 ug/m^3 for n-hexane exposure.[94] This RfC has been given a confidence rating of medium due to medium confidence in the underlying study and medium confidence in the database. The database lacks chronic exposure information on the pure compound via any route of exposure, a multigenerational developmental and reproductive toxicity study and a developmental neurotoxicity study.

Acute inhalation exposure of humans to high levels of n-hexane causes mild central nervous system (CNS) depression and irritation of the skin. Nervous system effects include dizziness, giddiness, slight nausea, and headache in humans.[95]

1.3.10. Methyl Tertiary Butyl Ether (MTBE)

Methyl *tert*-butyl ether (MTBE) has been used in the United States since the late-1970's as an octane-enhancing agent in gasoline.

In 1994, EPA's Office of Research and Development concluded that, under the 1986 EPA cancer risk assessment guidelines, inhalation cancer test results support placing MTBE in Group C as a "possible human carcinogen."[96] An Interagency Assessment of Oxygenated Fuels similarly concluded that "While there are no studies on the carcinogenicity of MTBE in humans, there is sufficient evidence to indicate that MTBE is an animal carcinogen and to regard MTBE as having a human hazard potential. However, estimates of human risk from MTBE contain large uncertainties in both human exposure and cancer potency."[97] The Agency is currently conducting a reassessment of MTBE.

By the inhalation route, MTBE has been found to cause increases in liver and kidney weights and increased severity of spontaneous kidney lesions, as well as swelling around the eyes and increased prostration in laboratory rats[98]. These effects are cited as the basis for EPA's current inhalation reference concentration (RfC) of 3 mg/m^3 for MTBE. The RfC has a medium to high confidence rating.

1.3.11. Styrene

Styrene is found in the exhaust from both gasoline- and diesel-powered engines. Several epidemiologic studies suggest that there may be an association between styrene exposure and an increased risk of leukemia and lymphoma. However, the evidence is inconclusive due to confounding factors. Animal studies have produced both negative and positive results. EPA is currently assessing the potential of styrene to cause cancer.

Chronic exposure of humans to styrene results in effects on the central nervous system (CNS), such as headache, fatigue, weakness, depression, peripheral neuropathy, minor effects on some kidney enzyme functions and on the blood. Human studies are inconclusive on the reproductive and developmental effects of styrene. The data from human studies looking at central nervous system effects was found to be sufficient for EPA to develop an RfC of 1 mg/m^3 for styrene exposure. The RfC is assigned an overall confidence rating of medium. Data from animal oral exposure studies was found to be sufficient for EPA to also develop an RfD of 200 ug/kg-day for styrene oral exposure. The RfD is assigned an overall confidence rating of medium.

Acute exposure to styrene results in mucous membrane and eye irritation, and central nervous system effects in humans. [99, 100]

1.3.12. Toluene

Toluene is found in evaporative as well as exhaust emissions from motor vehicles.

Under the 2005 Guidelines for Carcinogen Risk Assessment, there is inadequate information to assess the carcinogenic potential of toluene because studies of humans chronically exposed to toluene are inconclusive, toluene was not carcinogenic in adequate inhalation cancer bioassays of rats and mice exposed for life, and increased incidences of mammary cancer and leukemia were reported in a lifetime rat oral bioassay.[101]

The central nervous system (CNS) is the primary target for toluene toxicity in both humans and animals for acute and chronic exposures. CNS dysfunction (which is often reversible) and narcosis have been frequently observed in humans acutely exposed to low or moderate levels of toluene by inhalation; symptoms include fatigue, sleepiness, headaches, and nausea. Central nervous system depression has been reported to occur in chronic abusers exposed to high levels of toluene. Symptoms include ataxia, tremors, cerebral atrophy, nystagmus (involuntary eye movements), and impaired speech, hearing, and vision. Chronic inhalation exposure of humans to toluene also causes irritation of the upper respiratory tract, eye irritation, dizziness, headaches, and difficulty with sleep.[102]

Human studies have also reported developmental effects, such as CNS dysfunction, attention deficits, and minor craniofacial and limb anomalies, in the children of women who abused toluene during pregnancy. A substantial database examining the effects of toluene in subchronic and chronic occupationally exposed humans exists. The weight of evidence from these studies indicates neurological effects (i.e., impaired color vision, impaired hearing, decreased performance in neurobehavioral analysis, changes in motor and sensory nerve conduction velocity, headache, dizziness) as the most sensitive endpoint. The data from these human studies was found to be sufficient for EPA to develop an RfC of 5 mg/m^3 for toluene exposure. The overall confidence in this RfC is high. Additional data from animal oral exposure studies was found to be sufficient for EPA to also develop an RfD of 80 ug/kg-day for toluene oral exposure.[103] The overall confidence in the RfD is medium.

1.3.13. Xylenes

Mixed xylenes are blended into gasoline and are present in diesel fuels. Xylenes are emitted in the exhaust emissions and evaporative emissions of both gasoline- and diesel-powered engines.

Inadequate information is available on the carcinogenic effects of mixed xylenes in humans, and animal studies have been inconclusive. Under the 1999 Draft Revised Guidelines for Carcinogen Risk Assessment, data are inadequate for an assessment of the carcinogenic potential of xylenes.[104]

Chronic inhalation exposure in humans to mixed xylenes results primarily in central nervous system effects, such as headache, nausea, fatigue and also included eye and nose irritation and sore throat.[105] Animal studies have reported developmental effects, such as an increased incidence of skeletal variations in fetuses, and fetal resorptions via inhalation. EPA developed an RfC of 100 ug/m^3 for xylenes based on impaired motor coordination in rats. The confidence rating assigned to the RfC for

xylenes is medium. Data from animal oral exposure studies, looking at decreased body weight and increased mortality were found to be sufficient for EPA to develop an RfD of 200 ug/kg-day for oral xylene exposure. The RfD was assigned an overall confidence rating of medium.[106]

Acute inhalation exposure to mixed xylenes in humans results in irritation of the nose and throat, gastrointestinal effects such as nausea, vomiting, and gastric irritation, mild transient eye irritation, and neurological effects.[107]

1.3.14. Polycyclic Organic Matter (POM)

POM is a class of chemicals consisting of organic compounds having multiple benzene rings and boiling points in excess of 100 degrees Celsius. POM is a byproduct of the incomplete combustion of fossil fuels and, as such, is a component of diesel and gasoline engine emissions. At least eight of the compounds included in the class of compounds known as POM are classified by EPA as probable human carcinogens based on animal data. These include acenaphthene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, chrysene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene. One POM, naphthalene, is discussed separately in this section.

Recent studies have found that maternal exposures to polyaromatic hydrocarbons (PAHs), a subclass of POM, in a population of pregnant women were associated with several adverse birth outcomes, including low birth weight and reduced length at birth.[108] These studies are discussed later in Chapter 3.

1.3.15. Diesel Exhaust

In EPA's Diesel Health Assessment Document (HAD),[109] diesel exhaust was classified as likely to be carcinogenic to humans by inhalation at environmental exposures, in accordance with the revised draft 1996/1999 EPA cancer guidelines. A number of other agencies (National Institute for Occupational Safety and Health, the International Agency for Research on Cancer, the World Health Organization, California EPA, and the U.S. Department of Health and Human Services) have made similar classifications. EPA concluded in the Diesel HAD that it is not possible currently to calculate a cancer unit risk for diesel exhaust due to a variety of factors that limit the current studies, such as limited quantitative exposure histories in occupational groups investigated for lung cancer.

However, in the absence of a cancer unit risk, the EPA Diesel HAD sought to provide additional insight into the significance of the cancer hazard by estimating possible ranges of risk that might be present in the population. An exploratory analysis was used to characterize a possible risk range by comparing a typical environmental exposure level for highway diesel sources to a selected range of occupational exposure levels. The occupationally observed risks were then proportionally scaled according to the exposure ratios to obtain an estimate of the possible environmental risk. A number of calculations are needed to accomplish this, and these can be seen in the EPA Diesel HAD.

The outcome was that environmental risks from diesel exhaust exposure could range from a low of 10^{-4} to 10^{-5} to as high as 10^{-3}, reflecting the range of occupational exposures that could be associated with the relative and absolute risk levels observed in the occupational studies. Because of uncertainties, the analysis acknowledged that the risks could be lower than 10^{-4} or 10^{-5}, and a zero risk from diesel exhaust exposure was not ruled out.

Noncancer health effects of acute and chronic exposure to diesel exhaust emissions are also of concern to the Agency. EPA derived an RfC from consideration of four well-conducted chronic rat inhalation studies showing adverse pulmonary effects.[110, 111, 112, 113] The RfC is 5 $\mu g/m^3$ for diesel exhaust as measured by diesel PM. This RfC does not consider allergenic effects such as those associated with asthma or immunologic effects. There is growing evidence, discussed in the Diesel HAD, that diesel exhaust can exacerbate these effects, but the exposure-response data are presently lacking to derive an RfC. The EPA Diesel HAD states, "With DPM [diesel particulate matter] being a ubiquitous component of ambient PM, there is an uncertainty about the adequacy of the existing DE [diesel exhaust] noncancer database to identify all of the pertinent DE-caused noncancer health hazards" (p. 9-19).

The Diesel HAD also briefly summarizes health effects associated with ambient PM and discusses the EPA's annual National Ambient Air Quality Standard (NAAQS) of 15 $\mu g/m^3$. There is a much more extensive body of human data showing a wide spectrum of adverse health effects associated with exposure to ambient PM, of which diesel exhaust is an important component. The $PM_{2.5}$ NAAQS is designed to provide protection from the noncancer and premature mortality effects of $PM_{2.5}$ as a whole, of which diesel PM is a constituent.

1.4. Emerging Issues

Beyond the specific areas of quantifiable risk discussed above in Chapter 1.1.2, EPA is interested in emerging mobile source toxics issues that might require action in the future. The emerging issues currently under investigation by EPA are gasoline PM and metals.

1.4.1. Gasoline PM

Gasoline exhaust is a complex mixture that has not been evaluated in EPA's IRIS. Gasoline exhaust is a ubiquitous source of particulate matter, contributing to the health effects observed for ambient PM which is discussed extensively in the EPA Particulate Matter Criteria Document.[114] The PM Criteria Document notes that the PM components of gasoline and diesel engine exhaust are hypothesized, important contributors to the observed increases in lung cancer incidence and mortality associated with ambient $PM_{2.5}$.[115] Gasoline PM is also a component of near-roadway emissions that may be contributing to the health effects observed in people who live near roadways (see Chapter 3.1.3.1). There is also emerging evidence for the mutagenicity and cytotoxicity of gasoline exhaust and gasoline PM. Seagrave et al. investigated the combined particulate

and semivolatile organic fractions of gasoline and diesel engine emissions in various animal and bioassay tests.[116] The authors suggest that emissions from gasoline engines (including both the semi-volatile organic compounds and the particulate matter) are mutagenic and can induce inflammation and have cytotoxic effects.

EPA is working to improve the understanding of PM emissions from gasoline engines, including the potential range of emissions and factors that influence emissions. EPA led a large cooperative test program that recently completed testing approximately 500 randomly procured vehicles in the Kansas City metropolitan area. The purpose of this study was to determine the distribution of gasoline PM emissions from the in-use light-duty fleet. Results from this study are expected to be available shortly. This work shows how PM emissions vary for light-duty gasoline vehicles (automobiles and light-duty trucks) for different model years. It also shows how colder temperatures increase gasoline PM emissions. The data from this program are being evaluated. Some source apportionment studies in various areas of the country, including Denver and California, show gasoline and diesel PM can result in larger contributions to ambient PM than predicted by EPA emission inventories.[117,118] These source apportionment studies were one impetus behind the Kansas City study.

Another issue related to gasoline PM is the effect of mobile source on ambient PM, especially secondary PM. Ambient PM is composed of primary PM emitted directly into the atmosphere and secondary PM is formed in the atmosphere from chemical reactions in the atmosphere. Sulfates and nitrates are major examples of inorganic secondary PM, both of which have been well studied and quantified. Carbonaceous PM, from both primary PM emissions and secondary PM formed in the atmosphere, is a major source of PM, especially in urban areas. Various studies show that carbonaceous PM specifically from mobile sources is a major PM constituent in many urban areas over many portions of the country (including urban areas in the Northeast, Southeast, Midwest, and California/Washington portions of the United States). This information is included in EPA reports and various source apportionment studies.[119,120,121,122,123,124,125]

Primary carbonaceous mobile source emissions can be evaluated from emission inventories. The ambient PM levels from these emissions and secondary PM formed in the atmosphere from mobile sources can then be estimated by air quality modeling studies using the CMAQ (Community Multi-scale Air Quality) model. In addition to primary carbonaceous (organic aerosol) emissions, some specific compounds contribute to atmospheric PM loadings via formation of secondary organic aerosols (SOA). These compounds include monoterpenes and possibly isoprene and sesquiterpenes, as well as anthropogenic aromatic hydrocarbons such as toluene (and probably higher molecular weight non-aromatic hydrocarbons).

Smog chamber studies show that benzene forms SOA possibly through reactions with NOx. Prior smog chamber work[126] suggested benzene might be relatively inert in forming SOA, although this early study may not be conclusive. However, the more recent work shows that benzene does form SOA in smog chambers. This new smog chamber work shows that benzene can be oxidized in the presence of NOx to form SOA

with maximum mass of SOA being 8-25% of the mass of benzene.[127] Work is needed to determine if a tracer compound can be found for benzene SOA which might indicate how much of ambient SOA comes from benzene.

Upon release into the atmosphere, these numerous compounds can react with free radicals in the atmosphere to form SOA. While SOA formation from many reactive hydrocarbons has been investigated in the laboratory, there is relatively little information available on the chemical composition of SOA compounds from specific hydrocarbon precursors. This lack of information is largely due to having few reliable methods for measuring the polar, high molecular weight compounds that are thought to make up much of ambient SOA. The absence of compositional data has largely prevented identifying aromatically-derived SOA in ambient samples which, in turn, has prevented observation-based measurements of the aromatic and other SOA contributions to ambient PM levels.

Recently EPA has taken the first step in addressing these issues by developing a tracer-based method for detecting SOA precursors in ambient samples. The method consists of irradiating the SOA precursor of interest in a smog chamber in the presence of NOx, collecting the SOA produced on filters, and then analyzing the samples for highly polar compounds using advanced organic chemistry methods. Employing this method, candidate tracers have been identified for several hydrocarbon compounds which are emitted in significant quantities and known to produce SOA in the atmosphere. Some of these compounds forming SOA that have been investigated in the current study are toluene, a variety of monoterpenes, isoprene, and β-caryophyllene, the latter three of which are emitted by vegetation.[128, 129, 130, 131, 132,133] The tracers provide a means to identify the hydrocarbon SOA precursors present in ambient $PM_{2.5}$ samples and show promise for estimating their contributions to the organic carbon concentrations.

The results of a recent EPA field study, to be published in the peer-reviewed literature, suggest aromatic hydrocarbon emissions, including toluene and possibly xylenes, contribute to SOA in Research Triangle Park, North Carolina, with initial estimates as high as 0.7 $\mu g/m^3$ during smog events in July/August. The level of toluene-derived SOA is the lowest in the November-February time frame (about 0.2 $\mu g/m^3$) with intermediate levels in the other months. Currently, EPA is conducting similar analyses of ambient $PM_{2.5}$ samples in Cincinnati, OH, Northbrook, IL, Detroit, MI, Bondville, IL, and St. Louis, MO, the results of which will be available by the end of 2006. After acceptance of the EPA field study results in the peer-reviewed literature, they will be used to assess whether current treatment of aromatic SOA in the EPA CMAQ model need to be modified. Along with most of the other state-of-the-science air quality models, CMAQ predicts low levels of aromatic SOA.

One caveat regarding this work is that a large number of gaseous hydrocarbons emitted into the atmosphere having the potential to form SOA have not yet been studied in this way. It is possible that hydrocarbons which have not yet been studied produce some of SOA species which are being used as tracers for other gaseous hydrocarbons. This means that the present work could overestimate the amount of SOA in the atmosphere to the gaseous hydrocarbons studied to date.

The issue of SOA formation from aromatic precursors is an important one to which EPA and others are paying significant attention. Due to the large contribution of mobile source emissions to overall aromatic levels in the atmosphere, this issue is a crucial one for assessing what further reductions are possible in mobile source PM.

1.4.2. Metals

The emission of metals to the environment is receiving increasing attention. Metals comprise a complex class of elements, some of which are toxic at very low exposure levels. The chemical form in which a metal or metal compound is emitted often determines the potential toxicity and ultimate fate of the element in the environment. Research in recent years suggests that some metals (e.g., transition metals) play an important role in the toxicity of ambient PM, and inhalation as well as ingestion of metals is known to cause a diverse array of cancer and noncancer effects in mammals. Since metals do not degrade in the environment, concerns arise regarding their accumulation in plants, animals, soil and water. The emission of metals from mobile sources is an emerging area of interest since the emissions are in the breathing zone and are distributed in a concentrated fashion in the roadway environment.

Emission of metals from mobile sources occurs as the result of metallic impurities in lubricating oil and fuel, catalyst wear, engine wear, brake wear, and tire wear. Emission rates of most metals from mobile sources are quite low, presenting challenges for many common measurement methods. In recent years, improvements in analytical chemistry allow both the quantification of very low levels of metals in mobile source exhaust as well as some characterization of the form of the metals emitted.[134] Currently, there are many gaps in our understanding of the quantity, chemical form and size distribution of metals in exhaust or from tire and brake wear. Application of state-of-the-art measurement techniques to mobile source metal emissions is just beginning. For example, EPA is currently conducting an emissions characterization program to understand the emission rate and chemical form of mercury in motor vehicle exhaust and the total mercury concentration in gasoline, diesel fuel, lubricating oil, and brake wear emissions. This work will help us understand the potential sources of motor vehicle mercury emissions, and the contribution of motor vehicles relative to other sources of mercury emissions. This information is necessary for any future consideration of control options. Other metals are also being evaluated in various studies.

Metals can also be emitted from mobile sources as a result of their use as an additive to gasoline and/or diesel fuel. As discussed in Chapter III.G of the preamble, Clean Air Act section 211 provides EPA with the authority to require a fuel additive manufacturer to collect necessary data to enable EPA to make a determination about the potential for risk to public health.

References for Chapter 1

[1] Rao, S.; Pollack, A.; Lindhjem, C. 2004 Expanding and updating the master list of compounds emitted by mobile sources – Phase III Final Report. Environ International Corporation.

[2] www.epa.gov/ttn/atw/toxsource/summary.html. Tables of dose-response values on this website, used in EPA Office of Air Quality Planning and Standards risk assessments, are available in Docket EPA-HQ-OAR-2005-0036.

[3] National Academy of Sciences. 1983. Risk Assessment in the Federal Government: Managing the Process. Committee on the Institutional Means for Assessment of Risks to Public Health, National Research Council. Found in various EPA library collections through http://www.epa.gov/natlibra/ols.htm by its OCLC catalog no.09374015.

[4] EPA. 1986. Guidelines for carcinogen risk assessment. Federal Register 51:33992-34003. September 24.

[5] EPA. 2005. Guidelines for carcinogen risk assessment and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/P-03/001F.

[6] EPA. 1986 Guidelines for carcinogen risk assessment. Federal Register 51:33992-34003. September 24.

[7] U. S. EPA. 2005 Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. Report No. EPA/630/R-03/003F. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283

[8] EPA. 1986. Guidelines for mutagenicity risk assessment. Federal Register 51:34006-34012. Sept. 24.

[9] EPA. 1991. Guidelines for developmental toxicity risk assessment. Federal Register 56:63798-63826.

[10] EPA. 1998. Guidelines for neurotoxicity risk assessment. Federal Register 63:26926. May 14. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12479.

[11] EPA. 1996. Guidelines for reproductive toxicity risk assessment. EPA/630/R-96/009. Federal Register 56274-56322, 31 October 1996. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2838.

[12] EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington D.C. EPA/600/8-90/066F.

[13] EPA (2002) A review of the reference dose and reference concentration processes. EPA/630/P-02/002F.

[14] EPA (1998) Methods for exposure-response analysis for acute inhalation exposure to chemicals: development of the acute reference exposure. Review draft. Office of Research and Development, Washington, D.C. EPA/600/R-98/051.

[15] EPA (2002) A review of the reference dose and reference concentration processes. EPA/630/P-02/002F.

[16] EPA 2005 "Full IRIS Summary for Benzene (CASRN 71-43-2)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0276.htm.

[17] U.S. EPA (1985) Environmental Protection Agency, Interim quantitative cancer unit risk estimates due to inhalation of benzene, prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC. for the Office of Air Quality Planning and Standards, Washington, DC., 1985. Document no. EPA600-X-85-022.

[18] Clement Associates, Inc. (1991) Motor vehicle air toxics health information, for U.S. EPA Office of Mobile Sources, Ann Arbor, MI, September 1991. Available in Docket EPA-HQ-OAR-2005-0036.

[19] Hayes, R. B., S. N. Yin, M. S. Dosemici, et al. (1997) Benzene and the dose-related incidence of hematological neoplasms in China. *J. Nat. Cancer Inst*. 89:1065-1071.

[20] International Agency for Research on Cancer (IARC) (1982) IARC monographs on the evaluation of carcinogenic risk of chemicals to humans, Volume 29, Some industrial chemicals and dyestuffs, International Agency for Research on Cancer, World Health Organization, Lyon, France, p. 345-389.

[21] U.S. EPA (1998) Carcinogenic Effects of Benzene: An Update, National Center for Environmental Assessment, Washington, DC. EPA600-P-97-001F. Enter report number at the following search page, http://yosemite.epa.gov/ncepihom/nsCatalog.nsf//SearchPubs?Openform.

[22] Irons, R.D., W.S. Stillman, D.B. Colagiovanni, and V.A. Henry (1992) Synergistic action of the benzene metabolite hydroquinone on myelopoietic stimulating activity of granulocyte/macrophage colony-stimulating factor in vitro, Proc. Natl. Acad. Sci. 89:3691-3695.

[23] U.S. EPA (1998) Carcinogenic Effects of Benzene: An Update, National Center for Environmental Assessment, Washington, DC. EPA600-P-97-001F. Enter report number at the following search page, http://yosemite.epa.gov/ncepihom/nsCatalog.nsf//SearchPubs?Openform.

[24] U.S. EPA (1998) Carcinogenic Effects of Benzene: An Update, National Center for Environmental Assessment, Washington, DC. EPA600-P-97-001F. Enter report number at the following search page, http://yosemite.epa.gov/ncepihom/nsCatalog.nsf//SearchPubs?Openform.

[25] U. S. EPA (2005) Guidelines for Carcinogen Risk Assessment. Report No. EPA/630/P-03/001F. http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283.

[26] U.S. EPA (1998) Carcinogenic Effects of Benzene: An Update. EPA/600/P-97/001F. . Enter report number at the following search page, http://yosemite.epa.gov/ncepihom/nsCatalog.nsf//SearchPubs?Openform.

[27] Rothman, N; Li, GL; Dosemeci, M; et al. (1996) Hematotoxicity among Chinese workers heavily exposed to benzene. Am J Ind Med 29:236-246.

[28] Rappaport, S.M.; Waidyanatha, S.; Qu, Q.; Shore, R.; Jin, X.; Cohen, B.; Chen, L.; Melikian, A.; Li, G.; Yin, S.; Yan, H.; Xu, B.; Mu, R.; Li, Y.; Zhang, X.; and Li, K. (2002) Albumin adducts of benzene oxide and 1,4-benzoquinone as measures of human benzene metabolism. *Cancer Research*. 62:1330-1337.

[29] Rappaport, S.M.; Waidyanatha, S.; Qu, Q.; Yeowell-O'Connell, K.; Rothman, N.; Smith M.T.; Zhang, L.; Qu, Q.; Shore, R.; Li, G.; Yin, S. (2005) Protein adducts as biomarkers of human enzene metabolism. *Chem Biol Interact*. 153-154:103-109.

[30] Lin, Y-S., Vermeulen, R., Tsai, C.H., Suramya, W., Lan, Q., Rothman, N., Smith, M.T., Zhang, L., Shen, M., Songnian, Y., Kim, S., Rappaport, S.M. (2006) Albumin adducts of electrophilic benzene metabolitesin benzene-exposed and control workers. Environ Health Perspec.

[31] Hayes, R.B.; Yin, S.; Dosemeci, M.; Li, G.; Wacholder, S.; Travis, L.B.; Li, C.; Rothman, N.; Hoover, R.N.; and Linet, M.S. (1997) Benzene and the dose-related incidence of hematologic neoplasms in China. *J. Nat. Cancer Inst*. 89:1065-1071.

[32] Hayes, R.B.; Songnian, Y.; Dosemeci, M.; and Linet, M. (2001) Benzene and lymphohematopoietic malignancies in humans. Am J Indust Med, 40:117-126.

[33] Lan, Q.;, Zhang, L., Li, G., Vermeulen, R., et al. (2004). Hematotoxicicity in Workers Exposed to Low Levels of Benzene. Science 306: 1774-1776.

[34] Shu, X.O,; Gao, Y.T.; Brinton, L.A.; et al. (1988) A population-based case-control study of childhood leukemia in Shanghai. Cancer 62:635-644.

[35] McKinney P.A.; Alexander, F.E.; Cartwright, R.A.; et al. (1991) Parental occupations of children with leukemia in west Cumbria, north Humberside, and Gateshead, Br Med J 302:681-686.

[36] Keller, KA; Snyder, CA. (1986) Mice exposed in utero to low concentrations of benzene exhibit enduring changes in their colony forming hematopoietic cells. Toxicology 42:171-181.

[37] Keller, KA; Snyder, CA. (1988) Mice exposed in utero to 20 ppm benzene exhibit altered numbers of recognizable hematopoietic cells up to seven weeks after exposure. Fundam Appl Toxicol 10:224-232.

[38] Corti, M; Snyder, CA. (1996) Influences of gender, development, pregnancy and ethanol consumption on the hematotoxicity of inhaled 10 ppm benzene. Arch Toxicol 70:209-217.

[39] U. S. EPA. (2002). Toxicological Review of Benzene (Noncancer Effects). National Center for Environmental Assessment, Washington, DC. Report No. EPA/635/R-02/001F. http://www.epa.gov/iris/toxreviews/0276-tr.pdf.

[40] Ford, AM; Pombo-de-Oliveira, MS; McCarthy, KP; MacLean, JM; Carrico, KC; Vincent, RF; Greaves, M. (1997) Monoclonal origin of concordant T-cell malignancy in identical twins. Blood 89:281-285.

[41] Aksoy, M. (1989) Hematotoxicity and carcinogenicity of benzene. Environ. Health Perspect. 82: 193-197.

[42] Goldstein, B.D. (1988) Benzene toxicity. Occupational medicine. State of the Art Reviews. 3: 541-554.

[43] Aksoy, M. (1991) Hematotoxicity, leukemogenicity and carcinogenicity of chronic exposure to benzene. In: Arinc, E.; Schenkman, J.B.; Hodgson, E., Eds. Molecular Aspects of Monooxygenases and Bioactivation of Toxic Compounds. New York: Plenum Press, pp. 415-434.

[44] Goldstein, B.D. (1988) Benzene toxicity. Occupational medicine. State of the Art Reviews. 3: 541-554.

[45] Aksoy, M., S. Erdem, and G. Dincol. (1974) Leukemia in shoe-workers exposed chronically to benzene. Blood 44:837.

[46] Aksoy, M. and K. Erdem. (1978) A follow-up study on the mortality and the development of leukemia in 44 pancytopenic patients associated with long-term exposure to benzene. Blood 52: 285-292.

[47] Rothman, N., G.L. Li, M. Dosemeci, W.E. Bechtold, G.E. Marti, Y.Z. Wang, M. Linet, L.Q. Xi, W. Lu, M.T. Smith, N. Titenko-Holland, L.P. Zhang, W. Blot, S.N. Yin, and R.B. Hayes (1996) Hematotoxicity among Chinese workers heavily exposed to benzene. Am. J. Ind. Med. 29: 236-246.

[48] EPA 2005 "Full IRIS Summary for Benzene (CASRN 71-43-2)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0276.htm.

[49] Qu, Q., R. Shore, G. Li, X. Jin, L.C. Chen, B. Cohen, et al. (2002). Hematological changes among Chinese workers with a broad range of benzene exposures. Am. J. Industr. Med. 42: 275-285.

[50] Lan, Q.;, Zhang, L., Li, G., Vermeulen, R., et al. (2004). Hematotoxicity in Workers Exposed to Low Levels of Benzene. Science 306: 1774-1776.

[51] Turtletaub, K.W. and Mani, C. (2003). Benzene metabolism in rodents at doses relevant to human exposure from urban air. Health Effects Inst. Research Report No.113.

[52] U.S. EPA. (2002). Health Assessment of 1,3-Butadiene. Office of Research and Development, National Center for Environmental Assessment, Washington Office, Washington, DC. Report No. EPA600-P-98-001F at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54499.

[53] EPA 2005 "Full IRIS Summary for 1,3-butadiene (CASRN 106-99-0)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0139.htm.

[54] Delzell, E., Sathiakumar, N., Hovinga, M., Macaluso, M., Julian, J., Larson, R., Cole, P. and Muir, D.C.F., 1996. A Follow-up Study of Synthetic Rubber Workers. *Toxicology*, 113, 182-189.

[55] U.S. EPA. (2002). Health Assessment of 1,3-Butadiene. Office of Research and Development, National Center for Environmental Assessment, Washington Office, Washington, DC. Report No. EPA600-P-98-001F at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54499.

[56] EPA 2005 "Full IRIS Summary for 1,3-butadiene (CASRN 106-99-0)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0139.htm.

[57] EPA 2005 "Full IRIS Summary for 1,3-butadiene (CASRN 106-99-0)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0139.htm.

[58] Delzell, E., Sathiakumar, N., Graff, J., Macaluso, M., Maldonado, G., Matthews, R. (2006) An updated study of mortality among North American synthetic rubber industry workers. Health Effects Institute Report Number 132.

[59] Bevan, C.; Stadler, J.C.; Elliot, G.S.; et al. (1996) Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation. Fundam. Appl. Toxicol. 32:1-10.

[60] U.S. EPA (1987) Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde, Office of Pesticides and Toxic Substances, April 1987. Found in various EPA library collections through http://www.epa.gov/natlibra/ols.htm by its OCLC catalog no.16989049.

[61] Hauptmann, M..; Lubin, J. H.; Stewart, P. A.; Hayes, R. B.; Blair, A. 2003. Mortality from lymphohematopoetic malignancies among workers in formaldehyde industries. Journal of the National Cancer Institute 95: 1615-1623.

[62] Hauptmann, M..; Lubin, J. H.; Stewart, P. A.; Hayes, R. B.; Blair, A. 2004. Mortality from solid cancers among workers in formaldehyde industries. American Journal of Epidemiology 159: 1117-1130.

[63] Pinkerton, L. E. 2004. Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup. Environ. Med. 61: 193-200.

[64] Coggon, D, EC Harris, J Poole, KT Palmer. 2003. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. J National Cancer Inst. 95:1608-1615.

[65] Bundesinstitut für Risikobewertung (BfR) Toxicological Assessment of Formaldehyde. Opinion of BfR No. 023/2006 of 30 March 2006. www.bfr.bund.de/cm/290/toxicological_assessment_of_formaldehyde.pdf

[66] Conolly, RB, JS Kimbell, D Janszen, PM Schlosser, D Kalisak, J Preston, and FJ Miller. 2003. Biologically motivated computational modeling of formaldehyde carcinogenicity in the F344 rat. Tox Sci 75: 432-447.

[67] Conolly, RB, JS Kimbell, D Janszen, PM Schlosser, D Kalisak, J Preston, and FJ Miller. 2004. Human respiratory tract cancer risks of inhaled formaldehyde: Dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. Tox Sci 82: 279-296.

[68] Chemical Industry Institute of Toxicology (CIIT).1999. Formaldehyde: Hazard characterization and dose-response assessment for carcinogenicity by the route of inhalation. CIIT, September 28, 1999. Research Triangle Park, NC.

[69] Health Canada (2001) Priority Substances List Assessment Report. Formaldehyde. Environment Canada, Health Canada, February 2001. The document may be accessed at

http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/formaldehyde/index_e.html .

[70] U.S. EPA (2004) National Emission Standards for Hazardous Air Pollutants for Plywood and Composite Wood Products Manufacture: Final Rule. (69 FR 45943, 7/30/04)

[71] Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Formaldehyde. Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available at http://www.atsdr.cdc.gov/toxprofiles/tp111.html.

[72] EPA 2005 "Full IRIS Summary for Acetaldehyde (CASRN 75-07-0)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0290.htm.

[73] Appleman, L. M., R. A. Woutersen, V. J. Feron, R. N. Hooftman, and W. R. F. Notten. (1986). Effects of the variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol. 6: 331-336.

[74] Appleman, L.M., R.A. Woutersen, and V.J. Feron. (1982). Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology. 23: 293-297.

[75] EPA 2005 "Full IRIS Summary for Acetaldehyde (CASRN 75-07-0)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0290.htm.

[76] EPA 2005 "Full IRIS Summary for Acetaldehyde (CASRN 75-07-0)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0290.htm.

[77] Myou, S.; Fujimura, M.; Nishi K.; Ohka, T.; and Matsuda, T. (1993) Aerosolized acetaldehyde induces histamine-mediated bronchoconstriction in asthmatics. Am Rev Respir Dis 148(4 Pt 1): 940-3.

[78] Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Acrolein. Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 2005. Publication # PB/91/180307/AS at http://www.atsdr.cdc.gov/toxprofiles/tp124.html

[79] EPA 2005 "Full IRIS Summary for Acrolein (CASRN 107-02-8)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0364.htm.

[80] EPA 2005 "Full IRIS Summary for Acrolein (CASRN 107-02-8)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0364.htm.

[81] Agency for Toxic Substances and Disease Registry (ATSDR). Draft Toxicological Profile for Acrolein. 2005 Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available at http://www.atsdr.cdc.gov/toxprofiles/.

[82]US EPA .2004. Toxicological Review of Naphthalene. (Reassessment of inhalation cancer risk), Environmental Protection Agency, Integrated Risk Information System (IRIS), Research and Development, National Center for Environmental Assessment, Washington, DC http://www.epa.gov/iris/subst/0436.htm

[83] Oak Ridge Institute for Science and Education. (2004) External Peer Review for the IRIS Reassessment of the Inhalation Carcinogenicity of Naphthalene. August 2004. http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=86019

[84] California EPA (2004) Long Term Health Effects of Exposure to Naphthalene. Office of Environmental Health Hazard Assessment at http://www.oehha.ca.gov/air/toxic_contaminants/draftnaphth.html

[85] International Agency for Research on Cancer (IARC) (2002) Monographs on the Evaluation of the Carcinogenic Risk of Chemicals for Humans. Vol. 82. Lyon, France.

[86] USEPA. 1998. Toxicological Review of Naphthalene. Environmental Protection Agency, Integrated Risk Information System (IRIS), Research and Development, National Center for Environmental Assessment, Washington, DC http://www.epa.gov/iris/subst/0436.htm.

[87] EPA 2005 "Full IRIS Summary for 2,2,4-Trimethylpentane (CASRN 540-84-1)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0614.htm.

[88] Hazardous Substances Data Bank (HSDB) on Isooctane 2005. National Library of Medicine Bethesda, MD found at http://toxnet.nlm.nih.gov/index.html. Enter "isooctane" at search screen.

[89] ATSDR (1999) Toxicological Profile for Ethylbenzene (update). USDHHS, PHS, ATSDR. Publication PB/99/166647 at http://www.atsdr.cdc.gov/toxprofiles/tp110.html.

[90] EPA 2005 "Full IRIS Summary for Ethylbenzene (CASRN 100-41-4)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati,

OH http://www.epa.gov/iris/subst/0051.htm.

[91] Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Ethylbenzene. 1999 Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available at http://www.atsdr.cdc.gov/toxprofiles/.

[92] ATSDR. 1999. Toxicological Profile for n-Hexane. USDHHS, PHS, ATSDR. Publication# PB/99/166688. http://www.atsdr.cdc.gov/toxprofiles/tp113.html.

[93] EPA 2005 "Full IRIS Summary for n-Hexane (CASRN 110-54-3)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0486.htm.

[94] EPA 2005 "Full IRIS Summary for n-Hexane (CASRN 110-54-3)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0486.htm.

[95] Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for n-Hexane. 1999 Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available at http://www.atsdr.cdc.gov/toxprofiles/.

[96] EPA. 1994. Health risk perspectives on fuel oxygenates. Washington, DC: Office of Research and Development; Report No. EPA 600/R-94/217.

[97] Interagency Oxygenated Fuels Assessment Steering Committee. 1997. Interagency assessment of oxygenated fuels. Washington, DC: National Science and Technology Council, Committee on Environment and Natural Resources and Office of Science and Technology Policy. http://www.epa.gov/otaq/regs/fuels/ostpfin.pdf.

[98] EPA 2005 "Full IRIS Summary for Methyl-tertiary-butyl Ether (MTBE, CASRN 1634-04-4)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0545.htm.

[99] EPA 2005 "Full IRIS Summary for Styrene (CASRN 100-42-5)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0104.htm.

[100] Agency for Toxic Substances Disease Registry (1992) Toxicological profile for styrene. Atlanta: ATSDR. http://www.atsdr.cdc.gov/toxprofiles/tp53.html.

[101] EPA 2005 "Full IRIS Summary for Toluene (CASRN 108-88-3)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and

Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0118.htm.

[102] EPA 2005 "Full IRIS Summary for Toluene (CASRN 108-88-3)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0118.htm.
[103] EPA 2005 "Full IRIS Summary for Toluene (CASRN 108-88-3)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0118.htm.
[104] EPA 2005 "Full IRIS Summary for Xylenes (CASRN 1330-20-7)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0270.htm.
[105] EPA Toxicological Review of Xylenes. January 2003. EPA 635/R-03/001.

[106] EPA 2005 "Full IRIS Summary for Xylenes (CASRN 1330-20-7)" Environmental Protection Agency, Integrated Risk Information System (IRIS), Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH http://www.epa.gov/iris/subst/0270.htm.
[107] Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Xylene. 2005 Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available at http://www.atsdr.cdc.gov/toxprofiles/.

[108] Perera, F.P.; Rauh, V.; Tsai, W-Y.; et al. (2002) Effect of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect 111: 201-205.

[109] U.S. EPA (2002) Health Assessment Document for Diesel Engine Exhaust. EPA/600/8-90/057F Office of Research and Development, Washington DC. This document is available electronically at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=29060 .

[110] Ishinishi, N; Kuwabara, N; Takaki, Y; et al. (1988) Long-term inhalation experiments on diesel exhaust. In: Diesel exhaust and health risks. Results of the HERP studies. Ibaraki, Japan: Research Committee for HERP Studies; pp.11-84.

[111] Heinrich, U; Fuhst, R; Rittinghausen, S; et al. (1995) Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhal Toxicol 7:553-556.

[112] Mauderly, JL; Jones, RK; Griffith, WC; et al. (1987) Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. Fundam Appl Toxicol 9:208-221.

[113] Nikula, KJ; Snipes, MB; Barr, EB; et al. (1995) Comparative pulmonary toxicities and

carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. Fundam Appl Toxicol 25:80-94.

[114] U.S. Environmental Protection Agency (2004) Air Quality Criteria for Particulate Matter. Research Triangle Park, NC: National Center for Environmental Assessment – RTP Office; Report No. EPA/600/P-99/002aF.

[115] U.S. Environmental Protection Agency (2004) Air Quality Criteria for Particulate Matter. Research Triangle Park, NC: National Center for Environmental Assessment – RTP Office; Report No. EPA/600/P-99/002aF, p. 8-318.

[116] Seagrave, J.; McDonald, J.D.; Gigliotti, A.P.; Nikula, K.J.; Seilkop, S.K.; Gurevich, M. and Mauderly, J.L. (2002) Mutagenicity and in Vivo Toxicity of Combined Particulate and Semivolatile Organic Fractions of Gasoline and Diesel Engine Emissions. Toxicological Sciences 70:212-226.

[117] Watson,J., Fujita,E., Chow,J., Zielinska,B., Richards,L., Neff,W., Dietrich,D. Northern Front Range Air Quality Study Final Report: Volume 1. June 30, 1998. For Colorado State University, Cooperative Institute for Research in the Atmosphere, by Desert Research Institute, Reno, NV. This document is available in the EPA Docket as EPA-HQ-OAR-2005-0036-1179.

[118] Schauer, J.J.; Rogge, W.F.; Hildemann, L.M.; et al. (1996) Source apportionment of airborne particulate matter using organic compounds as tracers. Atmos Environ 30(22):3837-3855.

[119] EPA, 2001, "National Air Quality and Emission Trends Report, 1999," EPA 454/R-01-004.

[120] Watson,J., Fujita,E., Chow,J., Zielinska,B., Richards,L., Neff,W., Dietrich,D. Northern Front Range Air Quality Study Final Report: Volume 1. June 30, 1998. For Colorado State University, Cooperative Institute for Research in the Atmosphere, by Desert Research Institute, Reno, NV. This document is available in the EPA Docket as EPA-HQ-OAR-2005-0036-1179.

[121] Schauer, James J., Wolfgang F. Rogge, Lynn M. Hildemann, Monica A. Mazurek, Glen R. Cass, and Bernd Simoneit, 1996, "Source Apportionment of Airborne Particulate Matter Using Organic Compounds as Tracers," Atmospheric Environment, 30, 3837-3855.

[122] Zheng, Mei, Glen R. Cass, James J. Schauer, and Eric S. Edgerton, 2002, "Source Apportionment of PM2.5 in the Southeastern United States Using Solvent-Extractable Organic Compounds as Tracers," Environmental Science and Technology, 36, 2631-2371.

[123] Hannigan, Michael P., William F. Busby, Jr., Glen R. Cass, 2005, "Source Contributions to the Mutagenicity of Urban Particulate Air Pollution," Journal of the Air and Waste Management Associatio*n*, 55, 399-410.

[124] Kleeman, Michael J.., Glen R. Cass, 1999, "Identifying the Effect of Individual Emission Sources on Particulate Air Quality Within a Photochemical Aerosol Processes Trajectory Model," Atmospheric Environment, 33, 4597-4613.

[125] Schauer, James J., Glen R. Cass, 2000, "Source Apportionment of Wintertime Gas-Phase and Particle-Phase Air Pollutants Using Organic Compounds as Tracers, Environmental Science and Technology, 1821-1832.

[126] Izumi, L. and T. Fukuyama. 1990, Photochemical aerosol formation from aromatic hydrocarbons in the presence of NOx., Atmospheric Environment, 24A, 1433.

[127] Martin-Reviego, M. and K. Wirtz, 2005. "Is benzene a precursor for secondary organic aerosol?" Environmental Science and Technology, 39, 1045-1054.

[128] Kleindienst, T.E., T.S. Conver, C.D. McIver, and E.O. Edney. 2004. Determination of secondary organic aerosol products from the photooxidation of toluene and their implications in ambient $PM_{2.5}$. *J. Atmos. Chem. 47*, 79-100.

[129] Edney. E.O., T.E. Kleindienst, M. Jaoui, M. Lewandowski, J.H. Offenberg, W. Wang, M. Claeys. 2005. Formation of 2-methyl tetrols and 2-methylglyceric acid in secondary organic aerosol from laboratory irradiated isoprene/NO_X/SO_2/air mixtures and their detection in ambient $PM_{2.5}$ samples collected in the Eastern United States. *Atmospheric Environment 39*: 5281-5289.

[130] Claeys, M., R. Szmigielski, I. Kourtchev, P. Van der Veken, R. Vermeylen, W. Maenhaut, M. Jaoui, T.E. Kleindienst, M. Lewandowski, J.H. Offenberg, E.O. Edney. 2007. Hydroxydicarboxylic acids: Markers for secondary organic aerosol from the photooxidation of α-pinene. *Environ. Sci. Technol.* (Web Edition, 01/23/2007).

[131] Jaoui, M., T.E. Kleindienst, M. Lewandowski, J.H. Offenberg, E.O. Edney. 2005. Identification and quantification of aerosol polar oxygenated compounds bearing carboxylic or hydroxyl groups. 2. Organic tracer compounds from monoterpenes. *Environ. Sci. Technol.39*:5661-5673.

[132] Edney. E.O., T.E. Kleindienst, T.S. Conver, C.D. McIver, and W.S. Weathers. 2003. Polar organic oxygenates in $PM_{2.5}$ at a southeastern site in the United States. *Atmospheric Environment 37*, 3947-3965.

[133] Lewandowski, M., M. Jaoui, T.E. Kleindienst, J.H. Offenberg, E.O. Edney. 2007. Composition of $PM_{2.5}$ during the summer of 2003 in Research Triangle Park, North Carolina. *Atmos. Environ.* (in press; available on line 01/30/2007).

[134] Schauer, James J., Glynis C Lough, Martin M Shafer, William F Christensen, Michael F Arndt, Jeffrey T DeMinter and June-Soo Park. 2006. Characterization of metals emitted from motor vehicles. Health Effects Institute Research Report Number 133.