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Mobile-Source Air Toxics: A Critical Review of the Literature on Exposure and Health Effects

A Special Report of the Institute's Air Toxics Review Panel

Mobile-Source Air Toxics

A Critical Review of the Literature on Exposure and Health Effects

HEI Air Toxics Review Panel

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The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the Institute

- Identifies the highest-priority areas for health effects research;
- Funds and oversees the conduct of research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI research and analyses to public and private decision makers.

Typically, HEI receives half of its core funds from the U.S. Environmental Protection Agency and half from the worldwide motor vehicle industry. Additional funds for this Special Report were provided by the U.S. Federal Highway Administration.

HEI has funded more than 250 studies in North America, Europe, and Asia that have produced important research to inform decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. The results of these studies have been published in more than 200 Research and Special Reports.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop the Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and HEI Commentaries are widely communicated through HEI's Web site (*www.healtheffects.org*), annual conferences, publications, and presentations to legislative bodies and public agencies.

EXECUTIVE SUMMARY

INTRODUCTION

Air toxics are emitted into ambient air from many different sources. They comprise a diverse group of air pollutants that, with sufficient exposure, are known or suspected to cause adverse effects on human health, including cancer, effects on the development of organs or tissues, and damage to the immune, neurologic, reproductive, or respiratory systems. Tools and techniques for assessing project-specific health effects of mobile-source air toxics (MSATs) are very limited. Indeed, there are substantial uncertainties about the health effects of ambient levels of air toxics in general, irrespective of their source allocation. While acknowledging these uncertainties, the U.S. Environmental Protection Agency (EPA), in its model-based National Air Toxics Assessment (NATA), estimated that 92% of the U.S. population is at some increased risk for adverse effects on the respiratory system (including irritation and other effects) because of exposure to air toxics from outdoor sources. The NATA also estimated that, in most of the U.S., people have a slightly increased lifetime risk of cancer from air toxics (between 1 and 25 in a million) if they are exposed to 1999 concentrations of these pollutants over the course of their lifetimes. Comparisons of total air toxics emissions by state indicated that heavily industrialized urban areas have the highest emissions.

MSATs are a subset of these air toxics. They are compounds emitted by on-road vehicles and nonroad equipment that are known or suspected to cause cancer or other serious health effects and environmental effects (*http://epa.gov/otaq/toxics.htm*). In its 2001 rule, the EPA listed 21 compounds or compound classes as MSATs. In the more recent 2007 rule, the EPA expanded this list. Mobile sources are the principal sources of exposure for only a few of these MSATs because many are also emitted by non-mobile sources. The EPA estimates that mobile sources are responsible for about 44% of estimated outdoor emissions of air toxics. Almost 50% of the estimated cancer risk and 74% of the estimated noncancer risk from air toxics is estimated to come from mobile sources.

Hazardous air pollutants, of which air toxics can be considered a subset, were defined in the authorizing legislation for the 1970 Clean Air Act as "pollutants which present, or may present, through inhalation or other routes of exposure, a threat of adverse human health effects (including, but not limited to, substances which are known to be, or may reasonably be anticipated to be, carcinogenic, mutagenic, teratogenic, neurotoxic, which cause reproductive dysfunction, or which are acutely or chronically toxic)." A U.S. air toxics regulatory program was authorized under the Act and redesigned under the 1990 Clean Air Act amendments. The legislation required the EPA to characterize, prioritize, and address the effects of air toxics on public health and the environment. It also required the EPA to regulate or consider regulating air toxics from motor vehicles in the form of standards for fuels, vehicle emissions, or both. The 1990 amendment to the Act specifically included acetaldehyde, benzene, 1,3-butadiene, and formaldehyde—all known or suspected carcinogens.

The EPA also addressed urban air toxics in its Integrated Urban Air Toxics Strategy. The strategy addressed toxic emissions from all outdoor sources, including stationary, area, and mobile sources. It promised a rulemaking on mobile-source standards in 2000 and new area-source standards to take effect by 2009. The Integrated Urban Air Toxics Strategy included a list of 33 high-priority hazardous air pollutants, including acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, and polycyclic organic matter (POM).

By considering pollutants that originate at least in part from mobile sources and taking into account health and risk-assessment information in the Integrated Risk Information System (IRIS), the EPA in 2001 defined a list of 21 MSATs, which was expanded in 2007. This approach, including the regulation of fuels and vehicle emissions as well as the introduction of emission-control devices such as catalytic converters, has led to substantial reductions in the emission of MSATs since the

enactment of the Clear Air Act. It contrasts with the approach taken for the criteria air pollutants (CO, SO_x, NO_2, O_3, lead, and particulate matter [PM]), for which national ambient air quality standards for compounds were established.

Taking into account expected future reductions in air toxics from existing regulatory programs designed to reduce ozone and PM (including the reformulated-gasoline program, the national low emission vehicle program, emissions standards for passenger vehicles, gasoline sulfur-control requirements [Tier 2], and heavy-duty diesel-fuel sulfur-control requirements), the EPA has elected only recently to issue additional fuel and vehicle standards to further control MSATs.

In 2007, the EPA issued a new rule to reduce hazardous air pollutants from mobile sources. This rule identifies 1162 MSATs, but singles out 8 MSATs as key: benzene, 1,3-butadiene, formaldehyde, acetaldehyde, acrolein, POM, naphthalene, and diesel exhaust (DE). The 2007 rule also limits the benzene content of gasoline and reduces emissions from passenger vehicles and gas cans. Reformulated or alternative fuels have been introduced since 1992 with expectations of substantial environmental benefits, as their emission profiles are different from those of traditional fuels. These changes are resulting in decreases in the emissions of some MSATs and increases in others. However, the introduction of reformulated or alternative fuels might pose its own risks, and the removal of individual fuel components does not automatically ensure safe fuels.

In addition to the broad public-health issues they pose, a concern over the health risks of MSATs influences the development of transportation projects at the federal, state, and local levels. Under the National Environmental Policy Act of 1969 as amended in 1982, agencies such as the U.S. Federal Highway Administration are expected to address MSAT effects associated with transportation projects that are intended to create new capacity or add significantly to urban highways or highways close to potentially vulnerable populations. Local projects that lead to improvements in traffic flow, expansion of bus routes, and vehicle-technology retrofits all influence the quantities and sites of MSAT emissions. In some cases, the possible environmental and public-health effects of MSATs have been part of the basis for legal challenges to such projects. In this climate of increased regulatory, public, and judicial concern about MSATs, an MSAT review panel was formed by the Health Effects Institute (HEI) in the winter of 2005. The panel was charged with the following tasks:

- Use information from the peer-reviewed literature to summarize the health effects of exposure to the 21 MSATs defined by the EPA in 2001;
- Critically analyze the literature for a subset of priority MSATs selected by the panel; and
- Identify and summarize key gaps in existing research and unresolved questions about the priority MSATs.

In creating this review of the literature on MSATs, the panel focused on a subset of MSATs for which mobile sources are a sizable source of human exposure and for which existing data suggested that health effects might be observed at concentrations approaching those found in ambient air. The panel elected not to focus on a critical review of DE, a substantial contributor to human exposure and to health risks in the overall context of MSATs, because HEI and many others (e.g., the EPA and the California Air Resources Board) have recently reviewed these issues. Instead, the panel has provided an expanded summary of DE reviews. The seven priority MSATs selected for detailed review by the panel were acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, naphthalene, and POM. For each of these, the panel asked three questions—(1) To what extent are mobile sources a significant source of exposure to this MSAT? (2) Does this MSAT affect human health? and (3) Does this MSAT affect human health at environmental concentrations? The panel then reviewed the peer-reviewed literature, reached key conclusions, and made recommendations for future research.

SUMMARY

Ambient MSATs usually occur as part of complex mixtures. They are emitted into ambient air from many different sources and can also be present in water, food, and soil. MSATs can exist in the gas phase as well as in association with PM. Moreover, after emission, some MSATs can undergo atmospheric transformations that produce other known MSATs, products of unknown chemistry and toxicity, and nontoxic degradation products. In this report, the panel focused on the sources of MSATs—motor vehicles, particularly on-road motor vehicles—for which the broadest evidence exists. Non-road sources, such as trains, planes, and marine vessels, which are important but less studied, were not considered. Substantial exposures to many MSATs also come from sources other than motor vehicles.

Source attribution suggested that the contribution of mobile sources to overall emissions is greatest for 1,3-butadiene, followed by benzene, formaldehyde, acetaldehyde, and acrolein. Mobile-source contributions to overall POM exposure vary depending on the POM species; however, it is clear that mobile sources are contributors to POM associated with PM. There are insufficient data on mobile-source

contributions to naphthalene exposure, but it appears likely that the contributions of mobile sources to exposures are limited. Given that substantial exposures to certain MSATs can arise from non-mobile sources (e.g., smoking, food, and indoor environments) and can occur through air, water, food, and soil, regulatory authorities beyond those specified in the Clean Air Act would be required to substantially reduce overall human exposure to these toxic agents.

Because exposures to MSATs occur as complex mixtures (which can also include non-MSAT compounds), it is especially difficult to deconvolute the contributions of any given compound to human health risks. Animal toxicology studies, typically concerning exposure to single compounds, provide insights into targets and underlying mechanisms of toxicity and dose–response. But these insights are constrained by uncertainties about extrapolations from high to low doses and about interspecies comparisons. Because relatively high levels of exposure are found in occupational settings, studies of occupational cohorts provide opportunities for understanding associations between exposure to individual MSATs and health effects. Epidemiologic studies in occupational cohorts have served, accordingly, to define risks associated with exposures to several MSATs. Identifying effects in community studies is more challenging, however, because of low ambient concentrations, exposures to multiple possible toxicants, and other confounders. Nonetheless, newer studies incorporating biomarkers that directly reflect individual exposure and early biologic consequences can reduce confounding due to misclassification errors in exposure and provide important insights into possible health effects of certain MSATs. They may be especially useful in occupational studies with low exposure concentrations and, to a more limited extent, in community settings.

ACETALDEHYDE

1. To what extent are mobile sources an important source of exposure to acetaldehyde?

Mobile sources are a significant, but not the principal, source of exposure to acetaldehyde. Concentrations tend to be lowest outdoors; they are 2 to 10 times higher indoors and in vehicles. Acetaldehyde is also present in many foods.

2. Does acetaldehyde affect human health?

Like all aldehydes, acetaldehyde is chemically reactive. It causes irritation to the eyes, skin, and respiratory tract and induces cellular inflammation. Although acetaldehyde is a carcinogen in rodents, the data on the possibility of its carcinogenicity in humans are inadequate. Data on respiratory effects are limited mainly to small clinical studies of asthmatic patients using exposure challenges with aerosols of acetaldehyde. The effects of exposures to multiple aldehydes, all of which can be irritants to the respiratory tract, are not known.

3. Does acetaldehyde affect human health at environmental concentrations?

There has been only one epidemiologic study of environmental exposure to acetaldehyde. This was a study of children with asthma, and it was small and unable to distinguish the effect of acetaldehyde from that of other pollutants. Inasmuch as indoor sources of acetaldehyde account for most personal exposure and ambient concentrations appear to be far below those producing irritation, it is doubtful that acetaldehyde in ambient air at concentrations observed in recent years has adversely affected human health. It is likely, however, that acetaldehyde emissions will increase with current requirements for increased use of ethanol, although the exact effect on future concentrations is not known.

ACROLEIN

1. To what extent are mobile sources an important source of exposure to acrolein?

Because of the limited number of studies of acrolein, its highly reactive nature, and the limitations of sampling methods, the available environmental data for acrolein might not be sufficient to allow an assessment of ambient, indoor, or personal exposures. Additional limitations include the number and type of environments sampled, the number of samples collected, the absence of accounting for the presence or absence of sources, the absence of data on geographic and seasonal variability, the representativeness of residences and populations sampled, and the lack of sampling for sensitive or at-risk populations. Limited urban roadside and in-vehicle data do not suggest elevated exposures. Surprisingly low concentrations were observed in tunnel studies—a finding at odds with EPA estimates that overall contributions of acrolein from mobile sources are considerably higher. Substantial mobile-source contributions to exposure might result from the formation of acrolein from 1,3-butadiene in the air. Environmental tobacco smoke is a major indoor source of acrolein.

2. Does acrolein affect human health?

Acrolein is very irritating to the respiratory tract of humans and animals. Studies showed that chronic inhalation resulted in inflammation. Although acrolein might damage DNA, several animal bioassays have not provided substantive evidence of carcinogenicity. Because of its

high chemical reactivity, acrolein is unlikely to be distributed throughout the body.

3. Does acrolein affect human health at environmental concentrations?

There are insufficient data for an assessment of the effect of ambient exposures to acrolein on human health. However, it should be noted that measured environmental concentrations and personal exposures were only slightly lower than concentrations shown to cause irritation.

BENZENE

1. To what extent are mobile sources an important source of exposure to benzene?

There are more air-monitoring data for benzene than for any other MSAT considered in this report. The highest concentrations were found at urban roadside and urban in-vehicle locations. Mobile sources are an important component of overall exposure to benzene. Consistent with this observation, levels of personal exposures to benzene appeared to be in the same range as those found in ambient settings.

2. Does benzene affect human health?

There is clear and widely accepted evidence from a variety of occupational epidemiologic studies that exposure to benzene increased the risks of acute myeloid leukemia; there is less certainty about other lymphohematopoietic cancers. Extended follow-up of an existing cohort further confirmed this association. Moreover, data from several new cohorts (petroleum workers and gas and electric utility workers) demonstrated increased leukemia risks at lower estimated exposures than previously observed.

3. Does benzene affect human health at environmental concentrations?

Some studies have indicated that an increased risk of childhood leukemia was associated with proximity to petrochemical works and gasoline stations, although identifying such effects in community studies is challenging. Studies have yielded mixed results with regard to associations between traffic and childhood leukemia. There has been substantial progress in the development of biomarkers for benzene. Studies using biomarkers have indicated a relationship between benzene concentrations in urine and the presence of cytogenetic abnormalities in community studies (e.g., in street vendors, gasoline-service-station attendants, and children attending schools near major roads). Variations in the enzymes involved in the metabolism of benzene have been identified and linked to increased sensitivity to benzene hematotoxicity. Several newer studies have revealed effects on hematologic indices at lower exposure concentrations than those reported before. However, there remains considerable uncertainty as to the lowest concentration that might be associated with adverse hematologic effects.

1,3-BUTADIENE

1. To what extent are mobile sources an important source of exposure to 1,3-butadiene?

Mobile sources are the most important contributors to 1,3-butadiene concentrations in ambient air in most locales. Because of 1,3-butadiene's short atmospheric lifetime, concentrations of 1,3-butadiene are highest near sources. However, its high reactivity results in the production of other MSATs, such as formaldehyde, acetaldehyde, and acrolein. Several recent studies indicated that indoor concentrations might be higher than outdoor concentrations—an effect not entirely accounted for by environmental tobacco smoke (a known source of indoor exposure). Thus, there might be other important sources of indoor exposure.

2. Does 1,3-butadiene affect human health?

The human evidence, though limited, is consistent with the possibility that 1,3-butadiene causes lymphohematopoietic cancers in high-exposure occupational settings. This is plausible, moreover, because there is good evidence that certain metabolites of 1,3-butadiene cause cancer and adverse reproductive effects in mice. In humans, however, the metabolism of 1,3-butadiene appears to be more like that of rats, a less susceptible species. At high exposure concentrations, such as those once found in the U.S. in certain industries, 1,3-butadiene is likely to be a human health hazard because of its carcinogenicity. The confounding of 1,3-butadiene's health effects by coexposure to styrene and dimethyldithiocarbamate cannot be ruled out. But on epidemiologic and toxicologic grounds, 1,3-butadiene seems likely to be the active agent. Biomarkers of exposure for 1,3-butadiene have been developed and validated. However, biomarkers of effect were identified inconsistently in exposed workers and were not correlated with biomarkers of exposure.

3. Does 1,3-butadiene affect human health at environmental concentrations?

In community studies, there is no direct evidence of health effects of exposure to 1,3-butadiene at ambient concentrations. However, community studies have limitations in sensitivity because of the low exposure concentrations and other pollutants present.

FORMALDEHYDE

1. To what extent are mobile sources an important source of exposure to formaldehyde?

Indoor sources of formaldehyde appear to be the principal source of exposures. Indoor concentrations are three to five times higher than outdoor concentrations. However, mobile sources are an important source of ambient concentrations. The highest ambient concentrations were found at urban roadside sites. It appears that summer photochemical activity contributes more formaldehyde to ambient air than do direct vehicle emissions, as strong seasonal effects are observed. It is important to note that in Brazil, ambient formaldehyde concentrations have increased fourfold over the past few years, following the expansion of the fleet of vehicles using compressed natural gas.

2. Does formaldehyde affect human health?

Like the other aldehydes, formaldehyde is an irritant to the eyes, skin, and respiratory tract in humans. It has recently been classified as a human carcinogen, in part because of evidence of nasopharyngeal cancer at concentrations historically encountered in industrial settings. The underlying mechanisms of this carcinogenicity are not fully understood but include DNA–protein crosslinking and increased cell proliferation.

3. Does formaldehyde affect human health at environmental concentrations?

There is limited and inconclusive evidence that indoor exposure to formaldehyde increases the occurrence of asthma in children. There is no evidence about health effects of outdoor exposures to ambient concentrations of formaldehyde, but given the likelihood of the expanded use of alternative fuels in the U.S. and the probable resulting increases in formaldehyde emissions, some attention should be paid to possible effects of increased emissions from mobile sources in the future.

NAPHTHALENE

1. To what extent are mobile sources an important source of exposure to naphthalene?

Naphthalene is the most abundant polycyclic aromatic hydrocarbon (PAH) found in ambient air. Mobile sources (both fuel combustion and evaporation) are an important, but not the primary, source of naphthalene. There is limited evidence to suggest that concentrations of naphthalene are higher at roadside sites and in vehicles. Indoor concentrations are typically 5 to 10 times higher than ambient concentrations and may be derived from environmental tobacco smoke and moth repellents. However, trends toward the reduction of these indoor sources might lead to the increased importance of outdoor sources as determinants of exposure.

2. Does naphthalene affect human health?

There is evidence in rodents that exposure to naphthalene leads to inflammation of the nasal tract and tumors of the nasal epithelium and olfactory epithelium. However, there are no data on carcinogenicity in humans. Several case reports, which were deficient in quantitative exposure assessments, suggest that single or repeated exposures can cause effects in blood cells, such as hemolysis and hemolytic anemia.

3. Does naphthalene affect human health at environmental concentrations?

There are no epidemiologic or other studies that assess the health effects of exposure to naphthalene at ambient concentrations.

POM

1. To what extent are mobile sources an important source of exposure to POM?

POM is a term commonly used to describe a mixture of hundreds of chemicals, including PAHs, their oxygenated products, and their nitrogen analogs. Some POMs are found in the gas phase, some in the particle phase, and some in both. Different measurement studies have looked at different POM mixtures; there is no standard exposure- or health-based definition of POM. There is a lack of consistency in PAH groupings and indicator compounds for POM. Mobile sources might be significant contributors to ambient concentrations of POM in urban settings. However, other combustion processes, such as wood burning, cigarette smoking, road paving, and roof tarring might lead to substantial additional exposures. Food-derived sources of POM are likely to be the principal source of exposure in many settings where there is limited combustion of wood and industrial fossil fuel. Diesel vehicles emit more PAHs than gasoline-fueled vehicles; "cold starts" account for up to 50% of their PAH emissions.

2. Does POM affect human health?

A few PAH components of POM are potent animal carcinogens. Some of these (e.g., benzo[*a*]pyrene) are classified as human carcinogens. At high occupational exposures, there is sufficient evidence for increased risk of lung cancer in coke-oven workers and possibly in asphalt-industry workers. An association between lung cancer and the use of "smoky" coal in China has also been observed. In highly polluted industrial sites, adverse effects on reproductive (lower birth weights), respiratory (obstructive lung disease),

cardiovascular (ischemic heart disease), and immune (enhanced allergic inflammation) systems have been reported, but the linkages to POM are not firm.

3. Does POM affect human health at environmental concentrations?

While there is evidence that air pollution containing PAHs is genotoxic and has effects on reproductive health, there is no direct evidence from community studies that POM specifically, at ambient exposure concentrations, causes health effects. Because community studies involve exposures to complex mixtures, they have limited ability to address the effects of POM alone. Additional identification of relevant biomarkers of exposure is needed.

GAPS AND RECOMMENDATIONS

Several common themes emerged when the panel considered the gaps in current research on exposure to MSATs and their health effects. It is evident that exposure to many MSATs comes from sources other than vehicles. Indeed, mobile sources are the primary sources of exposure for only a few of the 21 MSATs listed by the EPA in its 2001 mobile-source rule. There is a clear need for better attribution of the sources of these MSATs by, for example, measuring concentrations at roadsides and in vehicles. There is also a need for better attribution of the other sources of MSATs, as well as better characterization of concentrations in microenvironments, such as homes and workplaces, and of factors that affect these concentrations. In addition, there is a need for better characterization of the contributions of outdoor concentrations to indoor concentrations and personal exposures. The atmospheric transformation products of some MSATs and the factors regulating their production need to be identified and characterized. Efforts should also be made to collect existing MSAT data from local and state monitoring networks and enter these data into useable, readily accessible databases to support further analyses.

Improved analytical chemistry methodologies are needed to better understand exposure measures. For example, measured concentrations of acrolein appear to be lower than the actual ambient concentrations. This discrepancy might reflect technical limitations of conventional measurement techniques. There is a strong need to compile spatial and trend data on MSATs in the U.S. Very limited information on these topics is available in the peer-reviewed literature. There is also a need to continue improving the NATA modeling estimates of exposures to MSATs. While in many instances the NATA estimates were similar to exposure concentrations reported in the literature, there were some instances, particularly among aldehydes, in which the NATA modeling appeared to substantially underestimate measured exposure concentrations. Improved modeling and better characterization of spatial and temporal trends are vital to the assessment of the effect of regulatory changes on the emissions of MSATs. They are also needed to assess possible changes in MSAT emissions arising from increased utilization of alternative fuels. Indeed, the widespread introduction of ethanol and compressed natural gas as vehicle fuels in some regions of the world that have less advanced engine and emission control technologies than the U.S. has already led to increases in ambient concentrations of aldehydes in these regions. Whether or not the same increases will be seen in the U.S. as alternative-fuel use increases is unknown.

The risk of cancer has dominated health concerns about the MSATs. The panel concluded the following:

- Quantitative estimates of the relationship between cancer risk and exposure concentrations have been derived largely from studies of occupational cohorts in which exposure to high concentrations of one or more MSATs could be documented. Data from these occupational cohorts might be of limited utility in the evaluation of health effects at ambient concentrations because of the magnitude of the exposure differences. At this point, the panel does not recommend initiating new cohort studies in areas where exposures come from ambient settings to improve quantitative estimates of the cancer-causing potential of MSATs. Moreover, the cost, methodologic difficulties, and data challenges make it unlikely that there are feasible epidemiologic approaches capable of addressing the risks associated with ambient exposures on a compound-by-compound basis. Substantial improvements in the analytical sensitivity and specificity of biomarkers for key MSATs might provide firmer linkages between exposures and health effects; however, it will be important to validate these biomarkers first. Epidemiologic studies coupled with the use of such biomarkers will be of value in investigating the health effects of mobile-source emissions as a whole—for example, looking at populations living or working in proximity to roadways. Research opportunities for use of biomarkers might also arise in connection with emerging "hot spots."
- Some quantitative cancer-potency estimates for MSATs have been derived from animal models. However, extrapolating from these results to humans remains troublesome. A better understanding of the toxicokinetics (including biotransformation pathways) of MSATs in both animals and humans, particularly at ambient concentrations, might provide clearer perspectives on

the similarities and dissimilarities between animal and human metabolism. However, the issue of potential species differences in toxicodynamics will remain.

- Animal studies and especially epidemiologic studies have tended not to focus on noncancer endpoints in investigating the toxicity of MSATs. It remains an open question as to whether developmental, reproductive, and neurologic effects result from mobile-source exposures and to what extent the MSAT aldehydes, singly and collectively, contribute to pulmonary irritation, cough, and asthma. Subpopulations susceptible to the health effects of MSATs also need to be better defined.

CONTRIBUTORS

The HEI Board of Directors appointed a panel to summarize the health effects of exposure to the 21 MSATs defined by the EPA in its 2001 rule. The panel used information from the peer-reviewed literature to critically analyze the literature for a subset of key MSATs and to assess and summarize research gaps and unresolved questions regarding these key MSATs. The Air Toxics Review Panel was made up of members of the HEI Research and Review Committees and was supplemented by other independent subject-matter experts as needed. Experts in four general areas of expertise were sought: exposure, toxicology, epidemiology, and clinical medicine. The report of the panel was submitted for outside peer review and benefited from the thoughtful critiques of the peer reviewers. However, the views expressed in this report are those of the Air Toxics Review Panel, and no endorsement by the external reviewers should be inferred.

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CRITICAL REVIEW

Overview

Air toxics are a subset of a diverse group of hazardous air pollutants that are known or suspected to cause adverse health effects in humans sufficiently exposed to them. These health effects include cancer; damage to the immune, neurologic, reproductive, and respiratory systems; effects on the development of organs or tissues; and other health problems. The U.S. air toxics regulatory program was authorized under the 1970 Clean Air Act and redesigned under the 1990 Clean Air Act amendments (U.S. Congress 1991). The legislation requires the U.S. Environmental Protection Agency (EPA) to characterize, prioritize, and address the effects of air toxics on public health and the environment. In the amendments of 1990, Congress identified 189 hazardous air pollutants (also referred to as HAPs) from stationary sources as air toxics. In 1999, the EPA identified 33 of these (as well as diesel particulate matter [DPM]) as important urban air toxics (EPA 1999a).

Since then, governmental agencies, in particular the EPA, have worked to compile toxicity information and identify gaps in the data on hazardous air pollutants in order to help set priorities for research and regulation.

The EPA has performed a National Air Toxics Assessment (NATA) (EPA 2006b). Based on emissions data from 1999, the NATA presented information on emission of the 33 urban air toxics from various outdoor sources (including stationary sources, area sources, and both on-road and nonroad mobile sources) and on the subsequent modeled concentrations of these air toxics in various regions of the U.S. The NATA also projected population exposures to these pollutants and estimated the risk of both cancer and noncancer health effects resulting from them. Although state and local agencies have conducted some limited monitoring, there is still significant uncertainty about ambient concentrations of air toxics and, thus, about exposure. The NATA estimates of exposure are severely limited by inadequate monitoring data on ambient concentrations of most air toxics. Based on model-to-monitor comparisons for air toxics that have monitoring data, the EPA has found that the NATA probably underestimates some exposures, particularly for "hot spots" (areas that have elevated concentrations of air toxics).*

The Clean Air Act also requires the EPA to regulate or consider regulating mobile-source air toxics (MSATs) in the form of standards for fuels, vehicles, or both. The Act specifically included acetaldehyde, benzene, 1,3-butadiene, and formaldehyde as MSATs (U.S. Congress 1991). By including key pollutants that originate, at least in part, from mobile sources and taking into account health and risk-assessment information in the Integrated Risk Information System (IRIS), the EPA created a more inclusive list of 21 MSATs (Table 1) (EPA 2001b). Many MSATs are also emitted by non-mobile sources. In 2002, based on an earlier version of the NATA using 1996 emissions data, the EPA (2002d) estimated that mobile sources accounted for as much as half of all cancers attributed to outdoor sources of air toxics. Using these data and taking into account expected future reductions in air toxics resulting from existing regulatory programs designed to reduce ozone and particulate matter (PM) (including the reformulated-gasoline program, the national low-emission-vehicle program, emissions standards for passenger vehicles, gasoline sulfur-control requirements [Tier 2], and the heavy-duty diesel-fuel sulfur-control requirements), the EPA elected not to issue additional vehicle standards to control air toxics at that time (EPA 2001b).

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

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* In this report the NATA was used in a very limited way, and therefore a critical review of the NATA is beyond the scope of and has little relevance to this review. Specifically, the NATA was used to estimate the proportion of total emissions of each of the priority mobile-source air toxics (MSATs) that originate from mobile sources. Because the NATA is the only national emissions database that is available for all of the priority MSATs, there was no opportunity to compare these estimates with other emissions information. Use of NATA emissions is always reported as such. In addition, the NATA ambient air model results were used as one source of information to compare urban with rural concentrations of the priority MSATs. In most cases measurement data were also used to compare urban and rural concentrations, in addition to the NATA model results.

Table 1. Twenty-One Mobile-Source Air Toxics (MSATs) Identified by the EPA in 2001[a]

Acetaldehyde
Acrolein
Arsenic
Benzene
1,3-Butadiene
Chromium compounds
Diesel engine exhaust
Dioxins and furans
Ethylbenzene
Formaldehyde
n-Hexane
Lead compounds
Manganese compounds
Mercury compounds
Methyl *tert*-butyl ether
Naphthalene
Nickel compounds
Polycyclic organic matter
Styrene
Toluene
Xylene

[a] EPA 2001b.

In 2007, the EPA finalized a new rule to reduce hazardous air pollutants from mobile sources. It defines a more comprehensive list of MSATs and defines eight MSATs as "key": benzene, 1,3-butadiene, formaldehyde, acetaldehyde, acrolein, polycyclic organic matter (POM), naphthalene, and diesel exhaust (DE). It also limits the benzene content of gasoline and reduces emissions from passenger vehicles and gas cans (EPA 2007).

Apart from federal and state efforts related to the Clean Air Act, air toxics have increasingly become the focus of local efforts as well. In many urban areas, they have become an environmental justice issue because disadvantaged populations can potentially experience disproportionate exposures to, and health effects from, air toxics. These potential exposures and effects have also been part of the basis for legal challenges, under the National Environmental Policy Act of 1969, as amended (U.S. Congress 1982), to major transportation projects in a number of metropolitan areas.

Understanding the toxicity of MSATs is challenging because of the wide range of compounds in the group, health endpoints of concern, and available information on exposure and toxicity. Benzene, for example, is considered a known human carcinogen. Ambient benzene concentrations are measured in many locations worldwide, biomarkers for benzene have been developed and validated, and many epidemiologic and toxicity studies have been performed. By contrast, POM, another MSAT, is a broad class of aromatic organic compounds having more than one benzene ring. POM includes a wide range of compounds, includ-ing polycyclic aromatic hydrocarbons (PAHs); substituted PAHs, such as nitro-PAHs and alkyl-PAHs; heterocyclics, such as aza-arenes and thio-arenes; and other subclasses, such as lactones. Some POM compounds are carcinogenic in animal models, and many are mutagenic in bacterial or mammalian cell systems; others do not appear to be toxic at ambient exposure concentrations. While some POM compounds (such as benzo[*a*]pyrene) have been studied extensively, others have not. Further complicating our under-standing is the range of atmospheric transformation reactions that many POM compounds can undergo, giving rise to numerous additional compounds.

The assessment of risks to human health calls for identification of the hazardous properties of a compound, the dose–response for key adverse health effects, and accurate data on human exposure. Risk assessments make it possible to determine the "margin of exposure," the difference between a given human exposure and the no observed adverse effect level (NOAEL). In cases of irreversible effects, such as genotoxic carcinogenesis, risk assessments also make linear extrapolation to humans possible from dose–responses observed in long-term animal studies and from human exposures observed in epidemiologic studies. The precision of species-to-species extrapolation or high-to-low-dose extrapolation is improved by the availability of toxicokinetic and mode-of-action data in animals and humans.

The aim of this report is to assemble and critique relevant information on key MSATs; to assess the completeness of the MSAT data on toxic potential, dose–response, and human exposure needed for accurate risk assessments; and to identify the research needed in the years ahead to fill today's data gaps.

THE AIR TOXICS REVIEW PANEL

The Board of Directors of the Health Effects Institute (HEI) appointed an Air Toxics Review Panel to review and critique the literature and create this Special Report. The panel included members of the HEI Research and Review Committees and other independent experts in exposure, toxicology, epidemiology, and clinical medicine:

Thomas Kensler, Chair, *Professor, Division of Toxicology, Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health*

H. Ross Anderson, *Professor of Epidemiology and Public Health, Division of Community Health Sciences, St. George's Hospital Medical School and Environmental Research Unit, University of London*

Michael Brauer, *Professor, School of Occupational and Environmental Hygiene, University of British Columbia*

Elizabeth Delzell, *Professor, Department of Epidemiology, University of Alabama–Birmingham*

Mark Frampton, *Professor of Medicine and Environmental Medicine, University of Rochester*

Helmut A. Greim, *Professor, Institute of Toxicology and Environmental Hygiene, Technical University of Munich*

Rogene Henderson, *Senior Scientist Emeritus, Lovelace Respiratory Research Institute*

Brian Leaderer, *Susan Dwight Bliss Professor and Vice Chair, Department of Epidemiology and Public Health, Deputy Dean of Yale School of Public Health, and Co-director of the Yale Center for Perinatal, Pediatric and Environmental Epidemiology at the Yale University School of Medicine*

William N. Rom, *Sol and Judith Bergstein Professor of Medicine and Environmental Medicine and Director of Pulmonary and Critical Care Medicine, New York University Medical Center*

The panel was charged with reviewing the exposure and health literature on MSATs and preparing a report that would be concise and understandable to decision-makers who are not health scientists. The report does the following:

- Summarizes exposure and health data from peer-reviewed literature for the 21 MSATs defined by the EPA in its 2001 rule.
- Critically analyzes the literature for a subset of seven priority MSATs selected by the panel. (These are the MSATs for which mobile sources are important sources of human exposure and for which existing data suggest that health effects might be observed at concentrations approaching those found in ambient air.)
- Identifies research gaps and unresolved questions in the context of today's regulatory agenda.

After the panel had prepared a draft of the report, it was critiqued by peer reviewers. The reviewers had expertise in a variety of relevant scientific disciplines; they also provided a perspective on how the report might be viewed by policymakers. Comments from the reviewers were taken into consideration by the panel in its final report.

SOURCES OF INFORMATION

As an initial step in creating the report, a literature survey was undertaken in the winter of 2004–2005 by Gradient Corporation of Cambridge, Mass., to identify and summarize published exposure and toxicity information on the 21 MSATs. (Summaries are included in Appendices B, C, and D of this report, which are available on the HEI Web site and on a compact disk [CD] that accompanies the printed version.)

The resulting exposure-summary information was used by the panel in its evaluation of MSATs and is included in Appendix B as follows:

- Table B.1 is a summary of key information on the exposure-data studies for each MSAT, including brief study descriptions and details of time periods, locations, location types (i.e., urban, suburban, rural, in-vehicle, roadside, and tunnel), and location details.
- Table B.2 is a data matrix showing the MSATs investigated in each study.
- Tables B.3 through B.23 are data summaries for each of the MSATs. Certain MSATs are represented by one or more surrogate compounds. (POM, for example, is represented by data both for total PAHs and for the seven specific PAHs identified by the EPA as probable human carcinogens—benz[*a*]anthracene, benzo[*b*]-fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, chrysene, 7,12-dimethylbenz[*a*]anthracene, and indeno-[1,2,3-*cd*]pyrene).

The toxicity and health portions of the literature survey took advantage of peer-reviewed secondary sources of information, such as the EPA's Health Assessment Documents, U.S. Agency for Toxic Substances and Disease Registry (ATSDR) reports, and International Agency for Research on Cancer (IARC) monographs. Information on acute, chronic, and subchronic health effects (including cancer and noncancer endpoints) was collected from these sources. In addition, the primary sources on which key toxicity criteria were based were identified and obtained. The survey was updated and augmented with information from primary sources in the spring of 2006 for six of the seven priority MSATs. The survey was also augmented for

the remaining MSATs in cases where the secondary sources were out of date (i.e., 2001 or earlier).

The glossary at the beginning of this report provides information on health effects terms and defines various standards and guidelines.

The resulting toxicity- and health-summary tables were used by the panel in its evaluation of MSATs and are included in Appendix C as follows:

- Tables C.1 and C.2 summarize the toxicity criteria that were readily available in the secondary sources and online, showing whether a given MSAT is considered a carcinogen, how toxic or potent it is (as indicated by the cancer and noncancer criteria), and the date of the most recent evaluation. The principal focus was on the inhalation exposure route, because this is the predominant route of exposure to MSATs. However, when an MSAT—e.g., chromium(III)—had no available quantitative cancer or noncancer toxicity criteria for the inhalation route, toxicity criteria were identified for the oral route of exposure and included in the tables. To facilitate the comparison of criteria, units were converted where necessary, such that all cancer and noncancer toxicity criteria are expressed in units per $\mu g/m^3$ for the inhalation route and mg/kg-day for the oral route.
- Table C.3 provides information on chronic noncancer health effects. For each MSAT, the details of the key chronic-toxicology studies that formed the basis of the toxicity criteria were summarized, starting with IRIS and adding other sources if they were more recent. In addition, the studies on which the toxicity criteria were based are listed in the last column of the table. Criteria based on oral-route studies—e.g., chromium(III)—were included in the table only when no toxicity criteria were identified for the inhalation route.
- Table C.4 provides information on chronic cancer health effects. In addition, the studies on which the toxicity criteria were based are listed in the last column of the table. Criteria based on oral-route studies (e.g., benzo[*a*]pyrene) were included in the table only when the inhalation unit risk was not provided and the compound was classified as a carcinogen (when inhaled); in these cases, the oral unit risk and associated critical study were provided.

For classes of compounds (e.g., POM and dioxins), information on the individual compounds was provided in the summary table (Table C.1), but detailed information was provided only for those that are the most toxic. For POM, for example, detailed information was provided for benzo[*a*]pyrene; for dioxins, detailed information was provided for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD).

- Table C.5 summarizes the acute-toxicity criteria available for each MSAT. Note that both the acute-exposure guideline levels (AEGLs) and the *Emergency Response Planning Guidelines* have three levels of severity. This report does did not include level 3, which pertains to life-threatening effects, because it was deemed too extreme to be useful in the report.
- Table C.6 summarizes the studies that served as the basis for the acute-toxicity criteria for each MSAT. The literature searches in this table were updated, like the literature searches in Tables C.3 and C.4, although to a lesser extent, because most of the exposure guidelines were of recent origin. Literature searches were also conducted for compounds for which no acute criteria were available, but these uncovered no relevant studies.

SELECTION OF MSATs FOR CRITICAL REVIEW

CRITERIA FOR SELECTING PRIORITY MSATS

Starting with the 189 hazardous air pollutants listed in the Clean Air Act (U.S. Congress 1991), the panel sought to identify the MSATs likely to pose the greatest risk to humans at ambient exposure concentrations. To make the task manageable, the panel elected to focus on the 21 MSATs listed by the EPA in its 2001 rule (EPA 2001b): acetaldehyde, acrolein, arsenic compounds, benzene, 1,3-butadiene, chromium compounds, DPM and DE organic gases, dioxin and furans, ethylbenzene, formaldehyde, *n*-hexane, lead compounds, manganese compounds, mercury compounds, methyl *tert*-butyl ether (MTBE), naphthalene, nickel compounds, POM, styrene, toluene, and xylene.

Exposure

The following questions about exposure were established as criteria to help focus discussion of the individual MSATs:

- Are there emissions data suggesting that mobile sources are a substantial contributor to the burden that this MSAT places on the environment? Are the concentrations measured by roadsides or in vehicles higher than those measured in ambient air? (Consider excluding the MSAT from review if there is a major indoor source of it.)
- Do mobile-source exposures to this MSAT occur in significant quantities?
- Are there trends (up or down) in mobile-source exposure to this MSAT over time?
- Are new technologies or fuels likely to lead to higher emissions or other new problems with respect to this MSAT?

Health Effects

The following questions about health effects were also established as criteria:

- Is the MSAT on the IARC or EPA carcinogen list?
- Is the MSAT associated with noncancer endpoints of potential concern (e.g., health effects of the respiratory, immune, or reproductive system)?
- How potent is the MSAT? How do its ratios of exposure to toxicity (reference dose [RfD] and reference concentration [RfC]) compare?

Using the exposure and health information in Tables B.1 to B.31 and Table C.6, the panel reviewed the 21 MSATs and established a list of 7 priority MSATs consisting of acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, naphthalene, and POM. (Naphthalene was originally not included in the priority list. The panel discussed naphthalene, along with manganese compounds, at a later time and decided to add naphthalene to the list.) No single criterion served as the basis for inclusion. The aldehydes (acetaldehyde, acrolein, and formaldehyde) were included despite the fact that mobile sources of these compounds might not be the principal contributors to ambient exposures. The aldehydes are highly reactive irritants that might individually or collectively affect pulmonary function. Benzene and 1,3-butadiene were included because they have been classified as human carcinogens and because of the substantial contribution that mobile sources of both compounds are thought to make to ambient exposures. Naphthalene, a structurally simple POM, is considered individually because of its carcinogenicity in rodents and the recognition that it is the most abundant polycyclic hydrocarbon found in air. POM represents a broad class of carcinogenic and noncarcinogenic hydrocarbons with varying toxic potencies that arise from many sources. These are the seven priority MSATs discussed in detail in subsequent sections of this report. The panel chose not to include DE on its list of MSATs for critical review because several groups have recently reviewed the topic in detail. However, an expanded overview and summary of DE is provided in a later section of the report.

It should be noted that the criteria listed above did not all serve as the basis for excluding an MSAT from the panel's final priority list. There were three principal criteria for exclusion: (1) exposure to concentrations of the MSAT was low, both in absolute terms and as a proportion derived from mobile sources (e.g., for arsenic, chromium, dioxins and furans, *n*-hexane, manganese, mercury, and nickel compounds); (2) trends indicated that substantial declines in exposure to the MSAT could be expected in the years ahead (e.g., for lead and MTBE); and (3) concentrations of the MSAT in ambient air were low relative to indices of toxicity (e.g., for ethylbenzene, styrene, toluene, and xylene). Brief summaries of the key exposure and health information associated with the 13 nonpriority MSATs are provided in Appendix A of this report.

ADDITIONAL INFORMATION GATHERED FOR PRIORITY MSATS

In addition to the literature survey described earlier, information on indoor exposures was collected in the spring of 2006 for six of the seven priority MSATs (acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, and POM). Little exposure information was available for naphthalene. This information is included in Appendix D as follows:

- Table D.1 is a summary of the indoor exposure data sources for each MSAT, including brief study descriptions and details on study time periods, locations, and location types (e.g., residences, office buildings, and schools), as well as a description of each location and notes.
- Table D.2 is a data matrix showing the MSATs investigated in each study.
- Tables D.3 through D.8 are data summaries for each of the MSATs. Certain MSATs are represented by one or more surrogate compounds. (POM, for example, is represented by data both for total PAHs and for the seven specific PAHs identified by the EPA as probable human carcinogens.)

In addition, literature searches for six of the seven priority MSATs were updated as described earlier.

Glossary

The following terms are used in this report. The definitions given here were adapted from various sources available online at the URLs (uniform resource locators, or Internet addresses) cited at the end of each entry.

AEGLs

Acute exposure guideline levels A three-tier system of threshold exposure limits being developed by the National Advisory Committee on AEGLs of the U.S. Environmental Protection Agency to indicate the risk to humans resulting from "acute exposure" (a single, nonrepeating exposure lasting no more than eight hours) to a given hazardous airborne compound. AEGLs are intended to help government authorities and private organizations manage emergencies involving spills and other catastrophic exposures.

> **AEGL-1** The airborne concentration (expressed as parts per million [ppm] or mg/m^3) of a given substance above which it is predicted that the general population, including susceptible individuals, might experience noticeable discomfort, irritation, or certain asymptomatic nonsensory effects. The effects are not disabling and are transient and reversible upon cessation of exposure.
>
> **AEGL-2** The airborne concentration (expressed as ppm or mg/m^3) of a given substance above which it is predicted that the general population, including susceptible individuals, could might experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape from the exposure source.
>
> **AEGL-3** The airborne concentration (expressed as ppm or mg/m^3) of a given substance above which it is predicted that the general population might experience life-threatening health effects or death.

http://www.epa.gov/oppt/aegl/pubs/define.htm

Accessed March 26, 2007

BMC or BMD

Benchmark concentration or benchmark dose The concentration or dose of a given substance that produces a predetermined change in the response rate (the percentage rate at which the response occurs in a population) of a given adverse health effect (known as the benchmark response [BMR]) compared with the background rate.

http://www.epa.gov/iris/gloss8.htm#b

Accessed March 26, 2007

BMCL or BMDL

The statistical lower confidence limit of the exposure concentration or dose of a given substance at the BMC or BMD, respectively.

http://www.epa.gov/iris/gloss8.htm#b

Accessed March 26, 2007

Cancer Potency Factor

The theoretical upper bound of the probability of "excess" cancer cases (i.e., cases in excess of the number of expected cases) occurring in a population exposed to a given substance, assuming a lifetime exposure. The exposure dose is expressed in units of milligrams per kilogram-day (mg/kg-d).

http://www.oehha.ca.gov/air/hot_spots/pdf/apeni.pdf

Accessed March 26, 2007

Carcinogen Classifications, EPA

A five-category classification system developed by the U.S. Environmental Protection Agency (EPA) to characterize the extent to which available data (the "weight of evidence") support the hypothesis that given substances cause cancer in humans.

> **Group A (human carcinogen)** Substances for which human data are sufficient to demonstrate a cause-and-effect relationship between exposure and cancer incidence in humans. In the national scale assessment, seven air toxics currently classified as human carcinogens are arsenic compounds, benzene, 1,3-butadiene, chromium compounds, coke-oven emissions, nickel compounds, and vinyl chloride.

Carcinogen Classifications, EPA (*Continued*)

Group B (probable human carcinogen)

Group B1 Substances for which **limited** human data **suggest** a cause-and-effect relationship between exposure and cancer incidence in **humans**. In the national scale air toxics assessment, five air toxics are currently classified as probable (B1) human carcinogens: acrylonitrile, beryllium compounds, cadmium compounds, ethylene oxide, and formaldehyde.

Group B2 Substances for which animal data are **sufficient** to demonstrate a cause-and-effect relationship between exposure and cancer incidence in **animals**, and human data are inadequate or absent. In the national-scale assessment, 15 air toxics currently classified as probable (B2) human carcinogens are acetaldehyde, carbon tetrachloride, chloroform, 1,3-dichloropropene, ethylene dibromide, ethylene dichloride, hexachlorobenzene, hydrazine, lead compounds, methylene chloride, polychlorinated biphenyls, polycyclic organic matter, perchloroethylene, propylene dichloride, and trichloroethylene.

Group C (possible human carcinogen) Substances for which animal data **suggest** a cause-and-effect relationship between exposure and cancer incidence in **animals.** In the national scale assessment, four air toxics are currently classified as possible human carcinogens: acrolein, mercury compounds, quinoline, and 1,1,2,2-tetrachloroethane. (Because unit risk estimates have not been developed for acrolein and mercury compounds, the EPA has not estimated a cancer risk for these air toxics.)

Group D (not classifiable as to human carcinogenicity) Substances for which human and animal data are inadequate to either suggest or refute a cause-and-effect relationship between exposure and cancer incidence in humans. In the national scale assessment, the only air toxics currently considered to be not classifiable are manganese compounds.

Group E (evidence of noncarcinogenicity) Substances for which animal data are sufficient to demonstrate the absence of a cause-and-effect relationship between exposure and cancer incidence in animals. In the national scale assessment, no air toxics are currently classified as having sufficient evidence of noncarcinogenicity.

http://www.epa.gov/ttn/atw/nata/gloss1.html

Accessed March 26, 2007

Carcinogen Classifications, IARC

A four-category classification system developed by the International Agency for Research on Cancer (IARC) to characterize the extent to which available data support the hypothesis that a given substance causes cancer in humans. Substances are reviewed if (1) there is evidence of human exposure and (2) there is some evidence or suspicion of carcinogenicity.

Group 1 The agent is carcinogenic to humans.

Group 2

2A The agent is probably carcinogenic to humans.

2B The agent is possibly carcinogenic to humans.

Group 3 The agent is not classifiable as to its carcinogenicity to humans.

Group 4 The agent is probably not carcinogenic to humans.

http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php

Accessed March 26, 2007

Clean Air Act

The Clean Air Act is the comprehensive U.S. federal law that regulates air emissions from area, stationary, and mobile sources. The law authorizes the U.S. Environmental Protection Agency to establish National Ambient Air Quality Standards (NAAQS) to protect public health and the environment.

The goal of the Act was to set and achieve NAAQS in every state by 1975. The setting of maximum pollutant standards was coupled with directing the states to develop state implementation plans applicable to appropriate industrial-emission sources in the state.

The Act was amended in 1977 primarily to set new goals for achieving attainment of NAAQS because many areas of the country had failed to meet the earlier deadlines. The 1990 amendments to the Clean Air Act were intended in large part to meet unaddressed or insufficiently addressed problems, such as acid rain, ground-level ozone, stratospheric ozone depletion, and air toxics.

http://www.epa.gov/region5/defs/html/caa.htm

Accessed March 26, 2007

Equivalency Factor

See toxic equivalency factor (TEF).

HEC or HED

Human equivalent concentration or **human equivalent dose** The adjusted air concentration (for inhalation exposure) or adjusted dose (for other routes of exposure) of a given substance that is believed to induce the same degree of adverse health effects in humans as a given concentration or dose administered to laboratory animals. The adjustment can incorporate toxicokinetic information on the substance, if available, or use a standard default procedure, such as assuming that daily oral doses over a lifetime are proportional to body weight raised to the 0.75 power.

http://www.epa.gov/iris/gloss8.htm#b

Accessed March 26, 2007

Inhalation Unit Risk

See unit risk factor (URF).

IPCS

International Programme on Chemical Safety A joint program, established in 1980, of the International Labor Organization, the United Nations Environment Programme, and the World Health Organization (WHO). Its main roles are to establish the scientific basis for the safe use of chemicals and to strengthen national capabilities and capacities for chemical safety. The WHO is the IPCS's executing agency, which has the power to set guidelines.

http://www.who.int/ipcs/en/

Accessed March 26, 2007

LC_{50}

Lethal concentration 50% The concentration of a substance in air (generally) or water that kills 50% of exposed test animals in a given assay.

http://www.ccohs.ca/oshanswers/chemicals/ld50.html

Accessed March 26, 2007

LD_{50}

Lethal dose 50% The quantity of a given substance, administered all at once, that kills 50% of exposed test animals. It is a measure of the short-term poisoning potential (acute toxicity) of the compound.

http://www.ccohs.ca/oshanswers/chemicals/ld50.html

Accessed November 29, 2006

LOAEL

Lowest observed adverse effect level For a given airborne substance, the lowest exposure concentration at which significant increases in the frequency or severity of adverse health effects are observed in exposed humans or test animals compared with controls.

http://www.epa.gov/iris/gloss8.htm

Accessed March 26, 2007

MATES (I, II, and III)

Multiple Air Toxics Exposure Study A series of three air-sampling programs conducted between 1986 and 2006 by California's South Coast Air Quality Management District (SCAQMD). The programs were designed to assess concentrations of cancer-causing pollutants in ambient air and the risk they posed to residents of the region. SCAQMD is the air-pollution-control agency for Orange County and the urban portions of Los Angeles, Riverside, and San Bernardino counties.

http://www.aqmd.gov/news1/2005/matesiiifactsheet.html

Accessed March 26, 2007

MRL

Minimal risk level An estimate of daily human exposure to a substance at or below which the substance is believed unlikely to pose a measurable risk of adverse, noncancerous effects on human health. MRLs are calculated by the U.S. Agency for Toxic Substances and Disease Registry for inhalation and oral exposure routes as well as for acute, intermediate, and chronic forms of exposure. They should not be used as predictors of adverse health effects (*see* reference concentration or reference dose [RfC or RfD]).

http://www.atsdr.cdc.gov/glossary.html

Accessed March 26, 2007

NAAQS

National Ambient Air Quality Standards Air quality standards established by the U.S. Environmental Protection Agency in accordance with the Clean Air Act for pollutants considered harmful to public health and the environment. **Primary standards** set limits to protect public health, including the health of sensitive subpopulations, such as asthmatics, children, and the elderly. **Secondary standards** set limits to protect public welfare, including protection against decreased visibility and damage to animals, crops, vegetation, and buildings. The six principal, or "criteria," NAAQS pollutants are carbon monoxide, lead, nitrogen dioxide, particulate matter (PM), ozone, and sulfur oxides. NAAQS compounds are measured as parts

per million (ppm) by volume, milligrams per cubic meter of air (mg/m^3), and micrograms per cubic meter of air ($\mu g/m^3$).

http://epa.gov/air/criteria.html

Accessed August 14, 2007

NATA

National Air Toxics Assessment A comprehensive, ongoing evaluation, conducted by the U.S. Environmental Protection Agency, of air toxics in the U.S. The NATA aims to expand air toxics monitoring, improve and periodically update emissions inventories, improve national- and local-scale modeling, continue research on exposures and health effects in ambient and indoor air, and improve assessment tools.

http://www.epa.gov/ttn/atw/nata/gloss1.html

Accessed March 26, 2007

NOAEL

No observed adverse effect level For a given substance, the highest exposure concentration at which no significant increases in the frequency or severity of adverse health effects are observed in exposed humans or test animals compared with controls. (Certain effects might be observed at the NOAEL, but they are not considered adverse, or precursors of adverse, effects.)

http://www.epa.gov/iris/gloss8.htm

Accessed March 26, 2007

PMR

Proportionate mortality ratio The number of deaths from a specific cause in a specific period of time per 100 deaths from all causes in the same time period.

http://www.epa.gov/iris/gloss8.htm

Accessed March 26, 2007

REL

Reference exposure level The California Environmental Protection Agency defines REL as the concentration of a given substance in air at or below which adverse health effects in humans are not expected for a given acute, chronic, or other exposure. RELs are designed to protect sensitive subpopulations in particular by including margins of safety that reflect gaps and uncertainties in the data used.

http://www.oehha.ca.gov/air/hot_spots/pdf/apeni.pdf

Accessed November 29, 2006

RfC or RfD

Reference concentration or reference dose An estimate of a continuous inhalation exposure (RfC) or an estimate of the maximum daily oral exposure (RfD) to a given substance that is believed likely to be without appreciable risk of adverse health effects over a lifetime in humans, including sensitive subpopulations. It can be derived from a BMC (for RfC), BMD (for RfD), LOAEL, or NOAEL (see separate listings), with uncertainty spanning approximately an order of magnitude to reflect the limitations of the data used. Generally used in the U.S. Environmental Protection Agency's noncancer health assessments.

http://www.epa.gov/iris/gloss8.htm

Accessed March 26, 2007

RR

Relative risk (or risk ratio or rate ratio) The relative measure of the difference in risk between the exposed and unexposed populations in a cohort study. The relative risk is defined as the rate of disease among the exposed divided by the rate of the disease among the unexposed. A relative risk of 2 means that the exposed group has twice as high a risk of disease as the unexposed group.

http://www.epa.gov/iris/gloss8.htm

Accessed August 14, 2007

SMR

Standardized mortality ratio In a cohort study, the ratio of the risk or incidence of deaths in an exposed cohort to the expected risk or incidence of deaths in an unexposed control cohort. The SMR is usually standardized to control for differences in age, sex, race, or other factors between the two cohorts. It is frequently converted to a percent by multiplying it by 100. It is similar to relative risk.

http://www.epa.gov/iris/gloss8.htm

Accessed March 26, 2007

TEF

Toxic equivalency factor An estimate of the carcinogenic potency of a given polycyclic aromatic hydrocarbon (PAH) relative to the carcinogenic potency of benzo[*a*]pyrene. Benzo[*a*]pyrene is the most studied PAH compound. There are hundreds of known PAHs.

http://www.mass.gov/dep/toxics/pahs.htm

http://www.epa.gov/oswer/riskassessment/superfund_toxicity.htm

Accessed March 26, 2007

TLV

Threshold limit value An estimate of the concentration of an airborne substance in the workplace to which it is believed that normal, healthy adult workers can be exposed daily over a working lifetime without adverse health effects. (TLVs are established by the American Conference of Governmental Industrial Hygienists.)

http://www.acgih.org/Products

Accessed March 26, 2007

TWA

Time-weighted average The average concentration of a given hazardous compound in air over a given time period (such as an 8-hour work day or 40-hour work week), "weighted," or calculated, to reflect the durations of various changes in concentrations over the time period. TWAs are recommended by the National Institute for Occupational Safety and Health.

http://www.cdc.gov/niosh/npg/

Accessed March 26, 2007

UF

Uncertainty factor or safety factor A mathematical adjustment made for reasons of safety when data pertaining to an estimate or calculation are incomplete or uncertain. Uncertainty factors are applied to allow, for example, for differences between people's degrees of sensitivity to substances, between animal and human responses, and between LOAELs and NOAELs (see separate listings). These factors are applied to the LOAEL or the NOAEL to derive an MRL (see listing).

http://www.atsdr.cdc.gov/glossary.html

Accessed March 26, 2007

URE

Unit risk estimate An upper-bound estimate of the number of "excess" lifetime cancer cases (i.e., cases occurring in excess of the number of expected cases) in a population exposed by inhalation to a given substance at a concentration of 1 $\mu g/m^3$ in air over a lifetime, compared with an unexposed population. If a given URE were 1.5×10^{-6} per $\mu g/m^3$, for example, then 1.5 excess cases of cancer would be expected to develop per 1,000,000 people exposed. UREs are considered to represent a plausible upper limit to the true risk. (UREs do not usually represent a true statistical confidence limit.) The true risk is usually lower but can be higher. URE is an estimate used by the U.S. Environmental Protection Agency.

http://www.epa.gov/ttn/atw/nata/gloss1.html

Accessed March 26, 2007

URF

Unit risk factor An estimate of the upper-bound probability of an individual's contracting an "excess" case of cancer (i.e., a case in excess of the number of expected cases) in a hypothetical population exposed by inhalation to a given hazardous compound at a concentration of 1 $\mu g/m^3$ in air over a lifetime, compared with an unexposed control population. URF is an estimate used by the California Environmental Protection Agency.

http://www.oehha.ca.gov/air/hot_spots/pdf/apeni.pdf

Accessed March 26, 2007

Acetaldehyde

INTRODUCTION

Acetaldehyde (CAS Registry Number 75-07-0, C_2H_4O, molecular weight = 44.1) (Figure 1), also known as ethanal, is ubiquitous in the environment and is a product of numerous natural, industrial, and combustion processes.

Acetaldehyde is present in many ripe fruits, such as apples, grapes, and citrus fruits, as well as in roasted coffee beans, essential oils, wine, and other foods. It is the main metabolite of ethanol, the alcohol found in alcoholic beverages. Indeed, such beverages are the general population's principal source of exposure to acetaldehyde.

Acetaldehyde is used extensively as a chemical intermediate in the production of plastics and resins, the manufacture of paper, and the synthesis of organic chemicals. It is released into the environment by numerous industrial sources as well as the combustion of hydrocarbons found, for example, in wood, tobacco, and fossil fuels used in vehicles.

At one atmosphere pressure and 25°C, 1 ppm acetaldehyde is equivalent to 1.82 mg/m^3.

BENCHMARK LITERATURE

The following evaluation of research literature on acetaldehyde is based on data and source tables listed in Appendices B and D (available on the HEI Web site) of this report. Additional information was obtained from two large studies (Kinney et al. 2002; Weisel et al. 2005). Personal-exposure data also came from these two studies (Kinney et al. 2002; Weisel et al. 2005). Data summaries from the EPA Air Quality System database were used to calculate rural, suburban, and urban concentrations of acetaldehyde (EPA 2004a). Data used to assess exposures to acetaldehyde in ambient, outdoor, and indoor air were extracted from publications identified in Appendices B and D of this report. Evaluations of health endpoints were based on information from the International Agency for Research on Cancer (IARC 1999a), U.S. National Toxicology Program (NTP 2005), EPA (1999b, 2000b), and European Commission Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers (European Commission 2004) as well as various published papers cited as the findings are presented.

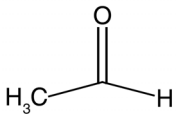

Figure 1. Structure of acetaldehyde.

EXPOSURE

SOURCES AND EMISSIONS

Acetaldehyde is ubiquitous in the environment. It is formed as a product of many processes, including the incomplete combustion of wood in fireplaces and woodstoves, the roasting of coffee beans, the combustion of gasoline and diesel fuel in motor vehicles, refining and waste processing in coal plants, the combustion of fossil fuels in power plants, the photochemical oxidation of hydrocarbons in the atmosphere, and (as an intermediate product) in respiration in plants (EPA 1994a, 2000b; Lakes Environmental Software 1998).

The National Air Toxics Assessment (NATA), conducted by the EPA, estimated that 32.4% of acetaldehyde emissions nationwide are from on-road mobile sources (including automobiles, trucks, and other vehicles) and that 40.8% and 19.1% of emissions are from on-road mobile sources in urban and rural areas, respectively (EPA 2006b). Acetaldehyde can also be produced photochemically in the atmosphere. It is estimated that 56% of ambient concentrations of acetaldehyde in California (in 1987) were from photochemical oxidation of organic precursors and that 44% were from direct-source emissions (California Environmental Protection Agency [California EPA] 1993). It is not known whether these findings are representative of other parts of the U.S.

Indoor sources of acetaldehyde are generally associated with combustion, such as smoke from tobacco or wood fires. Other indoor sources include building materials (e.g., polyurethane foams), cooking, certain consumer products (e.g., adhesives and nail-polish remover), volatilization from certain foods, and infiltration from ambient air sources (California EPA 1993; Lakes Environmental Software 1998).

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Table 2 and Figure 2 show the range of mean and maximum concentrations of acetaldehyde in μg/m^3 measured in outdoor (including in-vehicle) locations, in indoor environments, and by personal monitoring. The literature on ambient and outdoor concentrations reports acetaldehyde measurements in six different environments (urban, urban roadside, urban in-vehicle, suburban, rural, and combined urban–suburban–rural). Indoor concentrations are reported for three environments (residences, schools, and offices). One study reported personal-exposure concentrations among inner-city high school students (Sax et al. 2004); another reported personal-exposure concentrations for adults and children (Weisel et al. 2005).

Sampling times reported for ambient measurements ranged from 1 (Grosjean and Grosjean 2002) to 48 hours (Kinney et al. 2002), with concentration-averaging times

Table 2. Acetaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3) Mean	Concentration (μg/m^3) Maximum	Citations	Comments
Outdoor Areas						
Urban						
	91 averages*	Yearly	2.8	25.5**	EPA 2004a	
	68	Yearly	1.5	3.8	California Air Resources Board 2003	
	73	Yearly	2.8	8.5	California Air Resources Board 2003	
	82	Yearly	0.7	2.7	California Air Resources Board 2003	
	67	Yearly	2.9	10.0	California Air Resources Board 2003	
	76	Yearly	1.2	3.6	California Air Resources Board 2003	
	71	Yearly	1.8	6.1	California Air Resources Board 2003	
	36	8 wk	4.2	—	Kinney et al. 2002	Summer
	36	8 wk	2.8	—	Kinney et al. 2002	Winter
	~ 60	Yearly	3.2	—	South Coast Air Quality Management District 2000	
	~ 60	Yearly	5.2	—	South Coast Air Quality Management District 2000	
	395	Yearly	6.9	25.9	Weisel et al. 2005	2 seasons
	—	—	1.58	—	EPA 2006b	Model
	~ 350	≤ 2 months	1.9–5.4	12.0	Zielinska et al. 1998	
Urban in-vehicle						
	20	Travel time	2.8–63.0	—	Riediker et al. 2003	Bus runs
	50	Travel time	9.0	31.0	Riediker et al. 2003	Car
	115	Travel time	25.2	—	Weisel et al. 2005	Car
Urban roadside						
	8	2 hr	1.5–5.5	—	Grosjean and Grosjean 2002	Tunnel
	10	2 hr	1.1–2.3	—	Grosjean and Grosjean 2002	Tunnel
Suburban						
	33 averages*	Yearly	2.6	19.4**	EPA 2004a	
Rural						
	—	Yearly	0.71	—	EPA 2006b	Model
	33 averages*	Yearly	2.0	15.6**	EPA 2004a	
Urban–suburban–rural combined						
	1875	Yearly	2.5	17.0	EPA 2004d	
	2479	Yearly	1.1	8.8	Pratt et al. 2000	

Table continues on next page

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 10,515 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average.

ranging from a few days (e.g., Fitz et al. 2003) to 9 years (Pratt et al. 2000). The number of individual measurements per study ranged from a low of 20 for an in-vehicle study (Fitz et al. 2003) to a high of 10,515 for the combined urban–suburban–rural category (EPA 2004a). The 10,515 individual measurements contained in the largest combined data set (EPA 2004a) were acquired and concentrations were calculated for separate urban, suburban, and rural categories. The number of averages were then arranged as urban, suburban, and rural, and reported as the mean of the number of reported averages for use in this report.

The two remaining combined-category studies (EPA 2004d; Pratt et al. 2000), each with more than 1880 observations, reported data for the combined urban–suburban–rural category. The mean rural concentration of 0.71 μg/m^3 and mean urban concentration of 1.58 μg/m^3, shown in

Table 2 (*Continued*). Acetaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3) Mean	Concentration (μg/m^3) Maximum	Citations	Comments
Indoor Spaces						
Residences						
	30	100 min	18.0	38.0	Feng and Zhu 2004	75 homes
	6	—	—	43.0	Fortmann et al. 2001	Test house
	14	48 hr	12.1	18.0	Reiss et al. 1995	4 homes
	26	48 hr	9.2	30.0	Reiss et al. 1995	9 homes
	83	6 days	10.0	24.0	Sawant et al. 2004	Homes
	36	6 days	5.3	29.0	Zhang et al. 1994	6 homes
	40	2 days	15.0	36.0	Sax et al. 2004	Winter
	33	2 days	9.6	23.0	Sax et al. 2004	Fall
	41	2 days	15.0	92.0	Kinney et al. 2002; Sax et al. 2004	Summer
	37	2 days	16.0	54.0	Kinney et al. 2002; Sax et al. 2004	Winter
	398	Yearly	23.2	119.0	Weisel et al. 2005	2 seasons
Schools						
	—	School wk	6.8	25.0	Shendell et al. 2004	Heating and cooling in 20 classrooms
	28	6 days	12.0	25.0	Sawant et al. 2004	School rooms
Offices						
	199	6–8 hr	12.0	20.0	Whitmore et al. 2003b	201 classrooms in 67 schools
	23	2 years	5.0	—	Subramanian et al. 2000	Office building
Personal Exposures						
	38	2 days	13.0	—	Sax et al. 2004	Winter
	42	2 days	20.2	—	Sax et al. 2004	Summer
	409	2 days	22.9	86.1	Weisel et al. 2005	Adults
	169	2 days	24.9	112.0	Weisel et al. 2005	Children

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 10,515 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average.

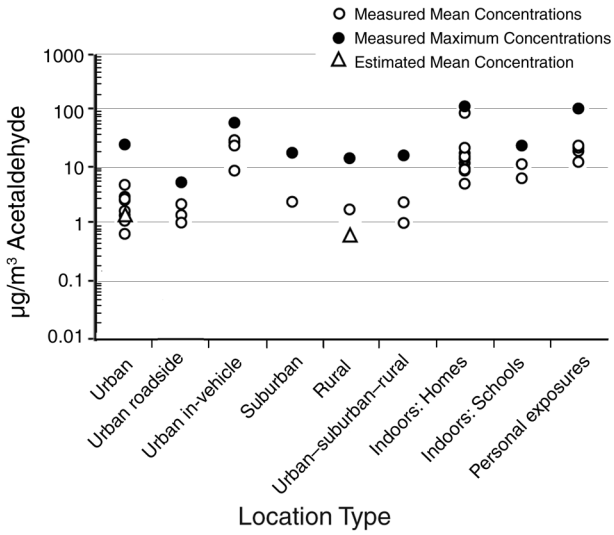

Figure 2. Concentrations of acetaldehyde (µg/m^3) at various locations. Data for figure are from Table 2.

Table 2 and Figure 2, were estimated using the NATA model (EPA 2006b). Sampling times for indoor measurements ranged from 90 minutes (Feng and Zhu 2004) to 1 school week (Shendell et al. 2004), with comparable concentration-averaging times. The number of samples per study ranged from 6 for a test-house study, in which a house was rented for the study (which afforded a more controlled environment) (Fortmann et al. 2001), to 398 for a residential-home study (Weisel et al. 2005). The personal-monitoring study, conducted in New York over a winter and summer monitoring campaign, focused on inner-city high school students, with personal samples collected over 48-hour periods (Sax et al. 2004). The largest database on personal exposures to acetaldehyde was obtained from data on adults and children in Elizabeth, N.J., Los Angeles, Calif., and Houston, Tex. (Weisel et al. 2005).

Although there was great variability in the number of measurements, season of measurement, and geographic area of measurement, Table 2 and Figure 2 suggest a trend. Mean concentrations in individual categories of location types—urban, urban-roadside, suburban, rural, and combined urban–suburban–rural—tended to be similar and to range from approximately 1 to 7 µg/m^3. Average urban in-vehicle concentrations tended to be higher than those in ambient air and were highly variable. Average home, school, and personal mean concentrations tended to be similar to each other (from 5 to 25 µg/m^3) and to range from approximately 2 to 10 times ambient and outdoor levels (Zhang et al. 1994; Sax et al. 2004; Weisel et al. 2005). Personal exposures of adults and children were similar to each other in the one study for which data were available (Weisel et al. 2005) and were higher than indoor residential levels. The highest average concentrations were measured inside vehicles in urban settings and ranged from 10 to more than 60 µg/m^3. Residences and personal exposures had the highest maximum concentrations, at 92 µg/m^3 (Kinney et al. 2002; Sax et al. 2004). The highest personal exposure, at 112 µg/m^3, was measured for a child. In general, peak concentrations of acetaldehyde, independent of sampling location, were in the 10 to 100 µg/m^3 range. Seasonal comparisons, though limited, indicated higher concentrations and exposures in summer than in winter. This is likely to be the result of increased atmospheric photochemical production of acetaldehyde in summer.

The NATA estimated the overall average ambient urban and rural mean concentrations for acetaldehyde to be 1.58 and 0.71 µg/m^3, respectively (EPA 2006b). The one study for which rural ambient monitoring data were available (EPA 2004d) reported a mean concentration of 2.0 µg/m^3. Several studies (Table 2 and Figure 2) reported mean urban concentrations for acetaldehyde in the range of 1 to 7 µg/m^3. Although the available monitoring data were not collected with the express intention of validating NATA estimates, it appears that the NATA model slightly underestimates ambient concentrations in both urban and rural settings.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average urban concentrations of acetaldehyde measured in several other countries are generally within the range of those for U.S. urban areas reported in Table 2 and Figure 2. Ambient concentrations in China, Japan, Denmark, Finland, France, Germany, Greece, Italy, and Sweden are in the range of those seen in the U.S. for urban, urban-roadside, suburban, and rural measurements (Kalabokas et al. 1988; Satsumabayashi et al. 1995; Slemr et al. 1996; Solberg et al. 1996; Granby et al. 1997; Ferrari et al. 1998; Christensen et al. 2000; Possanzini et al. 2000, 2002; Viskari et al. 2000; Nguyen et al. 2001; Sin et al. 2001; Ho et al. 2002; Bakeas et al. 2003; Feng et al. 2004, 2005; Hellén et al. 2004, 2005; Umweltbundesamt 1998).

Measurements in Mexico City (Baez et al. 1995, 2003) and Brazil (Tanner et al. 1988), however, show higher concentrations of acetaldehyde, in the range of 9.8 to 68 µg/m^3 in urban settings and 11 to 439 µg/m^3 in roadway tunnels (Nguyen et al. 2001; Grosjean et al. 2002; Vasconcellos et al. 2005). In recent years in Brazil, there has been increased use of oxygenated fuels, including hydrated ethanol and gasohol (a mixture of gasoline and 24% vol/vol ethanol), which currently account for more than 83% of the fuel used by vehicles in this country (Colón et al. 2001; Corrêa et al. 2003; Corrêa and Arbilla 2005). The use of natural gas in vehicles has been increasing by 20% per year in Brazil. The data from Brazil are of particular interest

because they demonstrate the effects of changes in fuel composition on atmospheric concentrations of aldehydes, such as acetaldehyde and formaldehyde. Montero and colleagues (2001) recorded average and peak acetaldehyde concentrations as high as 36.1 µg/m^3 and 103.6 µg/m^3, respectively, for São Paulo. The authors noted that while direct vehicle emissions appeared to be the primary source of both acetaldehyde and formaldehyde in the morning, photochemistry appeared to be the primary source at midday and in the evening. For Rio de Janeiro, average and peak acetaldehyde concentrations as high as 55.4 µg/m^3 and 83.5 µg/m^3, respectively, have been reported (Corrêa et al. 2003; Corrêa and Arbilla 2005). In general, the highest average and peak urban acetaldehyde concentrations in major Brazilian cities exceed those in U.S. urban areas by a factor of five. Recent increases in the use of natural gas in vehicles in Rio de Janeiro have had little effect on acetaldehyde concentrations but have resulted in a fourfold increase in formaldehyde concentrations and in the formaldehyde:acetaldehyde ratio (Corrêa and Arbilla 2005).

TEMPORAL TRENDS

Data that can be used to assess temporal trends in ambient concentrations of acetaldehyde are limited. Data on seasonal trends in ambient concentrations were reported for multiple sites in California's South Coast Air Basin from April 1998 through March 1999, as part of the Multiple Air Toxics Exposure Study (MATES-II) (South Coast Air Quality Management District 2000). Average concentrations were lowest during May (< 1.8 µg/m^3), rising to a maximum in August (approximately 5 µg/m^3) and then gradually tailed off. The seasonal pattern observed for formaldehyde closely followed that for acetaldehyde. These seasonal patterns suggest direct-source and photochemically generated contributions to the atmospheric concentrations of both acetaldehyde and formaldehyde.

Mohamed and colleagues (2002), using data collected as part of the EPA urban air toxics monitoring program at 13 urban locations in the U.S., reported no common seasonal trend for carbonyls (including acetaldehyde, acrolein, and formaldehyde) at all locations. They noted that the variations in trends from location to location might be a function of complex sources, photochemical processes, and anthropogenic processes that vary by location. Seasonal trend results, however, were not reported specifically for acetaldehyde but for carbonyls as a class. Weisel and colleagues (2005) reported average concentrations of acetaldehyde in Houston that were twice as high in fall and winter (approximately 9 µg/m^3) as in spring and summer. In this study, average concentrations measured in Elizabeth, N.J., were twice as high in spring, summer, and fall (increasing to approximately 10 µg/m^3) as in winter. No clear pattern was observed for Los Angeles. Sax and colleagues (2004) reported only a slight seasonal trend for acetaldehyde measured in New York and Los Angeles, where average concentrations were approximately 4 µg/m^3 or lower.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

The data on the biochemistry and metabolism of acetaldehyde were reviewed and summarized by Morris (1997), Health Canada (2000), and the European Commission (2004). Acetaldehyde is a highly reactive electrophilic compound and thus reacts readily with amino and sulfhydryl moieties of proteins and DNA to form DNA–protein crosslinks. After exposure and absorption via respiratory or oral routes, acetaldehyde is rapidly oxidized to acetic acid in the respiratory tract and liver by the enzyme NAD^+-dependent aldehyde dehydrogenase (Figure 3). The reported half-life of acetaldehyde in circulating blood is less than 15 minutes. Acetic acid is either further metabolized to carbon dioxide and water or enters the body's two-carbon pool for molecular synthesis reactions.

Aldehyde dehydrogenase–mediated metabolism of acetaldehyde in nasal tissue is of particular importance in the toxicity of inhaled acetaldehyde. In the rat, aldehyde dehydrogenase is present in all epithelial cells of the respiratory mucosa except the olfactory mucosa, where it is present only in the basal cells and Bowman's glands (Bogdanffy et al. 1986). This distribution correlates with the susceptibility of the epithelial region to the toxic effects of acetaldehyde. In general, the activities of rat olfactory enzymes are equivalent to those of humans (Bogdanffy et al. 1998).

Acetaldehyde is also produced endogenously in humans during sugar metabolism and thus occurs in trace quantities in human blood. It is the major metabolite of ethanol (Figure 3) and can reach relatively high concentrations in the blood of people who drink alcoholic beverages, especially if they are deficient in certain isoenzymic forms of aldehyde dehydrogenase 1.

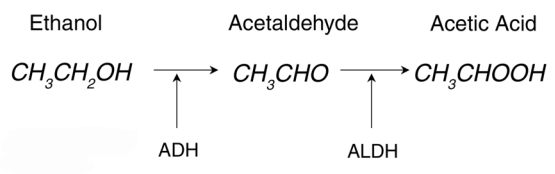

Figure 3. Metabolic pathway of acetaldehyde from ethanol. ADH = Alcohol dehydrogenase. ALDH = Aldehyde dehydrogenase.

NONCANCER HEALTH EFFECTS

Acute Effects

Data on acute toxicity summarized by the American Industrial Hygiene Association (AIHA 2004) show that acetaldehyde has low acute toxicity when inhaled or ingested. The 4-hour LC_{50} of acetaldehyde in rats was reported to be 24,200 mg/m^3 (AIHA 2004).

The primary effect of exposure to acetaldehyde through the air is irritation of the eyes, skin, and respiratory tract. In controlled exposure studies, a 15-minute exposure to 91 mg/m^3 caused eye irritation in most human subjects; some more sensitive subjects experienced irritation at 45 mg/m^3. At 364 mg/m^3, red eyes and transient conjunctivitis were observed. Concentrations greater than 364 mg/m^3 caused irritation of the nose and throat in most subjects (AIHA 2004). In susceptible persons with asthma, acetaldehyde can cause bronchial constriction (AIHA 2004).

Data on skin irritation and sensitization (the process in which a person becomes, over time, increasingly allergic to a substance through repeated exposure to that substance) were reviewed by the European Commission (2004). Exposures to concentrations of acetaldehyde greater than 1% in solution were found likely to be irritating to the skin. There is no clear evidence that acetaldehyde sensitizes skin in humans, although animal studies have demonstrated such a response.

Repeated-Dose Toxicity

Repeated-dose toxicity studies were reviewed and summarized by the AIHA (2004), Health Canada (2000), European Commission (2004), and EPA (1991). Whether acetaldehyde was inhaled or ingested, its toxic effects were limited principally to the sites of initial contact.

The no observed adverse effect level (NOAEL) for respiratory effects was 270 mg/m^3 in rats exposed by inhalation (6 hours/day, 5 days/week) for 4 weeks and 700 mg/m^3 in hamsters exposed for 13 weeks. At the lowest observed adverse effect levels (LOAEL), degenerative changes were observed at concentrations of 437 mg/m^3 in the olfactory epithelium in rats and 2400 mg/m^3 in the trachea in hamsters. Degenerative changes in the respiratory epithelium and larynx were observed at higher concentrations.

In a 28-day study in which acetaldehyde was administered to rats in drinking water to achieve an exposure of 675 mg/kg body weight/day, effects were limited to slight localized thickening of cells of the forestomach (NOAEL of 125 mg/kg body weight/day). After acetaldehyde was administered to rats at a concentration of 0.05% in drinking water for 6 months (yielding exposure of approximately 40 mg/kg body weight/day) synthesis of liver collagen was detected, an observation that was supported by in vitro data.

Reproductive and Developmental Effects

No information was found in the literature about the reproductive or developmental effects of acetaldehyde in humans.

No developmental studies in which acetaldehyde exposure was by the inhalation route were found. Numerous intraperitoneal and intravenous studies have been conducted in animals, mainly as part of investigations of the effects of ethanol, and were reviewed and summarized by the AIHA (2004), Health Canada (2000), and the World Health Organization (WHO 1995). These data suggest that acetaldehyde should probably be considered a potential developmental toxicant at high exposure concentrations or high metabolic-production levels. In fetal rats and mice exposed to acetaldehyde by intravenous or intraperitoneal injections of 50 to 400 mg/kg body weight between days 6 and 15 of gestation, skeletal malformations, reduced birth weight, and increased postnatal mortality have been reported. In the majority of these studies, maternal toxicity was not evaluated.

GENOTOXICITY

The genotoxicity of acetaldehyde was reviewed by Dellarco (1988), Feron and associates (1991), the IARC (1999a), and the WHO (1995). Acetaldehyde was not mutagenic in standard bacterial test systems (Ames test) with or without an exogenous metabolic activation system; it was, however, mutagenic in human lymphocytes and mouse lymphoma cells in the absence of an exogenous metabolism system. Chromosomal aberrations, sister-chromatid exchanges, and micronuclei were induced in in vitro test systems in the absence of exogenous metabolic activation. After intraperitoneal injection, acetaldehyde induced sister-chromatid exchanges in the bone marrow of Chinese hamsters and mice. However, acetaldehyde did not increase the frequency of micronuclei in early mouse spermatids. Acetaldehyde also induced protein–DNA crosslinks but only at concentrations that resulted in cell death (Lambert et al. 1994; Costa et al. 1997; WHO 1995). No conclusions can be drawn from the study's finding of acetaldehyde–DNA adducts in the peripheral white blood cells of alcoholics (Fang and Vaca 1997) in view of the lack of control for the effects of smoking in the study group and the well-known metabolic abnormalities observed in alcoholics. No conclusions can be drawn from the available studies in *Drosophila* either.

CANCER

An increased incidence of nasal tumors in rats and laryngeal tumors in hamsters was observed after inhalation of

acetaldehyde. In experiments in which rats were exposed to 0, 1365 mg/m^3, 2730 mg/m^3, or 5460 mg/m^3 acetaldehyde (reduced to 2730 mg/m^3 at 11 months because of toxicity) for 6 hours/day, 5 days/week for up to 27 months, dose-related increases in nasal adenocarcinomas and squamous-cell carcinomas (significant at all doses) were observed. All concentrations of acetaldehyde administered in these studies induced chronic tissue damage in the respiratory tract; the nasal olfactory mucosa was more sensitive than respiratory mucosa (Feron et al. 1982; Woutersen and Feron 1987). Increases in total malignant tumors, malignant mammary tumors, and hemolymphoreticular neoplasias were observed in rats administered acetaldehyde at concentrations between 50 and 2500 mg/L in drinking water (Soffritti et al. 2002). The overall incidence of carcinomas of the Zymbal gland, external ear ducts, nasal sinuses, and oral cavity increased only in animals treated with the highest concentration. The lack of a dose–response and limitations in reporting (e.g., no details on the methodology were available) make it impossible to draw firm conclusions from these data.

Although acetaldehyde is genotoxic in both in vitro and in vivo test systems, tumors were observed only at inhaled concentrations that produced significant cytotoxicity. Thus, it is likely that both the genotoxicity and irritancy of acetaldehyde play a role in its carcinogenicity. Acetaldehyde would, therefore, be expected to have in vivo activity only at sites such as the olfactory epithelium, where it is not rapidly metabolized to acetic acid and where cytotoxicity occurs.

HUMAN HEALTH

CANCER

Two epidemiologic investigations have examined the possible relationship between occupational exposure to acetaldehyde and cancer (Bittersohl 1974; Ott et al. 1989a,b). Bittersohl (1974) reported a fivefold higher than expected incidence of cancer among 200 German factory workers exposed to 1 to 7 mg/m^3 acetaldehyde as well as to other aldehydes. The workers had squamous-cell cancers of the bronchi (N = 5) and mouth (N = 2) and adenocarcinoma of the stomach (N = 1) and cecum (N = 1). All of the affected workers were smokers. No detailed information on the study design and population was reported. The interpretation of this study is also hampered by the fact that workers were exposed to other chemicals.

Ott and colleagues (1989a,b) conducted a nested case–control study of cancers of the lymphatic and hematopoietic tissues among chemical manufacturing workers. Subjects were identified from a review of the death certificates of male employees who had died between 1940 and 1978. They included 52 with non-Hodgkin's lymphoma, 20 with multiple myeloma, 39 with nonlymphocytic leukemia, and 18 with lymphocytic leukemia (Ott et al. 1989b). Five control subjects for each case subject were selected from the same group of workers. The investigators used subjects' job histories to classify them as ever- or never-exposed to acetaldehyde and 20 other agents and according to duration of exposure (less than 5 years or 5 or more years) (Ott et al. 1989a). The odds ratios associated with ever having been exposed to acetaldehyde were 2.5 for non-Hodgkin's lymphoma (7 cases), 2.3 for multiple myeloma (3 cases), and 1.3 for nonlymphocytic leukemia (3 cases). No subject with lymphocytic leukemia was classified as having been exposed. None of these results was statistically significant. Analysis of non-Hodgkin's lymphoma by duration of exposure found that the increased risk associated with acetaldehyde was concentrated in the subgroup with less than 5 years of exposure to this compound.

The cancer studies of Bittersohl (1974) and Ott and colleagues (1989a,b) have severe limitations for assessing the possible carcinogenic effect of acetaldehyde in humans. These limitations include (1) lack of exposure estimates and of exposure–response data, (2) possible confounding and effect modification by exposures to other agents present in the work environment and by age and smoking in the Bittersohl study (1974), and (3) inadequate statistical precision. Epidemiologic findings about the possible carcinogenic effects of acetaldehyde (Bittersohl 1974; Ott et al. 1989a,b) were not used in the latest EPA risk assessment for acetaldehyde (EPA 1991). The EPA judged the findings as weakly suggesting a possible association between acetaldehyde and various types of cancer but as inadequate for evaluating carcinogenic potential (EPA 1991, 1999b).

NONCANCER HEALTH EFFECTS

Acute health effects of acetaldehyde include eye irritation at 91 mg/m^3 (and occasionally at 45 mg/m^3) as well as bloodshot eyes and reddened eyelids at 364 mg/m^3 (Silverman et al. 1946). Irritation of the skin, mucous membranes, throat, and respiratory tract have also been reported (EPA 1993a).

Acetaldehyde exposure via ingestion and metabolism of alcohol has been reported to cause bronchoconstriction in Japanese adults with asthma (Shimoda et al. 1996; Takao et al. 1998). A polymorphism of the aldehyde dehydrogenase 1 gene, present in up to 50% of Asian populations and 40% of South American Indian populations, appears to contribute to racial variation in the susceptibility of individuals with asthma to bronchoconstriction after

ingestion of alcohol. After consuming alcoholic beverages, persons with a variant form of alcohol dehydrogenase 2 are also less able to metabolize acetaldehyde to acetic acid and are therefore susceptible to intolerance reactions, including bronchoconstriction and exacerbation of asthma. This alcohol-induced asthma is believed to be due to histamine release stimulated by abnormally high levels of metabolic acetaldehyde. These studies of exposure to acetaldehyde through ingestion of alcohol have limited relevance to the issue of the human health effects of exposure to acetaldehyde as an air pollutant.

Several studies have evaluated the effects of inhalation of aerosolized acetaldehyde on bronchoresponsiveness in individuals with asthma. A series of small, randomized, double-blind clinical studies in Japan, each including 9 to 18 subjects, found that inhalation of aerosolized acetaldehyde caused bronchoconstriction in adults with asthma (Myou et al. 1993, 1994a,b, 1995); no such effects were reported in nonasthmatic adults (Myou et al. 1993).

Only one investigation has evaluated the relationship between concentrations of acetaldehyde in outdoor air and the occurrence of asthma symptoms (Delfino et al. 2003). This panel study, conducted in California from November 1999 through January 2000, included 22 Hispanic children, ages 10 to 16 years, with physician-diagnosed asthma, living in an area of Los Angeles County characterized by high traffic density. The subjects were nonsmokers who lived in nonsmoking households. The investigators analyzed daily outdoor concentrations of acetaldehyde and 19 other pollutants in relation to the severity of asthma as self-reported daily in subjects' diaries. Acetaldehyde concentrations ranged from 1.9 to 10.5 $\mu g/m^3$, with a mean of 5.66 $\mu g/m^3$ (standard deviation [SD] = 1.82 $\mu g/m^3$) and an interquartile range of 2.38 $\mu g/m^3$. The concentrations strongly correlated with the concentrations of a number of other pollutants. The odds ratios for moderate asthma symptoms were 1.39 (95% confidence interval [CI], 0.80–2.41) for the interquartile range increase in acetaldehyde measured on the same day as the symptoms and 1.48 (95% CI, 1.16–1.87) for the interquartile range increase in acetaldehyde measured on the previous day. The odds ratios for more severe asthma symptoms were 1.57 (95% CI, 0.70–3.54) for the interquartile range increase in acetaldehyde measured on the same day as the symptoms and 1.36 (95% CI, 0.87–2.14) for the interquartile range increase in acetaldehyde measured on the previous day. Exposure to acetaldehyde was statistically correlated significantly and positively with exposure to other pollutants. For example, the Spearman correlation coefficient for exposure to acetaldehyde in addition to exposure to another pollutant was 0.79 for formaldehyde, 0.50 for benzene, 0.63 for ethylbenzene, 0.68 for toluene, and 0.65 for xylene. The effects of acetaldehyde were attenuated after adjustment for 8-hour maximum SO_2 concentration or 8-hour maximum NO_2 concentration. The study had a number of limitations, including small sample size and the resulting imprecision, the potential for inaccurate reporting of asthma symptoms resulting from the use of diaries, and the possibility of confounding by other pollutants as well as by other factors.

A single-blind study in patients from a clinic in Spain investigated differences in airway responsiveness to inhaled acetaldehyde and methacholine in 61 nonsmoking adult clinic patients with mild asthma and 20 nonsmoking healthy volunteers (Prieto et al. 2000). The study found that 56 (92%) of the 61 asthmatic patients showed evidence of bronchoconstriction. In the 56 asthmatic patients, FEV_1 (forced expiratory volume in 1 second) declined by at least 20% after inhalation of acetaldehyde (the geometric mean concentration that resulted in more than a 20% decline in FEV_1 was 17.55 mg/mL). None of the healthy subjects had bronchoconstriction after exposure.

A second study in clinic patients in Spain evaluated the effect of inhaled acetaldehyde (at concentrations up to 40 mg/mL) and methacholine on airway responsiveness (Sanchez-Toril et al. 2000). The main purpose was to determine whether challenge with acetaldehyde is a more specific test than challenge with methacholine for differentiating chronic bronchitis from asthma. The subjects were 62 clinic patients with asthma and 59 smokers with chronic bronchitis either alone (N = 32) or in combination with chronic obstructive pulmonary disease (N = 27). In 57 (92%) of the 62 asthmatic patients—compared with only 3 (5%) of the patients with chronic bronchitis—FEV_1 declined at least 20% after inhalation of acetaldehyde.

A third study in Spain examined the effect of inhaled acetaldehyde on lung function in 16 patients with asthma, 43 nonasthmatic patients with allergic rhinitis, and 19 healthy volunteers (Prieto et al. 2002b). All subjects were nonsmokers, and the study was single-blind. The study found that in 13 (81%) of the 16 patients with asthma, 8 (19%) of the 43 patients with allergic rhinitis, and none of the 19 healthy subjects, FEV_1 declined at least 20% after inhalation of acetaldehyde (the geometric mean concentration that resulted in a greater than 20% decline in FEV_1 was 35.5 mg/mL for asthmatic patients and 67.7 mg/mL for those with allergic rhinitis). The difference in the prevalence of a positive airway response between patients with allergic rhinitis and the healthy subjects was not statistically significant (P = 0.09). Bronchoconstriction

in response to acetaldehyde exposure depended on the presence of airway hyperresponsiveness to methacholine.

A fourth study in Spain investigated the relationship between airway responsiveness to inhaled acetaldehyde (up to 80 mg/mL), methacholine, and adenosine 5′-monophosphate and determined the repeatability and side effects of acetaldehyde challenge (Prieto et al. 2002a). All subjects were clinic patients, nonsmokers with mild, intermittent asthma. The study was single-blind. The first study component included 16 subjects and found that 12 (75%) of them experienced bronchoconstriction after exposure to acetaldehyde, that the geometric mean concentration producing a greater than 20% decline in FEV_1 was 38.9 mg/mL, and that responsiveness to the three agents was correlated. The second component, which included 14 subjects, found that the response to inhaled acetaldehyde was moderately repeatable; that the side effects of exposure included cough, dyspnea, and throat irritation; and that acute bronchoconstriction due to acetaldehyde inhalation was reversed within 15 minutes after the administration of inhaled salbutamol.

The findings in these studies of lung-function changes in response to inhaled acetaldehyde are limited in their generalizability to the human health effects of exposure to acetaldehyde as an air pollutant because of the special exposure settings and the focus on acute effects. Also, the procedures used to select subjects from clinic populations were not described in detail, and thus selection bias in these studies was possible.

REGULATORY SUMMARY

Acetaldehyde is classified by the National Institute of Occupational Safety and Health as "a potential human carcinogen," by the EPA (1991) as Group B2 ("a probable human carcinogen"), and by the U.S. NTP (2005) as "reasonably anticipated to be a human carcinogen via inhalation exposure," based on sufficient evidence in laboratory animals and inadequate evidence in humans. It is classified by the IARC (1999a) as Group 2B ("possibly carcinogenic to humans").

The reference concentration (RfC) for acetaldehyde is 9 $\mu g/m^3$ (EPA 1991), based on a NOAEL (human equivalent concentration, HEC) of 8.7×10^3 $\mu g/m^3$ for degeneration of olfactory epithelium in male rats after a 4-week inhalation exposure (Appelman et al. 1982, 1986) and an uncertainty factor of 1000.

A search of the literature and published regulations for North America, Asia, Australia, and Europe did not reveal any exposure standards for acetaldehyde.

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

Sources of acetaldehyde exist outdoors and indoors. Outdoor concentrations are the result of both direct emissions from mobile sources and photochemical reactions in the atmosphere. On-road mobile sources account for approximately 30% of total nationwide acetaldehyde emissions. Although potentially limited in numerous respects (sample collection and analysis methods, number and type of environments sampled, number of samples collected, methods of accounting for presence or absence of sources, extent of geographic and seasonal variability, representativeness of residences and populations sampled, extent of sampling for sensitive populations, and other factors), available data provide some general insights into acetaldehyde exposures. Concentrations tend to be lowest outdoors, ranging from 1 to 7 $\mu g/m^3$, and from 2 to 10 times higher in indoor spaces and inside vehicles. Personal-exposure concentrations tend to be higher than concentrations in residences and to be similar for adults and children. Overall, average and peak concentrations, independent of sampling location, appear to be below 100 $\mu g/m^3$. The highest average and peak ambient concentrations of acetaldehyde in São Paulo and Rio de Janeiro, Brazil, where over 83% of vehicles use either hydrated ethanol or a mixture of gasoline and 24% vol/vol ethanol, were higher by a factor of approximately 5 or more than those measured in U.S. urban areas.

TOXICOLOGY

In humans, acetaldehyde is an irritant of the eye, skin, and respiratory tract starting at concentrations of about 45 mg/m^3. In subchronic inhalation studies in animals, the NOAEL for respiratory effects is about 455 mg/m^3. Higher concentrations lead to degenerative changes in the olfactory and respiratory epithelia. These concentrations are generally several orders of magnitude higher than those typically observed in ambient, outdoor, or indoor air. In the body, acetaldehyde is formed from alcohol by alcohol dehydrogenase and is then metabolized to acetic acid. It is a clastogen both in vitro and in vivo. The nasal tumors observed in animals in inhalation experiments occurred at cytotoxic concentrations only, and it is likely that acetaldehyde's genotoxicity and irritating properties, with the consequent increased cell proliferation, both play a role in its carcinogenicity.

HUMAN HEALTH

The data on the possible carcinogenicity of acetaldehyde in humans are inadequate, and the data on respiratory effects are limited mainly to small clinical investigations using exposure challenges with aerosols of acetaldehyde in asthmatic patients. There has been only one epidemiologic study of environmental exposure to acetaldehyde. This was a study of children with asthma, and it was small and was unable to distinguish the effects of acetaldehyde from those of other pollutants. The effect of environmental exposure on other respiratory conditions has not been investigated. Indoor sources of acetaldehyde account for most environmental exposure, and both ambient and indoor air concentrations at present appear to be well below those that are known to produce adverse health effects. Thus, there is no conclusive evidence that acetaldehyde in ambient air, at current levels, adversely affects human health.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of acetaldehyde?

Mobile sources are an important, but not the only important, source of acetaldehyde. Urban concentrations of acetaldehyde measured in Brazil, where ethanol is widely used in motor vehicles as an alternative to conventional fuels, suggest that acetaldehyde concentrations elsewhere might increase in the future if the use of alcohols in fuels increases.

2. Does acetaldehyde affect human health?

Acetaldehyde is an irritant in humans at concentrations greater than 10 mg/m^3.

3. Does acetaldehyde affect human health at environmental concentrations?

There is no evidence to suggest that current ambient concentrations of acetaldehyde adversely affect human health.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

Data from studies in Brazil suggest that increased use of alcohols as alternative fuels and in fuel blends might increase ambient concentrations of acetaldehyde. The effect of such emissions on ambient air quality is unknown, as is whether such emissions increase the risk of adverse effects on human health. Research recommendations for acetaldehyde include the following:

- Continue to update, critically evaluate, and compare the NATA model to actual measurements to improve its usefulness in predicting the effects of increased use of alcohols in motor-vehicle fuels on ambient acetaldehyde concentrations.
- Average and peak concentrations of acetaldehyde are highest inside urban vehicles, in homes, schools, and personal exposures. Therefore studies are needed to better characterize the sources and factors associated with acetaldehyde concentrations in these settings.
- Establish a monitoring network capable of tracking long-term acetaldehyde concentrations because an increase in the use of alcohols as motor-vehicle fuels is likely.
- Assess acetaldehyde exposures of subpopulations that might be at especially high risk for adverse health effects (e.g., people with asthma).

TOXICOLOGY

The mechanisms of the induction of cancer by acetaldehyde are not yet understood. Data on the carcinogenic potency of acetaldehyde in animals have not been extrapolated to humans. Data on reproductive and developmental toxicity are inconclusive. Research recommen-dations for toxicology studies of acetaldehyde include the following:

- Extrapolate the data on acetaldehyde cancer potency across exposures and species.
- Clarify the mechanism of carcinogenicity in humans, including the quantitative relationship between DNA–protein crosslinks and mutations and the time course of the removal of these crosslinks.

HUMAN HEALTH

The simultaneous exposure of humans to acetaldehyde and other upper-respiratory-tract toxicants, such as acrolein, formaldehyde, crotonaldehyde, furfural, glutaraldehyde, and ozone, might lead to additive or synergistic effects, particularly sensory irritation and possibly cytotoxic effects on the nasal mucosa. Research recommendations for human-health studies of acetaldehyde include the following:

- Identify additive or synergistic effects on human health from simultaneous exposure to acetaldehyde and other upper-respiratory-tract toxicants, including other air toxics and particulate matter.

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Acrolein

INTRODUCTION

Acrolein (CAS Registry Number 107-02-8; C_3H_4O; molecular weight = 56.1) (Figure 4), also known as 2-propenal, is a volatile, highly electrophilic α,β-unsaturated aldehyde with a boiling point of 53°C. It is highly reactive in air and has a half-life of 1 day. It is commonly found in smoke from burning organic matter. Acrolein is released into the ambient air through the combustion of gasoline, oil, coal, and tobacco. It is also a by-product of fire and of 1,3-butadiene reactions in the atmosphere. In manufacturing processes, it is used to produce acrylic acid, which is used in turn to make acrylate polymers. In addition, it is used as a biocide to control aquatic flora and fauna. Acrolein is a metabolite of the cancer-chemotherapy agent cyclophosphamide.

At one atmosphere pressure and 25°C, 1 ppm acrolein is equivalent to 2.33 mg/m^3.

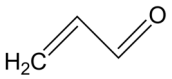

Figure 4. Structure of acrolein.

BENCHMARK LITERATURE

The following evaluation of research literature on acrolein is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from the EPA (2000c), the Agency for Toxic Substances and Disease Registry (ATSDR 2005c), and Weisel and colleagues (2005). Personal-exposure data are from a large study funded by HEI (Weisel et al. 2005). Data on outdoor and indoor residential concentrations of acrolein are also from the HEI study (Weisel et al. 2005) and represent one of the largest data sets available. Data summaries from the EPA Air Quality System database (2004a) were used to calculate urban, suburban, and rural concentrations of acrolein.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

EXPOSURE

SOURCES AND EMISSIONS

According to the National Air Toxics Assessment (NATA), in the U.S., on-road mobile sources account for 13.7% of acrolein emissions nationwide, 24.4% of all emissions in urban areas, and 5.4% of all emissions in rural areas (EPA 2006b). The oxidation of atmospheric 1,3-butadiene, which is emitted from motor vehicles, is an important source of acrolein in ambient air (ATSDR 2005a,c). The concentration of acrolein in motor vehicle exhaust is 0.47 mg/m^3 (Swarin and Lipari 1983). An important indoor source of acrolein is cigarette smoke (EPA 2000c; ATSDR 2005c). Acrolein is present in the vapor phase of cigarette smoke at 8.2 µg per 40-mL puff (Feron et al. 1978). Acrolein concentrations in mainstream smoke have been estimated to range from 3 to 220 $µg/m^3$ per cigarette (ATSDR 2005c) and in sidestream smoke from 100 to 1700 $µg/m^3$ (ATSDR 2005c). Proximity to a smoker or to enclosed spaces where smoking occurs might represent potentially important acrolein exposures.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Relatively little air-monitoring data exist for acrolein, in part because of its high reactivity, its short half-life (1 day), and measurement limitations. It has been suggested that some of the current methods for measuring acrolein have poor sensitivity, selectivity, and reproducibility. These limitations have in turn led to the speculation that concentration data reported in the literature might underestimate actual exposure concentrations. The limitations are associated with the use of sorbent-filled cartridges containing carbonyl-derivatizing agents for the collection of unsaturated carbonyls such as acrolein. The limitations include instability of the dinitrophenylhydrazine (DNPH)–acrolein hydrazone during collection and storage, poor chromatographic separation of complex carbonyl mixtures found in ambient and indoor air, and potential ozone interference (Seaman et al. 2006; Cahill et al. in press). A sampling method recently developed and used to monitor ambient urban, residential, and personal-exposure concentrations of acrolein might have overcome these limitations and might be yielding more reliable data (Weisel et al. 2005).

Table 3 and Figure 5 show the range of mean and maximum concentrations of acrolein in μg/m^3 measured outdoors, indoors, and by personal-exposure monitoring. Outdoor locations include urban, urban roadside, urban in-vehicle, suburban, and rural environments. Indoor spaces include residences and schools. Personal-exposure data are reported for adults and children. Sampling times ranged from 1 hour (Destaillats et al. 2002; Fitz et al. 2003) to 6 days (Sawant et al. 2004), with sample-averaging times ranging from a few hours (e.g., Destaillats et al. 2002) to 1 year (e.g., Sax et al. 2004). The number of measurements per study, from which the mean and maximum concentrations were determined, ranged from a low of 6 for a tunnel study (Destaillats et al. 2002) to a high of 2574 for the combined urban–suburban–rural category from the Air Quality System data set (EPA 2004a). The 2574 individual

Table 3. Acrolein Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3)		Citations	Comments
			Mean	Maximum		
Outdoor Areas						
Urban						
	27 averages*	Yearly	0.6	1.96**	EPA 2004a	
	—	Yearly	0.13	—	EPA 2006b	Model
	395	Yearly	6.3	11.9	Sax et al. 2004	Summer and winter
Urban in-vehicle						
	31	60–90 hr	—	0.5	Fitz et al. 2003	Bus
	50	7–15 hr	0.04	1.0	Riediker et al. 2003	Patrol cars
Urban roadside						
	6	4 hr	—	0.14	Destaillats et al. 2002	
	8	2 hr	—	0.6	Grosjean and Grosjean 2002	Tunnel
	10		—	0.31	Grosjean and Grosjean 2002	Tunnel
Suburban						
	30 averages*	Yearly	0.8	2.33**	EPA 2004a	
Rural						
	—	Yearly	0.03		EPA 2006b	Model
	10 averages*	Yearly	0.5	1.8**	EPA 2004a	
Indoor Spaces						
Residences						
	30	100 min	< 2.0	< 2.0	Feng and Zhu 2004	
	14	24 hr	< 0.1	< 0.1	Reiss et al. 1995	Winter
	26	24 hr	< 0.1	< 0.1	Reiss et al. 1995	Spring
	83	6 days	1.4	3.6	Sawant et al. 2004	
	62	24 hr	4.1***	21.0	Sheldon et al. 1992	
	398	2 seasons	1.7	14.8	Weisel et al. 2005	Summer and winter
Schools						
	28	6 days	1.2	2.1	Sawant et al. 2004	Classrooms
Personal Exposures						
	409	2 days	12.9	11.2	Weisel et al. 2005	Adults
	169	2 days	10.9	> 8.3$^+$	Weisel et al. 2005	Children

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 2,574 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average; *** = median; $^+$ 99th percentile = 504 μg/m^3 (this appears to be an outlier, so 95th percentile is used).

measurements contained in this data set were broken down as mean urban, suburban, and rural concentrations. The mean urban concentration of 0.14 μg/m^3 and the mean rural concentration of 0.04 μg/m^3 shown in Figure 5 were estimated by using the NATA model (EPA 2006b).

Only seven of all the studies reviewed reported concentrations of acrolein in ambient air. Although data are limited, there does appear to be an increasing gradient in mean and maximum concentrations from rural to suburban to urban, with mean values ranging from 0.5 to 6.3 μg/m^3 and maximum values ranging from 1.8 to 11.9 μg/m^3. The NATA reported a nationwide estimated mean concentration of 0.11 μg/m^3, with estimated concentrations of 0.13 μg/m^3 and 0.03 μg/m^3 for urban and rural areas, respectively (EPA 2006b). These estimated concentrations are an order of magnitude lower than measured concentrations. Although limited, the data for urban roadside and urban in-vehicle acrolein measurements suggest that exposures in these environments are considerably lower at both mean and maximum concentrations than in other outdoor spaces, residences, schools, or personal exposures. Measurements from tunnel studies indicate that acrolein concentrations are surprisingly low (< 0.6 μg/m^3), given that on-road mobile sources account for 24% of urban acrolein emissions.

Six studies reported acrolein concentrations in residences, and one reported concentrations measured in school classrooms. In three of the six residential studies, concentrations were below the limit of detection. In the remaining three—one of which used a collection system designed to overcome the limitations of existing methods (Weisel et al. 2005)—residential concentrations were similar to outdoor concentrations, with mean concentrations of less than 10 μg/m^3 and one maximum concentration of 21 μg/m^3. Two of the studies were conducted in households of nonsmokers (Sheldon et al. 1992; Sax et al. 2004). Although environmental tobacco smoke is an important source of acrolein indoors, none of the studies reviewed here included households of smokers. The one study reporting classroom measurements found acrolein concentrations to be low, with a mean concentration of 1.2 μg/m^3 and maximum concentration of 2.1 μg/m^3 (Sawant et al. 2004).

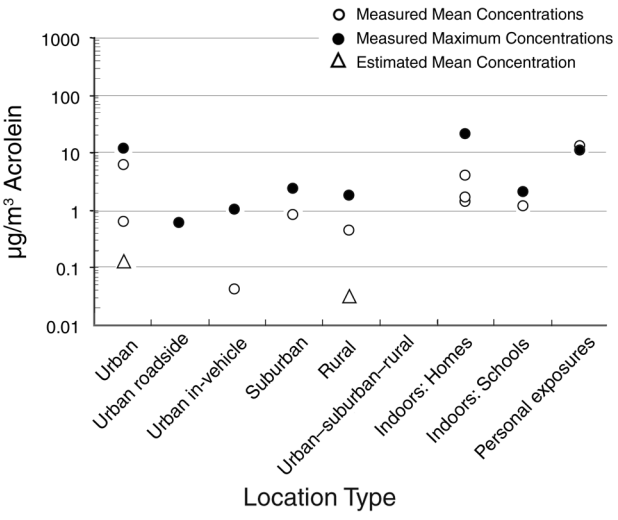

Figure 5. Concentrations of acrolein (μg/m^3) at various locations. Data for figure are from Table 3.

The one study that used the improved collection system made extensive measurements of personal acrolein exposure as well as indoor residential and outdoor exposure for a group of nonsmoking adults and children (Weisel et al. 2005). Mean and maximum personal exposures for adults tended to be similar and in the range of 11 to 12 μg/m^3. Mean personal-exposure concentrations were twice those measured outdoors and six times those measured inside the residence. Maximum personal-exposure concentrations tended to be similar to those measured both outside and inside the home. The study compared two types of samplers used to measure concentrations of acrolein (an active sampler with DNPH-coated filters and a passive sampler with dansylhydrazine-coated filters). In the study (Weisel et al. 2005) and in two prior studies (Zhang et al. 1994; Zhang et al. 2000), the samplers containing DNPH-coated collection media were found to underestimate acrolein concentrations by a factor of two. Many of the available data on acrolein concentrations were collected using DNPH-coated samplers like these, leading to the conclusion that measurements made with such samplers might be underestimating acrolein concentrations.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

A survey of the published literature found only one study with a measurement of detectable ambient acrolein concentrations outside the U.S. This measurement (1.48 μg/m^3 in a bus station in China) was in the range of measurements obtained in the U.S. (Feng et al. 2005).

TEMPORAL TRENDS

At present, the limited number of measurements and the unreliability of sampling methods make an assessment of temporal trends in ambient concentrations of acrolein impossible.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

Inhalation is the main route of exposure to acrolein. The metabolism of acrolein in rats has been described (Draminski et al. 1983) (Figure 6). Acrolein reacts readily with glutathione, depleting this antioxidant in tissues, and is excreted as a mercapturic acid in the urine. This is the major pathway for detoxification. Acrolein can be oxidized in the liver by alcohol dehydrogenase to acrylic acid or by liver or lung microsomal cytochrome P450s to form the epoxide glycialdehyde, which is hydrolyzed in turn to form glyceraldehyde.

BIOMARKERS

No reliable biomarkers have been reported for either exposure to or effects of acrolein (ATSDR 2005c). Early studies suggested that 3-hydroxypropyl mercapturic acid in urine might be useful as a biomarker for acrolein, but it did not correlate well with exposure (Alarcon 1976).

NONCANCER HEALTH EFFECTS

The LC_{50} for 4- to 6-hour inhalation exposures of acrolein in mice, rats, rabbits, and guinea pigs is approximately 23 mg/m^3 (Kane et al. 1979; Beauchamp et al. 1985). The major toxicologic properties of the compound are that it is extremely irritating and that it binds irreversibly to the tissues of the respiratory tract when inhaled. For

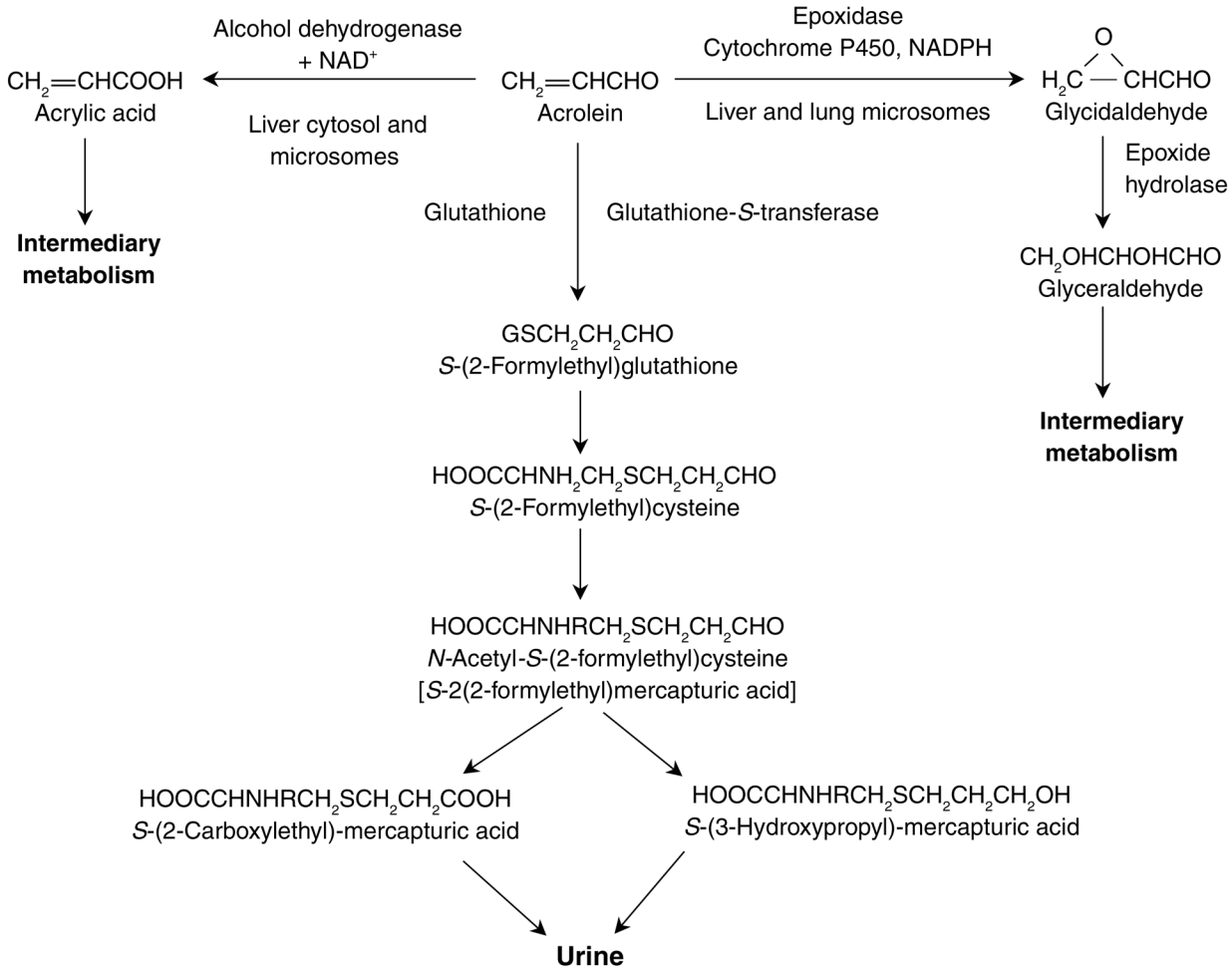

Figure 6. Metabolic pathway of acrolein. R = COCH. (Modified from Draminski et al. 1983, with the permission of Springer Science and Business Media.)

this reason, inhaled acrolein does not distribute well to other organs. Acrolein inhibited the respiratory rate in mice at a concentration of 1.6 mg/m^3 (Steinhagen and Barrow 1984) and in rats at a concentration of 14 mg/m^3 (Babiuk et al. 1985). As reviewed by the World Health Organization (WHO 1992; International Agency for Research on Cancer [IARC] 1995), repeated inhalation of acrolein in rats, guinea pigs, rabbits, Syrian hamsters, monkeys, and dogs caused reduction in body weight and interference with pulmonary function as well as a variety of histopathological changes in the nose, airways, and lungs. The exposure concentrations ranged from 0.5 to 11 mg/m^3 for periods of up to 13 weeks.

In obligate nose breathers, the nose was a sensitive target organ because of the reactive nature of the compound. In all species studied, neutrophilic infiltration and focal squamous-cell hyperplasia and metaplasia were observed in the upper respiratory tract. Repeated exposure of dogs to 4 mg/m^3 for 24 hours/day for 90 days resulted in confluent bronchopneumonia. Guinea pigs and rats showed focal liver necrosis after similar exposures to 2 mg/m^3. In rats and rabbits exposed to acrolein for 13 weeks at 1 to 11 mg/m^3, tracheal inflammation, mucous-gland hyperplasia, epithelial metaplasia, bronchiolitis, accumulations of alveolar macrophages, and focal interstitial pneumonitis (at high doses only) were observed (Feron et al. 1978). More recent studies have focused on the molecular interactions of acrolein with tissues (Kehrer and Biswal 2000). At low doses, as would be expected in tissues after inhalation exposure, acrolein inhibited cell proliferation without causing cell death and might have enhanced apoptosis induced by other toxins. Kehrer and Biswal suggested that the acrolein-mediated decrease in cell proliferation was caused by changes in expression of growth- or stress-related genes or transcription factors secondary to the depletion of glutathione known to be caused by acrolein. Acrolein was ciliostatic in rabbit tracheal slices (Dalhamn and Rosengren 1971). No reproductive toxicity was seen in rats or rabbits treated with acrolein by gavage.

GENOTOXICITY

In Vivo

No studies have reported genotoxic effects of acrolein in humans or animals by any route of exposure (ATSDR 2005c). Acrolein did not induce DNA damage in rats or dominant-lethal mutations in mice treated in vivo (Epstein et al. 1972). Acrolein induced both somatic and germinal mutations in insects (IARC 1995).

In Vitro

Acrolein binds chemically with proteins and DNA in vitro, but DNA adducts have not been detected in exposed animals (Nelsestuen 1980; Chung et al. 1984). Acrolein induced DNA damage and mutation in bacteria (IARC 1995). Based on a recent summary of the genotoxicity of acrolein (ATSDR 2005c), acrolein is weakly mutagenic in bacteria without an exogenous metabolism system and nonmutagenic in bacteria with an exogenous metabolism system. In yeast, acrolein was not mutagenic unless there was exogenous metabolism.

In cultured mammalian cells, acrolein induced gene mutation, sister-chromatid exchange, and DNA damage in some, but not all, mammalian-cell test systems (ATSDR 2005c). It also acted as a potent inhibitor of the DNA repair enzyme O^6-methylguanine-DNA methyl transferase (ATSDR 2005c).

Acrolein forms DNA adducts on synthetic oligonucleotides at deoxyguanosine sites, and this lesion might be responsible for mutagenic activity (D'Isa et al. 2004). There were many of these adducts on telomeric repeat regions, and preliminary results suggested that acrolein can form adducts on synthetic oligodeoxyribonucleotides containing such telomeres (D'Isa et al. 2004).

Acrolein causes DNA adducts in human tissues and this adduct formation is related to exposure—presumably to cigarette smoke. Nath and Chung (1994) developed a sensitive ^{32}P-postlabeling method combined with high-performance liquid chromatography to detect exocyclic adducts resulting from binding at two sites of bases involved in the hydrogen bonding that maintains the double-helical structure of DNA. They found 1,N^2-propanodeoxyguanosine adducts of acrolein and crotonaldehyde in human liver DNA; the number of acrolein adducts detected was 0.3 to 2.0 adducts in 10^6 guanine bases, which was considered to be a very high concentration and indicative of exposure to cigarette smoke. In another study, Nath and colleagues (1998) noted that acrolein was present in cigarette smoke at 100 to 1000 µg/cigarette (depending on the brand) and in automobile exhaust, and that acrolein could also be a product of endogenous lipid peroxidation. They analyzed the aforementioned adducts in gingival DNA from 11 smokers and found that mean acrolein-derived 1,N^2-propanodeoxyguanosine concentrations were 1.36 ± 0.90 µmol/mol guanine in the 11 smokers compared with 0.46 ± 0.26 µmol/mol guanine in 12 nonsmokers (P = 0.003). Cohen and colleagues (1992) reported that acrolein induced bladder cancer in rats when 2 mg/kg body weight of acrolein was injected intraperitoneally twice a week for 6 weeks, followed by

administration of uracil as 3% of the diet for 20 weeks (18 of 30 rats, compared with 8 of 30 rats exposed to control solvent). An identical 6-week acrolein protocol followed by a control diet produced no tumors. A 26-week acrolein exposure protocol had to be stopped at 21 weeks because of severe toxicity. Most important, Feng and colleagues reported that in cultured cells from normal human bronchial epithelia, acrolein formed DNA adducts on the p53 tumor-suppressor gene at mutational hot spots at CpG sites where G→T transversions occur (Feng et al. 2006). In addition, acrolein can form DNA adducts at p53 codon 249, which is a lung cancer mutational hot spot that does not form adducts with benzo[*a*]pyrene. Acrolein greatly reduces nucleotide-excision repair capacity, the major repair pathway for bulky DNA damage.

CANCER

In Vivo

Acrolein is metabolized in vitro by liver and lung microsomes to glyceraldehyde, which is carcinogenic to mice after skin application and to mice and rats after subcutaneous injection, producing tumors at the site of application (IARC 1987). In three carcinogenicity studies of orally administered acrolein (two in rats and one in mice), no treatment-related increases in tumor frequency were observed (IARC 1987). One inhalation study was conducted in Syrian hamsters for 52 weeks (with an exposure concentration of 0 or 9 mg/m^3); no increase in neoplasia was observed (IARC 1987). In another study of mice, application of acrolein to skin did not increase the number of papillomas (IARC 1995). An increased incidence of urinary bladder papillomas was observed in rats receiving intraperitoneal injections of acrolein in combination with uracil in the diet; no papillomas were observed with acrolein treatment alone (IARC 1987). In a study at the National Center for Toxicological Research, 150 or 75 nmol acrolein was injected intraperitoneally twice into neonatal B6C3F1 mice. Liver adenomas were observed in 5 of 96 male mice injected with the 75 nmol dose. These results showed that neonatal mice were relatively insensitive to acrolein (Von Tungeln et al. 2002).

HUMAN HEALTH

CANCER

No studies of the carcinogenicity of acrolein in human populations were identified.

NONCANCER HEALTH EFFECTS

Acrolein is a respiratory irritant starting at concentrations as low as 700 µg/m^3 in humans and is reactive in cell cultures; it causes growth inhibition, increased cell-membrane permeability, and apoptosis (Feron et al. 1978; Kehrer and Biswal 2000; Finkelstein et al. 2001; Biswal et al. 2002). Acrolein is highly reactive with sulfhydryl groups (cysteine, histidine, and lysine) and is endogenously produced during lipid peroxidation. Studies of firefighters exposed to wood smoke in prescribed burns in the western U.S. found a work-shift effect of −125 mL for FEV_1 (forced expiratory volume in one second). However, the presence of acrolein in smoke was correlated with that of other compounds, making it impossible to distinguish the effects of the acrolein (Slaughter et al. 2004).

Acrolein can inhibit human alveolar-macrophage release of interleukin (IL)-1β, IL-12, and tumor necrosis factor-α (TNF-α) after in vitro exposures, probably by inhibiting effects on nuclear factor-κB (NFκB) (Li L et al. 1999). In cell culture exposures, 5 to 25 µM acrolein reduced levels of IL-8 mRNA and protein, apparently through effects on NFκB (Valacchi et al. 2005). Earlier studies (Cantral et al. 1995) showed that cigarette smoke inhibited the ability of cultured normal human bronchial epithelial cells to attach to the extracellular matrix and to migrate in response to chemotactic stimuli. When such cells were exposed to acrolein concentrations (5, 10, or 25 µM) chosen to mimic doses that lung epithelial-lining fluid would receive after exposure to mainstream or sidestream tobacco smoke, a dose-related decline in IL-8 protein and mRNA and subsequent TNF-α stimulation were observed. Because IL-8 has NFκB binding sites on its promoter, the authors speculated that these effects were mediated through the oxidation of cysteines in the DNA-binding domain of NFκB, thus affecting DNA-binding capacity. Acrolein also caused an increase in the inhibitory IKKβ, which might prevent the release of NFκB from the cytoplasm to the nucleus, and inhibited activated protein-1 activity in A549 lung-adenocarcinoma cells because of altered glutathione imbalance (Biswal et al. 2002). Thioredoxin also contains thiol groups and was reduced in A549 cells after exposure to acrolein (Yang et al. 2004).

Acrolein causes apoptosis of human alveolar macrophages (Li L et al. 1997) and bronchial epithelial cells when administered in vitro. These effects occur through the mitochondrial pathway by liberating cytochrome c, activating the initiator caspase-9, activating the effector caspase-7, and inhibiting the enzymatic activity of caspase-3 (Tanel and Averill-Bates 2005). Apoptosis occurs at doses ranging from 5 to 25 µM of acrolein. Higher doses might cause cell necrosis. Both α-tocopherol and

ascorbic acid can modulate the apoptotic effects (Nardini et al. 2002).

Acrolein induces a dose-dependent increase in reactive oxygen species from brain mitochondria and decreases glutathione content (Luo and Shi 2005). It can induce mitochondrial stress in brain mitochondria or spinal-cord tissue (Shi et al. 2002; Luo and Shi 2004). Acrolein exposure can lead to time- and dose-dependent reactive oxidant species generation and lipid peroxidation in spinal-cord tissue. Antioxidants can reduce acrolein-induced membrane damage and cell death. All of these studies involved in vitro exposures; their relevance to human in vivo exposures is not known.

REGULATORY SUMMARY

In its evaluation of the carcinogenicity of acrolein, the IARC concluded that there is inadequate evidence for the carcinogenicity of acrolein in humans. The IARC also stated that there is inadequate evidence for the carcinogenicity of acrolein in laboratory animals and concluded that the carcinogenicity of acrolein is therefore not currently classifiable in humans (IARC 1995).

The reference concentration (RfC) for acrolein is 0.02 $\mu g/m^3$ (EPA 2003a), based on a human equivalent concentration lowest observed adverse effect level (LOAEL [HEC]) of 20 $\mu g/m^3$ for nasal lesions in rats exposed for 13 weeks (Feron et al. 1978) and an uncertainty factor of 1000.

A search of the literature and published regulations for North America, Asia, Australia, and Europe did not reveal any exposure standards for acrolein.

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

On-road mobile sources account for approximately 24% of ambient acrolein emissions in urban areas. The oxidation of 1,3-butadiene, a component of mobile-source emissions, is an important source of acrolein emissions. Environmental tobacco smoke is a major source of acrolein indoors. Because of the limited number of studies, the highly reactive nature of acrolein, and the limitations in sampling methods, the available environmental data for acrolein do not appear to be sufficient to allow an assessment of ambient, indoor, or personal exposures. Additional limitations include the number and type of environments sampled, the number of samples collected, the method of accounting for the presence or absence of sources, the extent of geographic and seasonal variability, the representativeness of residences and populations sampled, and the extent of sampling for sensitive or at-risk populations. The available data did suggest, however, that personal mean and peak exposures for adults and children were similar and were lower than 15 $\mu g/m^3$ and that mean personal exposures were two or more times higher than measured ambient or indoor concentrations. Peak personal-exposure concentrations were similar to peak ambient concentrations. The highest peak concentration, at 21 $\mu g/m^3$, was recorded in a residence. The limited data for urban roadside and urban in-vehicle acrolein concentrations suggested that exposures in these environments were considerably lower, both as mean and peak concentrations, than for other outdoor areas, residences, schools, or personal exposures. Measurements from tunnel studies indicated concentrations that were surprisingly low (< 0.6 $\mu g/m^3$), given that on-road mobile sources, again, account for 24% of urban acrolein emissions. Differences in sampling and sample analysis might affect the absolute concentrations reported in the various studies, but it was beyond the scope of this report to assess sampling and sample analysis.

TOXICITY

Acrolein is a reactive, water-soluble compound that is strongly irritating at concentrations of 2 to 4 mg/m^3 in laboratory animals and approximately 2.33 mg/m^3 in humans. Because of these properties, the inhaled compound is not likely to be distributed beyond the nasal cavity and the upper respiratory tract, nor is it likely to be able to reach the DNA of a living cell. In Syrian hamsters exposed for 52 weeks, neither orally administered acrolein nor inhaled acrolein resulted in cancer. Studies in vitro demonstrated that the compound is weakly mutagenic and shows some evidence of binding to biomolecules, particularly those with sulfhydryl groups (proteins containing cysteine, histidine, and lysine). Other studies in vitro indicated that acrolein inhibits cytokine release from macrophages through inhibition of transcription factors and induces apoptosis and generation of reactive oxygen species. The significance of these in vitro findings for expected effects in vivo is limited because of the poor distribution of the inhaled compound due to its high reactivity.

HUMAN HEALTH

Acrolein is a respiratory irritant in humans at relatively low concentrations (700 $\mu g/m^3$). In vitro, acrolein causes inhibition of glutathione, a key antioxidant in the lower respiratory tract. Reductions in glutathione are seen in diseases such as idiopathic pulmonary fibrosis, cystic

fibrosis, and bronchopulmonary dysplasia. When glutathione was administered to patients with idiopathic pulmonary fibrosis, increases in glutathione levels in the epithelial-lining fluid were observed. Reductions in antioxidant protection and scavengers predispose individuals to emphysema, lung inflammation, and fibrosis. The EPA has determined that the potential carcinogenicity of acrolein cannot be determined from the available data (EPA 2003a).

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of acrolein?

Mobile-source emissions account for some (approximately 24%) of the ambient concentrations of acrolein. Other mobile-source emission air toxics (e.g., 1,3-butadiene) might contribute to acrolein concentrations through atmospheric reactions. Shortcomings in the sampling techniques used for these measurements and a paucity of air-sampling data limit confidence in these numbers.

2. Does acrolein affect human health?

Acrolein is a potent respiratory irritant, especially in the upper airway. Because acrolein is a highly reactive, water-soluble molecule, it might not reach other areas of the body in appreciable concentrations.

3. Does acrolein affect human health at environmental concentrations?

Provided that measured ambient concentrations of acrolein (approximately 15 $\mu g/m^3$) are correct, these concentrations are much lower than those that cause irritation in humans (approximately 700 $\mu g/m^3$). However, maximum exposure concentrations indoors are in the same range as those observed to cause irritation in humans.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

Studies measuring acrolein in urban settings (e.g., near roadways, refineries, incinerators, and where smokers congregate) are limited. Many of these studies use collection systems in which acrolein is unstable, leading to possible underestimation of actual exposures. Research recommendations for acrolein-exposure studies include the following:

- Conduct further research to develop and validate improved exposure monitors for acrolein.
- Collect exposure data on acrolein in urban, suburban, and rural settings as well as in indoor environments and for personal exposures.

TOXICOLOGY

Acrolein is a reactive, irritating compound. Research recommendations for acrolein toxicology studies include the following:

- Further evaluate doses and inflammatory responses to acrolein, particularly in the lower respiratory region in animal studies.
- Conduct additional studies to address the distribution of inhaled acrolein in the respiratory tract and the exposure concentration required to induce inflammation. Of greater concern than the inhalation of the parent compound is the possible formation of acrolein as a metabolite of 1,3-butadiene, a form in which acrolein could be much more widely distributed in the body. For this reason, studies to determine the percentage of inhaled 1,3-butadiene that is metabolized to acrolein should be conducted.

HUMAN HEALTH

There is a striking lack of information about the effects of acrolein on human health. Research recommendations for human-health studies of acrolein include the following:

- Conduct epidemiologic studies if suitable populations can be found.

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INTRODUCTION

Benzene (CAS Registry Number 71-43-2; C_6H_6; molecular weight = 78.1) (Figure 7) is a clear, colorless, volatile, highly flammable liquid with a characteristic odor. It is the smallest of the aromatic compounds, with a single six-member unsaturated carbon ring. Benzene is soluble in lipids and has an octanol–water partition coefficient of 2.14. At 1 atmosphere and 20°C, benzene has a density of 0.879, a boiling point of 80.1°C, and a melting point of 5.5°C. It is derived from petroleum and is used extensively as a solvent or raw material in many manufacturing processes. Benzene is one of the leading chemicals produced and used around the world.

At one atmosphere pressure and 25°C, 1 ppm benzene is equivalent to 3.26 mg/m^3.

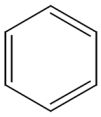

Figure 7. Structure of benzene.

BENCHMARK LITERATURE

The following evaluation of research literature on benzene is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from the Agency for Toxic Substances and Disease Registry (ATSDR 2005b,d), EPA (1998a, 2000d, 2002e), and the International Agency for Research on Cancer (IARC 1987).

EXPOSURE

SOURCES AND EMISSIONS

Although natural sources of benzene include volcanoes and forest fires, the sources of most ambient benzene are emissions from coal and oil combustion, motor-vehicle exhaust, evaporation from gasoline service stations, evaporation of industrial solvents, and hazardous waste sites. According to National Air Toxics Assessment (NATA) data, the major source of benzene emissions into ambient air in the U.S. is on-road mobile-source emissions, which account for 49% of all emissions nationwide and 57% of all emissions in urban areas (EPA 2006b). In the outdoors, the highest exposures to benzene are likely to occur in heavy traffic, during the filling of vehicle gas tanks, and at or near gasoline filling stations. Sources of indoor benzene exposure include tobacco smoke, several household products, and ambient air entering the home through ventilation or infiltration (EPA 2000d; ATSDR 2005d). Tobacco combustion is a major source of indoor benzene exposure. Estimates of the amount of benzene released by cigarette smoking range from 5.9 to 75 µg per cigarette in mainstream smoke and from 345 to 653 µg per cigarette in sidestream smoke (ATSDR 2005d; National Toxicology Program 2005).

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

The literature search yielded 34 ambient, outdoor, indoor, and personal-exposure studies of benzene. More air-monitoring data are available for benzene than for any other MSAT considered in this report. Table 4 and Figure 8 show the range of mean and maximum concentrations of benzene

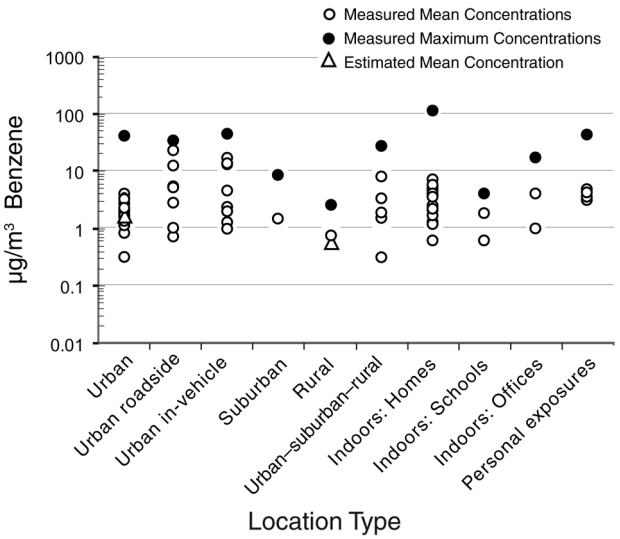

Figure 8. Concentrations of benzene (µg/m^3) at various locations. Data for figure are from Table 4.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

Table 4. Benzene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration ($\mu g/m^3$) Mean	Concentration ($\mu g/m^3$) Maximum	Citations	Comments
Outdoor Areas						
Urban						
	152 averages*	Yearly	1.6	6.1**	EPA 2004a	
	69	17 months	3.2	10.0	California Air Resources Board 2003	
	74	16 months	3.9	22.0	California Air Resources Board 2003	
	81	1.5 yr	0.1	1.9	California Air Resources Board 2003	
	65	1 yr	1.8	8.2	California Air Resources Board 2003	
	83	1.5 yr	2.0	7.5	California Air Resources Board 2003	
	60	1 yr	2.2	9.5	California Air Resources Board 2003	
	33	18 months	1.8	3.1^{+}	Payne-Sturges et al. 2004	
	50	9 hr	0.3	2.0	Riediker et al. 2003	
	10	5 wk	1.1***	1.6^{+}	Adgate et al. 2004b	
	8	4 wk	1.3***	2.2^{+}	Adgate et al. 2004b	
	35	8 wk	1.3	—	Kinney et al. 2002	
	36	8 wk	2.6	—	Kinney et al. 2002	
	132	7 months	1.6	3.3^{+}	Sexton et al. 2004	
	≈ 60	1 yr	3.5	—	South Coast Air Quality Management District 2000	
	≈ 60	1 yr	3.1	—	South Coast Air Quality Management District 2000	
	≈ 30	1 yr	—	4.1**	Mohamed et al. 2002	
	16	—	—	6.6**	Rodes et al. 1998	Samples taken during commuting times
	12	—	—	2.9**	Rodes et al. 1998	Samples taken during commuting times
	—	Yearly	1.56	—	EPA 2006b	Model
	250	1 yr	—	39.0	Zielinska et al. 1998	
	555	Yearly	2.2	11.1	Weisel et al. 2005	2 seasons
Urban in-vehicle						
	20	Bus commutes	—	9.5**	Fitz et al. 2003	Bus commutes
	42	Police patrols	1.3	44.0	Riediker et al. 2003	Police patrols
	74	4 days	4.5	11.0	Batterman et al. 2002	
	1	90 min	2.4	—	Fedoruk and Kerger 2003	1 car test

Table continues on next page

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 113,343 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average; *** = median value; $^{+}$ = 90th percentile; $^{++}$ = 95th percentile; $^{+++}$ = 99th percentile.

Table 4 (*Continued*). Benzene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration ($\mu g/m^3$) Mean	Concentration ($\mu g/m^3$) Maximum	Citations	Comments
Outdoor Areas (*Continued*)						
Urban in-vehicle (*Continued*)						
	3	90 min	1.0	14.0	Fedoruk and Kerger 2003	3 car tests
	3	90 min	—	14.0	Fedoruk and Kerger 2003	3 car tests
	32	Commute time	13.0–17.0	22.0	Rodes et al. 1998	Cars
	26	Commute time	2.0–14.0	16.0	Rodes et al. 1998	Cars
Urban roadside						
	50	9.1 hr	0.7	2.6	Riediker et al. 2003	Samples taken 3PM–12AM
	56	7 days	2.7–22.0	33.0	Sapkota and Buckley 2003	Tunnel roadside
	24	Commutes	5.2–12.0	20.0	Rodes et al. 1998	
	18	Commutes	1.0–5.0	5.9	Rodes et al. 1998	
Suburban						
	155 averages*	Yearly	1.5	8.6**	EPA 2004a	
Rural						
	—	Yearly	0.6	—	EPA 2006b	Model
	64 averages*	Yearly	0.7	2.5**	EPA 2004a	
Urban–suburban–rural combined						
	1550	Yearly	1.5	8.8	EPA 2004d	
	3650	Yearly	1.8	26.0	Pratt et al. 2000	
	100	5 months	3.3	4.6^{++}	Adgate et al. 2004b	
	300	Yearly	0.3–7.9	24.0	Zielinska et al. 1998	
	—	1 hr	—	16.0**	Seigneur et al. 2003	
Indoor Spaces						
Tollbooths						
	280	3 hr	4.1	14.9	Sapkota et al. 2005	
Residences						
	282	6 days	4.6	13.0^{++}	Adgate et al. 2004b	
	101	6 days	3.9	7.5^{++}	Adgate et al. 2004b	
	88	4 wk	2.1***	7.2^{+}	Adgate et al. 2004a	
	93	2 days	2.2***	6.2^{+}	Adgate et al. 2004a	
	402	6 days	7.2	13.0^{+}	Clayton et al. 1999	
	185	6–7 days	1.3***	9.0	Gordon et al. 1999	
	9	3 wk	2.4***		Mukerjee et al. 1997	

Table continues on next page

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 113,343 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average; *** = median value; $^{+}$ = 90th percentile; $^{++}$ = 95th percentile; $^{+++}$ = 99th percentile.

Table 4 (*Continued*). Benzene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3) Mean	Concentration (μg/m^3) Maximum	Citations	Comments
Indoor Spaces (*Continued*)						
Residences (*Continued*)						
	6	10 days	2.4***		Mukerjee et al. 1997	
	33	3 days	3.7	8.3$^+$	Payne-Sturges et al. 2004	
	40	12 hr	0.6	14.0	Phillips et al. 2005	
	40	12 hr	1.2	110.0	Phillips et al. 2005	
	40	2 days	4.9	17.0	Sax et al. 2004	
	32	2 days	2.5	6.3	Sax et al. 2004	
	30	2 days	1.7	6.3	Sax et al. 2004; Kinney et al. 2002	
	36	2 days	5.3	39.0	Sax et al. 2004; Kinney et al. 2002	
	292	2 days	5.8	15.0$^+$	Sexton et al. 2004	
	104	2 days	2.2***	8.3$^+$	California Air Resources Board 1992	
	48	10 months	4.1	34.0	Van Winkle and Scheff 2001	
	554	Yearly	3.5	36.4	Weisel et al. 2005	2 seasons
Schools						
	47	5 wk	0.6***	1.0$^+$	Adgate et al. 2004a	
	39	4 wk	0.6***	1.6$^+$	Adgate et al. 2004a	
	—	—	—	3.4	Shendell et al. 2004	20 classrooms
	73	6–8 hr	1.8	4.1^{++}	Whitmore et al. 2003b	210 classrooms from 67 schools
Offices						
	—	8 hr	1.0	2.7	Daisey et al. 1994	
	> 200	8 hr	—	17.0	Girman et al. 1999	
Personal Exposures						
	36	2 days	4.7	—	Kinney et al. 2002	High school students, winter
	41	2 days	3.1	—	Kinney et al. 2002	High school students, summer
	545	2 days	3.6	27.4^{+++}	Weisel et al. 2005	Adults
	209	2 days	4.2	43.6^{+++}	Weisel et al. 2005	Children

[a] Data extracted from published studies.

* = Mean number of reported average concentrations derived from the full dataset of 113,343 measurements in EPA Air Quality System database (EPA 2004a); ** = maximum average; *** = median value; $^+$ = 90th percentile; $^{++}$ = 95th percentile; $^{+++}$ = 99th percentile.

in units of μg/m^3, as reported in the published literature. Ambient data are sorted into six categories: urban, urban roadside, urban in-vehicle, suburban, rural, and combined urban–suburban–rural. Indoor data are sorted into four categories: residences, schools, offices, and toll booths. Two recent studies reported personal-monitoring data for adults, high school students, and children.

This report focuses on benzene concentrations in the U.S. as found in publications dating from 2000 to the present. In the 1980s, the Total Exposure Assessment Methodology (TEAM) studies, a series of large-scale studies of nonoccupational exposures to volatile organic compounds (VOCs), funded by the EPA, compiled a large database on outdoor, indoor, and personal-exposure concentrations of benzene. A summary of the TEAM study design and findings as well as

a review and comparison of these findings with other large studies conducted in the early 1990s was published in 1996 (Wallace 1996). The earlier studies provided a global average and range of averages for ambient, indoor, and personal-exposure benzene concentrations during the 1980s. Although direct comparisons between the TEAM studies' results and those from the more recent studies used in this report are not appropriate, the TEAM results do provide a rough frame of reference. Benzene concentrations measured in the studies conducted in the early 1990s were in general similar to those reported both by Wallace (1996) and the TEAM studies.

Sampling times for the studies shown in Figure 8 and listed in Table 4 ranged from 1 hour (Seigneur et al. 2003) to 6 days (Adgate et al. 2004b). Sample-averaging times ranged from hours (e.g., Fitz et al. 2003) to 1.5 years (California Air Resources Board 1992). The number of observations per study, from which the mean and maximum concentrations were determined, ranged from a low of 1 for an in-vehicle study (Fedoruk and Kerger 2003) to a high of 113,343 for the combined urban–suburban–rural category (EPA 2004a). Three large studies (Pratt et al. 2000; EPA 2004a,d), all with more than 1000 observations, reported results as combined urban–suburban–rural. It should be noted that the mean rural concentration of 0.56 $\mu g/m^3$ and one of the mean urban values (1.6 $\mu g/m^3$) shown in Table 4 and Figure 8 were estimated by modeling (EPA 2006b).

There was great variability in the number of measurements, season of measurement, and geographic areas in which measurements were taken. The mean concentrations recorded in the Air Quality System database, the report with the largest number of observations in urban, suburban, and rural areas (EPA 2004a), indicated that concentrations in rural areas (0.7 $\mu g/m^3$) are approximately half those found in suburban and urban areas (1.6 $\mu g/m^3$ and 1.5 $\mu g/m^3$, respectively). This is consistent with the expectation that on-road mobile-source emissions would be lowest in rural areas and highest in urban areas. All studies taken together, however, and independent of the number of observations or constituent studies, suggest that the concentrations in urban, suburban, and rural areas are in the range of approximately 1 to 10 $\mu g/m^3$. Peak concentrations for urban, suburban, and rural air appear to be in the 15 to 50 $\mu g/m^3$ range, with the rural maximum being at the low end of the range.

Through the National Air Pollution Surveillance network of Canada, data on concentrations of a variety of air toxics are collected at urban, suburban, rural, and industrial sites. This effort is carried out in cooperation with provincial and municipal environmental agencies. It includes measurements of a large number of VOCs, including benzene. In 2004, there were 51 active sites where benzene measurements were taken. Thirty-eight sites were located in 18 cities across Canada, and the other 13 sites were in rural locations. For the urban sites, the annual mean concentrations ranged from 0.4 to 7.6 $\mu g/m^3$; 35 of the 38 sites recorded annual mean concentrations of less than 2.0 $\mu g/m^3$ (Dann T, unpublished).

The TEAM studies found an ambient global average for benzene of 6 $\mu g/m^3$ in the 1980s (Wallace 1996), with a range of mean concentrations between 2 and 19 $\mu g/m^3$ and a maximum concentration of approximately 100 $\mu g/m^3$. Current mean ambient concentrations appear to be somewhat lower than those measured in the 1980s in the TEAM studies.

Two studies (Rodes et al. 1998; Sapkota and Buckley 2003) found that urban roadside and urban in-vehicle concentrations were higher (10 to 22 $\mu g/m^3$) than the typical highest ambient concentrations measured in other studies (<10 $\mu g/m^3$). This is not surprising, given that higher benzene concentrations might be expected at such sites, where motor-vehicle emissions are highest. However, when all mean concentrations from all studies are considered together, urban roadside and urban in-vehicle concentrations appear similar to those in other outdoor settings. Peak concentrations for the urban roadside and urban in-vehicle categories are in the same range as those for the rural, suburban, urban categories.

Mean benzene concentrations in residences appear to be in the same range as those in ambient air—0.5 to 10 $\mu g/m^3$. The highest peak concentration found in all 34 benzene studies (110 $\mu g/m^3$) was measured in a residence. While some studies were careful to select homes without cigarette smokers (e.g., Kinney et al. 2002 and Weisel et al. 2005), smoking might have occurred in homes included in some of the studies. Although there were few studies with data on schools, schools tended to have mean and peak benzene concentrations at the low end of those found outdoors and in residences. The maximum peak value (3.4 $\mu g/m^3$) of all 34 studies was measured in a classroom. The one study reporting a mean benzene concentration in offices (1 $\mu g/m^3$) (Daisey et al. 1994) was at the low-to-middle end of the range of ambient concentrations, while another study reported a peak of 17 $\mu g/m^3$ (Girman et al. 1999). One study reported a peak concentration (99th percentile observation) in schools of 4.1 $\mu g/m^3$ (Whitmore et al. 2003b). Mean and peak concentrations reported for toll booths were similar to those in the urban roadside and urban in-vehicle categories. Residential concentrations of benzene measured in the TEAM studies (Wallace 1996) averaged approximately 10 $\mu g/m^3$, with a range of 2 to 19 $\mu g/m^3$ and a peak concentration near 100 $\mu g/m^3$. Current residential concentrations

of benzene appear to be lower than those recorded in the 1980s in the TEAM studies.

Mean personal benzene exposures reported for adults, high school students, and children showed a very narrow range of concentrations (3.1 to 4.7 μg/m^3). The maximum personal exposure (43.6 μg/m^3) was similar to that recorded for ambient air and lower than the maximum concentration recorded for residences. The TEAM studies reported a global average personal exposure to benzene for nonsmokers of 15 μg/m^3, with a range of 7 to 29 μg/m^3 and several maximum readings of well over 100 μg/m^3 (Wallace 1996). A rough comparison of the TEAM studies and the more current data shown in Table 4 and Figure 8 suggests that personal exposures to benzene have decreased since the 1980s.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average urban concentrations of benzene measured in several other countries are generally higher than those measured in the U.S. In urban areas of China, for example, concentrations of 7.9 to 120.9 μg/m^3 were measured (Zhao et al. 2004). In residential areas of India, concentrations of 26 to 195 μg/m^3 were measured (Srivastava et al. 2004). Concentrations measured at urban roadside locations tended to be higher than those measured in the U.S., ranging from 5.2 to 73 μg/m^3 in China (reported in Chang et al. 2005) and 15.8 to 18,816 μg/m^3 in India (Samana et al. 1998; Srivastava et al. 2004) and concentrations measured at urban roadside locations tended to be higher than those measured in ambient air. The higher concentrations of benzene at ambient locations were also seen in Korea (9.4 μg/m^3, Baek et al. 1997), Pakistan (17 μg/m^3, Barletta et al. 2002), the Philippines (12.6 μg/m^3, Gee and Sollars 1998), and Turkey (38 to 57 μg/m^3, Muezzinoglu et al. 2001). Concentrations in Japan, however, were measured at 1.8 to 2.9 μg/m^3, closer to those in the U.S. (reported in Chang et al. 2005; Japan Ministry of the Environment 2005b). Ambient concentrations of benzene ranged from nondetectable to 47 μg/m^3 in the Philippines (Gee and Sollars 1998), 3.6 to 228 μg/m^3 in Taiwan (Chang et al. 2005; Lin et al. 2005), and 3.5 to 50.2 μg/m^3 in Thailand (Gee and Sollars 1998; Muttamara and Leong 2000; Gioda et al. 2004).

In Europe, ambient concentrations of benzene varied considerably, ranging from 3 to 534 μg/m^3 in Denmark (reported in Gioda et al. 2004), 1.1 to 2.1 μg/m^3 in Finland (Hellén et al. 2005), 3.3 to 16 μg/m^3 in France (Ferrari et al. 1998), 1 to 30 μg/m^3 in Germany (Slemr J et al. 1996; reported in Gioda et al. 2004; Umweltbundesamt 1998), 13 to 26 μg/m^3 in Greece (Chatzis et al. 2005), 1.3 to 12.6 μg/m^3 in Italy (Crebelli et al. 2001; Bono et al. 2003), and 0.7 to 1.94 μg/m^3 in the U.K. (U.K. National Air Quality Archive 2006a). Only minor differences were seen between ambient and urban roadside measurements in most of these countries.

In Latin American countries, benzene concentrations were more consistent, ranging from around 4 to 40 μg/m^3 (Baez et al. 1995; Gee and Sollars 1998; Bravo et al. 2002; Serrano-Trespalacios et al. 2004), although concentrations were higher in Brazil, ranging from 11.3 to 11,800 μg/m^3 (Grosjean and Miguel 1988; Gee and Sollars 1998; Fernandes et al. 2002; Gioda et al. 2004).

TEMPORAL TRENDS

The National Air Pollution Surveillance benzene-monitoring program began in 1989. For the years 1991 to 2004, there were complete annual data records (with valid annual means in at least 10 of the 14 years) for 20 urban sites in 12 cities. The composite annual mean for this group of sites is shown in Figure 9. Also shown in the figure are composite annual means for a group of rural sites with complete (8 of 11 years) data for the years 1994 to 2004 (Dann T, unpublished).

These Canadian data indicate a trend toward decreasing concentrations of benzene in the air in both urban and rural areas. Data from the U.S. for 95 sites monitoring urban ambient air indicate a 47% decrease in benzene concentrations between 1994 and 2000 (EPA 2006b). During this period, the mean urban concentration in Canada dropped from approximately 3.3 to 1.8 μg/m^3. In 1994, 90% of the sites reported concentrations below 6.2 μg/m^3, and by 2004 the concentrations were below 3.0 μg/m^3. Over the same time period, there was a corresponding decrease in the benzene content of Canadian gasoline,

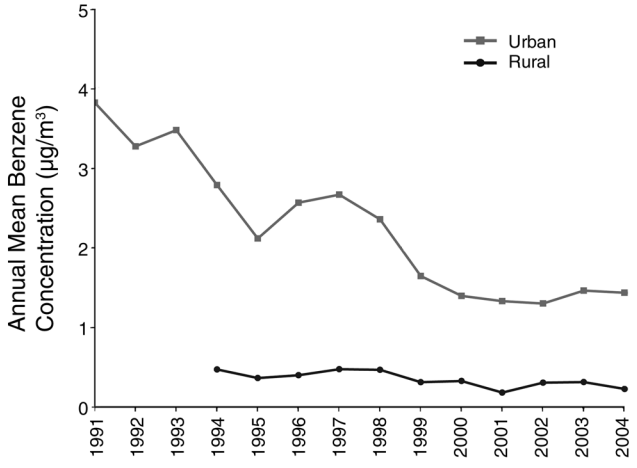

Figure 9. Annual mean concentrations of benzene measured in Canadian urban and rural locations from 1991 to 2004. (Courtesy of T. Dann, Head, Air Toxics Analysis and Air Quality, Environment Canada, 2007. Data are available from the National Air Pollution Surveillance (NAPS) Network at *www.etc-cte.ec.gc.ca/naps/index_e.html*.)

with the largest decrease in concentration occurring during the second half of 1999, as a result of regulatory action (Environment Canada 2003b).

Measurements of ambient benzene concentrations at sites in California's South Coast Air Basin from 1990 through March 1997, reported as part of the Multiple Air Toxics Exposure Study (MATES) (South Coast Air Quality Management District 2000), demonstrated a trend similar to that observed for Canada and urban areas in the U.S., with concentrations dropping from approximately 2.8 to 0.8 $\mu g/m^3$ (a 70% drop).

The MATES-II study, conducted from April 1998 through March 1999, again measured benzene at sites in California's South Coast Air Basin (South Coast Air Quality Management District 2000). Benzene concentrations demonstrated a pronounced seasonal trend, with peak concentrations occurring during the colder months of October through January (2 to 2.25 $\mu g/m^3$) and the lowest concentrations occurring during the warmer months of April through October, when concentrations were typically less than 1 $\mu g/m^3$. In this study, seasonal trends for 1,3-butadiene closely followed the seasonal benzene trends. Sax and colleagues (2004) also reported maximum benzene concentrations in the colder months, in both Los Angeles and New York.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

Some of the metabolites of benzene are responsible for its toxicity and carcinogenicity (Longacre et al. 1981; Snyder and Hedli 1996). This is supported by the observation that benzene toxicity is inhibited by toluene, a competitive inhibitor of benzene metabolism; by the reduced toxicity of benzene in animals that have had a partial hepatectomy, reducing their ability to metabolize benzene; and by the reduced toxicity of benzene in mice lacking the enzyme CYP2E1, known to be the major determinant of in vivo benzene metabolism (Sabourin et al. 1988). The metabolism of benzene is illustrated in Figure 10.

Benzene is first oxidized to benzene oxide, which can spontaneously rearrange to phenol, be further oxidized to the ring-breakage compound muconaldehyde, or form a conjugate with glutathione and be excreted in the urine as *S*-phenylmercapturic acid (SPMA). Phenol is excreted in the urine or oxidized to catechol or hydroquinone. Catechol can be further oxidized to trihydroxybenzene, and hydroquinone can be oxidized to the highly reactive bipolar benzoquinone. All of the phenolic metabolites can

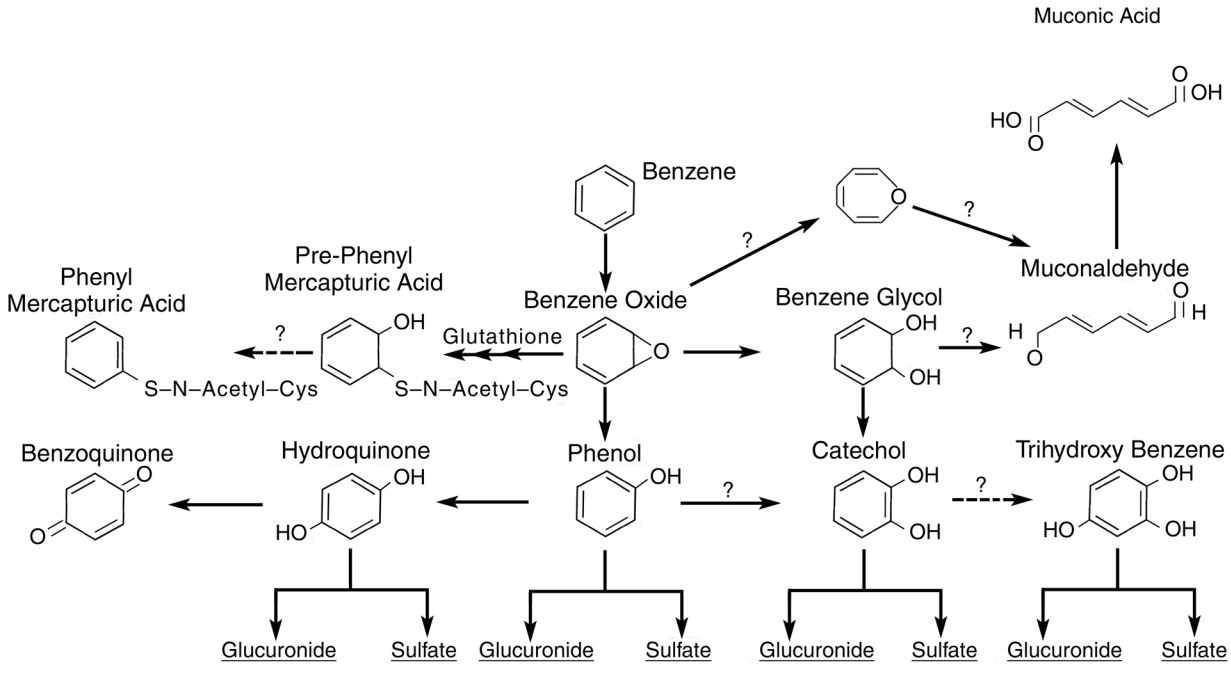

Figure 10. Metabolic pathway of benzene. (Reprinted from Sabourin et al. 1988, with the permission of Elsevier.)

form conjugates (glucuronides or sulfates) prior to excretion in the urine. Muconaldehyde is further oxidized to muconic acid, which is excreted in the urine (Sabourin et al. 1988).

The key toxic metabolites for cytotoxicity and the induction of leukemia are thought to be benzoquinone, benzene oxide, and muconaldehye. The formation of muconic acid and the quinones is favored at low exposure concentrations (Sabourin et al. 1988). The genotoxicity is thought to be clastogenic (i.e., consisting of chromosomal damage) in nature rather than being caused by point mutations.

There are species differences in the metabolism of benzene (Sabourin et al. 1988). In metabolizing benzene, rats convert a large portion of the benzene to phenol, a marker of a detoxication pathway. By contrast, mice form much greater amounts of hydroquinone, hydroquinone glucuronide, and muconic acid, all markers of pathways leading to putative toxic metabolites. Metabolism in humans appears to resemble that in mice (Sabourin et al. 1989).

There are two key enzymes involved in the detoxication of benzene metabolites (Recio et al. 2005). One is NAD(P)H:quinone oxidoreductase-1 (NQO1), which reduces the benzene quinone metabolites, and the other is the microsomal epoxide hydrolase, which hydrolyzes the epoxide group on benzene oxide. NQO1-knockout mice have increased sensitivity to benzene-induced hematotoxicity and demonstrate myeloid hyperplasia after benzene exposure (Ross 2005).

BIOMARKERS

Biomarkers of benzene exposure have been studied in animals for potential use in assessing exposure in humans. Exposure biomarkers in humans are discussed below, in the section on human health. Biomarkers of benzene health effects are based on hematotoxicity and on indicators of genotoxicity. Hematotoxicity is detected by alterations in complete blood counts, including hemoglobin concentration, hematocrit, erythrocyte count, leukocyte count, and differential and platelet counts. For genotoxicity, chromosomal aberrations in bone marrow and peripheral-blood lymphocytes and sister-chromatid exchange can be used (ATSDR 2005d). However, none of the biomarkers of effect are specific for benzene.

NONCANCER HEALTH EFFECTS

In Vivo

Exposure to high concentrations of benzene is acutely toxic because of narcotic effects on the central nervous system and cardiac sensitization (Bingham et al. 2001). Inhalation exposures of animals (in rats, mice, and rabbits) to benzene concentrations greater than 32,600 mg/m^3 benzene for several minutes up to several hours usually result in death from central nervous system depression or ventricular fibrillation (in rabbits).

Hematopoietic effects have been studied mainly in mice, showing reduced bone-marrow cell counts and anemia after 2 weeks of exposure, 4 or 5 days/week, 6 hours/day, to 980 mg/m^3. Exposure of mice to as little as 32.6 mg/m^3 benzene for 6 hours/day for 5 days resulted in a decrease in bone-marrow cells.

Animal studies indicate that benzene exposure affects humoral and cellular immunity. Mice exposed to 81 mg/m^3 benzene for 6 hours/day for 5 days had a decrease in spleen weight as well as in the number of circulating leukocytes (Wells and Nerland 1991). Mitogen-induced blastogenesis of B and T lymphocytes was depressed in mice exposed to 33 mg/m^3 benzene (Rozen et al. 1984). Mice exposed to 33 mg/m^3 also showed delayed splenic reaction to foreign antigens when evaluated in vitro (Rosenthal and Snyder 1987). Prior exposure of mice to 98 mg/m^3 benzene decreased resistance to subsequent infections (Rosenthal and Snyder 1985).

Benzene-induced effects on the reproductive system have been observed in animals, but most studies were conducted at exposure concentrations well above those currently found in occupational settings or ambient air (ATSDR 2005d). In one 13-week study (Ward et al. 1985), mice were exposed to 980 mg/m^3 benzene, and gonadal alterations were observed, with greater severity in males.

In Vitro

Bioactivation of benzene has also been shown to produce reactive oxygen species, which are cytotoxic and can lead to oncogene activation (Wan et al. 2005). Muconic acid and muconaldehdye are both hematotoxic (Witz et al. 1996) and cytotoxic (Zhang et al. 1997).

The studies cited above on the effects of benzene exposure on the immune system often used in vitro tests to assess effects on lymphocyte function.

GENOTOXICITY

Benzene acts mainly as a clastogenic agent, as opposed to causing point mutations. Benzene-induced chromosomal aberrations in bone marrow and lymphocytes have been observed in mice, rats, Chinese hamsters, and humans. An increase in micronuclei has been observed in the bone marrow and peripheral blood of mice, rats, and Chinese hamsters. An increase in sister-chromatid exchanges has been observed in bone marrow or lymphocytes of mice, rats, and humans (ATSDR 2005d).

CANCER

In Vivo

After chronic exposures of rats and mice, benzene was found to be carcinogenic in both, but mice are the more sensitive of the two species (Cronkite et al. 1984; Huff et al. 1989; Maltoni et al. 1989). Tumors induced by exposures to 326 or 980 mg/m^3 benzene for 104 weeks or longer include hepatomas, Zymbal-gland tumors, and tumors of the lung and ovary as well as thymic and nonthymic lymphomas. Intermittent lifetime exposure to 980 mg/m^3 benzene was found to be more tumorigenic than short-term exposure (10 weeks) to 3900 mg/m^3 followed by lifetime observation (Snyder et al. 1988).

The toxicity of benzene in animals has been studied widely, but no animal model of the induction of the acute myeloid leukemia (AML, also referred to as acute myelogenous leukemia) observed in exposed humans (see *Human Health* section below) has been found. However, genetically modified mice, in which key detoxication enzymes are missing, have been shown to develop myeloid-cell hyperplasia after benzene exposure (Ross 2005).

In Vitro

The mechanisms of benzene's carcinogenicity and its ultimate toxic metabolite(s) are not known, although recent studies are adding to our knowledge. Cytogenetic studies have indicated that benzene acts as a clastogenic agent (rather than causing point mutations) (Whysner et al. 2004). It has been postulated that 1,4-benzoquinone (Irons 1985; Pellack-Walker et al. 1985; Jowa et al. 1986) and *t,t*-muconaldehyde (Goldstein et al. 1981; Witz et al. 1985) are toxic metabolites of benzene. Both of these compounds are bipolar, which is consistent with the clastogenic properties of benzene.

In vitro studies of the inhibition of enzymes involved in DNA replication and maintenance, such as topoisomerases, have indicated that these enzymes play a role in benzene-induced chromosomal aberrations (Eastmond et al. 2005; Lindsey et al. 2005). Other epigenetic studies indicated that benzene modifies the chromatin structure, giving rise to heritable changes not affecting DNA (Morgan and Alvares 2005).

HUMAN HEALTH

BIOMARKERS

The use of biomarkers in benzene studies has been reviewed by Albertini and colleagues (2003a). Biomarkers fall into three general categories—biomarkers of exposure, susceptibility, and effect. While not in themselves health effects, these biomarkers indicate that an individual or group has been exposed to benzene or that benzene is causing metabolic or cellular effects that might be part of the mechanistic chain leading to effects on human health such as cancer (Albertini et al. 2003a). All three categories of biomarkers might be useful in assessing the risk of exposure to benzene from mobile-source emissions by extending investigative opportunities at the low end of exposure concentrations in occupational settings and in ambient air.

Biomarkers of Exposure

Biomarkers of exposure include metabolic products such as S-phenylmercapturic acid, *t,t*-muconic acid (*t,t*-MA), and adducts of benzene oxide, albumin, and hemoglobin. The relative sensitivity and usefulness of exposure biomarkers have been explored in a number of studies.

A study of Chinese workers concluded that S-PMA was a sensitive marker for exposure at around 32.6 mg/m^3 but was affected by a polymorphism (genetic variants in enzymes) in glutathione-S-transferase T1 (GSTT1) (Qu et al. 2005). Two genetic variants in the enzymes that metabolize benzene, myeloperoxidase and NAD(P)H:quinone oxidoreductase, were related to changes in cell counts.

In another study of Chinese workers, a variety of urinary metabolites were found to be elevated after benzene exposure, including *t,t*-MA and S-PMA at 0.65 mg/m^3 benzene, phenol and hydroquinone at 1.63 mg/m^3 benzene, and catechol at 6.5 mg/m^3 benzene (Kim et al. 2006). The study also indicated that metabolism of benzene to hydroquinone and *t,t*-MA was favored at low exposures, confirming earlier studies in mice (Sabourin et al. 1988).

The technologies used in the new "omics" fields of study (genomics, proteomics, etc.) have been used to study alterations in DNA and proteins in humans exposed to benzene (Forrest et al. 2005; Smith et al. 2005; Vermeulen et al. 2005; Zhang et al. 2005a). More than 100 genes were shown to be differentially expressed, and serum protein profiles indicated that several proteins were differentially expressed in benzene-exposed subjects compared with controls. Such changes, if confirmed, might be useful as exposure biomarkers in the future.

In contrast, in a study of occupational exposure, S-PMA and *t,t*-MA were found to be useful as biomarkers only in the most highly exposed workers and the most sensitive biomarker was the presence of benzene in the urine at exposure concentrations of less than 32.6 mg/m^3 (Farmer et al. 2005). In a study of school children in Thailand, measures of *t,t*-MA and benzene in the blood were significantly different in two groups exposed to ambient concentrations of 27.71 µg/m^3 and 8.8 µg/m^3 benzene, respectively (Navasumrit et al. 2005).

This evidence suggests that exposure biomarkers are sensitive indicators of benzene exposure at the lower end of occupational concentrations and the higher end of concentrations in the community. It appears, however, that the

most sensitive and specific method of measuring exposure is by direct measurement of benzene in urine, exhaled air, or blood. This method avoids unwanted variations associated with other substances that might share the same metabolic pathways and with age and genetic differences in benzene metabolism.

Biomarkers of Effect

The distinction between biomarkers of effect and health effects is not clear-cut. Indicators of hematotoxicity, for example, such as a reduction in circulating blood cells, can be regarded variously as markers of exposure, as health effects in their own right, or as evidence of a link in the causal chain leading to cancer. These biomarkers of effect might be connected mechanistically to the eventual development of cancer through damage to DNA. The main markers investigated have been direct DNA damage, mutations, and structural and numerical chromosomal aberrations (Albertini et al. 2003a).

In a study of a Chinese cohort exposed in an occupational setting, there was evidence of chromosomal aberrations (chromosomal loss and an increase in breakage of chromosomes) at benzene concentrations as low as 1.6 mg/m^3. Exposure was associated with increased concentrations of urinary metabolites of benzene and reductions in blood counts. The various biomarkers tended to correlate with one another (Qu et al. 2003). There was no evidence of aneuploidy (an abnormal number of chromosomes) in peripheral-blood cells in this study. But in another study of a Chinese occupational cohort, aneuploidy was associated with exposures greater than 16 mg/m^3 (Zhang et al. 2005b). A third study, of 250 Chinese workers, found that white blood cell counts and platelet counts were significantly lower than for 140 controls even with exposures of less than 3.25 mg/m^3 (Lan et al. 2004).

In a recent study from Thailand, ambient benzene concentrations, individual benzene exposure, blood benzene, urinary *t,t*-MA, and cytogenetic markers (DNA-strand breaks and DNA-repair capacity) were investigated in gasoline service station attendants, roadside street vendors, and students in schools within 500 meters of a main road and compared with control populations exposed to low concentrations of benzene (Navasumrit et al. 2005). Differences in ambient concentrations were demonstrated and corresponded to differences in measurements of personal exposure and blood benzene. Exposure was correlated with urinary *t,t*-MA and cytogenetic abnormalities. Median ambient concentrations were 28 µg/m^3 for schools near main roads in Bangkok and 8.2 µg/m^3 for schools in provincial areas. These results suggested that biomarkers of exposure and effect might be sensitive to benzene concentrations experienced in community settings.

Biomarkers of Susceptibility

Biomarkers of susceptibility would be very useful in helping to determine acceptable exposure concentrations for susceptible individuals. Two genetic markers, CYP2E1 and NQO1, are associated with the variations in the ways benzene is metabolized. Little is known about the distribution of these genotypes in the general population. It has also been found that polymorphisms in the genes that regulate hematopoiesis through cytokines, chemokines, and cellular-adhesion molecules modify the hematotoxic effects of benzene (Lan et al. 2005). Knowledge of such genetically based variations in the response to benzene will be important in helping to define susceptible subpopulations.

CANCER

Most of the epidemiologic evidence on benzene and cancer is based on a relatively small number of studies of occupational cohorts. These cohorts tended to be studied repeatedly as additional workers died over the course of the years. Perhaps the most influential was the cohort of rubber-hydrochloride workers in three U.S. factories (the Pliofilm cohort) in a study conducted through the mid-1970s. The strengths of this cohort included good characterization of exposure to benzene and little coexposure to other potentially toxic substances (Rinsky et al. 1981, 1987). There was an increased risk of leukemia, predominantly of myeloid origin, with increasing exposure to benzene.* The risk of multiple myeloma was also increased, but this did not seem to be related to exposure. Another important study was of workers in 12 Chinese cities (Hayes et al. 1996, 2000). A variety of industrial processes were included, all of which involved exposure to benzene, among other substances. There was an increased risk for the larger grouping of "all hematologic neoplasms," with mixed evidence of dose-related responses for subcategories. Specifically, increased risks were observed for acute nonlymphocytic leukemias with or without myelodysplastic syndrome (preleukemia) and nonsignificant increases for non-Hodgkin's lymphoma. The benefit of the large sample size of this study was offset to some extent by the less well-characterized and more heterogeneous exposure, less standardization and validation of outcome measurements, and

* The classification of cancers of the lymphohematopoietic system has undergone considerable change over the time spanned by these cohort studies. Leukemia mainly arises from stem or progenitor cells in the bone marrow. Leukemias are classified as myeloid or lymphoid according to whether they resemble normal cells of myeloid phenotype (granulocytic, monocytic, megakaryocytic, or erythroid) or lymphoid type (lymphocytes or plasma cells). If the malignant cells are well differentiated, the leukemia is classified as chronic; if undifferentiated, as acute. The main types of leukemia are chronic lymphocytic leukemia, chronic myeloid leukemia, acute lymphocytic leukemia, and acute myeloid leukemia (AML, also referred to as acute myelogenous leukemia). Myelodysplastic syndromes can develop into AML. Nonlymphocytic leukemia, a classification used by some studies, is leukemia of myelogenous origin.

less convincing reference populations. It has been argued that the exposure of these Chinese workers might have been underestimated (Wong 2002). Overall, however, the epidemiologic evidence points fairly convincingly toward a causal association between benzene exposure and leukemia.

It is reasonably clear that an association with leukemia exists under the exposure conditions in these occupational cohorts. However, it is less clear which model of exposure–response should be adopted for risk assessment at the lower end of occupational exposures and, by extrapolation, to the general population, which is exposed to benzene at even lower levels and as part of a different mixture of compounds arising from different sources. These uncertainties arise because nearly all the key inputs into models of exposure–response can be (and, in the literature, have been) questioned. For example, for the Pliofilm cohort, different approaches to estimating exposure and to statistical modeling resulted in large differences in risk estimates (Crump 1994). In the Chinese studies, questions have been raised about possible underestimation of exposures, confounding by other exposures, bias in the ascertainment of cases, the validation of causes of death, and the suitability of comparison populations (Wong 2002). The shape of the exposure–response curve is critical for extrapolation to ambient concentrations. While there have been arguments for various nonlinear models with or without a threshold, most investigators conclude that based on available evidence a linear model cannot be excluded.

New Evidence from Existing Occupational Cohort Studies

An extended follow-up of the Pliofilm cohort through 1996 was reported by Rinsky and colleagues (2002). At the time of the follow-up, it had been 20 years since any cohort member had been exposed. The follow-up provided further confirmation of the association between benzene exposure and the risk of leukemia. This association tended to decrease with time since exposure. Another comprehensive examination of the benzene exposure of the Pliofilm cohort suggested that other studies had over- or underestimated exposures to varying degrees (Williams and Paustenbach 2003).

One of the uncertainties remaining from earlier analyses of the Pliofilm cohort had been an increased risk of multiple myeloma (Rinsky et al. 1987) reported by some other occupational studies. It was noted that the risk of multiple myeloma in the cohort was not related to gradients of exposure. In the follow-up through 1996, analysis showed an increased but nonsignificant risk of multiple myeloma, though again no evidence of an exposure–response relationship (Rinsky et al. 2002).

Results from a follow-up of Dow chemical workers provided modest evidence for an increase in leukemia with increased cumulative benzene exposure. This was compared with a reduced mortality from major causes. The average exposure concentration of 31 mg/m^3 and average cumulative exposure of 129 mg/m^3-year were higher than those in most studies of refineries and distribution workers but similar to those of the lowest exposure grouping in the Pliofilm cohort (Bloemen et al. 2004). The study did not have the statistical power to provide a basis for extrapolation to the concentrations found in ambient air nor to clarify the specificity of benzene exposures for leukemia subgroups.

New Occupational Cohort Studies

Exposure to benzene might affect human health even at low concentrations. A nested case–control study of lymphohematopoietic cancers in the Health Watch cohort of Australian petroleum workers exposed to benzene concluded that excess leukemia risk (both acute nonlymphocytic and chronic lymphocytic leukemias) existed at cumulative benzene exposures lower than those observed in previous studies (higher than 6 mg/m^3-year) and that no threshold of cumulative exposure could be identified (Glass et al. 2003, 2005). No relationship with non-Hodgkin's lymphoma or multiple myeloma was found.

There is considerable interest in specifying the relationship between types of benzene (or benzene-related) exposures and types of lymphohematopoietic cancers. There is clear and widely accepted evidence from a variety of occupational studies that the risks of AML are increased, but the evidence for other lymphohematopoietic cancers is less clear. A review of available studies concluded that evidence for the risk of chronic lymphocytic leukemia was inconsistent and that evidence for the risk of chronic myeloid leukemia and acute lymphocytic leukemia was insufficient (Schnatter et al. 2005). In a meta-analysis of 26 occupational cohorts, no association with non-Hodgkin's lymphoma was observed overall or in any individual study (Wong and Raabe 2000). This conclusion was supported by a second review of existing evidence by the same investigators (Wong and Fu 2005).

Seventy-seven cases of leukemia in gas and electric utility workers were compared with 285 controls in a large nested case–control study in which benzene exposure was estimated using a job–exposure matrix (Guenel et al. 2002). The risk of leukemia was found to increase at cumulative exposures greater than or equal to 54.8 mg/m^3-year, with evidence of an exposure–response relationship. The risks of acute lymphocytic leukemia and AML were both increased, but there was apparently little affect on the risk of chronic leukemia. The exposures at which changes in risk were observed were lower than those reported for the Pliofilm cohort (130 mg/m^3-year). The median time-weighted

average (TWA) exposure to benzene was 0.52 mg/m^3 (90% of exposures were below 6.5 mg/m^3). The median cumulative exposure was 3.6 mg/m^3-year (90% of exposures were below 282 mg/m^3-year).

The association between peak and cumulative benzene exposure and lymphohematopoietic cancers was examined in a study of a cohort of chemical-production workers (Collins et al. 2003). The study suggested that peak exposures of more than 326 mg/m^3 are a better predictor of risk than cumulative exposure and that the risk of multiple myeloma might be more affected than that of other cancers. However, the study was too small to draw firm conclusions.

In a study from the U.K., a cohort of workers occupationally exposed to benzene in 233 companies since 1966 or 1967 was followed up for cancer registrations to 2001 and mortality to 2002 (Sorahan et al. 2005). Study subjects worked in a wide range of industries, some of which were associated with other potential hazards. Compared with population predictions, registrations and mortality for acute nonlymphocytic leukemia were increased, but there was no evidence of effects on other lymphohematopoietic cancers. While largely in line with other evidence that acute nonlymphocytic leukemia is associated with benzene exposure, the study did not yield information on exposure–response relationships at lower concentrations. The use of registrations was a strength of the study, given recent improvements in the survival rates for various leukemias. But in this study, the registration results were somewhat less conclusive than those for mortality.

Community Exposure Studies

A number of community studies have examined the association between the incidence of leukemia and proximity to sources of benzene (and other hydrocarbons), such as petrochemical works and gas stations (Knox and Gilman 1997; Harrison et al. 1999; Wilkinson et al. 1999; Reynolds et al. 2003; Steffen et al. 2004). All but one of these (Wilkinson et al. 1999) observed an association with childhood leukemia. An English study and a French study examined proximity to gas stations and reported positive associations (Harrison et al. 1999; Steffen et al. 2004). In the larger of these two studies, the risks of both acute nonlymphocytic leukemia and acute lymphocytic leukemia were increased (Steffen et al. 2004). A study in California found evidence of an association between childhood leukemia and modeled exposure to hazardous air pollutants originating from all sources (Reynolds et al. 2003). These studies pointed to the possibility that community exposure to organic compounds, including benzene, might cause childhood leukemia. Although it is not possible to single out benzene at this time, it is notable that both the English and French studies found an association with living near a gas station (benzene is a major constituent of gasoline vapor).

A number of studies have investigated the relationship between traffic exposure and childhood leukemia. Four of these found evidence of positive associations (Savitz and Feingold 1989; Nordlinder and Jarvholm 1997; Feychting et al. 1998; Harrison et al. 1999). Three found little or no evidence of an association (Raaschou-Nielsen et al. 2001; Langholz et al. 2002; Steffen et al. 2004).

The lack of consistency in the results of these community studies might be explained by variations in design, power, definition of exposure, window of exposure, and definition of outcome. Overall, however, the body of evidence points to an association between childhood leukemia and exposure to mixtures that contain benzene. Indeed, in view of what is already known from occupational and animal studies, a causal link between childhood leukemia and benzene exposure seems plausible.

Occupational Exposure during Pregnancy and Risk of Leukemia in Offspring

There is evidence associating childhood leukemia with the occupational exposure of parents to hydrocarbons (Buckley et al. 1989; McKinney et al. 1991; Shu et al. 1999), though some studies have found no association (van Duijn et al. 1994). The association, if causal, has important implications for the risks of community exposure, because it points to the possibility that the critical window of exposure is during the time of conception or in early pregnancy. None of these studies have been able to demonstrate that benzene is the hydrocarbon responsible for the association observed.

NONCANCER HEALTH EFFECTS

Acute exposure to very high concentrations of benzene (several thousand mg/m^3) is associated with anesthetic effects and severe damage to the blood-forming elements of the bone marrow. But this is not relevant to ambient exposures from mobile sources, which are lower by many orders of magnitude. The acute exposure guideline level one (AEGL-1), for minor effects on health, is based on a no observed adverse effect level (NOAEL) of 3.40×10^5 µg/m^3 observed in studies of humans (EPA 2006a). No new evidence is available since the guidelines were set. The AEGL-2, for more serious effects on health, is based on a NOAEL of 1.24×10^7 in inhalation studies in animals. These concentrations were far higher than those associated with mobile sources.

Effects on Reproductive Health

Animal studies have found that various reproductive outcomes, such as birth weight, are affected by benzene exposure; the evidence for effects on human fertility is inconclusive. There is little recent human evidence. The risk of congenital malformations was investigated in a study of women working in biomedical-research laboratories (Wennborg et al. 2005). Although it was a small study (1951 pregnancies), exposure to solvents before the third trimester was significantly associated with an increased risk of major malformations. The risk associated with the use of benzene around the time of conception or organogenesis was even higher.

Hematologic Effects

Benzene exposure can lead to hematotoxicity, which is important not only as a health effect in its own right, but also as a biomarker and risk factor for leukemia (Rothman et al. 1997). Criteria for studying the effects of benzene exposure (both orally and by inhalation) have been developed. The reference concentration (RfC) and California EPA reference exposure level (REL) for benzene (30 $\mu g/m^3$ and 60 $\mu g/m^3$, respectively; EPA 2003b; California EPA 2005a) are based on evidence that inhalation of benzene has effects on circulating blood cells in humans (EPA 2003b).The most influential study of hematologic effects was a study of 44 exposed workers and nonexposed control subjects in Chinese factories (Rothman et al. 1996). Reductions in circulating lymphocytes were observed at 8-hour TWA median exposures as low as 24 mg/m^3. The ATSDR inhalation minimal-risk level (MRL) is 0.2 mg/m^3 and is based on immunologic effects observed in mice.

More recent studies in occupational settings have revealed effects on hematologic indices at even lower benzene concentrations. Qu and colleagues (2002) studied peripheral-blood counts and white blood cell differential counts in 130 benzene-exposed workers and 51 age- and sex-matched controls. Personal benzene exposures in the exposed workers ranged from 0.2 to 398 mg/m^3 on the day of biologic sampling, and their 4-week averages ranged from 3.3 to 178 mg/m^3. The researchers observed an exposure–response relationship between increasing exposure and reductions in red and white blood cells, as well as in neutrophils. Compared with control subjects, effects were observed even in the group with the lowest exposures (0.82 mg/m^3 and lower). The reductions in red and white blood cells and in neutrophils were correlated with various biomarkers of exposure, including urinary metabolites and albumin adducts. A prospective study of 250 workers in three Chinese shoe factories and 140 controls found that white blood cell and platelet counts decreased, even in the group with the lowest exposures (Lan et al. 2004). Mean exposure concentrations ranged from less than 3 mg/m^3 to more than 33 mg/m^3. Hemoglobin concentrations were reduced only in the highest exposure group. Progenitor-cell-colony formation declined with increasing exposure and was the most sensitive of all the cell markers. Two genetic variants in the enzymes that metabolize benzene, myeloperoxidase and NAD(P)H:quinone oxidoreductase, were related to the declines in cell counts. A letter to the editor challenged the clinical significance of the findings at the lower exposures (Lamm and Grunwald 2006). The authors responded that the declines in blood cell counts were not of immediate concern but that the effects on progenitor cells were more pronounced and should be a matter of concern because they reflected alterations in bone marrow that might be associated with health effects in the future.

In contrast to the studies reported above, a recent study of U.S. petrochemical workers using routine monitoring data found no association between mean benzene exposures (8-hour TWA) of 0.46 to 1.9 mg/m^3 and any hematologic indicator (Tsai et al. 2004). This disparity might be explained by differences in the concentration and distribution of exposure between the U.S. and Chinese workers. Alternatively, the differences might lie in the fact that the Chinese studies were purposely designed to test the hypothesis and were thus superior in their exposure assessment and timing of biologic sampling in relation to exposure. While there is increasing evidence that effects on hematologic indices might occur at exposure concentrations lower than 3.26 mg/m^3, considerable uncertainty remains as to what is the lowest concentration associated with these effects.

REGULATORY SUMMARY

Benzene is classified by the IARC (1987) as Group 1 ("carcinogenic to humans") and by the EPA (1998a, 2003b) as Group A ("a known human carcinogen"). These classifications are based on evidence from both humans and animals. Various risk assessments have been carried out for the purpose of defining acceptable occupational and ambient exposure concentrations. These have generally relied on evidence from occupational studies (California EPA 2005a; U.K. Department for Environment, Food and Rural Affairs 2006; EPA 2000d; ATSDR 2005d).

The EPA (2003b) has estimated a lifetime cancer risk of 2.2×10^{-6} to 7.8×10^{-6} from 1 $\mu g/m^3$ benzene exposure over a lifetime—a concentration similar to that measured in ambient air. The risk estimate is based largely on evidence from a cohort of rubber workers (the Pliofilm cohort)

in which exposure to benzene was not associated with exposure to other chemicals (Rinsky et al. 1981, 1987; Paustenbach et al. 1993; Crump 1994). The California EPA calculated a cancer unit risk factor (URF) of 2.9×10^{-5} from 1 μg/m^3 benzene exposure over a lifetime (California EPA 2002), based on leukemia risk after occupational exposures (Rinsky et al. 1981).

For the purposes of reference values, however, much reliance has been placed on a small quantity of evidence from occupational studies that found an association between very low exposure concentrations and detectable abnormalities in blood cells, measured as absolute lymphocyte counts (Rothman et al. 1996). On this basis, together with some evidence from animal studies, the EPA determined a chronic inhalation RfC of 30 μg/m^3 benzene based on a benchmark concentration of 8.2 mg/m^3 benzene that was found to be associated with decreased lymphocyte counts in an occupational study (Rothman et al. 1996) and based on applying an uncertainty factor of 300. Using much the same evidence, the California EPA (2005a) determined an inhalation REL of 60 μg/m^3 for benzene based on a lowest observed adverse effect level (LOAEL) of 1.73 mg/m^3, an average occupational exposure of 60 μg/m^3, and an uncertainty factor of 10 (Tsai et al. 1983). In contrast, in the U.K., the occupational risk of cancer together with several safety factors was used to set an ambient standard of 16 μg/m^3 (with a target of 3 μg/m^3) (U.K. Department for Environment, Food and Rural Affairs 2006). Other regulatory standards include a maximum concentration of 1 mg/m^3 benzene in Cambodia (Kingdom of Cambodia 2000) and annual average concentrations of 3 μg/m^3 in Japan (Japan Ministry of the Environment 2005a), 20 μg/m^3 in Nepal, 10 μg/m^3 (with a target of 3.6 μg/m^3 to be achieved by 2010) in New Zealand, 10 μg/m^3 in Germany and Italy, 5 μg/m^3 in the Netherlands, and 16.25 μg/m^3 (as an annual running mean) in the U.K. (U.K. National Air Quality Archive 2006b). Austria has proposed an annual average concentration of 10 μg/m^3 as a standard and 2.5 μg/m^3 as a long-term target. Portugal has proposed an annual concentration of 10 μg/m^3 as a standard, and Sweden has set guidelines of 1.3 μg/m^3 for annual average concentrations (and a 5 μg/m^3 annual mean concentration to be achieved by 2010) (European Commission 1982; Swedish Environmental Protection Agency 1999; Bangladesh Department of Environment 2005; Netherlands Environmental Assessment Agency 2005; Clean Air Initiative–Asia 2006). The European Commission has recommended an annual average concentration of 5 μg/m^3 (with a 100% tolerance level of 10 μg/m^3) as a target to be met by 2010 (European Union 1998).

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

On-road mobile sources account for half of the benzene found in ambient air; tobacco combustion is a major source in indoor air. A relatively large and growing database of measures of environmental concentrations exists for benzene, in contrast to other mobile-source air toxics. Mean ambient, outdoor, and indoor concentrations of benzene typically range from 1 to 10 μg/m^3. Peak concentrations range from 14.9 μg/m^3 in rural settings to 110 μg/m^3 in residences. The highest mean concentrations are found in urban roadside (22 μg/m^3) and urban in-vehicle (17 μg/m^3) locations, where close proximity to direct motor-vehicle emissions is likely. Over the past several years, urban ambient concentrations of benzene have decreased. Seasonal data indicate that ambient benzene concentrations tend to peak during the cooler months. Personal exposures to benzene appear to be in the same range as ambient concentrations. Based on 1999 data, the NATA found mean benzene concentrations of 1.4 μg/m^3 overall, 1.56 μg/m^3 for urban areas, and 0.56 μg/m^3 for rural areas (EPA 2006b). A comparison with historical data suggests that current ambient and indoor concentrations and personal exposures to benzene are lower than those observed in the 1980s.

Differences in sampling and sample analysis might have influenced the absolute concentrations reported in the various studies, but it was beyond the scope of this report to assess such differences. Smoking, for example, in the environment sampled would probably have affected the observed concentrations. Additional limitations sometimes included the number and type of environments sampled, the number of samples collected, methods of accounting for the presence or absence of sources, the extent of geographic and seasonal variability, the representativeness of residences and populations sampled, and the extent of sampling for sensitive or at-risk populations.

TOXICITY

The carcinogenicity of benzene depends on how it is metabolized, but it is not certain which metabolites (or combinations of metabolites) are carcinogenic. Probable candidates are the metabolites benzoquinone and *t,t*-muconaldehyde, which are known to cause the type of clastogenic damage induced by exposure to benzene. Benzene metabolism also produces reactive oxygen species, which can lead to oxidative damage to DNA and interference with DNA repair. No good animal models are known for the benzene-induced AML associated with human exposures to

benzene. However, benzene is hematotoxic in mice. It is carcinogenic in both rats and mice; mice are the more sensitive of the two species. Humans metabolize benzene more like mice than like rats, suggesting that humans are sensitive to benzene in ways similar to mice.

HUMAN HEALTH

From epidemiologic studies, it is clear that there is an association between occupational exposure to benzene and the development of AML. There is less clarity about which model of exposure response should be adopted in assessing risk at the lower end of occupational exposures or, by extrapolation, to the general population, which is exposed to benzene at even lower concentrations and in mixtures of various compounds arising from various sources. The EPA's current risk assessment proposes a lifetime cancer risk of 2.2×10^{-6} to 7.8×10^{-6} for an exposure of 1 μg/m^3 over a lifetime (EPA 2003b)—an exposure that is similar to that measured in ambient air today. More recent studies have shown effects on hematologic indices even at low chronic occupational exposures—i.e., at or below 0.82 mg/m^3. Hematotoxicity is important not only as a human health effect in its own right, but also as a biomarker and risk factor for leukemia. Recent research on biomarkers of benzene exposure and its effects indicates that such markers might be sensitive to concentrations encountered in ambient air.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of benzene?

Mobile sources contribute almost half the benzene found in ambient air. There are other important sources of exposure, including smoking and environmental tobacco smoke.

2. Does benzene affect human health?

It is clear that there is an association between occupational exposure to benzene and the development of AML.

3. Does benzene affect human health at environmental concentrations?

Recent studies have shown effects on hematologic indices even at benzene concentrations that are lower than those of most occupational exposures (i.e., at or below 0.82 mg/m^3) but still higher than those of most ambient exposures. Community studies in which benzene is only one of many potential carcinogens in the air have shown inconsistent associations with cancer incidence.

RESEARCH GAPS AND RECOMMENDATIONS

It is known that benzene is a carcinogenic health hazard, specifically for acute nonlymphocytic leukemias with or without myeloidysplastic syndrome; the association with non-Hodgkin's lymphoma needs to be clarified. The exposure–response relationship, especially at the observed or extrapolated low concentrations found in occupational and ambient air, needs to be clarified as well. It is likely that there will be no feasible new epidemiologic approaches capable of directly assessing the risk of benzene exposure at current ambient concentrations. This is because exposures are characteristically low, the incidence of known relevant health effects is small, and benzene is encountered as part of a complex mixture of potential carcinogens. All of these make it very difficult to associate specific health effects with exposure to benzene in ambient air. There would appear to be little more to be gained by new analyses of existing cohorts or by meta-analysis. These have already been done. The only feasible epidemiologic approach would probably use biomarkers of benzene exposure and toxicity. Research recommendations for benzene include the following:

- New epidemiologic studies at low benzene exposure concentrations should include extensive use of biomarkers of exposure, effects, and susceptibility to permit better classification of exposure groups and determination of toxicity.
- Continue the development of sensitive analytical biomarkers of exposure, effect, and susceptibility.
- Validate biomarkers used as predictors of adverse health effects in worker cohorts exposed to benzene.
- Use the biomarkers to better characterize the shape of the benzene exposure–response curve at low ambient concentrations.
- Elucidate the possible association between exposure to benzene and non-Hodgkin's lymphoma.

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1,3-Butadiene

INTRODUCTION

1,3-Butadiene (CAS Registry Number 106-99-00, C_4H_6, molecular weight = 54.1) (Figure 11) is a colorless gas used as a monomer in the production of plastics, synthetic rubber, and other polymers. It was used in large volumes during World War II to make synthetic rubber when supplies of natural rubber were cut off. At the time, butadiene was assumed to have low toxicity.

At one atmosphere pressure and 25°C, 1 ppm butadiene is equivalent to 2.21 mg/m^3.

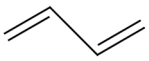

Figure 11. Structure of 1,3-butadiene.

BENCHMARK LITERATURE

The following evaluation of research literature on 1,3-butadiene is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from the International Agency for Research on Cancer (IARC 2004a), the EPA (2002b,c), the Agency for Toxic Substances and Disease Registry (ATSDR 1993), and Himmelstein and colleagues (1997). Most of the exposure information was summarized from recent studies and databases listed in the exposure tables in Appendices B and D. Most of the health-effects data were obtained from studies listed in the health tables in Appendix C, the California EPA (1992), the EPA (2002b,c), Albertini and colleagues (2003b), Delzell and colleagues (2001), and Sathiakumar and colleagues (2005).

EXPOSURE

SOURCES AND EMISSIONS

1,3-Butadiene is a component of motor-vehicle emissions, formed by the incomplete combustion of olefins in gasoline and diesel fuel. It is not a component of evaporative emissions. Except in areas near petrochemical plants, motor-vehicle emissions are the dominant source of 1,3-butadiene in ambient air. Other sources of non-occupational exposure include emissions from synthetic-rubber and plastics factories, cigarette smoke, and forest fires. 1,3-Butadiene reacts in the atmosphere, where it is oxidized by hydroxyl radicals, nitrate radicals, and ozone to produce acrolein and formaldehyde (Skov et al. 1992; Atkinson 1994). Because of its short half-life in air (1 to 9 hours), 1,3-butadiene at low concentrations is measurable only close to its emission sources (Atkinson and Carter 1984; Atkinson et al. 1989).

According to the 1999 National Air Toxics Assessment (NATA), on-road motor vehicles account for 51% of emissions in urban counties and 25% in rural counties in the U.S. Non-road motor vehicles account for 20% of emissions in urban counties and 12% in rural counties (EPA 2006b).

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Table 5 and Figure 12 show the range of mean and maximum concentrations of 1,3-butadiene in µg/m^3 measured in outdoor (including in-vehicle) locations, in indoor environments, and by personal monitoring.

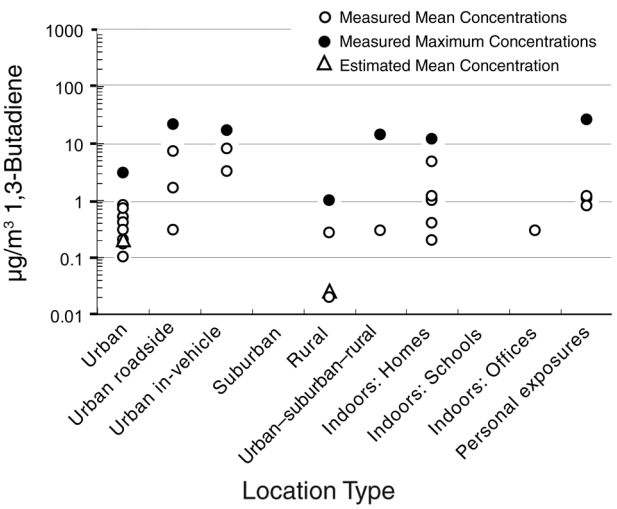

Figure 12. Concentrations of 1,3-butadiene (µg/m^3) at various locations. Data for figure are from Table 5.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

Table 5. 1,3-Butadiene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration ($\mu g/m^3$) Mean	Concentration ($\mu g/m^3$) Maximum	Citations	Comments[b]
Outdoor Areas						
Urban						
	> 1000	24 hr	0.16	0.78	Dann (Unpublished)	Canister measurement
	35	48 hr	0.14	—	Kinney et al. 2002	Summer
	36	48 hr	0.13	—	Kinney et al. 2002	Winter
	~ 600	24 hr	0.80	—	South Coast Air Quality Management District 2000	Canister measurement; MATES II Study
	4–17	24 hr	0.46	0.60	Zielinska et al. 1998	Canister measurement
	4–17	24 hr	0.44	0.84	Zielinska et al. 1998	Canister measurement
	4–17	24 hr	0.18	0.22	Zielinska et al. 1998	Canister measurement
	~ 60	24 hr	0.71	2.8	Zielinska et al. 1998	Canister measurement
	~ 60	24 hr	0.29	1.1	Zielinska et al. 1998	Canister measurement
	~ 480	24 hr	0.29	1.4	Dann (Unpublished)	Canister measurement; high-traffic sites
	60–83	24 hr	0.11–2.2	0.55–4.0	California Air Resources Board 2003	6 cities monitored
Urban in-vehicle						
	35	6 hr	7.9	—	Kim et al. 2001	
	50	~ 9 hr	3.3	17.2	Chan et al. 1991a,b	
	16	2 hr	0.24–2.7	5.7	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	13	2 hr	0.20–2.8	4.4	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	31	1–15 hr	2.0	2.9	Fitz et al. 2003	
Urban roadside						
	12	2 hr	—	4.9	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	9	2 hr	—	1.1	Rodes et al. 1998	Canister measurements: analyzed within 8 days of collection
	21	3 hr	7.2	20.5	Sapkota et al. 2005	Summer
	4–17	24 hr	1.6	4.8	Zielinska et al. 1998	Canister measurement
Suburban						
	~ 60	24 hr	0.20	1.1	Zielinska et al. 1998	Small community

Table continues on next page

[a] Data extracted from published studies.

[b] Given the gas-phase reactivity of 1,3-butadiene with NO_2, some investigators have suggested that sampling with canisters may result in post-sample degradation if canisters are stored for more than 1 week (Atkinson et al. 1984). Accordingly, studies using canister sampling for 1,3-butadiene may report measured concentrations that are lower than actual. Studies using canister measurements are noted.

Table 5 (*Continued*). 1,3-Butadiene Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3) Mean	Concentration (μg/m^3) Maximum	Citations	Comments[b]
Outdoor Areas (*Continued*)						
Rural						
	> 1000	4 hr	0.01	0.63	Dann (Unpublished)	Canister measurement
	~ 60	24 hr	0.26	0.99	Zielinska et al. 1998	Canister measurement
	~ 60	24 hr	0.02	0.60	Zielinska et al. 1998	Canister measurement
Urban–suburban–rural combined						
	1550	24 hr	0.29	1.4	EPA 2004d	Includes canister measurements
Indoor Spaces						
Residences						
	12	12 hr	1.1	—	Kim et al. 2001	
	35	48 hr	1.0	12	Kinney et al. 2002	Summer
	36	48 hr	1.2	5.8	Kinney et al. 2002	Winter
	32	48 hr	0.2	1.5	Sax et al. 2004	Fall
	62	24 hr	4.7	10	California Air Resources Board 1992; Sheldon et al. 1992	
	39	24 hr	0.42	2.5	Van Winkle and Scheff 2001	10 homes
Offices						
	12	12 hr	0.3	—	Kim et al. 2001	
Personal Exposures						
	473	2 hr	1.1	26.3	Kim et al. 2001	Day
	99	2 hr	0.8	7.9	Kim et al. 2001	Night
	35	48 hr	1.2	—	Kinney et al. 2002	Summer
	36	48 hr	0.87	—	Kinney et al. 2002	Winter

[a] Data extracted from published studies.

[b] Given the gas-phase reactivity of 1,3-butadiene with NO_2, some investigators have suggested that sampling with canisters might result in post-sample degradation if canisters are stored for more than 1 week (Atkinson et al. 1984). Accordingly, studies using canister sampling for 1,3-butadiene might report measured concentrations that are lower than actual. Studies using canister measurements are noted.

Ambient Air

In North America, annual mean concentrations of 1,3-butadiene range from 0.015 to 1.0 μg/m^3 (EPA 2004a; Environment Canada 2004) as shown in Figures 12–14. The overall U.S. mean concentration is 0.27 μg/m^3 (EPA 2006b). The Canadian National Air Pollution Surveillance system reported mean concentrations of 0.015 μg/m^3 for 14 rural sites and 0.16 μg/m^3 for 39 urban sites between 2002 and 2004 (Dann T, unpublished). In the U.S., the mean concentrations measured at two high-traffic sites ranged from 1.6 to 7.2 μg/m^3; the highest reported mean concentration was 20.5 μg/m^3 (Sapkota et al. 2005; Zielinska et al. 1998). Distributions and trend data for urban sites in the Canadian monitoring network are presented in Figures 13 and 14. The trend data indicate some decreases in ambient concentrations in the 1990s, with relatively small changes evident in more recent years. In the U.S., the NATA reported higher modeled mean concentrations in urban counties (0.17 μg/m^3) than in rural counties (0.03 μg/m^3) (EPA 2006b). This difference was also reported by Zielinska and colleagues (1998). The data from their monitoring program in Arizona showed that 1,3-butadiene concentrations ranged from 0.29 to 0.71 μg/m^3 in urban sites and was 0.02 to 0.26 μg/m^3 in rural sites. The mean background site (rural as opposed to urban) concentration was 0.02 μg/m^3. Concentrations of 1,3-butadiene at urban sites correlated with those of toluene, xylene, and benzene (Zielinska et al. 1998).

The California Children's Environmental Health Protection Program monitored six urban locations in California for approximately 1 year and reported site averages of

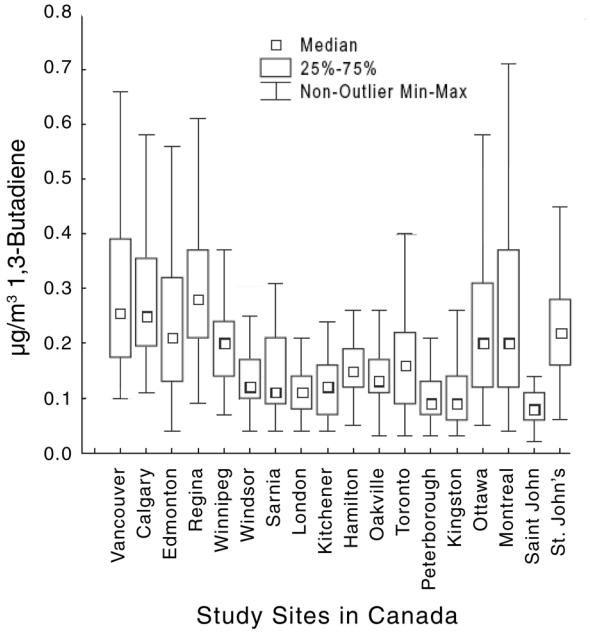

Figure 13. Annual mean concentrations of 1,3-butadiene in Canadian cities in 2001. (Reprinted from Environment Canada 2004, with permission.)

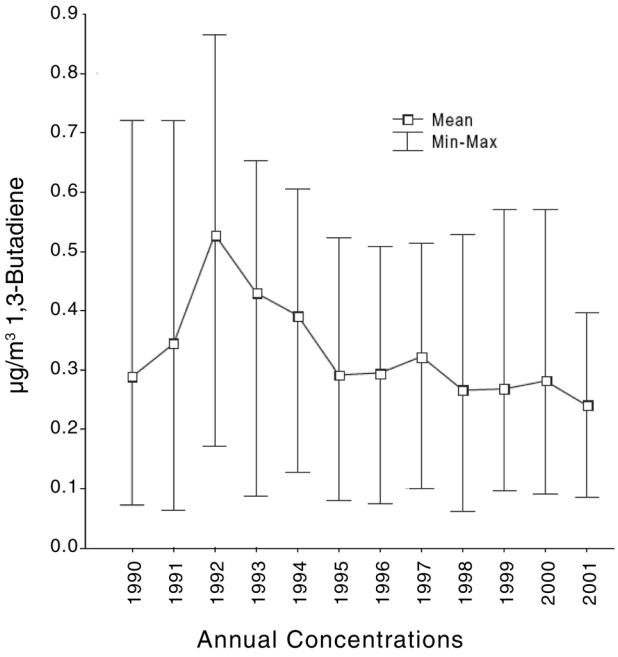

Figure 14. Concentrations of 1,3-butadiene measured in urban sites in Canada from 1990 to 2001 as part of the National Air Pollution Surveillance program. (Reprinted from Environment Canada 2004, with permission.)

0.1 to 2.2 µg/m^3 1,3-butadiene (the highest site average was measured in San Diego), with an overall mean of 0.76 µg/m^3 (California Air Resources Board 2003). The Multiple Air Toxics Exposure Study (MATES-II study) reported an overall mean concentration of 0.8 µg/m^3 at 10 monitoring sites over a 1-year period (South Coast Air Quality Management District 2000). Zielinska's monitoring program in Arizona reported a mean concentration (24-hour samples) of 1.6 µg/m^3 at a high-traffic urban roadside monitoring site (Zielinska et al. 1998). Sapkota and colleagues (2005) reported a mean concentration (3-hour samples) of 7.2 µg/m^3 near tollbooths in Baltimore, Md. At the tollbooths, the changes in 1,3-butadiene concentrations over time corresponded to the changes in traffic counts. Regression analyses suggested that vehicles with more than two axles were much larger contributors to concentrations than vehicles with two axles (based on significance of vehicle-class traffic counts in regression-model classes correlated at $r = 0.5$).

Zielinska and colleagues (1998) reported higher mean concentrations in winter than in summer and attributed the difference to lower levels of photochemical reactivity in winter. This contrasted with most of the other MSATs measured in the study. Kinney and associates (2002) measured 1,3-butadiene as part of a study of personal exposures of New York City high school students and found similar mean concentrations in summer (0.14 µg/m^3) and winter (0.13 µg/m^3). But when it came to mean personal exposures, they reported somewhat lower exposures in winter (0.87 µg/m^3) than in summer (1.2 µg/m^3).

Outside of North America, studies of ambient concentrations of 1,3-butadiene have been limited, but reported measures have been in the same range as those found in North American urban areas (Figure 12). A study in the U.K. (Kim et al. 2001) described in more detail below, also reported monitoring-site concentrations similar to those reported in the U.S. studies.

In-Vehicle Exposures

A study conducted in Raleigh, N.C., found that 1,3-butadiene concentrations measured in vehicles during commutes were about three times higher than those measured outdoors. A mean concentration of 3.3 µg/m^3 and a maximum of 17.2 µg/m^3 were measured (Chan et al. 1991a,b). Kim and colleagues (2001) also reported high mean concentrations in vehicles in the U.K. (7.9 µg/m^3 for 35 6-hour samples). Rodes and colleagues (1998) reported high mean concentrations (0.24 to 2.7 µg/m^3 for 16 2-hour samples with a maximum value of 5.7 µg/m^3) in single-occupant vehicles in Sacramento and Los Angeles. These concentrations were higher than urban roadside concentrations measured in both locations. In contrast, Fitz and colleagues

(2003) measured 1,3-butadiene concentrations in school buses on standard routes in Southern California and reported that 1,3-butadiene was detectable only on 8 of 31 windows-closed morning runs and on both of the 2 windows-open afternoon runs. Overall, 70% of their samples were below the 1.1 μg/m^3 limit of detection. In the remaining 30%, a mean 1,3-butadiene concentration of 2.0 μg/m^3 (maximum 2.9 μg/m^3) was measured.

Indoor Exposures

Only limited measurements of 1,3-butadiene have been made in indoor microenvironments. Additionally, in several such studies, the 1,3-butadiene in the majority of samples taken proved to be below the limits of detection (0.38 to 1.2 μg/m^3), which limited the conclusions that could be drawn from the studies (Chan et al. 1991a; California Air Resources Board 1992; Gordon et al. 1999; Sax et al. 2004). In New York City, Kinney and colleagues (2002) measured elevated concentrations of 1,3-butadiene in the homes of nonsmoking high school students. Personal exposures were similar to indoor concentrations and higher than ambient concentrations.

In the U.K., Kim and colleagues (2001) also reported elevated indoor concentrations, with a mean concentration (12-hour samples) of 1.1 μg/m^3 in 12 homes (6 with smokers) and an overall indoor/outdoor ratio of 6.6. Indoor concentrations in the homes with smokers were 3.4 times those in nonsmoking homes, and smoking was estimated to account for 60 to 70% of the 1,3-butadiene measured in these homes. In the nonsmoking homes, the changes in indoor concentrations over time generally followed the changes measured outdoors. A mean concentration (12-hour samples) of 0.3 μg/m^3 was measured in 12 office buildings. Concentrations in stores, cinemas, and libraries were between those in offices and homes; measurements in pubs (2-hour samples) were substantially higher (mean = 3 μg/m^3; N = 6) (Kim et al. 2001).

Similar instances of indoor concentrations exceeding those measured outdoors were reported by Mukerjee and colleagues (1997) for nine homes (six rural and three urban) in the Rio Grande Valley of Texas (median concentrations were 0.8 μg/m^3 indoors and 0.20 μg/m^3 outdoors) and by Van Winkle and Scheff (2001) for 10 nonsmoking homes in Chicago (median concentrations were 0.26 μg/m^3 indoors and 0.04 μg/m^3 outdoors). No specific activities or circumstances were found to be associated with these indoor 1,3-butadiene concentrations. It is possible that the concentrations result from reduced photochemical degradation of 1,3-butadiene indoors compared with outdoors, but this hypothesis has not been specifically addressed.

Personal Exposures

Kim and colleagues measured mean personal exposures to 1,3-butadiene in 12 nonsmoking adults in Birmingham, U.K., of approximately 1.1 μg/m^3 (Kim et al. 2001). Maximum daytime exposures were more than three times higher than night-time exposures. Exposure in the home was estimated to account for 50 to 90% of total 1,3-butadiene exposure. Kinney and colleagues (2002) observed average personal exposure measurements similar to those of Kim and colleagues (2001).

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

No studies were found of ambient 1,3-butadiene concentrations in Africa, and only one study was found for Asia, citing 1.8 μg/m^3 in Pakistan (Barletta et al. 2002). In Europe, 1,3-butadiene measurements have been taken in the U.K. and ranged from 0.06 to 0.88 μg/m^3 (Dollard et al. 2001; U.K. National Air Quality Archive 2006b). In Latin America, 1,3-butadiene concentrations of 2.7 μg/m^3 were measured in Brazil (Grosjean et al. 1998, 1999), and concentrations of 0.9 μg/m^3 were measured in Mexico (Serrano-Trespalacios et al. 2004). These are similar to ambient concentrations measured in the U.S. Ambient concentrations measured in Canada are shown in Figures 13 and 14 and are similar to those in the U.S.

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

The metabolism of 1,3-butadiene is shown in Figure 15 (as adapted from Himmelstein et al. 1997). Minor updates to the proposed pathways in Figure 15 can be found in Albertini and associates (2003a).

1,3-Butadiene can be oxidized by cytochrome P450 enzymes to three electrophilic epoxide forms: 1,2-epoxy-3-butene (a monoepoxide), 1,2:3,4-diepoxybutane (a diepoxide), and 3,4-epoxy-1,2-butanediol (an epoxy diol). The epoxides are detoxified by hydrolytic enzymes called epoxide hydrolases or by conjugation with glutathione. The initial metabolite in all species studied is 1,2-epoxy-3-butene, which can then be further metabolized by any or all of three pathways; it can be oxidized to 1,2:3,4-diepoxybutane, it can be conjugated with glutathione and then excreted in urine as M2 (a mercapturic acid); or it can be hydrolyzed to 3,4-epoxy-1,2-butanediol and, by a series of enzyme reactions, excreted in the urine as M1 (another mercapturic acid).

Concentrations of diepoxybutane in blood and of M1 and M2 in urine can be used to determine how much of the metabolism followed the oxidative pathway and how much

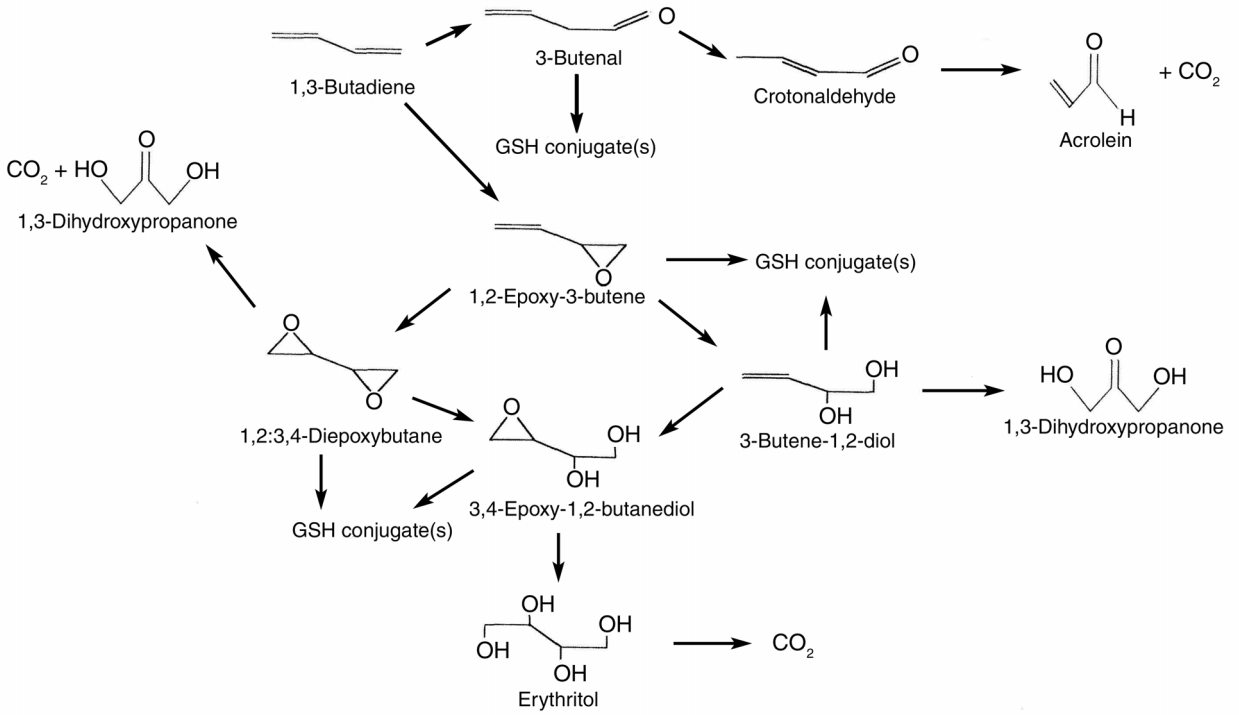

Figure 15. Proposed pathways of 1,3-butadiene metabolism. GSH = Glutathione. (Adapted from Himmelstein et al. 1997, with the permission of Informa Healthcare Journals and the author.)

followed the hydrolytic pathway. Mice have a much higher ratio of oxidizing enzymes to hydrolyzing enzymes than do rats or primates. The highly mutagenic 1,2:3,4-diepoxybutane can be readily detected in the blood of exposed mice but is difficult to detect in exposed rats. The ratio of M2 (the marker of the oxidative pathway) to M1 (a marker of a hydrolytic pathway) is higher in mice than in rats. The amount of 1,2:3,4-diepoxybutane formed in humans is not known, but the ratio of M2 to M1 in Czech rubber workers exposed to 1,3-butadiene was quite low, suggesting that humans metabolize 1,3-butadiene more by the hydrolytic (detoxifying) pathway than the oxidative pathway.

BIOMARKERS

The principal protein adduct formed in rodents and humans exposed to 1,3-butadiene is a trihydroxybutyl adduct, which appears to be formed from 3,4-epoxy-1,2-butane diol, but not from 1,2:3,4-diepoxybutane (Swenberg et al. 2000). In a study of Czech 1,3-butadiene workers, Albertini and colleagues (2003b) found this adduct to be the best biomarker of exposure. Various potential biomarkers of exposure were compared with careful measures of occupational exposure. The M1 urinary metabolite also proved to be useful as a biomarker of exposure (Albertini et al. 2003b). Later work by Swenberg's group (Boysen et al. 2004) developed a 1,2:3,4-diepoxybutane–specific adduct, which could be useful in determining the extent of the formation of 1,2:3,4-diepoxybutane (a potent mutagen) in various exposed species, including humans.

NONCANCER HEALTH EFFECTS

The noncancer effects of 1,3-butadiene exposure are well summarized in a review by Himmelstein and colleagues (1997). Some of the following information came from this review.

In Vivo

Single 6-hour exposures of rats and mice to high concentrations (1100 to 2200 mg/m^3) of 1,3-butadiene deplete the lung and liver of reduced glutathione. This depletion was more dramatic in mice (the highest depletion was 75% in lungs) than in rats (up to about 40% in liver) (Himmelstein et al. 1995). Many studies indicate that 1,3-butadiene exposure can induce metabolic enzymes, although the results depend on exposure conditions and the species of rodent used.

The toxicity of 1,3-butadiene in reproduction and development has been studied by the National Toxicology Program (NTP) (Morrissey et al. 1990). Rats and mice were exposed to up to 2200 mg/m^3 1,3-butadiene, 6 hours/day,

on days 6 to 15 of gestation. No developmental toxicity was observed in fetal rats, but the mice showed fetal anomalies after exposure to concentrations as low as 440 mg/m^3. Dominant-lethal and sperm-head-morphology studies suggested that 1,3-butadiene might also be a germ-cell mutagen in mice.

Gonadal atrophy is a major health effect observed in mice exposed to 1,3-butadiene. In the NTP studies, testicular atrophy was observed in male B6C3F1 mice exposed to 1380 mg/m^3 1,3-butadiene, and ovarian atrophy was observed in female mice exposed to concentrations as low as 13.8 mg/m^3 (Melnick et al. 1990). This effect was not observed in rats.

There are also large differences between rats and mice in the effect of 1,3-butadiene on the hematopoietic and immune systems. Sprague-Dawley rats exposed to up to 18,000 mg/m^3 1,3-butadiene for 6 hours/day, 5 days/week for 13 weeks showed no sign of hematologic toxicity nor any sign of general toxicity (Crouch et al. 1979). Similar exposures in B6C3F1 mice resulted in suppression of the immune system (spleen cell toxicity) and bone marrow toxicity (Thurmond et al. 1986). Later studies showed that 1,3-butadiene adversely affects hematopoiesis in mice (Irons et al. 1986; Leiderman et al. 1986; Colagiovanni et al. 1993).

In Vitro

In cell-culture studies, Irons and colleagues (1986) found that the 1,3-butadiene metabolite 1,2-epoxy-3-butene adversely affects cytokine-mediated cell differentiation in the bone marrow of mice but not of rats or humans. The authors concluded that mice have a unique hematopoietic progenitor-cell population that is sensitive to this metabolite and that does not exist in rats or humans.

Many in vitro studies have been conducted to determine the rate at which microsomal enzymes from mice, rats, and humans metabolize 1,3-butadiene (Himmelstein et al. 1997). The results of these studies are the same as those observed in vivo. Compared with rats and humans, mice have a much higher rate of oxidation of 1,3-butadiene and its metabolites than of hydrolysis of the metabolites. These metabolic differences lead to much higher concentrations of the potent mutagen 1,2:3,4-diepoxybutane in mice than in rats, which is consistent with the much higher observed toxicity of 1,3-butadiene in mice. No one has measured 1,2:3,4-diepoxybutane (the key metabolite in the oxidative pathway) in exposed humans. But the metabolite M1 (a key biomarker of the hydrolytic pathway) has been measured in the urine of workers exposed to 1,3-butadiene.

GENOTOXICITY

In Vivo

Mutations induced by 1,3-butadiene exposure of mice include chromosomal aberrations and *Hprt* mutations (Walker and Meng 2000; Walker et al. 2003). Extensive work has been conducted on the ability of 1,3-butadiene and its metabolites to induce *Hprt* mutations in the T lymphocytes of exposed rodents. The mutagenic potency of 1,3-butadiene and its metabolites was studied in female mice and rats (Walker and Meng 2000; Walker et al. 2003). Mice and rats were exposed by inhalation to 1,3-butadiene, 1,2-epoxy-3-butene, 1,2:3,4-diepoxybutane, or 3-butene-1,2-diol to determine: (1) if *Hprt* mutant frequencies in T cells from 1,3-butadiene–exposed mice and rats would correlate with the species differences in terms of cancer susceptibility and (2) if mutagenic potency data from mice and rats exposed to 1,3-butadiene and its individual epoxy metabolites would reveal the intermediates responsible for mutations in each species. These studies demonstrated important trends in mutagenic responses that begin to distinguish the relative contribution of specific intermediates to the induction of mutations in exposed mice and rats. The studies suggested that 1,2:3,4-diepoxybutane is the major contributor to the mutagenicity of the parent compound in mice and that 1,2-epoxy-3-butene is the principal mutagen in rats. Two weeks of exposure to 6.6 mg/m^3 1,3-butadiene yielded significant increases above background in *Hprt* mutant frequency in exposed mice, but repeated exposures to 1380 mg/m^3 1,3-butadiene were required to produce such mutations in rats. The mutagenic potency of 1,3-butadiene in mice at exposure concentrations of less than 138 mg/m^3 can be explained largely by its ultimate conversion to 1,2:3,4-diepoxybutane. In mice, when the exposure concentration of 1,3-butadiene exceeded 440 mg/m^3, the mutagenic effects of the metabolites derived from 3-butene-1,2-diol reached a plateau. They contributed less than 15% of the total mutagenic effects found in mice exposed to 1380 mg/m^3 1,3-butadiene. Most of the remainder of the mutagenic effects at high-concentration exposures in mice were probably attributable to 1,2:3,4-diepoxybutane, and minor amounts were attributable to 1,2-epoxy-3-butene–induced DNA adducts. In rats, minimal amounts of diepoxybutane have been measured in blood after exposures to 1,3-butadiene concentrations of 138 mg/m^3 and higher. Yet nearly all of the mutagenic effects observed after repeated exposures to 1380 mg/m^3 can be attributed to 1,2:3,4-diepoxybutane–derived metabolites.

Analyses of 1,3-butadiene–induced mutant fractions demonstrated that 1,3-butadiene exposure increased the frequencies of most types of spontaneous mutations occurring in *Hprt* (i.e., base substitutions, frameshifts, and deletions) in both mice and rats. The major difference between the two was the significant induction of base substitutions at GC and AT base pairs in exposed mice but only at AT base pairs in exposed rats (Walker and Meng 2000; Meng et al. 2004).

The stereochemistry of 1,3-butadiene metabolites is not a major factor in the mutagenicity of 1,3-butadiene (Walker and Meng 2000).

In Vitro

All three of the epoxide metabolites of 1,3-butadiene are mutagenic. But in a test system using human lymphocytes, 1,2:3,4-diepoxybutane was found to be approximately 100 times more mutagenic than the other two (Cochrane and Skopek 1994). The resulting mutational spectrum indicated that 1,2:3,4-diepoxybutane induced a substantial fraction of mutations with deletions and rearrangements of *HPRT.*

CANCER

In Vivo

Carcinogenicity studies indicated that 1,3-butadiene is a weak carcinogen in rats and a potent carcinogen in mice. Sprague-Dawley rats were exposed for 2 years to either 2200 or 18,000 mg/m^3 1,3-butadiene. There was an increase in the incidence of thyroid follicular adenomas, uterine tumors, and exocrine pancreatic tumors only at the high concentration (Owen et al. 1987). In females, the incidence of mammary tumors increased at both concentrations. By contrast, carcinogenicity studies conducted by the NTP (Huff et al. 1985; Melnick et al. 1990) indicated that 1,3-butadiene was a potent multisite carcinogen in B6C3F1 mice. Chronic low exposures (as low as 13.8 mg/m^3 for 2 years) resulted in an increased incidence of lung tumors in female mice. Chronic exposures to concentrations ranging from 44 to 138 mg/m^3 induced increases in lung carcinomas, hemangiosarcomas of the heart, and neoplasms of the forestomach, Harderian gland, preputial gland, liver, mammary gland, and ovary. Again, these dramatic differences in the responses of rats and mice appear to be based on the different patterns of 1,3-butadiene metabolism in the two species (Henderson et al. 1996).

Exposure of B6C3F1 mice to concentrations of 440 mg/m^3 1,3-butadiene or higher induced lymphomas that led to early deaths. This response was determined to have been caused by the activation of an endogenous retrovirus and was not considered applicable to humans.

HUMAN HEALTH

BIOMARKERS

Biomarkers of Exposure

One of the difficulties encountered in occupational studies has been exposure estimation. If valid and reliable measures of butadiene exposure could be identified, these could be investigated in relation to effects that are thought to be involved in genotoxicity, the main concern with 1,3-butadiene. A number of studies have investigated urinary metabolites or adducts of hemoglobin as possible biomarkers of 1,3-butadiene exposure in humans (reviewed in Albertini et al. 2003a). Most of these have reported associations between such biomarkers and occupational exposure. A recent comprehensive study by Albertini and colleagues (2003b), conducted among Czech workers, compared groups engaged in butadiene-monomer production, styrene-butadiene synthetic-rubber (SBR) production, or nonexposed administrative work. Smoking was less frequent in the nonexposed group. Detailed and comprehensive exposure assessment took place prospectively for 60 days before collection of biologic samples. Concentrations of both urinary metabolites (M1 and M2) and especially hemoglobin adducts correlated well with exposure. These biomarkers were not associated with genetic polymorphisms for glutathione *S*-transferase (GST) or P450 isoenzymes. Neither the urinary-metabolite nor the hemoglobin-adduct concentrations were affected by smoking.

Biomarkers of Effect

1,3-Butadiene is metabolized by a number of enzymes, including GST and P450, to various substances, including the potent mutagen 1,2:3,4-diepoxybutane. The biomarkers of effect investigated in the Czech study were T-cell variations in *HPRT* and cytogenetic changes in DNA, indicated by sister-chromatid exchanges and chromosomal aberrations. There was no association between 1,3-butadiene exposure and *HPRT* mutations or cytogenetic changes. Neither of these was associated with metabolic genotypes for GST and P450 isoenzymes. Results for the *HPRT* test were not consistent with positive evidence reported in a study of U.S. workers (Ward et al. 2001). Further, the study did not establish a connection between biomarkers of effect and actual exposure or biomarkers of exposure. Otherwise, it did provide evidence that biomarkers of the process of carcinogenesis are absent in workers exposed at concentrations up to 1.79 mg/m^3.

CANCER

Occupational Studies

In the current regulatory literature, the available human evidence is confined to studies of one large cohort of SBR workers in eight plants in the U.S. and Canada (Delzell et al. 1995, 1996) and three small cohorts of 1,3-butadiene–production workers at plants operated by Texaco (Divine and Hartman 1996), Union Carbide (Ward et al. 1995), and Shell (Cowles et al. 1994), respectively. By far the most influential is the study of SBR workers, among whom there was an increase in mortality from leukemia (compared with national rates) but not from lymphomas or other causes of death. The risk was greater in those with indications of higher and longer exposures. The leukemia mortality was not explained by exposure to benzene; however, the individual contributions of styrene and 1,3-butadiene could not be distinguished. Mortality at six of the plants was investigated using quantitative methods to assess exposure, focusing on leukemia as the outcome (Macaluso et al. 1996). An exposure–response relationship between 1,3-butadiene and leukemia was observed, even when styrene was in the model. There was a somewhat similar, but less convincing, association with styrene and leukemia. It was also found that the combined effects of 1,3-butadiene and styrene were less than additive. In a more detailed account of the SBR cohort, exposure was quantified retrospectively and analyzed with respect to a wide range of causes of death (Delzell et al. 1995). There were more leukemia deaths than expected for seven of the eight plants, with 11 excess deaths overall. Risk was related to length and intensity of exposure to 1,3-butadiene and styrene. As in the earlier analysis (Macaluso et al. 1996), the association with styrene was less convincing than that for 1,3-butadiene, but the high correlation between the two (0.5) made their effects difficult to disentangle statistically. There was little evidence for associations between either 1,3-butadiene or styrene and non-Hodgkin's lymphomas, and the incidence of other tumors was in line with that expected for the general population. Benzene exposure was uncommon and low and did not confound these associations.

Despite the small number of studies, there is reasonable evidence that exposure to 1,3-butadiene while working in SBR or 1,3-butadiene production is likely to be associated with an increased risk of lymphohematopoietic cancer. The large SBR-cohort study found an excess of leukemia; the 1,3-butadiene–production studies found an excess of non-Hodgkin's lymphoma and a lesser increase in leukemia. Although this has been presented as an inconsistency, it should be noted that the 1,3-butadiene–production studies did not have enough statistical power to show a significant increase in non-Hodgkin's lymphoma, a relatively uncommon cause of death, nor to exclude an association between 1,3-butadiene and this cancer. If the main evidence for the carcinogenicity of 1,3-butadiene comes from on the SBR-cohort study, then the question becomes whether the 1,3-butadiene associations are explained by correlations with the presence other chemicals, such as styrene and dimethyldithiocarbamate (DMDTC). The carcinogenicity of styrene is classified as Group 2A ("probably carcinogenic to humans") by the IARC, based on limited evidence in human populations and sufficient evidence in laboratory animals (IARC 2004a). The epidemiologic arguments in favor of 1,3-butadiene being a cause of cancer include exposure response, relative robustness to inclusion of styrene in 1,3-butadiene models, and the fact that styrene has not been associated with leukemia in workers exposed to high styrene concentrations in other industries (Delzell et al. 1996).

New Analyses of Occupational Studies

More recent human evidence is confined to updates and reanalyses of existing occupational studies. Mortality data on the 17,924 workers in the SBR cohort previously studied by Delzell and colleagues (1996) and Macaluso and colleagues (1996) have recently been updated by seven more years of follow-up and now include data on an additional 34% deaths (Sathiakumar et al. 2005, Delzell et al. 2006). The increased statistical power of this update has consolidated the evidence that working in the SBR industry is associated with an increased risk of leukemia, but it has not yet resolved uncertainties about the responsible agent. For all causes of death, the standardized mortality ratio (SMR), based on rates expected in the relevant state or province, was lower than expected (SMR = 92). For all leukemias combined, the SMR was 116 (71 observed leukemia deaths compared with 61 expected). There was no convincing evidence that this increase was confined to one type of leukemia. Among the lymphohematopoietic cancers, the association appeared to be specific for leukemia. There was no apparent increase in non-Hodgkin's lymphoma or multiple myeloma. The main increase in leukemia was seen among subjects who were ever-hourly workers with 20 to 29 years since hire and 10 or more years of employment. It was also largely confined to certain groups of workers, most of whom were exposed to multiple agents, including 1,3-butadiene, styrene, and DMDTC.

In an update of the Texaco cohort of 2800 1,3-butadiene–production workers, mortality from all causes and from cancers was lower than expected. But mortality from all lymphohematopoietic cancers was significantly higher, because of increases in these cancers in workers first employed before 1950 and in short-term workers (Divine

and Hartman 2001). However, using an estimate of cumulative 1,3-butadiene exposure, no exposure–response relationship with lymphohematopoietic cancers was found. Mortality was increased for most of the main subgroups, non-Hodgkin's lymphoma and leukemia, though these increases were not statistically significant. Mortality data on the small cohort of 614 workers with potential exposure to 1,3-butadiene in the Shell petrochemical plant was updated (Tsai et al. 2001). Total mortality and all-cancer mortality were low compared with rates in the reference population. Mortality from lymphohematopoietic cancers was similar to that of the reference population. The small size of this cohort, with only three deaths from lymphohematopoietic cancer, does not allow conclusions to be drawn about the effects of 1,3-butadiene.

Workers in the SBR industry are also exposed to DMDTC. It has been postulated that the apparent differences in types of lymphohematopoietic cancer observed in 1,3-butadiene–production workers as compared with SBR workers might be explained by coexposure of the latter to DMDTC (Irons et al. 2001). DMDTC has not been evaluated for carcinogenicity by the IARC (2005a,b), and it has no toxicologic profile in the ATSDR (2005f). It is not generally thought to be carcinogenic, although it has immunosuppressant qualities and is known to inhibit the activity of CYP2E1, a major enzyme responsible for the oxidation of 1,3-butadiene to its epoxide intermediates (Bird et al. 2001). Thus, one might expect DMDTC to inhibit, rather than enhance, the carcinogenicity of 1,3-butadiene.

NONCANCER HEALTH EFFECTS

Biomarkers of Reproductive Effects

Studies in mice suggest that 1,3-butadiene can cause testicular and ovarian atrophy. Testicular injury in men is associated with suppression of inhibin B, a Sertoli-cell secretory protein, and with an increase in follicle-stimulating hormone through a feedback mechanism. In an exploratory study, the utility of these molecules as biomarkers was investigated in stored serum from a group of workers exposed to a variety of potential reproductive toxins, including styrene, acrylonitrile, and 1,3-butadiene, at a polymer-production plant in the mid-1970s (Lewis et al. 2002). Using an index that combined the measured levels of inhibin B and follicle-stimulating hormone, there was an increase in abnormal values in exposed workers compared with controls. There was a correlation between abnormal values and subsequent changes in fertility, but it was not statistically significant. These results require confirmation.

REGULATORY SUMMARY

Current regulatory risk assessments are based mainly on occupational evidence for cancer risk and on animal studies for noncancer risk. 1,3-Butadiene is classified by the IARC (2004a) as a Group 2A carcinogen ("probably carcinogenic to humans") based on limited evidence in humans and sufficient evidence in animals. It is classified by the EPA (2002b,c) as "carcinogenic to humans by inhalation." The difference in classification between the IARC and EPA reflects uncertainty about the interpretation of available epidemiologic evidence.

The EPA has estimated a lifetime risk ("unit risk") of 3×10^{-5} for a 1 μg/m^3 exposure. This estimate is based entirely on the evidence from the cohort of SBR workers (Delzell et al. 1995, 1996; Macaluso et al. 1996) and uses linear extrapolation below the lowest observed concentrations in these occupational data. A similar estimate was made by Health Canada (Hughes et al. 2001). Based on the occupational evidence, a cancer-potency factor of 1.7×10^{-4} was determined by the California EPA (1992). In the U.K., the Expert Panel on Air Quality Standards considered that the occupational evidence indicated no increased risk in workers exposed to less than 2250 μg/m^3 1,3-butadiene and arrived at a recommendation of 2.25 μg/m^3 as a running annual average, taking into account ambient lifetime exposure and the likelihood of individual variability (U.K. Department for Environment, Food and Rural Affairs 2002). All of these risk assessments have recognized that 1,3-butadiene is a known carcinogen in animals. The risk assessments are founded on numerous assumptions, including the specificity of 1,3-butadiene's association with occupational health effects and the accuracy of exposure estimates for worker cohorts.

Noncancer risk assessments by both the EPA and California EPA have relied on evidence of reproductive and developmental effects in mice, including testicular and ovarian atrophy. This information led to an inhalation reference concentration (RfC) of 2 μg/m^3, based on a benchmark concentration of 1.94×10^3 μg/m^3 for ovarian atrophy and an uncertainty factor of 1000 (EPA 2002b,c). The California EPA (2000) set a chronic reference exposure level (REL) of 20 μg/m^3, based on a lowest observed adverse effect level (LOAEL) of 600 μg/m^3 and an uncertainty factor of 30. The occupational evidence on the reproductive effects of 1,3-butadiene is limited to the study discussed above.

The U.K. has set an ambient air quality objective of 2.25 μg/m^3 of 1,3-butadiene as a running mean average concentration (U.K. National Air Quality Archive 2006a).

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

Long-term average ambient concentrations of 1,3-butadiene are typically less than 1 to 2 $\mu g/m^3$. These concentrations are generally much lower than occupational exposures. Concentrations measured at high-traffic sites have been found to be higher than those typically found at general urban and rural locations. Mobile sources contribute 51% of the exposure in urban locations and 25% in rural locations. Based on only a small number of studies, it is believed that indoor concentrations are typically higher than ambient concentrations; personal exposures are similar to indoor concentrations. Total exposure is therefore dominated by exposure to indoor sources. Ambient sources are different from occupational sources and are accompanied by different coexposures. 1,3-Butadiene is subject to atmospheric reactivity and can produce atmospheric acrolein and formaldehyde.

TOXICITY

Species differences in susceptibility to cancer are related to differences in metabolism. Mice, which metabolize 1,3-butadiene mainly by oxidative reactions to form a toxic diepoxide, are more susceptible than rats, which have a higher capacity to hydrolyze the epoxide metabolites of 1,3-butadiene to nontoxic forms. Humans are more similar to rats than mice in this respect. Adverse reproductive outcomes are also observed in mice but not rats.

HUMAN HEALTH

Working in the SBR industry is associated with increased hematopoietic cancer. On epidemiologic evidence alone, it is not possible to completely distinguish with confidence the effects of 1,3-butadiene from those of other coexposures. The extrapolation of occupational risk to risk at ambient concentrations is highly sensitive to a variety of assumptions. Biomarkers of exposure have been identified. Biomarkers of effect are identified inconsistently in exposed workers and are not correlated with biomarkers of exposure.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of 1,3-butadiene?

Emissions estimates and comparisons of measurement data between urban and rural areas—as well as comparisons of roadside and in-vehicle with urban background measurements—indicate that mobile sources are important contributors to ambient concentrations of 1,3-butadiene. Limited indoor and personal-exposure measurements also indicate, however, that indoor concentrations are higher than outdoor concentrations. Environmental tobacco smoke is a source of indoor 1,3-butadiene. But even in nonsmoking environments, indoor concentrations of 1,3-butadiene are higher than outdoor concentrations, suggesting the presence of other indoor sources or the absence of indoor photochemical degradation as possible explanations for the observed differences in concentrations.

2. Does 1,3-butadiene affect human health?

The human evidence, though limited, is consistent with the possibility that 1,3-butadiene causes lymphohematopoietic cancers in high-exposure occupational settings. This is plausible, moreover, because there is good evidence that certain metabolites of 1,3-butadiene cause cancer and adverse reproductive effects in mice. In humans, however, the metabolism of 1,3-butadiene appears to be more like that of rats, a less susceptible species. At high exposure concentrations, such as those once found in the U.S. in certain industries, 1,3-butadiene is likely to be a human health hazard because of its carcinogenicity. The confounding of 1,3-butadiene's health effects by coexposure to styrene and DMDTC cannot be ruled out. But on epidemiologic and toxicologic grounds, 1,3-butadiene seems likely to be the active agent.

3. Does 1,3-butadiene affect human health at environmental concentrations?

If a monotonic exposure–response relationship with no threshold is assumed (as for a genotoxic substance), then 1,3-butadiene can be assumed to be a hazard at ambient concentrations. It is not realistic to expect that this hazard can be demonstrated using epidemiologic methods, because the relevant outcome is uncommon and because community exposure to 1,3-butadiene is almost always associated with coexposure to other agents from the same sources, principally emissions from traffic and tobacco smoke. Estimates of community effect can be made by extrapolation from the exposure–response relationships in the SBR cohort evidence. But they are sensitive to a variety of assumptions about the magnitude and slope of the exposure–response relationship. Possibly there are subgroups that are especially sensitive to 1,3-butadiene because of age or genetic polymorphisms in the genes involved in 1,3-butadiene metabolism or because of combined exposures from a number of sources.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

The current NATA estimates of 1,3-butadiene exposure appear to be low, compared with measured ambient concentrations. Research recommendations for 1,3-butadiene–exposure studies include the following:

- Develop improved emissions estimates, including a better understanding of the relative effect of different vehicle types (e.g., light versus heavy duty) for future risk assessments.
- Identify the determinants of indoor 1,3-butadiene concentrations and personal exposures given that several studies have found indoor concentrations to be higher than outdoor concentrations.
- Systematically analyze the trends in ambient concentrations of 1,3-butadiene at U.S. monitoring locations, especially high-traffic sites.
- Assess the effect of alternative fuels on ambient 1,3-butadiene concentrations.

TOXICOLOGY

Given the large differences in the metabolism of 1,3-butadiene in mice and rats, there is a need to conduct well-controlled metabolism and toxicity studies in species more similar to humans, such as nonhuman primates. Humans are more like rats than mice in how they metabolize 1,3-butadiene. Exposed rats do not show the hematologic toxicity observed in exposed mice and develop tumors (mainly mammary) only after chronic high exposures to 1,3-butadiene. Research recommendations for 1,3-butadiene–toxicology studies include the following:

- Conduct parallel metabolism and toxicity studies in primates to improve the assessment of risk to humans, particularly in hematopoietic tissues, by linking the concentration of specific metabolites to specific toxic effects.

HUMAN HEALTH

There is a need for more research on cancer incidence in high-exposure populations. These are only found in occupational settings. However, it is unlikely that suitable opportunities now exist for such research. These studies would require very large and well-characterized cohorts followed over many years. Research recommendations for human-health studies of 1,3-butadiene include the following:

- Carry out additional investigations of biomarkers of exposure and effect in occupational settings. This can be done in smaller and better-characterized occupational cohorts than those typically needed in cohort studies examining cancer occurrence as an endpoint. Hemoglobin adducts are promising as biomarkers of exposure. Additional research on these should be carried out to help in the development of valid biomarkers for community studies.
- Further research on biomarkers in general, with refinements to make them sufficiently sensitive for use in community studies. Biomarkers for use in more highly exposed community samples should be considered, too, but these should be part of an integrated assessment that includes other air toxics, such as benzene. In addition, biomarkers, such as hemoglobin adducts, and *HPRT*-mutant assays should be validated in primates in order to better understand human responses to low exposures to 1,3-butadiene.

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Formaldehyde

INTRODUCTION

Formaldehyde (CAS Registry Number 50-00-0; CH_2O; molecular weight = 30.0) (Figure 16), also known as methanal, is a colorless gas having a strong, irritating odor. It is ubiquitous in the environment as a result of natural processes. It is also a major industrial chemical and is used extensively as a chemical intermediate (e.g., in the production of resins and fertilizers) and as a disinfectant and preservative in many industrial and consumer applications. Formaldehyde is also produced in the body as part of normal metabolism.

At one atmosphere pressure and 25°C, 1 ppm formaldehyde is equivalent to 1.2 mg/m^3.

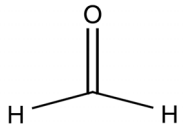

Figure 16. Structure of formaldehyde.

BENCHMARK LITERATURE

The following evaluation of research literature on formaldehyde is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from HEI research reports by Kleinman and Mautz (1991), Leikauf (1991), Fennell (1994), and Grosjean and Grosjean (2002); the Agency for Toxic Substances and Disease Registry (ATSDR 1999a); WHO (2002); the Chemical Industry Institute of Toxicology (CIIT 1999); the EPA (1990, 2000e); the Organisation for Economic Co-operation and Development Screening Information Data Set (OECD 2002); the International Agency for Research on Cancer (IARC 1997a, 2006); and selected key articles.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

EXPOSURE

SOURCES AND EMISSIONS

Formaldehyde is formed in all living cells. It is also formed from the photochemical oxidation of volatile organic compounds (VOCs) present in vehicle exhaust and from incomplete combustion of gasoline and diesel fuels. As formaldehyde is not present in appreciable quantities in fuels per se, it is not a component of evaporative emissions. Formaldehyde is also formed during other major combustion processes, such as the burning of forests, other wood, cigarettes, and coal in coal-fired power plants. Formaldehyde is a common component of resins in pressed-wood products and is emitted indoors in considerable quantities by building materials and furnishings. In the atmosphere, formaldehyde is subject to photolysis and reaction with hydroxyl radical. Photolysis is thought to be the most important atmospheric mechanism of formaldehyde removal. It is an important component in the production of atmospheric NO_2 and ozone. Formaldehyde has an atmospheric lifetime of approximately 4 hours (Seinfeld and Pandis 1998).

According to the National Air Toxics Assessment (NATA), on-road mobile sources account for 40% of emissions in urban counties and 13% of emissions in rural counties in the U.S. Non-road motor vehicles account for 27% of emissions in urban counties and 11% in rural counties (EPA 2006b). Using the Assessment System for Population Exposure Nationwide (ASPEN) model, Pratt and colleagues (2000) estimated that mobile sources contributed 58% of ambient concentrations in Minnesota.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Table 6 and Figure 17 show the range of mean and maximum concentrations of formaldehyde in μg/m^3 measured in outdoor (including in-vehicle) locations, in indoor environments, and by personal monitoring.

Ambient Concentrations

In the U.S., annual mean ambient concentrations of formaldehyde in air range from 0 to 49 μg/m^3, with an overall national mean concentration of 4.3 μg/m^3 (EPA 2006). The NATA reported higher modeled mean concentrations in urban counties (1.8 μg/m^3) than in rural counties

Table 6. Formaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging Sampling Time	Concentration (μg/m^3) Mean	Concentration (μg/m^3) Maximum	Citations	Comments
Outdoor Areas						
Urban						
	—	1 yr	1.8	—	EPA 2006b	Model
	437	24 hr	3.2	14.8	Manchester-Neesvig et al. 2003	
	> 1000	24 hr	2.4	15.0	Dann (Unpublished)	
	~ 600	24 hr	5.5		South Coast Air Quality Management District 2000	
	4–17	24 hr	1.3	2.0	Zielinska et al. 1998	
	4–17	24 hr	2.1	2.8	Zielinska et al. 1998	
	4–17	24 hr	0.8	1.1	Zielinska et al. 1998	
	~ 60	24 hr	4.4	24.5	Zielinska et al. 1998	
	~ 60	24 hr	1.4	4.2	Zielinska et al. 1998	
	395	Yearly	6.4	12.4*	Weisel et al. 2005	2 seasons
	36	48 hr	5.3		Kinney et al. 2002	
	36	48 hr	2.1		Kinney et al. 2002	Winter
Brazil						
	37	2 hr	15.1	56.9	Montero et al. 2001	
	13	3 hr	10.8	34.6	Grosjean and Grosjean 2002	Tunnel measurements excluded
Urban in-vehicle						
	50	~ 9 hr	20.7	65.3	Riediker et al. 2003	
	15	2 hr		23.6	Rodes et al. 1998	
	13	2 hr		18.5	Rodes et al. 1998	
Urban roadside						
	9	2 hr		8.3	Rodes et al. 1998	
	4–17	24 hr	5.1	7.8	Zielinska et al. 1998	
	10	2 hr		20.3	Rodes et al. 1998	
Urban roadside in Brazil						
	28	2 hr	16.8	66.8	Corrêa et al. 2003	1998–2001 (changing fuel composition)
	24	2 hr	80.2	122.8	Corrêa and Arbilla 2005	2001–2002 (changing fuel composition)
	101	1–2 hr	1.5–54.1	93.5	de Andrade et al. 1998	

Table continues on next page

[a] Data extracted from published studies.

* 99th percentile.

Table 6 (*Continued*). Formaldehyde Measured in Ambient Air, Outdoor and Indoor Areas, and Personal Exposures[a]

Sample Location and Type	Observations (*n*)	Averaging (Time)	Concentration (μg/m^3) Mean	Concentration (μg/m^3) Maximum	Citations	Comments
Outdoor Areas (*Continued*)						
Suburban						
	~ 60	24 hr	1.1	5.3	Zielinska et al. 1998	Small community
Rural						
	—	1 yr	0.64	—	EPA 2006b	Model
	~ 840	4 hr	1.5	11.0	Dann (Unpublished)	
	~ 60	24 hr	1.3	5.6	Zielinska et al. 1998	
	~ 60	24 hr	1.3	6.2	Zielinska et al. 1998	
Urban–suburban–rural combined						
	> 1000	24 hr	4.3	182.0	EPA 2006b	
	> 1000	24 hr	3.2	49.2	EPA 2004d	
	> 1000	24 hr	1.7	21.0	Pratt et al. 2000	
Indoor Spaces						
Residences						
	75	1.5 hr	28.0	85.0	Feng and Zhu 2004	
	398	yearly	21.6	53.8*	Weisel et al. 2005	2 seasons
	36	48 hr	20.9		Kinney et al. 2002	Summer
	36	48 hr	12.1		Kinney et al. 2002	Winter
	26	24 hr	19.8	66.2	Reiss et al. 1995	
	36	3 hr	67.1	125.1	Zhang et al. 1994	
Schools						
	911	7–10 days	33.0	76.0	Whitmore et al. 2003b	
	199	6–8 hr	16.0	29.0	Whitmore et al. 2003a	
Personal Exposures						
	409	48 hr	21.7	45.4*	Weisel et al. 2005	Adults
	169	48 hr	20.8	47.4*	Weisel et al. 2005	Children
	42	48 hr	28.5		Kinney et al. 2002	Summer
	38	48 hr	11.5		Kinney et al. 2002	Winter

[a] Data extracted from published studies.

* 99th percentile.

(0.64 μg/m^3) (EPA 2006b). Pratt and colleagues (2000) also reported higher concentrations in urban than in rural areas in Minnesota. In contrast, Zielinska and colleagues (1998) did not find appreciably higher mean concentrations in urban (0.8 to 4.4 μg/m^3) than in rural locations (1.3 μg/m^3) or background (1.3 μg/m^3) in Arizona and suggested that atmospheric transport of formaldehyde could be affecting non-urban locations. Mean concentrations at an urban roadside site, however, were the highest in the study (5.1 μg/m^3). The California Children's Environmental Health Protection Program monitored six urban California locations for approximately 1 year and reported site averages ranging from 1.9 to 4.7 μg/m^3 (the highest site average was measured in Los Angeles), with an overall mean concentration of 3.2 μg/m^3 (Manchester-Neesvig et al. 2003). The Multiple Air Toxics Exposure Study (MATES-II) reported a mean concentration of 5.5 μg/m^3 from 10 monitoring sites over a 1-year period (South Coast Air Quality Management District 2000). In Minnesota, Pratt and colleagues (2000) reported mean concentrations from multiple monitoring sites

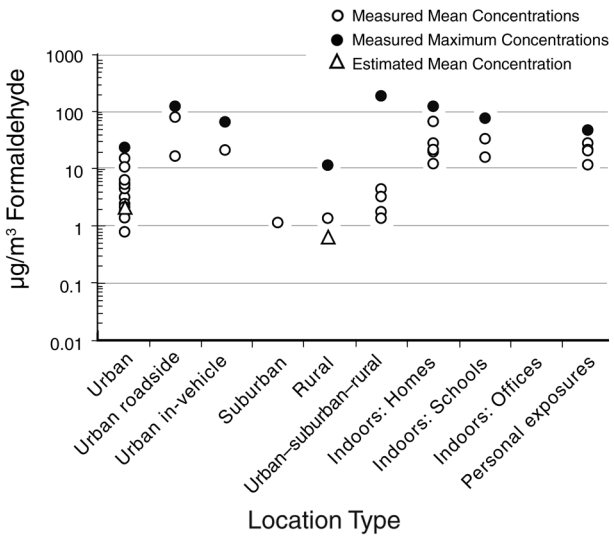

Figure 17. Concentrations of formaldehyde (µg/m^3) at various locations. Data for figure are from Table 6.

ranging from 0.8 to 2.9 µg/m^3, with an overall mean of 1.7 µg/m^3. A study of outdoor and indoor concentrations for approximately 100 residences in Elizabeth, N.J., Houston, Tex., and Los Angeles, Calif., over two seasons reported an average of 6.4 µg/m^3 with a 99th percentile concentration of 12.4 µg/m^3 (Weisel et al. 2005). Measurements from the Canadian National Air Pollution Surveillance system show an overall mean concentration of 2.4 µg/m^3 for nine urban sites and 1.5 µg/m^3 for seven rural sites over the same period (2002 to 2004) (Environment Canada 2003a, 2004, 2005).

In Los Angeles, short-term measurements (2-hour samples) of formaldehyde showed a range of ambient (7 to 20 µg/m^3) and urban roadside (11 to 15 µg/m^3) concentrations. Short-term measurements in Sacramento showed a range of somewhat lower ambient (2 to 4 µg/m^3) and roadside (4 to 6 µg/m^3) concentrations. Although Grosjean and Grosjean (2002) measured 2-hour concentrations as high as 21 µg/m^3 in a tunnel study, there is little evidence to suggest elevated in-vehicle exposures (discussed below). Measurements of formaldehyde from Brazil (discussed below) indicate short-term concentrations of up to 100 µg/m^3 in urban areas.

Measurements from Brazil provide an interesting case study of the effect of fuel composition on ambient concentrations of aldehydes. In Brazil, ethanol was introduced in the late 1970s as part of a national program to decrease dependency on imported oil. By 1998, approximately 40% of the fuel used in vehicles was ethanol. Some vehicles ran on pure ethanol (at peak, approximately 26% of vehicles) and others on gasoline–ethanol mixtures (e.g., gasohol, which contains 76% gasoline and 24% ethanol, vol/vol) (Colón et al. 2001). At its peak, total ethanol-containing fuels accounted for over 83% of the fuel used by vehicles (Colón et al. 2001; Corrêa et al. 2003; Corrêa and Arbilla 2005). Annual mean concentrations of 18 to 50 µg/m^3 formaldehyde and short-term measurements (1- to 2-hour samples) as high as 100 µg/m^3 were measured in Brazilian cities (de Andrade et al. 1998; Montero et al. 2001; Grosjean et al. 2002; Corrêa et al. 2003). Measurements made in Rio de Janeiro between 1998 and 2002 document an increase in annual mean formaldehyde concentrations from 20 µg/m^3 in 2000 to 80 µg/m^3 in 2002. At the same time, there was an 18-fold increase in vehicles fueled by compressed natural gas (6% in 2002) and a decrease in the percentages of vehicles fueled by 100% ethanol (to 14% from a peak of approximately 26%) and gasohol (Corrêa and Arbilla 2005).

In-Vehicle Exposures

Rodes and colleagues (1998) measured in-vehicle formaldehyde concentrations of 7 to 21 µg/m^3 in Los Angeles and 5 to 12 µg/m^3 in Sacramento over 2-hour driving periods. These concentrations were not higher than those measured in Los Angeles at an ambient monitoring site (7 to 20 µg/m^3) or urban roadside sites (11 to 15 µg/m^3). In Sacramento, where ambient concentrations were lower than in Los Angeles, in-vehicle concentrations were somewhat lower than roadside concentrations (4 to 6 µg/m^3) but slightly higher than ambient concentrations (2 to 4 µg/m^3). These results suggest that in-vehicle exposures to formaldehyde are only slightly higher than ambient exposures and that ambient background concentrations are a more significant source of exposure than are direct vehicle emissions.

However, Fitz and colleagues (2003) measured elevated in-vehicle concentrations of formaldehyde in a recent school-bus study on standard routes in Southern California. Compared with the mean concentration at an ambient monitoring site (0.4 µg/m^3), the means ratio was 5.3 for windows-closed morning runs and 2.8 for windows-open afternoon runs. Comparison of sampling runs of 1 to 1.5 hours with closed or open windows suggested some indoor production or reentrainment of formaldehyde. Supporting the possibility of reentrainment was the finding that samples collected on a windows-closed compressed-natural-gas bus had concentrations of formaldehyde that were two to three times higher than those in windows-closed diesel buses. Overall, mean concentrations were higher when the bus windows were closed: On runs with windows closed, mean concentrations were 2.1 µg/m^3 (ranging from 0.89 to 4.8 µg/m^3). On runs with windows open, mean concentrations were 1.1 µg/m^3 (ranging from 0.55 to 2.1 µg/m^3). On rural and suburban runs with windows open, mean concentrations were 0.93 µg/m^3 (ranging from 0.34 to 2.0 µg/m^3). In a North Carolina state-trooper study (Riediker et al. 2003), in-vehicle concentrations (7- to

14-hour samples) of total aldehydes were higher than roadside or ambient concentrations. The overall in-vehicle mean concentration was 21 μg/m^3.

Indoor Exposures

In a study of New York City high school students, Kinney and colleagues (2002) reported personal formaldehyde exposures to be similar to indoor concentrations but higher than outdoor concentrations, reflecting the potential importance of indoor formaldehyde sources. At 21 μg/m^3, summer indoor concentrations (48-hour samples) were higher than winter indoor concentrations (12 μg/m^3). Personal exposures were also higher in summer (14 μg/m^3) than in winter (5 μg/m^3). Overall, indoor concentrations ranged from 5 to 22 μg/m^3 in winter (with a mean of 12 μg/m^3) and from 6 to 50 μg/m^3 in summer (with a mean of 18 μg/m^3). Similar measurements made in Los Angeles as part of the same study showed higher indoor concentrations in winter, ranging from 8 to 60 μg/m^3 (with a mean of 21 μg/m^3). In the study by Weisel and colleagues (2005) of Elizabeth, N.J., Houston, Tex., and Los Angeles, Calif., the average indoor residential concentration for all three cities was 21.6 μg/m^3 for both seasons, with a 99th percentile value of 53.8 μg/m^3.

Numerous other studies have reported indoor concentrations of formaldehyde that are higher than corresponding outdoor concentrations (Zhang et al. 1994; Gordon et al. 1999; Subramanian et al. 2000), with mean indoor concentrations in homes, office buildings, and schools typically three to five times higher than mean outdoor concentrations (Sawant et al. 2004). Typical median indoor concentrations (24-hour samples) ranged from 5 to 50 μg/m^3 in homes, slightly higher in schools (13 to 55 μg/m^3), and slightly lower in office buildings (Subramanian et al. 2000). Mean short-term concentrations (6-hour samples) in six residences in New Jersey were 67 μg/m^3, with a maximum concentration of 125 μg/m^3 (Zhang et al. 1994). Mean concentrations (100-minute samples) in 75 residences in Ottawa were somewhat lower, at 28 μg/m^3, and ranged from 6 to 85 μg/m^3. Substantially higher indoor concentrations (1.5- to 5-hour samples) have been found in association with certain activities in the kitchen, such as broiling fish (129 μg/m^3) and cleaning the oven (200 to 400 μg/m^3) (Fortmann et al. 2001).

Personal Exposures

Two recent studies (Kinney et al. 2002; Weisel et al. 2005) have investigated personal-exposure concentrations of formaldehyde. Both measured personal exposures over a 48-hour periods in summer and winter. In the study by Kinney and colleagues, 46 high school students in New York City were monitored. Average concentrations were 28.5 μg/m^3 in summer and 11.5 μg/m^3 in winter. Personal-exposure concentrations in both seasons were approximately five times higher than outdoor concentrations and comparable to indoor residential concentrations. In the study by Weisel and colleagues, 312 adults and 118 children in Elizabeth, N.J., Houston, Tex., and Los Angeles, Calif., were monitored. Average concentrations were similar for both adults (21.7 μg/m^3) and children (20.8 μg/m^3). The 99th-percentile concentrations were similar as well (45.4 μg/m^3 for adults and 47.4 μg/m^3 for children). Personal-exposure concentrations were approximately three times higher than outdoor concentrations and similar to indoor residential concentrations. These studies suggest that in the U.S. indoor concentrations of formaldehyde are the predominant source of personal exposures.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average urban concentrations of formaldehyde measured in several other countries are generally within the range of those reported for U.S. urban areas (see Table 6 and Figure 17). Ambient concentrations in China, Japan, Turkey, Australia, Denmark, Finland, France, Germany, Greece, Italy, Sweden, and Canada are in the range of those seen in the U.S. for urban, roadside, suburban, and rural measurements (Kalabokas et al. 1988; Shepson et al. 1991; National Environmental Protection Council 1993; Satsumabayashi et al. 1995; Possanzini et al. 1996, 2000, 2002; Slemr et al. 1996; Solberg et al. 1996; Granby et al. 1997; Khare et al. 1997; Ferrari et al. 1998; Christensen et al. 2000; Viskari et al. 2000; Mathew et al. 2001; Sin et al. 2001; Ho et al. 2002; Bakeas et al. 2003; Feng et al. 2004, 2005; Hellén et al. 2004; Chang et al. 2005; Chiu et al. 2005; Odabasi and Seyfioglu 2005; Tago et al. 2005; Japan Ministry of the Environment 2005b). Ambient concentrations in Taiwan and Africa were somewhat higher (ranging from 4.8 to 109 μg/m^3 in Taiwan, although the area included local industries that might have contributed). Ambient concentrations of 40 μg/m^3 were measured in Cairo, Egypt (Khoder et al. 2000; Chiu et al. 2005).

Measurements of formaldehyde concentrations in Mexico City (Baez et al. 1995, 2003; Grutter et al. 2005), however, were higher, ranging from 5 to 44 μg/m^3 in urban settings. In Brazil, measurements were somewhat higher (compared with the U.S.) in Rio de Janeiro (10.7 to 32 μg/m^3), but not in São Paulo (2.8 μg/m^3) (Nguyen et al. 2001; Grosjean et al. 2002). Average concentrations in roadway tunnels in several Brazilian cities were elevated, ranging from 17 to 80 μg/m^3 (Corrêa et al. 2003; Corrêa and Arbilla 2005; Vasconcellos et al. 2005) and up to 65 μg/m^3 near heavy traffic

(Corrêa et al. 2003). Brazil is of particular interest because of the widespread use of ethanol in fuels, as discussed earlier. Montero and colleagues (2001) recorded 2-hour mean and maximum formaldehyde concentrations in São Paulo that were as high as 22 μg/m^3 and 55 μg/m^3, respectively. Mean and maximum concentrations in Rio de Janeiro as high as 16 μg/m^3 and 65 μg/m^3, respectively, have been reported (Grosjean et al. 2002; Corrêa et al. 2003). In recent years, the use of compressed natural gas in vehicles has been increasing by 20% per year. Over the same time period, mean formaldehyde concentrations in Rio de Janeiro have risen fourfold, to 96 μg/m^3 (with peak 2-hour concentrations as high as 135 μg/m^3) (Corrêa and Arbilla 2005). In general, the highest mean formaldehyde concentrations in major Brazilian cities have proved to be nine or more times higher than the highest mean concentrations in U.S. urban areas; the differences in maximum concentrations are roughly similar.

SEASONAL CHANGES IN FORMALDEHYDE CONCENTRATIONS

Formaldehyde is both produced and degraded in ambient air by photochemistry. The highest seasonal ambient concentrations of formaldehyde are associated with the highest rates of photochemical activity. Zielinska and colleagues (1998), for example, reported a strong seasonal variation in formaldehyde concentrations. The highest concentrations were measured in June and July, when photochemical activity was highest. Measurements at roadside locations suggested that photochemical activity in summer contributes more formaldehyde to ambient concentrations than do direct vehicle emissions. (Random samples were taken every 6 days in summer and during periods of stagnant air in winter. Yet summer concentrations were still higher than winter concentrations.)

In New York City, Kinney and colleagues (2002) also reported higher ambient concentrations in summer (5.3 μg/m^3) than in winter (2.1 μg/m^3). Interestingly, they also reported that summer indoor concentrations (48-hour samples), at 21 μg/m^3, were higher than winter indoor concentrations, at 12 μg/m^3, possibly as a result of increased off-gassing from indoor sources and infiltration of ambient formaldehyde in summer (Kinney et al. 2002). Indoor formaldehyde concentrations that are higher in summer than in winter have also been reported elsewhere (Reiss et al. 1995). These are possibly related to higher concentrations of indoor ozone, which lead to increased formaldehyde formation indoors. Mean personal exposures were higher in summer (28.5 μg/m^3) than in winter (11.5 μg/m^3) (Kinney et al. 2002).

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

More than 90% of inhaled formaldehyde gas is absorbed and rapidly metabolized to formate in the upper respiratory tract (Figure 18). In primates, some absorption takes place in the nasal cavity as well as in the nasopharynx, trachea, and bronchi. It has been shown that when formaldehyde is mixed with particles, more of it is retained by the respiratory tract than when it is inhaled alone (Kleinman and Mautz 1991). This suggests that some particles can bind with gases and increase the retained dose of a gas. However, Rothenberg and colleagues (1989) estimated that the deposited dose of formaldehyde in the particle phase was substantially smaller than the dose from the vapor phase. Formate, the metabolic product of formaldehyde, is incorporated in normal metabolic pathways or further oxidized to carbon dioxide. Endogenous formaldehyde is present in all human cells. Exposure of humans, monkeys, or rats to formaldehyde by inhalation does not alter the concentration of formaldehyde in the blood (the concentration of endogenous formaldehyde in human blood is about 2 to 3 mg/L).

NONCANCER HEALTH EFFECTS

Acute Effects

In animals, after inhalation of formaldehyde, lesions are typically found in the upper respiratory tract; after oral administration, they are typically found in the stomach. The nature of the lesions depends on the ability of the tissues involved to respond to the exposure and on the local concentration of formaldehyde. Atrophy and necrosis as well as hyper- and metaplasia of epithelia can occur. The most sensitive no observed adverse effect levels (NOAELs) for morphologic lesions resulting from inhalation exposure to formaldehyde were concentrations ranging from 1.2 to 2.4 mg/m^3 (Greim 2002).

Reproductive and Developmental Effects

Because inhaled formaldehyde is rapidly metabolized and detoxified on contact with the respiratory tract, it is unlikely to reach the reproductive organs in concentrations sufficient to cause damage. In animal studies, the inhalation of formaldehyde had no effect on reproduction or fetal development (IARC 2006). Thrasher and Kilburn (2001) reviewed Russian and Japanese studies reporting birth defects and affects on enzyme function in the mitochondria, lysosomes, and endoplasmic reticulum of laboratory

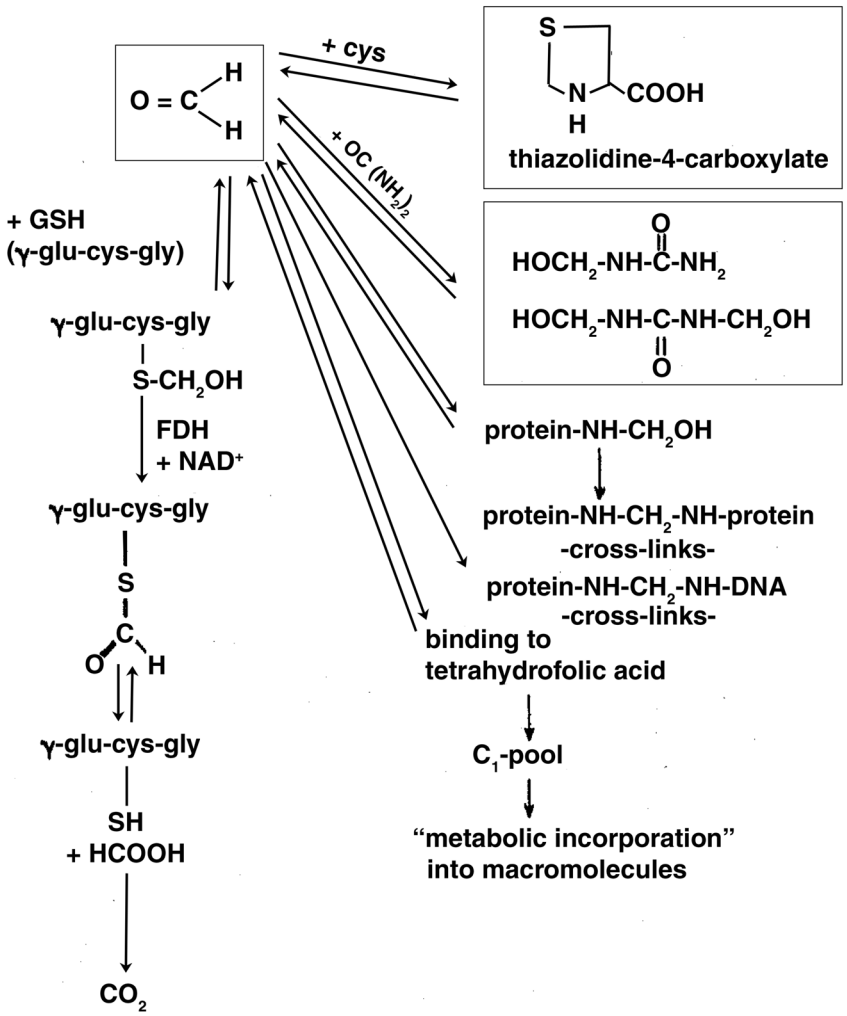

Figure 18. Metabolic pathway of formaldehyde. (Reprinted from Bolt 1987, with the permission of Springer Science and Business Media and the author.)

animals exposed to airborne formaldehyde. Because of severe limitations in these studies (e.g., simultaneous exposure to other chemicals and the lack of analytical concentration measures), they were not suitable for evaluating the reproductive and developmental toxicity of formaldehyde.

GENOTOXICITY

Upon absorption at the site of contact, formaldehyde forms intra- and intermolecular crosslinks with proteins and nucleic acids. Formaldehyde is genotoxic at high concentrations and can induce gene mutations and chromosomal aberrations in mammalian cells. However, the genotoxic effects are limited to cells in direct contact with formaldehyde; no effects are observed in vivo in distant-site tissues. DNA–protein crosslinks are a sensitive measure of DNA modification by formaldehyde. In conclusion, formaldehyde is a direct-acting, locally effective mutagen.

CANCER

In rats, inhalation exposure to formaldehyde induced squamous-cell carcinomas of the nasal cavity. The dose response was highly nonlinear, with sharp increases in tumor incidence occurring only at concentrations greater than 7.2 mg/m^3. No increased incidence of tumors was found in other organs. Nasal cancer was only found at concentrations that induced damage to nasal tissues, including epithelial degeneration and increased cell proliferation, leading to the conclusion that damage to nasal tissue plays a crucial role in the tumor-induction process for formaldehyde. No significant increase in tumors was seen in mice or Syrian hamsters (IARC 2006).

These species differences appear to be related to the local dosimetry and disposition of formaldehyde in nasal tissues. Species differences in nasal anatomy and respiratory physiology might have a profound effect on susceptibility to

formaldehyde-induced nasal tumors. Exposure of rats to formaldehyde in drinking water increased the incidence of forestomach papillomas, leukemias, and gastrointestinal tract tumors in one study (Sofritti et al. 1989) but not in others (IARC 2006). However, the study by Sofritti and colleagues has been questioned because of methodologic shortcomings (Feron et al. 1990).

HUMAN HEALTH

BIOMARKERS

Biomarkers of Exposure

Biomarkers of exposure have not been developed for use in epidemiologic research on the health effects of formaldehyde. Carraro and colleagues (1999) suggested that an immunologic assay that measures the humoral immune response to adducts of formaldehyde and human serum albumin could be used as a marker of environmental exposure to formaldehyde, but such a marker has not been developed.

CANCER

A relatively large number of cohort, nested case–control, and proportional-mortality studies have examined the relationship between occupational exposure to formaldehyde and cancer in two types of populations—people who work with formaldehyde in industrial settings and people in professions in which the use of formaldehyde is fairly common. The industrial settings included those in which formaldehyde is made and those that use formaldehyde in making other products. Workers in the garment industry have also been studied. The professional groups included embalmers, pathologists, laboratory technicians, and anatomists. Population-based case–control studies of selected cancers have also evaluated the association between these cancers and environmental exposure or occupational exposure to formaldehyde.

In 2004, the IARC reviewed formaldehyde and classified it as Group 1 ("an established human carcinogen") (IARC 2006). The IARC review indicated that there is sufficient epidemiologic evidence that formaldehyde causes nasopharyngeal cancer in humans, that there is strong but not sufficient evidence of a causal association between leukemia and occupational exposure to formaldehyde, and that there is only limited epidemiologic evidence that formaldehyde causes sinonasal cancer in humans. The review did not find that the epidemiologic evidence supported a causal role for formaldehyde in relation to cancer at other sites (oral cavity, oropharynx, hypopharynx, larynx, lung, brain, or pancreas). At present, formaldehyde is classified by the National Institute for Occupational Safety and Health as a "potential human carcinogen," by the EPA as Group B1 ("a probable human carcinogen"), and by the National Toxicology Program as "reasonably anticipated to be a human carcinogen."

The conclusion that formaldehyde causes nasopharyngeal cancer in humans has been controversial (Marsh and Youk 2005; Tarone and McLaughlin 2005). In 1997, a meta-analysis of 47 epidemiologic studies of formaldehyde and upper-respiratory-tract cancer reported a weak positive association between exposure to formaldehyde and nasopharyngeal cancer in case–control studies (meta rate ratio [mRR] = 1.3; 95% CI, 0.90–2.10) (Collins et al. 1997). A weak positive association was also present in cohort studies (mRR = 1.6; 95% CI, 0.80–3.00), but no association remained in an analysis that took reporting problems into account (mRR = 1.0; 95% CI 0.50–1.80).

There are seven additional studies, not included in the meta-analysis by Collins and colleagues (1997), that have data on formaldehyde and nasopharyngeal cancer. Of these, two reported a positive association and five reported no association or a very weak association that was not statistically significant.

The additional studies include updates of the three largest studies of industrial workers exposed to formaldehyde. These evaluated mortality from cancer and other diseases among 11,039 workers employed at three U.S. garment factories (Pinkerton et al. 2004), among 25,619 workers at 10 U.S. factories that made or used formaldehyde (Hauptmann et al. 2003, 2004), and among 14,014 workers at six British factories that made or used formaldehyde (Coggon et al. 2003). Their results were inconsistent for nasopharyngeal cancer. No deaths from nasopharyngeal cancer (compared with an expected number of 0.96), occurred among the garment workers, who were estimated to have had exposure to constant low concentrations of formaldehyde (ranging from 0.11 to 0.24 mg/m^3) without intermittent exposure to much higher concentrations ("peaks") (Pinkerton et al. 2004). Among the British workers, 28% of whom were estimated to have been exposed to concentrations of formaldehyde at or above 2.4 mg/m^3, there was only one death from nasopharyngeal cancer (compared with 2.0 expected deaths). In contrast, among workers at the 10 U.S. factories, the ever-exposed group experienced a total of eight observed deaths (compared with 3.81 expected) from nasopharyngeal cancer (standardized mortality ratio [SMR] = 2.10; 95% CI, 1.05–4.21), and the nonexposed group experienced two observed deaths (compared with 1.28 expected) (SMR = 1.56; 95% CI, 0.39–6.23). Further analyses suggested a positive exposure–response relationship both for peak exposure

(seven naso-pharyngeal-cancer deaths were observed in workers in the highest-exposure category, i.e., at or above 4.8 mg/m^3 formaldehyde) and for cumulative exposure (three nasopharyngeal-cancer deaths were observed in workers in the highest-exposure category, i.e., 6.6 mg/m^3-years).

A fourth study of occupational exposure to formaldehyde compared the proportional cancer incidence among exposed men with the proportional incidence among unexposed men in Denmark from 1970 to 1984 (Hansen and Olsen 1995). Exposure was estimated on the basis of job titles (obtained from Danish pension data) and by linking job histories to records that identified all Danish companies that made or imported formaldehyde. The study found four cases of nasopharyngeal cancer among exposed men, compared with 3.2 expected cases (standardized proportionate incidence ratio [SPIR] = 1.3; 95% CI, 0.30–3.20).

In addition to these recent studies of industrial cohorts, there have been three population-based case–control studies of nasopharyngeal cancer. Armstrong and colleagues (2000) studied 282 cases of nasopharyngeal cancer in Chinese individuals and 282 Chinese control subjects living in two areas of Malaysia where people of southern Chinese ancestry have relatively high rates of this cancer. A semiquantitative measure of exposure to formaldehyde was estimated on the basis of self-reported occupational histories. The study found essentially no association with formaldehyde. Among 49 exposed pairs of cases and controls, the median difference in hours of exposure to formaldehyde was 0.6 (P = 0.25 after adjusting for diet and cigarette smoke). The adjusted odds ratio for any estimated exposure to formaldehyde was 0.71 (95% CI, 0.34–1.43), and the adjusted odds ratio for a tenfold exposure increase was 0.88 (95% CI, 0.70–1.12).

Vaughan and colleagues (2000) studied 194 cases of nasopharyngeal cancer identified between 1987 and 1993 in five U.S. cancer registries and 244 controls. Industrial hygienists used self-reported work histories to classify subjects' jobs according to the probability of exposure to formaldehyde (as "possible," "probable," or "definite") and according to estimated intensity of exposure ("none"; "low" as less than 0.12 mg/m^3; "moderate" as 0.12 to 0.60 mg/m^3; or "high" as greater than 0.60 mg/m^3). Odds ratios were 1.3 (95% CI, 0.80–2.10) for any possible, probable, or definite exposure, based on 79 exposed cases and 79 exposed controls; 1.6 (95% CI, 0.30–7.10) for the highest intensity of exposure (more than 0.60 mg/m^3), based on 5 exposed cases; and 2.1 (95% CI, 1.00–4.50) for the longest duration of exposure (more than 18 years), based on 29 exposed cases. Analyses restricted to cases with differentiated squamous-cell or epithelial nasopharyngeal cancers found a statistically significant positive association with duration of exposure and with cumulative exposure (average concentration-years), both when all possible, probable, or definite exposures to formaldehyde were included and when only definite exposures were included. The investigators concluded that their results supported a causal relationship between occupational exposure to formaldehyde and nasopharyngeal cancer.

Hildesheim and colleagues (2001) studied 375 cases of nasopharyngeal cancer and 325 community controls, all from Taipei, Taiwan. Exposure to formaldehyde was estimated on the basis of self-reported occupational data. The study found, at most, a weak association with formaldehyde. Odds ratios were 1.4 (95% CI, 0.93–2.20) for ever having been exposed, 1.6 (95% CI, 0.91–2.90) for greater than 10 years of exposure, 1.2 (95% CI, 0.67–2.20) for greater than 10 years of exposure after excluding the most recent 10 years before diagnosis, and 1.5 (95% CI, 0.88–2.70) for the highest cumulative exposure. Epstein-Barr virus is a well-established risk factor for nasopharyngeal cancer. Hildesheim and colleagues found that subjects who were seropositive for Epstein-Barr virus (360 cases and 94 controls) had an odds ratio of 2.7 (95% CI, 1.20–6.20) for ever having been exposed to formaldehyde, but there was no exposure–response trend in this group.

Marsh and Youk (2005) and Tarone and McLaughlin (2005) challenged the suggestion that the data from the study by Hauptmann and colleagues (2004) reflected a causal association between formaldehyde and nasopharyngeal cancer. Their arguments included the observation that all of the excess nasopharyngeal cancers among the exposed workers were confined to only 1 of the 10 plants in the study. This plant had 6 observed (compared with 0.66 expected) deaths; the other 9 plants, combined, had only 2 observed (compared with 3.15 expected) deaths. Also, the British study found no excess nasopharyngeal cancer, unlike the U.S. study, even though it included five times as many subjects with relatively high formaldehyde exposure (2.4 mg/m^3 or higher) (Tarone and McLaughlin 2005). At present, it is not known if differences in formaldehyde exposure, chance, or other factors explain the inconsistent results of these studies.

The IARC's conclusion in its 2004 review that there is "strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde" (IARC 2006) is also controversial. At the time of the IARC's 1995 review (IARC 1997a), there were three large studies of industrial workers (that were subsequently updated, see below), as well as a number of smaller studies, that reported data consistent with the absence of

an association between exposure to formaldehyde and leukemia. Seven of eight studies that evaluated professional groups and that were available in 1995 reported that leukemia was weakly associated with work as an embalmer or funeral director, as a pathologist or laboratory technician, or as an anatomist. For a number of reasons, however, the results of these studies did not constitute a satisfactory scientific basis for concluding that formaldehyde causes leukemia. The reported associations typically were weak (with rate or risk ratios of about 1.5), based on small numbers, and not statistically significant. The studies did not obtain direct, quantitative estimates of exposure to formaldehyde, did not evaluate exposure–response relationships, and did not assess possible confounding by other agents to which members of the professional groups might have been exposed. Thus, the research had not ruled out the possibility that the weak associations were caused by occupational exposures other than to formaldehyde, by nonoccupational exposure, or by chance or bias.

Among the updated studies of industrial workers, published after the 1995 IARC review (IARC 1997a), two reported a positive association between formaldehyde and myeloid leukemia. The first, by Pinkerton and colleagues (2004), found that the rate of death from all forms of leukemia, combined, among garment workers was similar to the rate in the general U.S. population (24 observed and 22 expected deaths), reflecting an SMR of 1.09, which was not statistically significant. The rate of death from lymphocytic leukemia was lower than expected (3 observed and 5 expected deaths, SMR = 0.60, not statistically significant). The rate of deaths from myeloid leukemia was higher than expected (15 observed and 10 expected deaths, SMR = 1.44, not statistically significant), particularly among workers who had 10 or more years of potential exposure to formaldehyde (8 observed and 3.7 expected deaths, SMR = 2.19, not statistically significant) and for workers with 20 or more years since first exposure (13 observed and 6.8 expected deaths, SMR = 1.91, statistically significant [$P < 0.05$]). Of the total of 15 myeloid leukemias observed among these workers, 9 were acute, 5 were chronic, and 1 was unspecified as acute or chronic. Quantitative estimates of individual subjects' exposure to formaldehyde were not available. The analysis controlled for sex, race, age, and calendar period but not for lifestyle exposures, such as smoking, which is suspected of being weakly associated with leukemia.

The second updated study, by Hauptmann and colleagues (2003), of U.S. plants that produced and used formaldehyde, reported that exposed workers had an overall leukemia-mortality rate that was 15% lower than in the general U.S. population (65 observed and 76 expected deaths, SMR = 0.85, not statistically significant), after adjusting for gender, race, age, and calendar period. Other analyses did not compare the death rates of workers with those of the general U.S. population; instead, they compared the death rates of workers who had relatively high exposure with those of workers who had relatively low exposure. These analyses used several measures of exposure, including duration of exposure, estimated cumulative exposure, average intensity of exposure, and exposure to peaks. Leukemia in general was not strongly or consistently associated with duration of exposure or with cumulative exposure. But myeloid leukemia was positively associated both with exposure to peak levels of formaldehyde greater than 4.8 mg/m^3 (rate ratio [RR] = 3.46, statistically significant) and with an average intensity of exposure of greater than 1.2 mg/m^3 (RR = 2.49, statistically significant). The researchers did not report on acute and chronic forms of leukemia separately. They attempted to adjust their results for possible confounding by benzene and other agents and reported that such adjustments had little effect on the results for formaldehyde and leukemia.

The association between formaldehyde and leukemia seen in this study has been challenged for several reasons (Marsh and Youk 2004; Casanova et al. 2004; Cole and Axten 2004). The biologic mechanism by which formaldehyde might cause leukemia has not been established (Hauptmann et al. 2003, 2004; Collins 2004; Heck and Casanova 2004; Cogliano et al. 2005; Golden et al. 2006). No plausible biologic mechanism has been suggested to explain why there might be a true association between peak or average-intensity exposures and leukemia but no association between cumulative exposure and leukemia. The higher RRs for workers in the high peak and average-intensity exposure groups were caused by a rate of leukemia that was quite low in the low-exposure group compared with the general U.S. population (Marsh and Youk 2004). The explanation of this pattern is unknown, but the possibility that the positive results for myeloid leukemia are attributable wholly or in part to an unidentified confounder or bias cannot at present be excluded.

The British study found that the rate of death from leukemia was lower among formaldehyde-exposed workers than in the population at large, both for workers with any amount of exposure (31 observed and 34 expected deaths, SMR = 0.91) and for workers in high-exposure jobs (eight observed and 11 expected deaths, SMR = 0.71) (Coggon et al. 2003). The study did not present detailed results of analyses of leukemia according to alternative exposure indices, nor did it present results for specific forms of leukemia. The Danish study (Hansen and Olsen 1995) of proportional cancer incidence also did not find any evidence

of a positive association between potential exposure to formaldehyde and leukemia (39 observed and 47.0 expected cases; SMR = 0.8, 95% CI, 0.6–1.6).

Overall, the epidemiologic evidence of an association between formaldehyde and leukemia is inconsistent. A positive relationship between formaldehyde and myeloid leukemia was recently reported in studies of two groups of industrial workers. But these results are not supported by studies of several other groups of industrial workers. Studies of professional groups have reported that working as an embalmer, undertaker, pathologist, or anatomist is weakly associated with leukemia, but the association might be caused by other occupational exposures or unidentified sources of bias.

NONCANCER HEALTH EFFECTS

Formaldehyde is a skin sensitizer and one of the more common causes of contact dermatitis. High concentrations can cause asthmatic reactions by way of an irritant mechanism. Whether formaldehyde can cause bronchial asthma by way of immunologic mechanisms is unresolved at present. Studies in animals indicate that formaldehyde might enhance sensitization to inhaled allergens.

Short-term exposure to formaldehyde can lead to noncancer health effects in nonsensitized people, including irritation of the eyes, nose, and other upper-respiratory sites as well as small, reversible decrements in pulmonary function. (All of these are rare at concentrations below 0.36 mg/m^3.) Lachrymation, sneezing, coughing, nausea, dyspnea, and concentration-dependent discomfort are the chief symptoms of formaldehyde exposure. Individual responses to formaldehyde vary substantially, although the eyes are generally most sensitive to exposure. About 5 to 20% of individuals report eye irritation at concentrations ranging from 0.6 to 1.2 mg/m^3, but some begin to feel irritation even at airborne concentrations below 0.12 mg/m^3. Moderate to severe irritation of the eyes, nose, and throat occurs at exposures ranging from 2.4 to 3.6 mg/m^3. In healthy nonsmokers and asthmatics, lung function was generally unaffected even after 3 hours of exposure to up to 3.6 mg/m^3 formaldehyde. Concentrations ranging from 60 to 125 mg/m^3 caused death. Based on a review of chamber, community, and occupational studies of human exposure to formaldehyde, however, it was not possible to identify a specific NOAEL or lowest observed adverse effect level (LOAEL) for formaldehyde (Bender 2002).

In addition to contact dermatitis, epidemiologic studies have reported several other possible effects, but the evidence for a causal relationship is insufficient. These effects include asthma, neurobehavioral effects, histologic changes in the nasal epithelium of workers with occupational exposure, and adverse reproductive effects among occupationally exposed women, including spontaneous abortion, low birth weight, and congenital malformations.

Repeated exposure to formaldehyde typically causes toxic effects at the site of first contact. These are characterized by local cytotoxicity and subsequent repair of the damage. A limited number of studies have investigated histopathological changes in the nasal epithelium of relatively small populations of workers who were repeatedly exposed to formaldehyde. Some histopathological changes in the nasal epithelium were reported at 0.3 mg/m^3 formaldehyde, but the available data do not allow adequate dose–response evaluations.

In a meta-analysis of epidemiologic studies (Collins et al. 2001), no evidence of an increased risk of spontaneous abortions among workers exposed to formaldehyde was found.

Some studies report an association between long-term, low-concentration exposure to formaldehyde and chronic neurobehavioral deficiencies (Williams and Lees-Haley 1998). But because of severe limitations, such as selection biases and unblinded research, no firm conclusions about the neurotoxicity of formaldehyde can be drawn from these studies.

In the past 15 years, investigators have reported associations between formaldehyde in indoor air and asthma or asthma-like symptoms (Krzyzanowski et al. 1990; Czap et al. 1993; Norback et al. 1995; Wantke et al. 1996; Smedje et al. 1997; Wieslander et al. 1997; Garrett et al. 1999; Franklin et al. 2000; Smedje and Norback 2001). Most recently, Rumchev and colleagues (2002) carried out a population-based case–control study in Perth, Australia, to determine whether formaldehyde in indoor air is related to the risk of serious asthma in children. The subjects were 88 children, six months to three years of age, having a primary hospital-discharge diagnosis of asthma between 1997 and 1999. The controls were 104 children who were identified from birth records and did not have a history of asthma. Formaldehyde concentrations in the subjects' bedrooms and living rooms were measured twice, once in winter and once in summer. Mean formaldehyde concentrations were 30.2 $\mu g/m^3$ in subjects' bedrooms and 27.5 $\mu g/m^3$ in living rooms. Exposure concentrations were higher for cases than for controls. After adjusting for a large number of potential confounders, a statistically significant positive association between formaldehyde and asthma was found, with an odds ratio of 1.39 for exposure at or above 60 $\mu g/m^3$ and an estimated 3% increase in the risk of serious asthma per increase of 10 $\mu g/m^3$ in indoor formaldehyde concentration. The study had a number of limitations, including its rather small size, the large number of potential confounders, and the possibility of residual confounding, selection bias, and diagnostic uncertainty.

Only one investigation, by Delfino and colleagues (2003), has evaluated the relationship between formaldehyde in ambient air and asthma. A panel study conducted from November 1999 to January 2000 included 22 Hispanic children, 10 to 16 years of age, with physician-diagnosed asthma, living in Los Angeles County in an area characterized by high traffic. Subjects were nonsmokers who lived in nonsmoking households. The investigators analyzed daily ambient concentrations of formaldehyde and 19 other pollutants in relation to asthma severity as self-reported in daily diaries. Formaldehyde concentrations (69 measurements) ranged from 5.12 to 16.82 μg/m^3, with a mean of 8.65 μg/m^3 (SD = 2.89 μg/m^3) and an interquartile range of 3.79 μg/m^3; they were strongly correlated with the concentrations of a number of other pollutants. The odds ratios for moderate asthma symptoms were 1.09 (95% CI, 0.70–1.60) for the interquartile-range increase in formaldehyde measured on the same day as the symptoms and 1.37 (95% CI, 1.04–1.80) for the interquartile-range increase measured on the previous day. The odds ratios for more severe asthma symptoms were 1.90 (95% CI, 1.13–3.19) for the interquartile-range increase in formaldehyde measured on the same day as the symptoms and 1.30 (95% CI, 0.76–2.22) for the interquartile-range increase measured on the previous day. The apparent effects of formaldehyde were attenuated after adjustment for 8-hour maximum SO_2 or 8-hour maximum NO_2. The study had a number of limitations, including small size and resulting imprecision, a high potential for inaccurate reporting of asthma symptoms, and the possibility of confounding by other pollutants and factors.

REGULATORY SUMMARY

Formaldehyde is classified by the IARC (2006) as Group 1 ("carcinogenic to humans") and by the EPA (1990) as Group B1 ("a probable human carcinogen"). These classifications are based on both human and animal evidence that indicates a risk of nasopharyngeal cancer. Various risk assessments have been carried out for the purpose of defining acceptable exposure concentrations in occupational settings and in ambient air. These have generally relied on evidence from animal studies (EPA 1990).

The EPA (1990) has estimated a lifetime cancer risk of 1.3×10^{-5} associated with an exposure of 1 μg/m^3 formaldehyde over a lifetime—a concentration in the same range as those measured in ambient air. The EPA's risk estimate is based largely on the occurrence of squamous-cell carcinoma in exposed male rats (Kerns et al. 1983). A new EPA Integrated Risk Information System (IRIS) cancer-risk assessment is underway in light of a CIIT analysis that supports a unit risk estimate (URE) of approximately 5.5×10^{-9} per μg/m^3. This value is substantially lower than the current IRIS URE of 1.3×10^{-5} per μg/m^3 (EPA 1990, 2000e; CIIT 1999; Conolly et al. 2004).

The EPA (1990) has not set an inhalation reference concentration (RfC) for formaldehyde at this time. It has set an oral reference dose (RfD) at 200 μg/kg-day, based on reduced weight gain and histopathology changes in rats (EPA 1990). The California EPA (1999) has set an acute 1-hour reference exposure concentration of 94 μg/m^3, with an interim 8-hour reference exposure concentration of 33 μg/m^3. Health Canada (2006) has set a residential indoor air quality guideline of 123 μg/m^3 for a 1-hour exposure and 50 μg/m^3 for an 8-hour exposure, with an action concentration of 60 μg/m^3 and a 1-hour average episode concentration of 370 μg/m^3 in British Columbia (British Columbia Ministry of Environment [Canada] 2006). The World Health Organization (WHO 2002) has set an air-quality guideline of 100 μg/m^3 for a 30-minute period.

Other regulatory standards worldwide call for a maximum air concentration of 12 μg/m^3 formaldehyde in Cambodia (Kingdom of Cambodia 2000) and an annual average air concentration of 48 μg/m^3 (30-minute average) in the Philippines (Republic of Philippines Department of Health 1999).

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

In the U.S., long-term mean ambient concentrations of formaldehyde typically range from 0 to 49 μg/m^3, with an overall national mean concentration of 4.3 μg/m^3. These concentrations are generally higher in urban than in rural environments, although atmospheric transport of formaldehyde might be affecting non-urban locations. Ambient measurements tend to be highest at roadside sites; some studies, but not all, report higher concentrations in vehicles than at roadside sites. Seasonally, the highest formaldehyde concentrations are associated with the highest rate of photochemical activity, and it appears that photochemical activity in summer contributes more formaldehyde to ambient concentrations than do direct vehicle emissions.

While mobile sources are clearly important contributors to ambient concentrations of formaldehyde, indoor sources are the predominant source of exposure. Indoor concentrations are generally three to five times higher than outdoor concentrations. Indoor concentrations and personal exposures show seasonal trends, with higher concentrations in summer than winter. However, the role of seasonal variability in ambient concentrations in determining these seasonal trends in indoor concentrations is not clear.

In Brazil, studies have shown that the widespread use of vehicles powered by ethanol-based fuels and compressed natural gas is associated with an increase in ambient formaldehyde, which has reached concentrations up to 10 times higher than those measured in U.S. urban areas and in the same range as the highest indoor concentrations recently measured.

TOXICITY

Formaldehyde is highly reactive. Direct contact with tissues, such as those of the upper respiratory tract, can cause local irritation and acute and chronic toxic and genotoxic effects. In rats, after long-term inhalation, formaldehyde causes tumors in the nasal mucosa. After long-term oral administration, it causes hyperplasia and keratinization in the forestomach as well as inflammation and ulcers in the glandular stomach.

HUMAN HEALTH

Formaldehyde has been classified as a human carcinogen, causing nasopharyngeal cancer at concentrations historically encountered in industrial settings. The mechanism of carcinogenesis is not fully understood. Nasopharyngeal cancer is rare in the U.S. and other Western countries; it is more common among people of southern Chinese ancestry. Formaldehyde, at concentrations found in occupational settings, might be associated with myeloid leukemia, although the evidence for this is not sufficient to conclude that a causal relationship exists. Again, the mechanism is not understood. There is limited evidence that exposure to formaldehyde in indoor air increases the occurrence of asthma symptoms in children. Formaldehyde is a respiratory irritant. Studies with volunteers yielded threshold concentrations of less than 0.6 mg/m^3 for odor perception, 0.6 to 1.2 mg/m^3 for eye irritation, and 1.2 mg/m^3 for nose and throat irritation. In workers with long-term exposure to formaldehyde, lesions in the nasal mucosa were observed at concentrations lower than 1.2 mg/m^3. At 0.4 mg/m^3, irritation of the eyes, which are considered to be the most sensitive to formaldehyde, is generally not observed. Formaldehyde causes sensitization of the skin. At present, there is little evidence that exposure to formaldehyde concentrations found in ambient air is hazardous.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of formaldehyde?

While mobile sources are clearly important contributors to ambient concentrations of formaldehyde, indoor sources are the predominant source of exposure. Indoor concentrations are higher than corresponding ambient concentrations and approximately the same as urban roadside and urban in-vehicle concentrations. In Brazil, studies have documented an increase in formaldehyde concentrations associated with the use of ethanol-based fuels and compressed natural gas. Ambient concentrations in Brazil have increased to the same range as the highest indoor concentrations recently measured in many countries.

2. Does formaldehyde affect human health?

Formaldehyde causes irritation of the eyes and respiratory system, with substantial variation in individual responses. Formaldehyde has been classified as a human carcinogen by regulatory agencies, but the human evidence is weak and inconsistent.

3. Does formaldehyde affect human health at environmental concentrations?

Ambient concentrations of formaldehyde are generally lower than those that cause irritation of the eyes and respiratory system. However, concentrations in certain outdoor environments, such as near roadways, can approach those at which sensitive people experience irritation. There is no evidence that ambient concentrations of formaldehyde cause any form of cancer.

RESEARCH GAPS AND RECOMMENDATIONS

EXPOSURE

An increased use of alcohols, particularly ethanol, as alternative vehicle fuels and in fuel blends might increase ambient concentrations of formaldehyde because the combustion of alcohols produces more formaldehyde than that of conventional fuels. Whether these increased emissions will increase the risk of adverse effects on human health, including cancer, is unknown. Research recommendations for formaldehyde-exposure studies include the following:

- Continue to update and critically evaluate the NATA model and compare the model with actual measurements to improve its usefulness in predicting the effect on ambient formaldehyde concentrations of increased use of alcohols as alternative motor-vehicle fuels.
- Develop a monitoring network capable of tracking long-term aldehyde concentrations in ambient air because such an increase in the use of alcohols in fuel is likely.

- Identify formaldehyde-exposure pathways and patterns of personal exposures (including diurnal and seasonal variations) in cities and rural areas throughout the U.S.

TOXICITY

Research recommendations for formaldehyde-toxicity studies include the following:

- Elaborate the quantitative relationship in humans between DNA–protein crosslinks and mutations and the time course of crosslink removal. This would help in understanding the mechanism of tumor induction and in establishing biomarkers of formaldehyde exposure and effect.

HUMAN HEALTH

Research recommendations for human-health studies of formaldehyde include the following:

- Identify populations with increased susceptibility to the irritant effects of formaldehyde (such as children, the elderly, and people with compromised lung function).
- Undertake additional research on the effect of long-term exposures to low formaldehyde concentrations on cancer, asthma, and other endpoints.
- Explore the effects on health of exposure to mixtures of aldehydes (and mixtures of aldehydes with other pollutants). Simultaneous exposure to formaldehyde and other upper-respiratory-tract toxicants, such as acetaldehyde, acrolein, crotonaldehyde, furfural, glutaraldehyde, ozone, and particulate matter might lead to additive or synergistic effects, especially with respect to sensory irritation and possible cytotoxic effects on the nasal mucosa.

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Naphthalene

INTRODUCTION

Naphthalene (CAS Registry Number 91-20-3; $C_{10}H_8$; molecular weight = 128) (Figure 19), also known as tar camphor, is a slightly water-soluble, two-ring aromatic hydrocarbon. A white, crystalline solid that readily changes from a solid to a gas at room temperature, it is used in moth repellents, lavatory scent discs, and soil fumigants and as a starting material in the manufacture of other organic compounds. Naphthalene is also found in light petroleum fractions and in residues from refineries. It is the most volatile member of the polycyclic aromatic hydrocarbons (PAHs), and inhalation is the principal pathway of exposure (Preuss et al. 2003).

BENCHMARK LITERATURE

The following evaluation of research literature on naphthalene is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from reviews by the Agency for Toxic Substances and Disease Registry (ATSDR 2005e), the European Union Risk Assessment Report (European Chemicals Bureau 2003), the International Agency for Research on Cancer (IARC 2002), the National Toxicology Program (NTP 2005), the California Environmental Protection Agency (California EPA 2004), the EPA (1998d, 2000f; 2004c), the World Health Organization (WHO 2000b), and selected key articles.

EXPOSURE

SOURCES AND EMISSIONS

A thorough review of the sources of, and potential exposures of humans to, naphthalene is given in a toxicologic profile of the compound published by the ATSDR (2005e) and in a study by Preuss and colleagues (2003). Sources of airborne naphthalene include various industrial, domestic, mobile-combustion, and natural processes. Naphthalene is widely used in industry and is a traditional constituent of mothballs. It is a product of incomplete combustion from a variety of sources, including industrial plants, residential heating with fossil fuels, motor vehicles, air traffic, and forest fires. Naphthalene is a constituent of gasoline as well as diesel and jet fuels. Motor vehicles contribute to naphthalene emissions by way of incomplete combustion and evaporation from liquid fuel. Other important sources of exposure are tobacco smoke and the numerous consumer products that contain naphthalene.

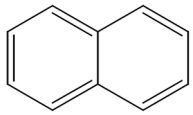

Figure 19. Structure of naphthalene.

The National Air Toxics Assessment (NATA) estimates indicate that on-road mobile-source emissions are responsible for approximately 20% of total naphthalene air emissions, with similar contributions in urban and rural areas. Non-road mobile-source emissions are estimated to contribute 6 to 7% of emissions (EPA 2006b). As with other PAHs, residential wood smoke is a major source of naphthalene emissions in areas with substantial wood-stove or fireplace use. Lu and colleagues (2005) reported data from Southern California showing that naphthalene concentrations were higher at urban sites with traffic sources nearby and that diurnal concentration patterns coincided with traffic patterns.

Naphthalene has been shown to react readily in the atmosphere with oxidant gases, such as nitrogen oxides and hydroxyl radicals (Reisen and Arey 2005). Concentrations of nitronaphthalenes, for example, can exceed those of naphthalene. The relative proportion of derivatives to the parent compound can vary depending on meteorology and the location of the mobile sources.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Ambient Air

The general public is exposed to naphthalene through inhalation of ambient and indoor air. Typical air concentrations for naphthalene are low—i.e., 1 $\mu g/m^3$ or less. The average daily intake of naphthalene from ambient air can

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

be estimated to be approximately 20 µg, based on a naphthalene concentration of 1 µg/m^3 in urban and suburban air and an inhalation rate of 20 m^3/day. Exposure has been estimated to range from 65 ng/kg body weight/day at the regional level to 0.25 mg/kg body weight/day at the local level in areas where naphthalene is emitted (for example, from releases associated with the manufacture of grinding wheels and mothballs) (European Chemicals Bureau 2003).

In the U.S., the NATA (EPA 2006b) estimated a national mean ambient naphthalene concentration of 0.07 µg/m^3. Estimated concentrations in urban areas (0.08 µg/m^3) were roughly four times higher than in rural areas (0.02 µg/m^3). Measured mean concentrations in urban and suburban areas agree well with these modeled estimates, with an overall mean of 0.08 µg/m^3 and individual-site means ranging from 0.01 to 0.4 µg/m^3 (EPA 2006b). Measurements in Southern California indicated slightly higher naphthalene concentrations (with site means ranging from 0.07 to 0.6 µg/m^3), while some measurements collected at urban sites in Arizona were even higher (with site means ranging from 0.01 to 0.9 µg/m^3 and individual measures as high as 2 µg/m^3 during episodes of summer photochemical air pollution) (Zielinska et al. 1998; Eiguren-Fernandez et al. 2004). Although summer episodes are associated with the highest concentrations, winter conditions (e.g., wood burning and surface inversions) can also result in high ambient concentrations. The measurements do not indicate strong seasonal variation in concentrations (Eiguren-Fernandez et al. 2004). Short-term urban in-vehicle concentrations (3- to 4-hour samples) as high as 3.8 µg/m^3 were measured in Detroit, but no concurrent fixed-site measurements were available for comparison (Batterman et al. 2002). Naphthalene is by far the most abundant vapor-phase PAH typically measured in ambient air, contributing, for example, 91% of the total (particle + vapor) PAH mass in measurements in Southern California (Eiguren-Fernandez et al. 2004).

Naphthalene can be converted in the atmosphere to naphthaquinones, a group of reaction products that are potent generators of reactive oxygen species and that are currently being investigated for their toxicity (Lu et al. 2005). Quinones and hydroquinones are described in more detail in the polycyclic organic matter (POM) section of this report.

Indoor Air

Although no recent studies of indoor naphthalene concentrations were found, studies from the early 1990s typically reported that average indoor air concentrations were less than 5 µg/m^3 (Lu et al. 2005) and that indoor concentrations were 5 to 10 times higher than those measured outdoors. Major indoor sources are tobacco smoke and moth repellents. It is likely that indoor concentrations have decreased in recent years because indoor smoking and the use of naphthalene in pesticides and mothballs have decreased (California EPA 2004).*

Personal Exposures

Consumers can be exposed to naphthalene through the use of moth repellents and tar shampoos and soaps as well as when damp-proofing homes. The European Union (European Chemicals Bureau 2003) estimated that the total daily intake from these exposures was 54.3 mg (0.77 mg/kg body weight/day). Infants, in particular, might have significant exposures to textiles (e.g., clothing and bedding) that have been in contact with naphthalene mothballs.

Although no personal-monitoring studies of naphthalene in the general community (non-workplace) were found, application of the regional human exposure (REHEX) model to Southern California indicated that indoor sources accounted for 40% of naphthalene exposure, in-vehicle exposure accounted for 4%, and environmental tobacco smoke accounted for 1 to 5%, depending on the season (Lu et al. 2005). Emissions estimates for California indicated that gasoline evaporation and engine exhaust accounted for 44% of total naphthalene emissions into ambient air; diesel exhaust was estimated to contribute another 9% of the total (Lu et al. 2005). Other major emissions sources, including asphalt and a large number of consumer products, contributed 15% of emissions.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average ambient and indoor concentrations of naphthalene measured in several other countries are generally in the same range as those reported in the U.S. (reviewed in IARC 2002).

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

The metabolism of naphthalene and its respiratory toxicity have been studied extensively and reviewed (Buckpitt et al. 2002; Stohs et al. 2002) (Figure 20). The toxicity of naphthalene results from its reactive metabolites. The first step, oxidation via cytochrome P450 monooxygenases, produces an unstable 1,2-epoxide that can convert nonenzymatically to 1-naphthol. The epoxide can also be

* Naphthalene was not included in the survey of indoor exposures and is thus not listed in the indoor exposure table in Appendix D.

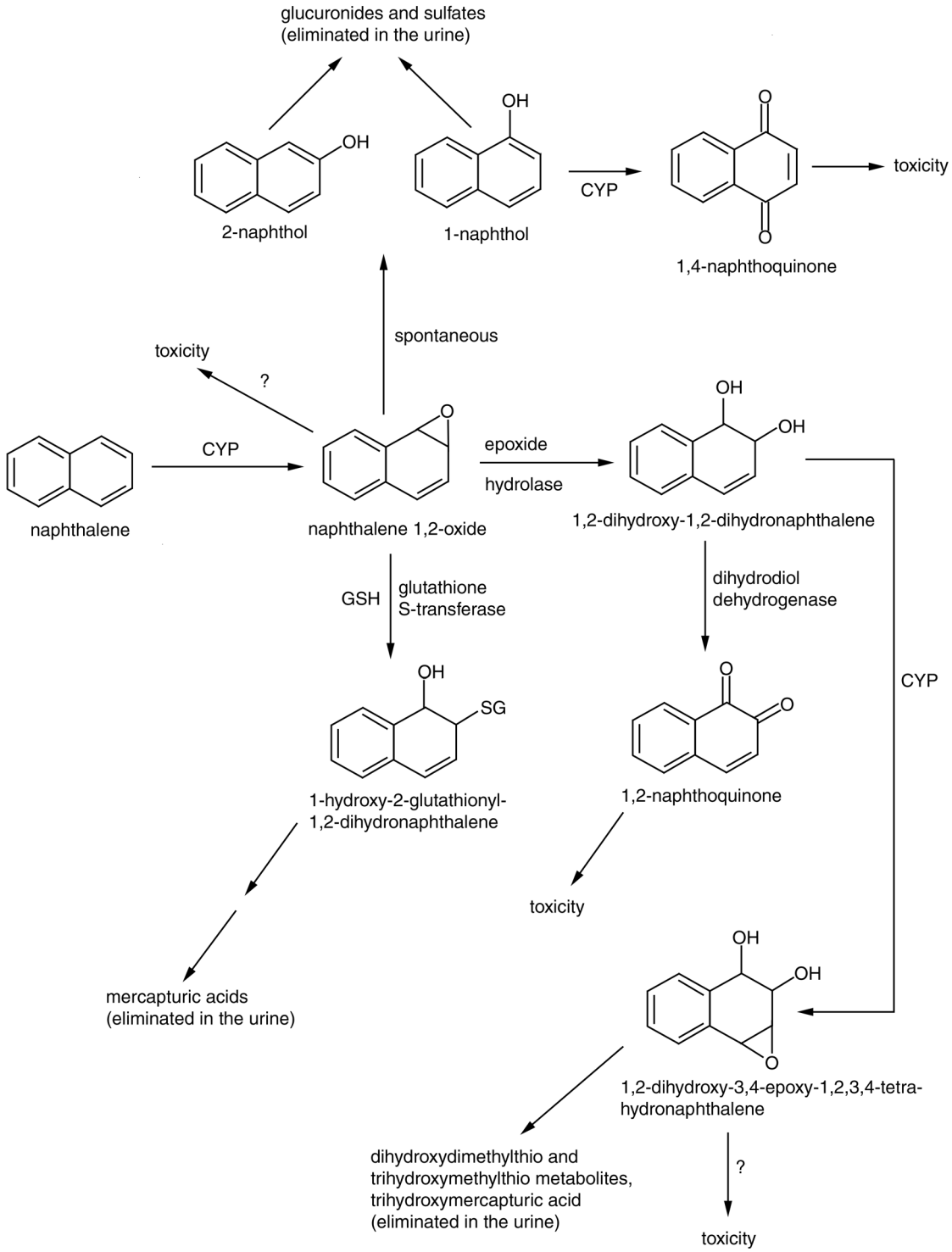

Figure 20. Metabolic pathway of naphthalene. CYP = cytochrome P450 enzymes; GSH = glutathione; SG = from glutathione. (From Agency for Toxic Substances and Disease Registry 2005e.)

converted via microsomal epoxide hydrolase to naphthalene dihydrodiol, via cytochrome P450 enzymes to naphthalene diepoxides, or via glutathione S-transferase to glutathione conjugates. The naphthol and the diol compounds can be further oxidized to form quinones, which, along with the epoxides, represent reactive toxic metabolites that can bind to macromolecules. Mice are the most sensitive (of the species tested) to the toxicity of inhaled naphthalene. They are also the most efficient at naphthalene oxidation. Humans and nonhuman primates are among the least efficient. Maximal rates of naphthalene metabolism measured in human lung microsomes are about 10 to 100 times lower than those in mice. These data suggest that the respiratory tract of humans is likely to be much less sensitive than that of mice to the toxicity of inhaled naphthalene (Figure 20).

In cellular systems from mice and rats, the enzyme CYP2F2 metabolizes naphthalene to 1R,2S-naphthalene oxide, which rearranges to 1-naphthol and forms the 1,2-dihydrodiol via epoxide hydrolase. Oxidation of 1-naphthol leads to 1,2- and 1,4-naphthoquinone. In nonciliated bronchiolar epithelial cells (Clara cells) isolated from the lungs of naphthalene-treated mice, covalent binding of 1,2-naphthoquinone to protein was reported. Treatment with the glutathione depletor diethylmaleate before naphthalene exposure decreased water-soluble naphthalene-metabolite formation by 48% yet increased naphthalene–protein adducts by 193% (Phimister et al. 2004). Recent studies (Baldwin et al. 2005) demonstrated a minimal pulmonary CYP2F2 expression in rats, indicating that CYP2F2 expression is the factor most clearly associated with susceptibility to naphthalene-induced pulmonary toxicity and might explain the limited susceptibility of rats.

In mice, glutathione depletion in Clara cells seems to be a determinant of the specific pulmonary toxicity of naphthalene. Plopper and colleagues (2001) have investigated early events in naphthalene-induced acute Clara-cell toxicity. Two hours after intraperitoneal injection of 200 mg/kg body weight naphthalene, they observed the highest glutathione depletion in the most susceptible distal bronchioles. Although severe glutathione depletion can lead to apoptosis and cell proliferation (Rahman et al. 1999), Phimister and colleagues (2005) concluded that, even though glutathione depletion might be responsible for certain aspects of naphthalene toxicity, it was not sufficient to cause cell death without additional stresses. Whereas these disruptive cellular changes seemed to be reversible after recovery of glutathione levels, they persisted after naphthalene exposure. Studies published recently by Lee and colleagues (2005) showed that the olfactory regions of the nasal septum and ethmoturbinates metabolize naphthalene at higher rates than the non-olfactory mucosa of the nasal septum. The regions of the nasal mucosa with high rates of naphthalene metabolism were the ones injured by inhaled or systemically administered naphthalene.

BIOMARKERS

Mercapturic acid and conjugates of naphthol in the urine have been used as biomarkers to indicate exposure to naphthalene.

NONCANCER HEALTH EFFECTS

Acute Effects

The toxicity of inhaled naphthalene has been shown to be greatest in the nasal cavity and in the Clara cells of the airways. These sites are also the location of high concentrations of cytochrome P450 enzymes, capable of oxidizing naphthalene to its reactive forms, and of the cellular systems with the highest rate of glutathione depletion (see above). Exposure of mice (but not rats) for 4 hours to concentrations as low as 10 mg/m^3 naphthalene resulted in detectable injury to Clara cells. Exposure of mice to the current 8-hour human occupational exposure standard (52 mg/m^3, time-weighted average [TWA]) resulted in substantial injury to epithelial cells in both the upper and lower respiratory tracts. In rats, after repeated exposures to 52 mg/m^3, non-neoplastic lesions were found in the olfactory and respiratory epithelia of the nose.

Interestingly, if naphthalene is administered to mice intraperitoneally, the injury site is still the epithelial cells of the respiratory tract. In mice exposed to cigarette smoke, recovery from naphthalene-induced injury to the bronchiolar epithelium was impaired. Clara cells of neonatal mice were more sensitive than those of adult mice to the cytotoxic effects of naphthalene. In rats and rabbits, repeated oral administration of naphthalene is known to cause cataract formation at doses of 700 mg/kg body weight/day and above.

There was no indication of hemolytic anemia in rodent studies. In isolated mouse Clara cells, 1,4-naphthoquinone and naphthalene 1,2-oxide were more toxic than naphthalene.

Reproductive and Developmental Effects

No studies of the effects of naphthalene exposure on the fertility of animals have been reported. Changes in the reproductive organs have not been detected in repeated-dose studies (including chronic-inhalation studies), and there are no available data on the effects of naphthalene exposure on reproductive function. In rats and rabbits exposed to naphthalene by gavage, signs of toxicity were observed in pregnant females (e.g., decreased body weight and lethargy) but not in fetuses. In mice exposed by

gavage, signs of toxicity were found both in pregnant females (increased mortality and reduced weight gain) and in fetuses (reduced number of live pups per litter).

GENOTOXICITY

The genotoxicity of naphthalene has recently been reviewed (Schreiner 2003).

In Vivo

In rats, inhalation of naphthalene caused oxidative stress and DNA damage in liver and brain tissue. Positive results were obtained for somatic mutations in *Drosophila melanogaster* and micronuclei in salamander-larvae erythrocytes. In mice given oral or intraperitoneal injections of naphthalene, negative results were obtained for micronuclei formation in bone marrow, and there was no induction of DNA single-strand breaks or unscheduled DNA synthesis in hepatocytes.

In Vitro

Naphthalene was not mutagenic in 16 bacterial assays and did not induce unscheduled DNA synthesis. In six cytogenetic assays, clastogenic effects (sister-chromatid exchanges and chromosomal aberrations) were seen in Chinese hamster ovary cells in the presence of metabolic activation. In human peripheral mononuclear leukocytes, the rate of sister-chromatid exchanges did not increase. Naphthalene induced chromosomal aberrations in mouse-embryo cultures and in micronuclei in human MCL-5 cells. It also induced DNA fragmentation in macrophages. Negative results were found in five cell-transformation assays, a gene-mutation assay in MCL-5 cells, three unscheduled-DNA-synthesis tests, and two alkaline-elution assays using primary rat hepatocytes. Because the cytogenetic effects were only seen at cytotoxic concentrations, they were considered to result from cytotoxicity rather than from gene mutations.

1,2-Naphthoquinone was mutagenic in *Salmonella typhimurium* without metabolic activation, formed N^7 adducts with deoxyguanosine, and caused DNA-strand scission in the presence of nicotinic adenine dinucleotide phosphate (NADPH) and copper via reactive oxygen species from an oxidation–reduction cycle. 1,4-Naphthoquinone induced chromosomal aberrations in Chinese hamster ovary and MCL-5 cells. Of other naphthalene metabolites tested, the 1,2-dihydrodiol and 1-naphthol were negative, and naphthoquinone was positive, for inducing sister-chromatid exchanges.

CANCER

Carcinogenicity studies have been completed in mice and rats by the NTP (1992, 2000). In mice, chronic-inhalation exposure to 0, 52, or 160 mg/m^3 naphthalene led to inflammation in the nose, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium, but not neoplasia. In rats, exposure to the same concentrations as well as a 314 mg/m^3 concentration led to a concentration-dependent increase in adenomas of the respiratory epithelium of the nose and neuroblastomas of the olfactory epithelium. Inflammation of the olfactory epithelium was observed at all concentrations. Because neuroblastomas are highly malignant and the cytochrome P450 isozymes that activate naphthalene in the nasal cavity of rodents are also present in humans, these neuroblastomas must be considered highly relevant. No liver tumors were induced by naphthalene in either mice or rats.

There are no adequate animal data available to assess the carcinogenic effects of oral or dermal exposure to naphthalene.

HUMAN HEALTH

BIOMARKERS

Biomarkers of Exposure

In Germany, a pilot study on naphthalene exposure in adults and children concluded that 1-naphthol and 2-naphthol concentrations in urine are accurate biomarkers for naphthalene exposure (Preuss et al. 2004). Naphthols could be detected in more than 90% of the urine samples. Concentrations of naphthols (the sum of 1-naphthol and 2-naphthol) were four times higher in adult smokers (median concentration, 37.6 µg/g creatinine) than in adult nonsmokers (8.2 µg/g creatinine). Compared with adults, children had slightly lower naphthol concentrations in urine (7.5 µg/g creatinine). Preliminary reference values proposed for the naphthols in urine (as means of the 95th percentile) were 41.2 µg/g creatinine (adult nonsmokers) and 23.5 µg/g creatinine (children). Chao and colleagues (2006) investigated the urinary excretion of 1- and 2-naphthol in workers exposed to naphthalene in jet fuel. Post-exposure urinary concentrations of both metabolites increased, although the concentrations of 2-naphthol were higher. The authors concluded that dermal exposure contributed significantly to urinary 2-naphthol concentrations, possibly because of naphthalene metabolism in the skin.

CANCER

Two case studies of cancer in humans exposed to naphthalene were reported. One describes four cases of laryngeal cancer (all in smokers) among workers in a naphthalene-purification plant in East Germany. The other describes 23 cases of colorectal carcinoma in people admitted to a hospital in Nigeria. The NTP (2005) and the IARC (2002) concurred that these studies provided inadequate evidence of naphthalene carcinogenicity in humans.

Naphthalene is metabolized to reactive intermediates. Of the species tested, mice are the most sensitive to inhaled naphthalene, and their metabolism is also the most efficient at naphthalene oxidation. Humans and nonhuman primates are among the least efficient at this oxidation. The data suggested that the respiratory tract of humans is likely to be much less sensitive to naphthalene than that of mice and rats. The higher rate of naphthalene metabolism in mice might lead to cytotoxic metabolites in the lung, causing increased cell turnover and tumors. The genotoxic effects of naphthalene are at present unclear. Although there is little evidence for the induction of gene mutations by naphthalene, there are indications of a clastogenic potential.

NONCANCER HEALTH EFFECTS

In humans, single or repeated exposures to naphthalene can cause severe hemolytic anemia. Hemolysis was observed in infants exposed to clothing and bedding that had been stored with naphthalene mothballs. However, no quantitative information on exposure concentrations was reported in these cases, and hence they cannot be used to establish a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) for this effect on health.

No information is available on the reproductive or developmental effects of naphthalene exposure in humans. The occurrence of hemolytic anemia in the neonates of anemic, naphthalene-exposed mothers demonstrates that naphthalene or its metabolites can cross the placental barrier. Hemolytic anemia has also been reported in infants born to mothers who "sniffed" or ingested naphthalene (as mothballs) during pregnancy.

REGULATORY SUMMARY

Naphthalene is listed in the NTP's *11th Report on Carcinogens* as "reasonably anticipated to be a human carcinogen" (NTP 2005). The EPA (2004c) has classified it as Group C ("possible human carcinogen") and has assigned it an inhalation unit risk of 0.1 per mg/m^3, based on time-to-tumor modeling and a summed risk for adenomas of the respiratory epithelium and neuroblastomas of the olfactory epithelium in male rats (the most sensitive sex and species in the NTP studies). The equivalent air concentrations for naphthalene, based on 1×10^{-6} and 1×10^{-5} cancer-risk levels, are 0.01 μg/m^3 and 0.1 μg/m^3, respectively (EPA 2004c). At present, the new unit risk factor has not yet been incorporated in the Integrated Risk Information System (IRIS). The California EPA considers naphthalene a toxic air contaminant and a substance that causes cancer. It has calculated a unit risk of 0.034 per mg/m^3 (3.4×10^{-5} per μg/m^3), based on data for the incidence of adenoma of the nasal respiratory epithelium and neuroblastoma of the nasal olfactory epithelium in male rats (California EPA 2004). The IARC has concluded that there is inadequate evidence in humans and sufficient evidence in laboratory animals for the carcinogenicity of naphthalene and has thus classified it as Group 2B ("possibly carcinogenic to humans").

For noncancer effects, the EPA (1998d) set a reference concentration of 3 μg/m^3 (0.67 ppb), based on a LOAEL for hyperplasia in respiratory epithelia and metaplasia in olfactory epithelia of 9.3 mg/m^3 and an uncertainty factor of 3000. The California EPA adopted a chronic inhalation reference exposure level (REL) of 9 μg/m^3, based on an adjusted LOAEL of 9.4 mg/m^3 and an uncertainty factor of 1000 (California EPA 2004, 2005b). This REL was based on respiratory effects (nasal inflammation, hyperplasia of the respiratory epithelium, and metaplasia of the olfactory epithelium) in mice.

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

Mobile sources are important contributors to ambient concentrations of naphthalene. But they are not the principal source of ambient emissions, nor are they major contributors to exposure. In some areas, wood combustion is the predominant source of emissions into ambient air, and environmental tobacco smoke, moth repellents, and other consumer products are major indoor sources. Given reduced exposures to environmental tobacco smoke and moth repellents in recent years, it is possible that ambient concentrations and mobile sources might become more important contributors to exposures than before. However, measurements to assess this possibility are not available at present.

TOXICITY

Animal studies have shown that exposure to naphthalene caused damage to the respiratory tract, including

chronic nasal inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium. In mice, naphthalene causes damage to both ciliated and Clara cells of the bronchiolar epithelium. Its toxicity is associated with naphthalene metabolism by cytochrome P450 enzymes, which are concentrated in Clara cells and are present in higher amounts in cells of mice than of rats or humans. Naphthalene is correspondingly more cytotoxic in the respiratory tract of mice than rats. It also depletes the detoxifying tripeptide glutathione.

Genotoxicity tests of naphthalene are generally negative, although naphthalene's quinone metabolites are known to be genotoxic. Chronic exposures induced nasal adenomas and neuroblastomas in rats but not mice. Chronic inflammation in addition to glutathione depletion might be a key factor in the development of tumors in animals. However, the mechanisms of tumor induction are not yet fully understood. It is also not yet possible to characterize the roles of cytotoxicity and genotoxicity in tumor induction.

HUMAN HEALTH

Although there are no epidemiology studies of naphthalene, there are case reports that exposure to high concentrations of naphthalene can induce methemoglobinemia and hemolysis in humans; this is not seen in rodents. There is limited evidence from animal bioassays that naphthalene can cause cancer, but it is not clear how to extrapolate these results to humans. Both the NTP and the IARC concluded that the evidence for naphthalene carcinogenicity in humans is inadequate. Humans might be less sensitive than rodents to toxic and carcinogenic effects of naphthalene because humans are less efficient at naphthalene oxidation.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of naphthalene?

Mobile sources are important contributors to ambient concentrations of naphthalene but are not the principal source of ambient emissions, nor are they major contributors to exposure.

2. Does naphthalene affect human health?

Naphthalene can cause hemolytic anemia in the neonates of naphthalene-exposed mothers and in infants exposed to bedding or clothing treated with mothballs. Although there is evidence of toxicity in animal studies for both cancer and noncancer effects, humans might be less sensitive than rodents to these effects because humans are less efficient at naphthalene oxidation.

3. Does naphthalene affect human health at environmental concentrations?

In the U.S., the average ambient concentration of naphthalene is 0.08 $\mu g/m^3$. The highest mean concentrations (approximately 0.5 to 1 $\mu g/m^3$) are measured indoors. The highest ambient and indoor concentrations approach the reference concentration for chronic inhalation (29 $\mu g/m^3$), but the mean ambient concentration is one to two orders of magnitude below this benchmark. Thus there is probably no risk of noncancer health effects from environmental exposures. Given the uncertainty about the shape of the dose–response curve at low concentrations in animals and questions about the carcinogenicity of naphthalene in humans, the available evidence is not adequate to determine human cancer risk at this time.

RESEARCH GAPS AND RECOMMENDATIONS

Research recommendations for naphthalene include the following:

- Characterize naphthalene-exposure pathways, patterns of personal exposures to naphthalene and its atmospheric reaction products (including air toxics "hot spots"), and exposures of children and other susceptible populations.
- Undertake additional studies of the toxicokinetics of inhaled naphthalene (including, in particular, studies of the nasal compartments that metabolize naphthalene). Comparative studies of naphthalene's toxicokinetics in various species should also be undertaken in order to help decrease the uncertainty in extrapolating data from animals to humans.
- Undertake studies of the mechanisms of tumor induction by naphthalene and its atmospheric reaction products (e.g., naphthaquinones), including the roles of genotoxicity and cytotoxicity caused by reactive oxygen species.

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Polycyclic Organic Matter

INTRODUCTION

Polycyclic organic matter (POM) consists of a mixture of hundreds of chemicals, including polycyclic aromatic hydrocarbons (PAHs), their oxygenated products, and their nitrogen analogs (nitro-PAHs). POM compounds with five or more benzene rings are generally associated with particulate matter (PM). Those with four or fewer rings are semivolatile and are partitioned between the particulate and gaseous phase.

The mixture of compounds in POM varies from place to place and from time to time. Sources of airborne POM include various mobile-source combustion, industrial, and domestic processes. In populated areas, the principal emission source in ambient air is exhaust from the combustion of gasoline, diesel fuel, and home-heating oil. In addition, there are industrial and municipal sources that can have a significant effect on human exposure, although most POM compounds have no commercial uses. In indoor air, the principal source is usually smoke from the burning of tobacco. Food is thought to be the major source of human exposure to PAHs, owing largely to PAH formation during cooking. Another source of dietary intake is the deposition of PAH-containing particles from ambient air onto fruits, vegetables, grains, and other foods grown outdoors. For nonsmokers living in relatively low-pollution areas, dietary intake of PAHs represents a larger source of POM exposure than does inhalation (Boström et al. 2002).

The EPA definition used for POM in the National Air Toxics Assessment (NATA) included only particle-phase POM; it defined POM as a group of 16 individual PAH species that are measured by the EPA's Method 610. They are known as the 16-PAH group and include acenaphthene, acenaphthylene, anthracene, benzo[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluorene, benzo[*ghi*]perylene, benzo[*k*]fluoranthene, chrysene, dibenz[*a*,*h*]anthracene, fluoranthene, fluorene, indeno[1,2,3-*cd*]pyrene, naphthalene, phenanthrene, and pyrene. Seven of these—benzo[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*a*,*h*]anthracene, and indeno[1,2,3-*cd*]pyrene—are known as the 7-PAH group and are classified as "probable human carcinogens." The structures of these compounds are included in Figure 21. Reactive bay regions and fjord regions are pointed out.

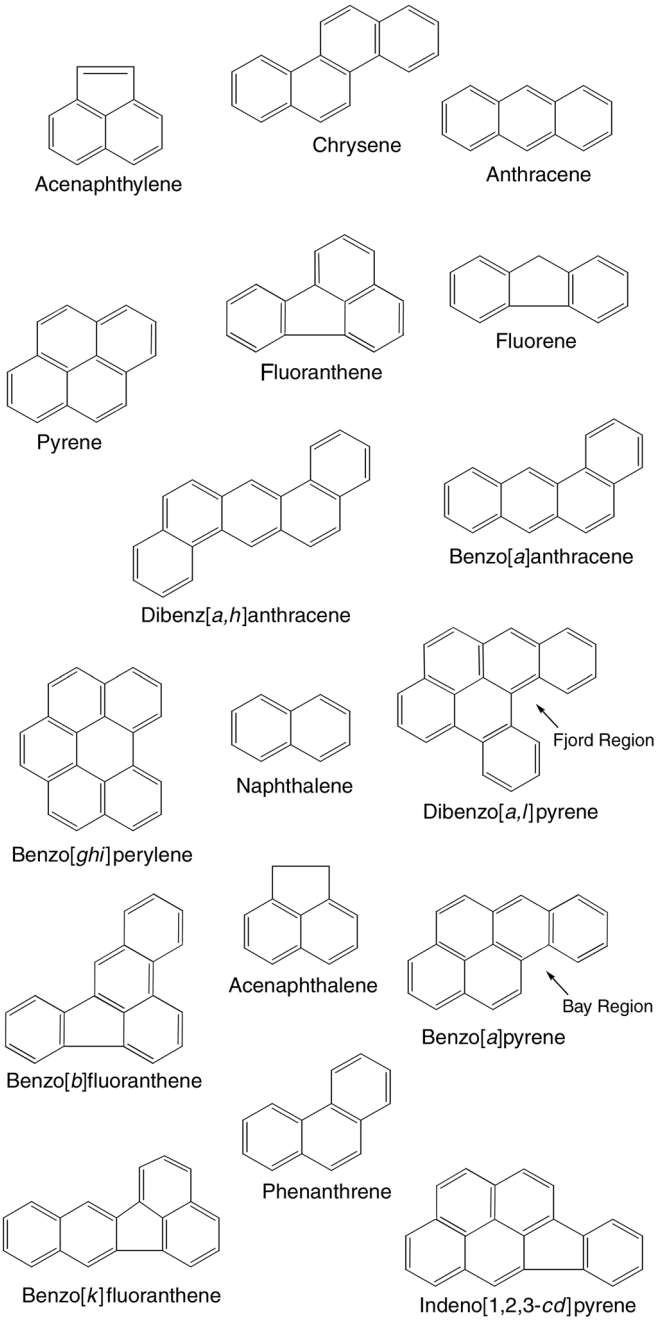

Figure 21. Structure of 17 POM compounds, with examples of bay and fjord regions indicated.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

BENCHMARK LITERATURE

The following evaluation of research literature on POM is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report as well as on key selected studies. Information on biomarkers of exposure is based on reviews in the Agency for Toxic Substances and Disease Registry (ATSDR 1995), Angerer and colleagues (1997), and Kyrtopoulos and colleagues (2001). Toxicologic information is based on reviews in the ATSDR (1995), EPA (1994b, 2000g), Rijksinstituut voor Volksgezondheid en Milieu (RIVM) (Sloof et al. 1989), and World Health Organization (WHO 1998; 2000a). Information on cancer risk is based primarily on a review for the Swedish government (Boström et al. 2002) and a risk assessment for benzo[*a*]pyrene developed by the WHO (1987). Additional information on health effects was summarized primarily from workplace studies and a limited number of community studies. In particular, sources of information central to the recent International Agency for Research on Cancer (IARC) review of PAHs (Cogliano et al. 2005) were reviewed.

EXPOSURE

SOURCES AND EMISSIONS

POM compounds result primarily from incomplete combustion and occur primarily as airborne particles. Emissions sources include vehicle-fuel combustion, cigarette smoking, road paving, roof tarring, meat grilling, and wood burning. Residential wood burning is believed to be the largest source of POM emissions, although vehicle-fuel combustion might be the largest source in urban areas (Boström et al. 2002). Nationally, however, the 1996 NATA estimates suggested that mobile sources accounted for only a small percentage of ambient exposure to the 7-PAH group in urban (2.9% on-road vehicles, 0.6% non-road vehicles) and rural counties (3.1% on-road, 0.8% non-road). Mobile-source contributions to the larger 16-PAH group accounted for less than 0.5% (EPA 2002d). Diesel vehicles generally emit more PAHs than gasoline-fueled vehicles, although different PAHs are emitted by the different types of engines. In a tunnel study, Marr and colleagues (1999) concluded that light-duty vehicles were an important source of higher molecular weight (four- and five-ring) PAHs, such as benzo[*b*+*k*]fluoranthene, benzo[*a*]pyrene, dibenz-[*a*,*h*]anthracene, and indeno[1,2,3-*cd*]pyrene, and that heavy-duty vehicles were a more important source of lower molecular weight PAHs, such as fluoranthene and pyrene. Another tunnel study also suggested that fluoranthene and pyrene are good tracers for exposure to diesel emissions (Chellam et al. 2005). In cold climates, emissions from "cold starts" might account for as much as 50% of the PAHs emitted by gasoline-fueled vehicles (Boström et al. 2002).

POM compounds are highly reactive and can be degraded in the atmosphere by photooxidation and reaction with atmospheric oxidants. Particle-bound PAHs are removed by deposition in 0.4 to 40 days (Seinfeld and Pandis 1998). PAH-particle sizes are bimodal. Fresh emissions range from 0.01 to 0.5 μm in size; urban aerosols also include an additional mode of particles that range from 0.5 to 1 μm. In the atmosphere, PAHs react with gaseous NO_2 (in the presence of HNO_3) to form mono- and di-nitro-PAHs. At 25°C, at equilibrium, benzo[*a*]pyrene, other PAHs with five or six rings, and chrysene exist predominantly in the aerosol phase. POM can be transported great distances and has been found even in locations remote from where the POM originated (Boström et al. 2002; Seinfeld and Pandis 1998).

Although recent research has begun to provide information on ambient concentrations of nitro-PAHs as well as quinones and hydroquinones (oxygenated products of PAHs) that might be important toxicologically, more information is still needed to support general conclusions about these compounds.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Ambient Air

Most measurements of POM involve collection of particles on filters and chemical analysis of the collected samples. A semicontinuous monitor is also available that measures total particle-bound PAH. This monitor was used by Levy and colleagues (2003) in a study in Roxbury, Mass. The mean total particle PAH concentration (averaged over 10 minutes) was 18 ng/m^3 (ranging from 4 to 57 ng/m^3, with a median of 8 ng/m^3). Higher concentrations were measured closer (within 20 m) to vehicle traffic. Regression models indicated an association between PAH concentrations and the numbers of nearby large diesel vehicles. The same total-PAH technique was used by Sapkota and colleagues (2005) in their study of tollbooth workers. The mean total particle PAH concentration (averaged over 3 hours) outside tollbooths was 135 ng/m^3 (ranging from 3 to 1130 ng/m^3) and correlated with the changes in traffic counts over time. The most extensive set of continuous particle-bound PAH data comes from the California Children's Environmental Health Protection Program measurements in Fresno, Calif. (California Air Resources Board 2003). Over a 1-year period, the mean concentration (averaged

over 1 hour) was 11.5 ng/m^3 (ranging from 0.4 to 291 ng/m^3).

Because of the complexity and cost of analysis, most studies of POM species include only a limited number of samples and are difficult to interpret in terms of their representativeness. Furthermore, different studies focused on different POM species and used different sampling and analytical techniques. Table 7 summarizes the range of concentrations of specific PAHs (particle phase only) measured in urban areas (including urban roadside high-traffic sites).

The NATA (EPA 2002d) reported higher modeled mean concentrations of PAHs in urban counties (108 ng/m^3) than in rural counties (21 ng/m^3). This finding was supported by data from Dachs and colleagues (2002), who reported PAH

Table 7. PAHs Measured in Ambient Air in Urban Areas

Compound	Number of Rings	Molecular Weight	Concentrations (ng/m^3) Minimum	Maximum	Citations	Notes
Benzo[*a*]anthracene	4	228	0.006	0.19	Manchester-Neesvig et al. 2003 Dachs et al. 2002 Naumova et al. 2002 Eiguren-Fernandez et al. 2004	a
Benzo[*b*]fluoranthene	5	252	0.01	0.26[b]	Sapkota et al. 2005 California Air Resources Board 2003 Naumova et al. 2002 Eiguren-Fernandez et al. 2004 Gigliotti et al. 2000	c
Benzo[*k*]fluoranthene	5	252	0.006	0.32	California Air Resources Board 2003 Manchester-Neesvig et al. 2003 Naumova et al. 2002 Eiguren-Fernandez et al. 2004 Gigliotti et al. 2000	d
Benzo[*a*]pyrene	5	252	0.009	0.28	California Air Resources Board 2003 Manchester-Neesvig et al. 2003 Dachs et al. 2002 Naumova et al. 2002 Eiguren-Fernandez et al. 2004 Gigliotti et al. 2000	e
Chrysene	4	228	0.008	0.3	Manchester-Neesvig et al. 2003 Dachs et al. 2002 Naumova et al. 2002 Eiguren-Fernandez et al. 2004 Gigliotti et al. 2000	e
Dibenz[*a,h*]anthracene	5	278	No measurements identified			
Indeno[1,2,3-*cd*]pyrene	6	276	0.003	0.59	California Air Resources Board 2003 Manchester-Neesvig et al. 2003 Dachs et al. 2002 Naumova et al. 2002 Eiguren-Fernandez et al. 2004 Gigliotti et al. 2000	f

[a] Measurements in tunnel studies as high as 10 ng/m^3 (Naumova et al. 2002; Eiguren-Fernandez et al. 2004).

[b] Maximum measurements as high as 1.1 ng/m^3 for unresolved benzo[*b*]fluoranthene + benzo[*k*]fluoranthene.

[c] Measurements in tunnel studies as high as 6.8 ng/m^3.

[d] Measurements in tunnel studies as high as 3.6 ng/m^3.

[e] Measurements in tunnel studies as high as 8.4 ng/m^3.

[f] Measurements in tunnel studies as high as 3.1 ng/m^3.

concentrations in urban Baltimore that were two to three times higher than concentrations measured over water in the Chesapeake Bay. (Their study was limited to 24 samples collected in a single month.) Gigliotti and colleagues (2000) measured similarly high concentrations in urban areas compared with rural areas in Southern California.

In Canada, data from approximately 2200 daily PAH samples collected at 35 sites between 1994 and 1997 were summarized (Environment Canada 1998). Mean PAH concentrations varied by more than three orders of magnitude from remote rural areas to industry-influenced sites (the range of means was 0.9 to 801 ng/m^3, and the range of 90th-percentile values was 4.8 to 2650 ng/m^3). For urban sites (with more than 10 sampling days of data), mean total-PAH concentrations ranged from 10 to 65 ng/m^3 and 90th-percentile concentrations ranged from 14 to 115 ng/m^3. Large population centers and sites with industrial emissions or wood-smoke sources had the highest concentrations. The most commonly measured PAH species were phenanthrene, fluoranthene, pyrene, and benzo[*b*+*k*+*j*]fluoranthene. Vapor-phase species accounted for the majority of the PAH mass. No consistent nationwide trends were observed.

As part of the Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study (Weisel et al. 2005), measurements were collected outside 55 homes of nonsmoking residents in Elizabeth, N.J., Houston, Tex., and Los Angeles, Calif. (Naumova et al. 2002). In the outdoor samples, total-PAH concentrations ranged from 12 to 110 ng/m^3 in Elizabeth, 10 to 160 ng/m^3 in Houston, and 4.2 to 64 ng/m^3 in Los Angeles. In the outdoor and corresponding indoor samples, total gas-phase-PAH concentrations were highest in Elizabeth, followed by Houston and then Los Angeles. Outdoor and corresponding indoor samples were highest in Elizabeth, followed by Los Angeles and then Houston. Significantly different profiles for five- to seven-ring PAHs in the outdoor samples suggested different PAH sources in the three cities. Benzo[*ghi*]perylene and coronene were the predominant high-molecular-weight PAHs in the outdoor samples in Los Angeles. Benzo[*b*+*k*]fluoranthene predominated in Houston. Such PAH-species variability was less striking in Elizabeth. The principal source of PAHs in Los Angeles is motor-vehicle emissions; in Houston it is petrochemical-industry emissions; and in Elizabeth it is both mobile-source and industrial emissions.

Given the interest in compounds that generate reactive oxygen species, measurements of four quinones (1,2-naphthoquinone, 1,4-naphthoquinone, 9,10-phenanthraquinone, and 9,10-anthraquinone) were made in airborne PM in Los Angeles. Substantial spatial variability in concentrations was observed, with downwind measurements showing elevated concentrations of 1,4-naphthoquinone and 9,10-phenanthraquinone, which are thought to be associated with vehicle emissions (Cho et al. 2004).

In-Vehicle Exposures

Measurements in vehicles are limited to total particle-bound PAHs. Riediker and colleagues (2003) reported a mean PAH concentration of 21.5 ng/m^3 in police patrol cars. No corresponding ambient or roadside measurements were available, but comparison with other roadside measurements did not suggest that in-vehicle concentrations were substantially higher than ambient concentrations at typical traffic sites. In a school-bus study in Southern California, Fitz and colleagues (2003) measured total particle PAH concentrations ranging from 36 to 198 ng/m^3, concentrations that were much higher than those measured at roadside locations.

Indoor Exposures

Only limited information is available about indoor concentrations of PAHs in developed countries. In China, high concentrations of PAHs have been measured in indoor settings in which biomass, and especially coal, is used for residential heating (Mumford et al. 1987). In addition to the outdoor RIOPA measurements at 55 homes in three cities described above, corresponding indoor measurements were made. The profiles for the five- to seven-ring PAHs in the indoor air in each of the three cities were similar to the outdoor profiles, which suggested that indoor concentrations of these PAHs were dominated by outdoor sources. Specifically, the measurements suggested that indoor concentrations of the particle-bound five- to seven-ring PAHs (e.g., benzo[*b*+*k*]fluoranthene, benzo[*a*]pyrene, indeno[1,2,3-*cd*]-pyrene, and dibenzo[*a*,*h*]anthracene) were dominated by outdoor sources; indoor sources were important for three-ring PAHs. Indoor concentrations of total PAHs were 22 to 350 ng/m^3 in Elizabeth, 21 to 310 ng/m^3 in Houston, and 16 to 220 ng/m^3 in Los Angeles; the ranking of mean concentrations by city corresponded to those of the outdoor samples.

Dubowsky and colleagues (1999) measured total particle-bound PAH in three (nonsmoking) Boston homes with varying proximities to traffic. The mean total PAH concentration at an urban site with traffic was 31 ng/m^3, more than three times higher than at a suburban site (8 ng/m^3). A daily peak in indoor PAH concentrations coincided with the morning rush hour at all three locations; higher concentrations were measured on weekdays than on weekends. Peaks also coincided with cooking, indicating the importance of this indoor source of PAHs in indoor air (Dubowsky et al. 1999). Total particle-bound PAHs measured in a variety of indoor environments in Boston were generally low, with mean concentrations ranging from approximately 5 to

10 ng/m^3. The highest concentrations were measured in a mall and a food court (Levy et al. 2002).

Personal Exposures

Tonne and colleagues (2004) measured personal PAH exposures (48-hour samples) of pregnant women in New York City. The mean total PAH concentration (for benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*ghi*]perylene, benzo[*a*]pyrene, chrysene and isochrysene, dibenz[*a,h*]anthracene, indeno[1,2,3]pyrene, and pyrene) was 8.0 ng/m^3 (ranging from 1.5 to 127 ng/m^3; SD = 9.5 ng/m^3). Mean concentrations of individual PAHs ranged from 0.06 ng/m^3 for dibenz[*a*,*h*]anthracene to 4.1 ng/m^3 for pyrene. Maximum concentrations ranged from 0.46 ng/m^3 for dibenz[*a*,*h*]anthracene to 96 ng/m^3 for pyrene. Both ambient concentrations and personal exposures were higher in winter than in summer for virtually all PAHs; the only exception was pyrene. The study identified significant predictors of PAH exposures, including amount of time spent outdoors, amount of time residential heating systems were running (more than 50% used fuel oil), and indoor burning of incense. No variables related to traffic sources were identified.

As part of the EXPOLIS (Air Pollution Exposure Distributions of Adult Populations in Europe) study (Zmirou et al. 2000), personal exposures to particle-phase PAHs were measured for 38 nonoccupationally exposed adult residents of Grenoble, France (Zmirou et al. 2002). Mean concentrations of nine PAHs (fluoranthene, pyrene, chrysene, benzo[*a*]-anthracene, benzo[*b*+*k*]fluoranthenes, benzo[*a*]pyrene, indeno[1,2,3-*cd*]pyrene, and benzo[*ghi*]perylene) were higher in winter than in summer. Annual mean concentrations ranged from 0.13 to 1.67 ng/m^3, depending on the species; the concentrations of fluoranthene and indeno[1,2,3-*cd*]pyrene were highest (Tonne et al. 2004). In Amsterdam, personal exposures of cyclists and drivers to total PAH during 1-hour trips along inner-city routes ranged from 7.5 to 24.7 ng/m^3 (van Wijnen et al. 1995).

SEASONAL TRENDS

Seasonal differences are evident for many of the PAHs. In general, concentrations of PAHs—especially those of higher molecular weight—are higher in winter than in summer, because emissions from heating sources increase and, to a lesser extent, because PAHs in the particle form are more abundant at lower temperatures (Naumova et al. 2002; Eiguren-Fernandez et al. 2004).

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Measured concentrations of PAHs in Canada are similar to those in the United States, as shown in Table 8.

TOXICOLOGY

The biologic properties of the majority of POM compounds are not yet fully understood. Benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene are the most extensively studied PAHs. The majority of the available information on POM toxicity is related to these two compounds.

BIOCHEMISTRY AND METABOLISM

The metabolism of POM is predominantly catalyzed by cytochrome P450-dependent monooxygenases (reviewed by the WHO International Programme on Chemical Safety 1998). The 1A1 and 1B1 forms of cytochrome P450 from animals and humans have been identified as being the most involved in metabolizing various carcinogenic PAHs to DNA-reactive diol epoxides. The presence of bay and fjord regions (see Figure 21) on many of these compounds makes them particularly reactive. These two major P450 forms are enzymes that are expressed in many mammalian tissues, either upon aryl hydrocarbon receptor–mediated induction (P450 1A1) or both constitutively and upon receptor-mediated induction (P450 1B1).

Benzo[*a*]pyrene is the most studied PAH with a bay region. It is first oxidized to form epoxide groups at several sites in its ring structure. These epoxides can be hydrated by epoxide hydrolase to form dihydrodiols or spontaneously rearrange to form phenols or quinone structures. The epoxide groups can also be detoxified by conjugation with glutathione; the phenol groups can be detoxified by conjugation with glucuronic acid. Benzo[*a*]pyrene is activated to

Table 8. PAH Measured in Canada[a]

Compound	Concentration (ng/m^3)	
	Rural Sites (n = 5)	Urban Sites (n = 12)
Indeno[1,2,3-*cd*]pyrene	0.04	0.24
Benz[*a*]anthracene	0.02	0.20
Benzo[*a*]pyrene	0.02	0.15
Benzo[*k*]fluoranthene	0.02	0.14
Benzo[*b*]fluoranthene	0.07	0.49
Chrysene	0.05	0.35
Dibenz[(*a,c*)+(*a,h*)] anthracene	0.01	0.04

[a] National Air Pollution Surveillance (NAPS) Air Toxics Monitoring Program (2002–2004). Data compiled by Tom Dann, Environment Canada (data available at *www.etc-cte.ec.gc.ca/NAPS/naps_data_e.html*). The urban Jonquiere site was excluded because it was affected by an aluminum smelter.

its ultimate DNA-reactive carcinogenic metabolite through the initial formation of (+)-benzo[*a*]pyrene-7,8-epoxide and its subsequent dihydrodiol metabolite (via epoxide hydrolase). This metabolite is subsequently activated to the ultimate reactive intermediate, (+)-*anti*-benzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxide, which can covalently interact with cellular DNA. In recent years, alternative metabolism mechanisms, such as formation of the radical cation (quinone and benzylic oxidation), have been proposed as contributors to the carcinogenic effects of PAHs.

In principle, the PAHs with fjord regions undergo the same metabolic activation and inactivation reactions as PAHs with bay regions. Of these, the most-studied compound is dibenzo[*a*,*l*]pyrene. Both P450 1A1 and P450 1B1 catalyze the formation of the 11,12-dihydrodiol and subsequently the 11,12-dihydrodiol-13,14-epoxide, of which the (−)-*anti*-dihydrodiol-epoxide is the most reactive and forms DNA adducts. Recent studies indicate that rat P450s form both the reactive 11,12-dihydrodiol-13,14-epoxide and the less reactive 7,8-dihydrodiol and that the human P450s 1A1 and 1B1 preferentially form the highly reactive (−)-*anti*-dihydrodiol-epoxide (Schober et al. 2006). This suggests that humans might be more susceptible to dibenzo[*a*,*l*]pyrene-induced cancers than rats.

NONCANCER HEALTH EFFECTS

Acute Effects

In animals, little is known about the adverse health effects associated with acute inhalation exposure to any of the PAHs, although some information is available on the effects of acute oral and dermal exposures to PAHs in animals, where the skin and liver have been identified as target organs of PAH toxicity.

Recently, toxicologic studies have suggested the importance of reactive oxygen species in the health effects of PM. To investigate the ability of PM to catalyze generation of reactive oxygen species, an assay was developed based on the reduction of oxygen by dithiothreitol. When the activity of this assay was correlated with measurements of the chemical composition of PM, high correlations were found for benzo[*g*]perylene ($r^2 = 0.82$), phenanthrene ($r^2 = 0.73$), pyrene ($r^2 = 0.73$), chrysene ($r^2 = 0.60$), and benzo[*b*]fluoranthene ($r^2 = 0.56$) and lower correlations ($r^2 = 0.32$ to 0.43) for other measured PAHs (fluoranthene, benz[*a*]anthracene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, and indeno[1,2,3-*cd*]pyrene) (Cho et al. 2005).

Repeated-Dose Toxicity

Animal studies of some of the PAHs have identified the skin, liver, and hematopoietic system as targets. Animal studies have also reported that oral exposure to benzo[*a*]pyrene affects the blood and liver, and acenaphthene, fluoranthene, and fluorene affect the liver and other organ systems. By contrast, no effects of anthracene were seen in the liver or any other organ system even at the highest dose of 1000 mg/kg body weight/day. Adverse skin effects have been noted in animals after application of solutions containing benzo[*a*]pyrene; skin exposure to mixtures of PAHs also caused skin disorders.

Benzo[*a*]pyrene and dimethylbenzanthracene have been found to be potent immunosuppressants. Effects have been documented on humoral immunity, cell-mediated immunity, and host resistance.

Reproductive and Developmental Effects

Oral- and parenteral-exposure studies of pregnant rodents have reported adverse effects of PAHs, including intrauterine growth retardation, fetal mortality, and teratogenesis. Toxic effects in adult rodents were often reversible, even after high exposure concentrations, but effects in fetuses and neonates were severe and persistent even at lower doses. Oral or parenteral exposure to benzo[*a*]pyrene decreased fertility and induced total sterility in F1 progeny of CD-1 mice and decreased the incidence of pregnancy in female rats. Developmental effects resulting from oral exposure to benzo[*a*]pyrene, such as reduced viability of litters and reduced mean pup weight, have also been noted.

GENOTOXICITY

The genotoxic potential of PAHs has been extensively investigated using both in vivo and in vitro assays. Most PAHs are genotoxic in bacterial and mammalian systems after the addition of an exogenous mammalian metabolic system or metabolization by P450 enzymes. It has been shown that macrophages are the primary cells capable of metabolizing PAHs; these cells generate 7,8-dihydroxy-9,10-epoxybenzo[*a*]pyrene, the reactive metabolite of benzo[*a*]pyrene. Limited genotoxicity tests conducted on urine obtained from humans exposed to PAHs have, however, been negative. The formation of benzo[*a*]pyrene–DNA adducts, as well as of benzo[*a*]pyrene–protein adducts and DNA adducts with metabolically generated reactive PAH intermediates, has been demonstrated.

Exposure to PAH might increase the risk of heritable mutations. Somers and colleagues (2004) exposed mice to ambient air in an urban-industrial area of Hamilton, Ontario, with high ambient concentrations of both PM and PAHs. Control groups were exposed to high-efficiency particulate air (HEPA)–filtered air at the same location and to air in a rural area with less pollution. HEPA filtration was

associated with a significant reduction in the heritable-mutation rate. This effect was primarily related to paternal mutations. PAHs bound to ambient air particles are the leading candidates for causing such mutations, as discussed in an editorial accompanying the Somers report (Samet et al. 2004). Whether this occurs in humans is unknown, but one study (Selevan et al. 2000) has suggested that exposure to elevated concentrations of ambient air pollution might affect sperm quality in young men. Furthermore, PAHs can be transferred across the placenta, exposing the fetus. In studies of mothers and newborns in Poland (Perera et al. 2002), PAH–DNA adducts in cord blood, determined using ^{32}P-postlabeling, were associated with the mutant frequency at the *HPRT* locus in the newborn ($\beta = 0.56$, $P = 0.03$). This suggests a possible link between exposure to PAHs in ambient air and somatic mutations in human newborns.

CARCINOGENICITY

There is a large database concerning the health effects in animals caused by exposure to complex mixtures that contain PAHs (such as crude oils, high-boiling-point distillates, petroleum products, coal tars, and creosote), and many PAHs are animal carcinogens by various routes. Studies have reported tracheal papillomas and carcinomas in hamsters from inhalation exposure to benzo[*a*]pyrene and squamous-cell tumors of the lung in rats from inhalation exposure to PAH mixtures. Leukemia and tumors in the liver, mammary gland, respiratory tract, and gastrointestinal tract were found in animals after oral exposure to benzo[*a*]pyrene, benz[*a*]anthracene, and dibenz[*a*,*h*]anthracene. The ability of inhaled benzo[*a*]pyrene to cause lung cancer can be enhanced by coexposure to other substances, such as cigarette smoke, asbestos, and (probably) airborne particles. The results of skin studies indicate that benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*a*,*h*]anthracene, and indeno[1,2,3-*cd*]pyrene are tumorigenic in rats and mice. Although many of these studies would be considered inadequate by current standards, the results nevertheless indicate that these PAHs can induce tumors, acting as both tumor initiators and promoters.

HUMAN HEALTH

BIOMARKERS OF EXPOSURE

The presence of PAHs and their metabolites in human urine and blood after inhalation, oral, or dermal exposures indicates that PAH absorption occurs. PAHs appear to be widely distributed in tissues after inhalation or oral exposure. The metabolism of some individual PAH compounds has been extensively studied in human- and animal-tissue homogenates, cultures, and perfused systems; information on interactions between individual components of POM is, however, insufficient.

PAHs have been identified and quantified in tissues of exposed humans, including lung, ovary, placenta, and uterine cervix, as well as leukocytes. Samples of lung tissue, for example, were obtained from 364 autopsies in Japan and analyzed for benzo[*a*]pyrene, benzo[*k*]fluoranthene, and benzo[*ghi*]perylene (Seto et al. 1993). PAH concentrations in the lung were higher in males than in females and higher in patients with lung cancer than in those without. Only benzo[*ghi*]perylene concentrations correlated with a history of smoking, and then only in males.

In general, POM (metabolized or unmetabolized) can be excreted into bile and urine as well as into breast milk. Secretion into the bile followed by elimination in the feces appears to be the major excretory route. The extent of elimination of PAHs varies among species. Tolos and colleagues (1990) measured concentrations of 1-hydroxypyrene in the urine of workers. Exposed workers had concentrations of 1-hydroxypyrene in the urine that were 17 times higher than those in unexposed controls; a history of smoking did not affect these results. In the study, ambient concentrations of pyrene were found to reflect environmental concentrations of coal tar pitch–derived PAHs.

Metabolites of POM can form adducts with DNA and proteins in tissues and blood; these can be measured in vivo. Using ^{32}P-postlabeling, Peluso and colleagues (2004) measured DNA adducts in blood lymphocytes and in bronchial and nasal brush biopsies from 55 patients undergoing diagnostic bronchoscopy. The quantity of adducts in bronchial tissue was weakly but significantly correlated with the quantity in blood lymphocytes ($r = 0.320$, $P < 0.05$) and tissue from the nasal brush biopsies ($r = 0.477$, $P < 0.01$). Specific adducts were not determined. The study suggests that nasal tissue is a potentially useful source for detecting PAH–DNA adducts. Other studies (Wiencke et al. 1995) have confirmed associations between DNA adducts in blood lymphocytes and lung tissue, although the relationship was generally weak.

Benzo[*a*]pyrene diol epoxide–DNA adducts were detected in bronchial epithelial cells in one of five lung specimens examined (Shamsuddin and Gan 1988). Smokers have higher concentrations of PAHs and DNA adducts than nonsmokers. Using the ^{32}P-postlabeling assay, Reddy and colleagues (1991) found that PAH–DNA adducts in blood leukocytes from foundry workers correlated with their exposure to benzo[*a*]pyrene, which was used as a surrogate for POM exposure.

PAH adducts were detected in placentas from live births in two regions of Bohemia in the Czech Republic—in Teplice, a polluted industrial area, and Prachatice, an agricultural area without heavy industry (Topinka et al. 1997). The quantities of adducts were higher in placentas from Teplice than from Prachatice (2.12 ± 1.46 compared with 1.48 ± 1.09 adducts per 10^8 nucleotides, respectively; $P = 0.0004$). However, little detail was provided on subject selection, ambient-air-monitoring methodology, or indoor exposure conditions, and the number of subjects was relatively small.

Using high-performance liquid chromatography and fluorescence detection, Pavanello and colleagues (1999) measured benzo[*a*]pyrene diol epoxide–DNA adducts in blood mononuclear cells from 130 people exposed to PAHs in various settings and by various routes—26 patients with psoriasis undergoing coal-tar treatment, 15 coke-oven workers, 19 chimney sweeps, 36 aluminum workers—and 34 nonexposed controls. Urinary levels of 1-pyrenol served as the biomarker of exposure. The quantities of adducts appeared to be most influenced by chronic, high-concentration respiratory exposure. No effect on the quantities of adducts was seen in patients undergoing coal-tar treatment, even though their daily dose of coal tar was 10 to 50 times higher than that of occupationally exposed workers. Eating grilled meats or smoking had no effect on the quantities of adducts. These findings suggest that the inhalation route of exposure to chronic, high concentrations of PAHs is the most important factor in adduct formation in occupational settings.

Breast milk has also been analyzed for DNA adducts following exposure to POM (Kalantzi et al. 2004). This is relevant not only with respect to determining exposure to POM, but also to the subsequent risk of breast cancer. Human mammary carcinoma cells were exposed to extracts from breast milk samples from four women in the U.K., and DNA adducts were measured using the ^{32}P-postlabeling assay. Effects were also examined when cells were exposed to breast milk extracts in combination with benzo[*a*]pyrene. Breast milk extracts increased micronuclei formation, independent of co-exposures to benzo[*a*]pyrene. All four extracts increased the percentage of p53-positive cells. One extract, when combined with benzo[*a*]pyrene, caused a 100-fold increase in benzo[*a*]pyrene–DNA adducts compared with benzo[*a*]pyrene alone. These findings suggest that environmental contaminants in breast milk other than benzo[*a*]pyrene might enhance the genotoxic effect of benzo[*a*]pyrene.

These studies illustrate that urinary concentrations of PAH metabolites, tissue concentrations of PAHs, and PAH–DNA and PAH–protein adducts in blood cells and tissue provide useful biomarkers of exposure to POM. However, because the exposures to POM in these studies are not known, the exposure–biomarker relationship is far from clear. Also unclear is the relationship between these biomarkers and the risk of cancer or noncancer health effects.

CANCER

The evidence for effects of exposure to POM on human health comes from epidemiologic studies. In general, these studies establish relationships between exposures and health outcomes but usually cannot prove causality. The exposures involve complex mixtures of POM and other gaseous and particulate pollutants and might be confounded by tobacco-smoke exposure. Therefore, human studies of POM exposure generally cannot ascribe health effects to POM alone nor to specific POM species.

Soot, coal tar, and pitch, all of which contain POM, have been known since the early 20th century to cause cancer in workers. Studies in the 1960s (Doll et al. 1972) demonstrated increased risk of mortality from lung and bladder cancers in "gasworkers" (workers exposed to coal-combustion products) in the U.K. More recent studies in occupational settings, where PAH concentrations can be one to two orders of magnitude higher than in ambient air, provided convincing evidence that POM is genotoxic and carcinogenic in humans (Kyrtopoulos et al. 2001; Mori 2002).

Armstrong and colleagues (2004) undertook a review and meta-analysis to quantify the lung-cancer risk associated with occupational exposure to benzo[*a*]pyrene. A 100 μg/m^3-years exposure to benzo[*a*]pyrene was associated with an average relative risk (RR) for lung cancer of 1.20 (CI, 1.11–1.29). The RR varied markedly with occupation; the highest risks were in the asphalt industry (RR = 17.5; CI, 4.21–72.78) and among chimney sweeps (RR = 16.2; CI, 1.64–160.7). Exposure to PM did not appear to be a confounder.

Studies in the Xuan Wei region of China provided evidence that cooking with "smoky" coal, which is high in PAHs and methylated PAHs, causes lung cancer (Mumford et al. 1987). The women in the study were virtually all nonsmokers yet, in some communes in the region, had a very high incidence of lung cancer. Lung-cancer mortality correlated closely with the use of smoky coal for cooking. In the commune of Cheng Guan, where 100% of homes used smoky coal, the lung-cancer mortality was 151.8 per 100,000 population. In the commune of Xi Ze, where no homes used smoky coal, lung-cancer mortality was 0.7 per 100,000. Tumors from 24 women who were nonsmokers showed high rates of mutations in both the *K-ras* and *P53* oncogenes, but their mutational spectra differed from those of smoking-related tumors (DeMarini et al. 2001).

These studies provided strong evidence for PAH exposure as a cause of lung cancer.

Studies of ambient exposure provided less definitive findings. Confounders included occupational exposures, indoor exposures to tobacco smoke and other sources, and dietary intake of PAHs. A series of studies have compared PAH concentrations in ambient air and PAH–DNA adducts in people living in an industrialized, highly polluted area and in a relatively clean area of Poland (Perera et al. 1998, 1992a,b, 2002; Whyatt et al. 1998). Estimated benzo[*a*]pyrene concentrations in the air of an industrialized area ranged from 0.057 μg/m^3 (in January) to 0.015 μg/m^3 (in May). The mean numbers of adducts per 10^8 nucleotides measured in subjects were 30.4×10^{-8} in winter and 4.2×10^{-8} in summer in the polluted area and 11.01×10^{-8} in winter and 3.0×10^{-8} in summer in the cleaner area. These findings suggested that variations in the amounts of PAH–DNA adducts by season and degree of pollution were related to variations in PAH concentrations in ambient air.

PAHs cause breast cancer in animals, but their role in causing breast cancer in humans is less clear. In a case–control study in Long Island, N.Y., Gammon and colleagues (2002) examined the relationship between breast cancer and blood PAH–DNA adducts (measured using an enzyme-linked immunosorbent assay [ELISA]) as a biomarker of exposure in women. Blood samples were tested from 576 women with cancer and 427 controls. The age-adjusted odds ratio (OR) for breast cancer for the highest compared with the lowest quintiles of adducts was 1.51 (CI, 1.04–2.20). However, there was no dose–response relationship and no relationship between the quantity of adducts and smoking or dietary PAH sources. The authors concluded that there might be a threshold above which additional effects are not observed. It is also possible that the ELISA lacked specificity for PAH adducts.

Taken together, these studies provided suggestive evidence that living in areas with high concentrations of ambient air pollution containing POM is genotoxic. However, the exposure–response relationship remains unclear, and the causality of POM in these relationships has not been established. Furthermore, there is little convincing evidence that the lower ambient concentrations of POM found in most Western industrialized cities are genotoxic in humans.

NONCANCER HEALTH EFFECTS

No reports of effects on human health after acute (short-term) exposure to POM were available. Epidemiologic studies of workers exposed to benzo[*a*]pyrene and PM by inhalation reported respiratory health effects. Recent studies suggest an effect of PAHs in conjunction with PM on the development of cardiovascular diseases, including atherosclerosis. Skin exposure to mixtures of PAHs might cause skin disorders or exacerbate existing lesions. Chronic exposure to benzo[*a*]pyrene has resulted in dermatitis, photosensitization, irritation of the eyes, and cataracts.

Reproductive and Neonatal Health

Only limited data were available on the effects of POM on reproduction and development in humans. Benzo[*a*]pyrene can adversely affect fertility, oocytes, and weight gain in animals. However these effects are observed at far higher concentrations than those found in ambient air. Although there are no studies directly addressing this issue in humans, the possibility exists that exposure to POM can cause noncancer health effects in humans, especially in conjunction with other exposures to PM.

Exposure to PAHs as part of ambient PM might contribute to low birth weight in infants. This possibility is supported by a study (Dejmek et al. 2000) of full-term births in two regions of Bohemia in the Czech Republic—Teplice, an area of industry and coal-burning power plants, and Prachatice, an agricultural area without heavy industry and with much lower concentrations of ambient PM than Teplice. However, both regions had similar ambient concentrations of PAHs. Data on full-term births to mothers of European origin were compared with ambient concentrations of PM and seven carcinogenic PAHs. In Teplice, for each 10-ng increase in PAH concentration, the adjusted OR for intrauterine growth retardation during the first gestational month was 1.22 ($P < 0.004$). A similar relationship was seen in Prachatice, but the data were not statistically significant.

Another study (Hertz-Picciotto et al. 2005), using the same data from these two areas, showed that ambient concentrations of both PM less than or equal to 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and PAHs were significantly associated with decreases in T lymphocytes in the cord blood of newborn infants. For a 100-ng/m^3 increase in PAHs, the percentage change in CD3+ T lymphocytes was −3.3% (95% CI, −5.6% to −1.0%). This effect was more than doubled for infants from homes that burned coal for heating. The findings suggested that the mother's exposure to ambient PAHs in the two weeks before birth might affect the immune status of the newborn. However, PAH and $PM_{2.5}$ concentrations were correlated in this study (Spearman correlation coefficient = 0.56, $P < 0.0001$), and independent effects were not determined.

Recent studies have examined birth outcomes in relation to environmental exposures in susceptible populations in New York City (Perera et al. 2004, 2005a). In 214 deliveries by nonsmoking women, maternal and cord blood was analyzed

for benzo[*a*]pyrene–DNA adducts and cotinine (as a measure of environmental tobacco-smoke exposure). There was a significant relationship between birth outcomes and both the amount of adducts in cord blood and cotinine. In the group with more DNA adducts and cotinine, birth weight was reduced 6.8% and head circumference 2.9% compared with the group with fewer adducts and less cotinine (Perera et al. 2004). Data were also examined following the World Trade Center disaster of September 11, 2001 (Perera et al. 2005b). In women pregnant at the time and living within one mile of the World Trade Center site on that date, amounts of DNA adducts in cord blood were inversely correlated with distance from the site. In the newborns of mothers exposed to environmental tobacco smoke (higher cotinine concentrations), a doubling of DNA adducts in cord blood corresponded to an 8% reduction in birth weight ($P = 0.03$) and a 3% reduction in head circumference ($P = 0.04$). In a pilot study performed in New Jersey, high ambient POM exposure was associated with fetal death (OR = 1.19), premature birth (OR = 1.25), and low birth weight (OR = 1.31) (Vassilev et al. 2001).

Cardiovascular and Respiratory Effects

Burstyn and colleagues (2003) studied a retrospective cohort of 58,862 men who started working in the asphalt industry between 1919 and 1939 in Denmark, Finland, France, Germany, Israel, the Netherlands, and Norway. Exposures to PAHs were modeled, based on workplace measurements. Deaths from obstructive lung disease were significantly associated with average exposures to PAHs ($P = 0.01$) and marginally associated with cumulative exposures ($P = 0.06$). However, data on smoking were not available, and confounding could not be excluded. Deaths from ischemic heart disease were examined in 12,367 of these workers employed between 1953 and 2000, with an average follow-up of 17 years (Burstyn et al. 2005). The risk of death from ischemic heart disease was significantly associated with both the average and the cumulative benzo[*a*]pyrene exposure concentrations. The relative risk associated with exposure to benzo[*a*]pyrene concentrations of 273 ng/m^3 or higher was 1.64 (CI, 1.13–2.38). The authors estimated that, if smoking were considered as a potential confounder, the highest PAH-exposure categories would be associated with an approximately 20 to 40% excess risk of ischemic heart disease.

POM is a component of combustion-related PM, especially diesel exhaust. Diesel PM (DPM) has been associated with airway inflammation in humans as well as allergic sensitization in nasal-instillation studies. However, diesel exhaust is a complex mixture, and there is little direct evidence to implicate POM as a causative factor of these health effects. In in vitro studies, ultrafine PM has been shown to enter cells and intracellular organelles, including the nucleus and mitochondria, by way of diffusion (Geiser et al. 2005). PM can interfere with one-electron transfers in the mitochondrial internal membrane; perturbation of the mitochondrial permeability transition pore can contribute to increased generation of superoxide anions and the induction of apoptosis (Li N et al. 2003). Organic extracts from DPM and quinone compounds appear to mimic these phenomena. Although the concentrations of PM and POM used in these studies are higher than those found in ambient air, they might provide insights into plausible mechanisms by which POM associated with ambient PM could mediate noncancer health effects.

One study provided insights into how POM might enhance responses to allergen challenge. Kepley and colleagues (2003) incubated human blood basophils with PAHs and measured the release of histamine and interleukin (IL)-4 with and without antigen. Several PAHs enhanced histamine and IL-4 release in response to crosslinking of the high-affinity IgE receptor FcϵRI. For one compound, 1,6-benzo[*a*]pyrene-quinone, signaling involved tyrosine phosphorylation and production of reactive oxygen species. Thus, PAHs might enhance allergic inflammation by increasing allergen-induced mediator release from basophils and possibly from mast cells, which are key effector cells in asthma.

REGULATORY SUMMARY

No specific guideline value has been recommended by the WHO for POM in air, although there are recommendations for individual PAHs. A unit lifetime risk for benzo[*a*]pyrene as an indicator air constituent for PAHs was estimated to be 8.7×10^{-5} per ng/m^3, based on epidemiologic data from studies in coke-oven workers (WHO 2000a). The European Union has proposed a target concentration of 1 ng/m^3 of benzo[*a*]pyrene (as a surrogate for PAH) in ambient air (Commission of the European Communities 2003). If this proposal is adopted, air monitoring would be required if the target is not met. The IARC has classified benzo[*a*]pyrene as a Group 1 carcinogen ("carcinogenic to humans") and dibenz[*a*,*h*]anthracene and dibenzo[*a*,*l*]pyrene as Group 2A ("probably carcinogenic to humans"), based on sufficient evidence in animals and strong mechanistic data. Several other compounds in the 16-PAH group were classified by the IARC as Group 2B ("possibly carcinogenic to human beings"), including benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, and indeno[1,2,3-*cd*]pyrene, based on sufficient evidence in animals (Cogliano et al. 2005; IARC 2007).

The cancer potency of PAH mixtures is often calculated using relative-potency values (in this case, benzo[*a*]-pyrene-equivalency factors). A recent analysis (Schneider et al. 2002), however, showed that this use of benzo[*a*]-pyrene-equivalency factors leads to underestimations of the carcinogenic potency of PAH mixtures in most cases. The EPA (1993b) and WHO (1998) have proposed using equivalent factors to estimate the toxic potency of PAH mixtures. The relative potencies are derived relative to benzo[*a*]pyrene in increments of multiples of 10. These factors are based on cancer bioassays using various routes of exposure and assuming that all PAHs have the same mode of action. Originally the EPA had used the 7-PAH group as a surrogate for the complex mixtures of hundreds of PAHs (EPA 1993b). The list has been repeatedly adapted as the EPA has developed new cancer potencies for individual PAHs. The WHO International Programme on Chemical Safety (1998) proposed a list of 13 compounds, which includes several PAHs with fjord regions, such as dibenzo[*a,l*]pyrene. Dibenzo[*a,l*]pyrene is metabolically activated by P450 1A1 and 1B1 to highly reactive and mutagenic species (Buters et al. 2002), and its carcinogenic potency has been estimated to be 100 times greater than that of benzo[*a*]pyrene (see Table 9). Dibenzo[*a,h*]anthracene, dibenzo[*a,e*]fluoranthene, dibenzo[*a,e*]pyrene, and dibenzo[*a,h*]pyrene have a relative carcinogenic potency similar to that of benzo[*a*]pyrene; that of dibenzo[*a,i*]pyrene is 10 times lower (WHO 1998). More recently, anthanthrene, benzo[*b*]naphthol[2,1-*d*]thiophene, naphthalene, phenanthrene, and pyrene have been proposed for addition to the list (see Table 9) (Jacob 2004). Note that the relative-potency range of this group of PAHs varies by five orders of magnitude.

SUMMARY AND KEY CONCLUSIONS

EXPOSURES

Food is thought to be the major source of human exposure to POM, owing to the formation of PAHs during cooking and also to the deposition of PAHs on fruits, vegetables, and grains from the atmosphere. Combustion of vehicle fuels and especially home-heating oil appears to be the principal source of exposure by the inhalation route for five- to seven-ring PAHs (e.g., benzo[*b*+*k*]fluoranthene, benzo[*a*]pyrene, indeno[1,2,3-*cd*]pyrene, dibenzo[*a,h*]-anthracene) that are associated with PM. Total PAH concentrations show some relationship to traffic proximity,

Table 9. Relative Carcinogenic Potencies of PAHs

Compound	EPA 1993b[a]	WHO 1998[b]	Jacob 2004
Anthracene	—	—	0.1
Benzo[*a*]pyrene	1	1	1
Benz[*a*]anthracene	0.1	0.1	0.1
Benzo[*b*]fluoranthene	0.1	0.1	0.1
Benzo[*j*]fluoranthene	—	0.1	0.1
Benzo[*k*]fluoranthene	0.01	0.1	0.1
Benzo[*b*]naphthol[2,1-*d*]thiophene	—	—	0.01
Chrysene	0.001	0.1	0.01
Cyclopenta[*cd*]pyrene	—	0.1	0.1
Dibenzo[*a,h*]anthracene	—	1	1
Dibenzo[*a,e*]fluoranthene	—	1	—
Dibenzo[*a,h*]pyrene	1	1	1
Dibenzo[*a,i*]pyrene	—	0.1	—
Dibenzo[*a,l*]pyrene	—	100	100
Indeno[1,2,3-*cd*]pyrene	0.1	0.1	0.1
Naphthalene, phenanthrene, pyrene	—	—	0.001

[a] Environmental Protection Agency (US) 1993b.

[b] World Health Organization International Programme on Chemical Safety 1998.

although the contribution of motor-vehicle emissions appears to be relatively small compared with that of other sources. Ambient concentrations and exposures are higher in winter than in summer because of atmospheric chemistry and increased emissions from heating systems. Preliminary measurements of a number of atmospheric transformation products suggest a contribution of motor-vehicle emissions.

TOXICOLOGY

Most POM are genotoxic in both in vitro and in vivo test systems. They generally require metabolism to epoxides and diol epoxides that can interact with DNA. The presence of PAHs and their metabolites in blood and tissues (including lung, ovary, placenta, and uterine cervix) indicate that PAHs are absorbed and distributed in tissues. Both metabolized and unmetabolized compounds are excreted into bile, feces, and urine as well as into breast milk. POM can induce tumors of the lung, skin, and breast. Effects on the blood and liver have also been observed. In pregnant rodents, intrauterine growth retardation, fetal mortality, and teratogenesis have been observed.

Biomarkers of exposure to PAHs are 1-hydroxypyrene in the urine as well as adducts with DNA and protein in tissues and blood. These are clearly elevated in exposed workers. Whether there is a correlation between increased environmental exposure and quantities of these biomarkers is less clear.

HUMAN HEALTH

POM as a mixture is a human carcinogen and is associated with lung, skin, esophageal, colon, pancreatic, and breast cancer. While different POM constituents have different degrees of carcinogenic potency, most studies have used benzo[*a*]pyrene as an indicator compound. Several PAHs are estimated to have relative carcinogenic potencies more than 10 times higher than that of benzo[*a*]pyrene. Epidemiologic studies of workplace and community exposures to complex mixtures that include POM have been used in carcinogenic-risk assessment. These studies were not able to ascribe effects to specific POM constituents, nor even to POM alone, but they did suggest that air pollution containing POM is genotoxic. Similar issues exist with regard to the effects of POM on reproduction. Exposure to ambient PM containing POM is associated with low birth weight and altered immune status in newborns. Occupational-exposure studies of asphalt workers indicated an association between long-term POM exposure and mortality from chronic obstructive pulmonary disease and ischemic heart disease. Together, these studies suggested that exposure to mixtures containing POM, including mixtures at concentrations found in ambient air, are associated with carcinogenic and reproductive effects, although it is not possible specifically to implicate POM or its individual components as being causally related to these health effects. Recent evidence from occupational and epidemiologic studies indicated associations between POM and mortality from respiratory and cardiovascular effects. But it is difficult to exclude confounding by exposure to cigarette smoke, and the concentrations of POM in these studies were often higher than those found in ambient urban air.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of POM?

Food is thought to be the major source of human exposure to POM. Combustion (of home-heating oil and, to some extent, of vehicle fuels) appears to be the dominant source of the particle-bound five- to seven-ring PAHs to which people are exposed by inhalation. For other POM species, insufficient data are available to determine the extent of mobile sources as contributors to exposure.

2. Does POM affect human health?

Occupational and community studies suggest that exposure to mixtures containing POM (and specifically PAHs) is associated with carcinogenic and reproductive effects, although it is not possible specifically to implicate POM or its individual components as being causally related to these health effects. Recent evidence from occupational epidemiologic studies indicated that exposure to high concentrations of PAHs is associated with mortality from respiratory and cardiovascular effects.

3. Does POM affect human health at environmental concentrations?

While there is evidence that air pollution containing PAHs is genotoxic and has effects on reproductive health, there is no direct evidence from community studies that POM specifically, at ambient exposure concentrations, causes health effects. Because community studies involve exposures to complex mixtures, they have limited ability to address the effects of POM alone. Additional identification of relevant biomarkers of exposure is needed.

RESEARCH GAPS AND RECOMMENDATIONS

POM is a complex mixture of PAHs in both gas and particle phases. Many different PAHs and mixtures of PAHs have been evaluated in different studies, making it difficult to compare results. General research recommendations for POM include the following:

- Identify a core set of specific species of POM for further study or indicator compounds to facilitate consistent research approaches.
- Although studies have investigated the effects of individual species of POM, studies of complex POM-containing mixtures should also be undertaken.

EXPOSURE

Specific research recommendations for POM-exposure studies include the following:

- Perform studies of ambient concentrations of nitro-PAHs, quinones, and hydroquinones.
- Further research the chemical reaction products of POM under typical atmospheric conditions and the possible biologic activities of these products.
- Determine regional variability (including "hot spots") in the concentrations of specific POM and total particle-bound POM. This information might be important for understanding the distribution and determinants of personal exposure.
- Add highly potent POM containing a fjord region to the NATA list of 16 particle-bound PAH species that define POM. Of these, the compounds in the 7-PAH group (benzo[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]-fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz-[*a,h*]anthracene, and indeno[1,2,3-*cd*]pyrene) are already classified as "probable human carcinogens."

TOXICITY

Specific research recommendations for POM-toxicity studies include the following:

- Undertake studies to determine the most appropriate animal species for extrapolation to humans, taking into account the potential toxic effects of reactive metabolites in various species and at various organ sites.
- Perform studies of the toxicokinetics and bioaccumulation of inhaled POM, including the dose for target tissues and the bioavailability of particle-bound POM.
- Initiate toxicity studies of the major atmospheric transformation products of POM.

HUMAN HEALTH

Specific research recommendations for human-health studies of POM include the following:

- Identify additional biomarkers of exposure to individual species of POM to facilitate epidemiologic studies (which heretofore have invariably involved mixtures).
- Determine the relative sensitivity of DNA adducts in order to help understand possible threshold concentrations of exposure.

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Summary of Studies of Diesel Exhaust

INTRODUCTION

Because numerous comprehensive reviews of the health effects of exposure to diesel exhaust (DE) have been published, the panel elected not to review the literature on diesel particulate matter (DPM) or diesel organic gases again in this special report. Instead, the following expanded summary of DE research has been provided.

DE is a complex mixture consisting of particulate-phase particulate matter (PM) and thousands of gaseous organic and inorganic components. DPM and diesel organic gases are designated as MSATs by the EPA. DPM is an agglomeration of nonvolatile elemental carbon particles with adsorbed semivolatile polycyclic organic matter (POM), metals, and sulfate ions. The size distribution of DPM is generally bimodal, with an accumulation mode, which accounts for most of the PM mass, and a nuclei mode, which accounts for most of the PM number (EPA 2002a; Kittelson et al. 2002; Sakurai et al. 2003). The PM in accumulation mode consists largely of soot (solid carbonaceous material and ash) and adsorbed organic and sulfur compounds and ranges from 30 to 1000 nm. PM in the nuclei mode consists of particles composed largely of the volatile organic and sulfur compounds and small amounts of solid, metallic compounds that are generally smaller than 30 nm (EPA 2002a; Kittelson et al. 2002). However, the boundary between the two modes can vary (Kittelson et al. 2002; Sakurai et al. 2003).

Several other MSATs are found in DE, including acetaldehyde, acrolein, benzene, formaldehyde, POM, and chromium compounds (EPA 2002a). DE contributes to ambient concentrations of PM, nitrogen oxides (NO_x, a component of smog), and ozone (also a component of smog—formed as a result of atmospheric reactions of semivolatile and volatile organic hydrocarbons and NO_x). Because other combustion products (such as smoke from burning wood and coal and industrial processes) also contribute to the concentrations of these pollutants to varying degrees in various places, it is difficult to assess exposure to DE in the general population. Allowable ambient concentrations of PM, nitrogen dioxide (NO_2), which is the most abundant species of NO_x, and ozone are set by U.S. National Ambient Air Quality Standards (U.S. Congress, House of Representatives 1977).

As part of an effort to reduce ambient PM and NO_x, the emission rates of these pollutants from diesel engines, as well as the emission rates of hydrocarbons and carbon monoxide, have been regulated since 1977. Regulatory efforts have historically been aimed at the heavy-duty diesel engines used in on-road trucks and buses. Beginning in 1996, efforts were broadened to include non-road equipment (EPA 1998b; EPA 2004b) and, beginning in 2000, railroad locomotives (EPA 1998c). In addition, effective as of 2004, PM and NO_x standards required both light-duty vehicles and diesel-fueled vehicles to meet the same emission standards as gasoline-fueled vehicles (EPA 2000a). Substantial additional reductions in PM and NO_x emissions are mandated for heavy-duty 2007-to-2010 on-road vehicles (EPA 2001a). These reductions require more advanced emission controls, such as catalyzed PM filters, exhaust-gas recirculation, and NO_x adsorbers, or selective catalytic reduction. Both the size and composition of the PM emitted by 2007-compliant engines are expected to be substantially different from those of earlier engines. The accumulation mode (particle mass) would be very low. Engine exhaust would consist largely of volatile or semivolatile nuclei-mode particles (Vaaraslahti et al. 2004). Certain particle filters might increase the NO_2:NO ratio in exhaust (Carslaw and Beevers 2004; Kittelson et al. 2006). PM emissions from 2010-compliant engines will be similar to those from 2007-compliant engines, but NO_x emissions will be substantially lower. However, the advanced NO_x-control technologies that will be used (such as the NO_x adsorbers and selective catalytic reduction) might generate new, potentially toxic chemical species.

The studies summarized here pertain mainly to the health effects of exposure to emissions from older or recent diesel engines. Although the expectation is that new diesel engines will contribute much less pollution to ambient air, it is still important to evaluate the exhaust from these engines, in particular to ensure that possible new emission species will not cause new adverse effects on human health.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

KEY LITERATURE REVIEWS

This expanded summary of the literature on exposure and health effects of DE is based on a review of original studies as well as reviews of the literature conducted by HEI (HEI Diesel Working Group 1995, HEI Diesel Epidemiology Expert Panel 1999), the California EPA (1998), and the EPA (2002a).

EXPOSURE SUMMARY

Because of the prevalence of diesel-fueled engines, DE and its by-products are present in most ambient environments. Urban and industrial areas—especially near roadways, truck and bus depots, and construction sites—typically have higher concentrations of DE pollutants (California EPA 2003). Current estimated ambient concentrations of DPM range from 3 to 10 $\mu g/m^3$; typical occupational concentrations range from 10 to 100 $\mu g/m^3$; the highest concentrations range from 100 to 1000 $\mu g/m^3$ and are found in poorly ventilated underground mines (EPA 2002a). Over the years, improvements in diesel fuel, such as decreases in sulfur content, and in diesel engines have reduced emissions of DE and many of its components (Gertler et al. 2002). Thanks to new regulations, this trend is expected to continue. Diesel engines designed to meet the 2007 emission standards will emit only very small quantities of PM and elemental carbon. Over a period of many years, these engines will gradually replace older engines. Retrofitting of the oldest diesel vehicles with PM filters will also contribute to emission reduction (LeTavec et al. 2002; Lanni 2003).

HEALTH EFFECTS AND REGULATORY SUMMARY

GENOTOXICITY

Since the late 1970s, extensive testing of the genotoxicity of DPM (and fractions of DPM) has been conducted using both in vitro assays (of bacterial and mammalian cells) and in vivo assays. The premise for conducting these studies was that the carcinogenic responses seen in earlier animal studies might have been caused by various organic compounds adsorbed to the particles (particularly polycyclic aromatic hydrocarbons [PAHs] and their nitrogen derivatives), many of which are mutagenic in in vitro assays (EPA 2002a). Most of the in vitro tests involved resuspended DPM or DPM extracts rather than whole DE.

The in vitro and in vivo assays used to evaluate the genotoxicity of DPM and particle extracts have been reviewed by Shirnamé-Moré (1995), the EPA (2002a), and the California EPA (1998). They found evidence of the following:

- Mutagenicity in bacterial assays (*Salmonella typhimurium*) and in mammalian cell cultures in the presence or absence of exogenous metabolic activation.
- Chromosomal damage in mammalian cell culture assays, measured as sister-chromatid exchanges (exchange of DNA between two chromatids of a chromosome), chromatid gaps and breaks, and formation of micronuclei (acentric chromosome fragments found in the cytoplasm). These changes have also been detected in bone-marrow cells of mice exposed to whole DE.
- Unscheduled DNA synthesis (a measure of the rate of DNA repair) measured either in cultured cells or in lung tissue of rodents exposed to whole DE.
- Small increases in DNA adducts in the lung tissue of rodents exposed to whole DE in some of the earlier diesel-inhalation studies but not in subsequent ones. Increases in DNA adducts were observed in workers exposed to DE (Hou et al. 1995; Hemminki et al. 1994). However, HEI's Diesel Working Group concluded that the adducts were not specific for diesel exposures (HEI 1995)

Regulatory Summary

The EPA (2002a) has reviewed the existing genotoxicity evidence in its *Health Assessment Document for Diesel Engine Exhaust* and concluded that "studies with *Salmonella* have unequivocally demonstrated mutagenic activity in both particulate and gaseous fractions of DE" and that "the induction of gene mutations and structural chromosomal aberrations have been reported in several mammalian cell lines after exposure to extracts of DPM." The EPA recognized, however, that "no single assay should be expected to either qualitatively or quantitatively predict rodent carcinogenicity."

The California EPA *Health Risk Assessment for Diesel Exhaust* (1998) also concluded that "diesel exhaust particles or their extracts are mutagenic in bacteria and several mammalian cell systems" and "induce chromosomal aberrations, aneuploidy and sister-chromatid exchange in rodent and human cells in culture."

These assays measure processes that might be relevant to some aspects of carcinogenesis, and agencies that assess risk have generally viewed them as useful for hazard identification.

CARCINOGENICITY

Animal Studies

The potential carcinogenic effects of DE from pre-1990 engines have been extensively investigated in long-term bioassays in rodents. The rat studies were conducted principally using exhaust from light-duty engines and showed an increase in lung tumors only at high exposure concentrations (several mg/m^3 DPM) (Heinrich et al. 1986, 1995; Ishinishi et al. 1986; Iwai et al. 1986, 1997; Mauderly et al. 1987, 1994; Brightwell et al. 1989). Only the rat study by Ishinishi and colleagues (1986) used exhaust from a heavy-duty engine (as well as a light-duty engine). All these engines had much higher emissions of DPM and gases than current and future diesel engines.

Two of the rat studies compared the carcinogenicity of whole DE with that of carbon-black particles (which lack gases and have much lower quantities of adsorbed organic compounds). The studies showed that exposure to high concentrations of either PM in whole DE or carbon black particles can cause lung tumors (Mauderly et al. 1994; Heinrich et al. 1995). These results have been widely interpreted as suggesting that the mechanisms of carcinogenesis in rats are likely to be related to exposures to high doses of the particles themselves and to possible lung overload rather than to the gases or adsorbed organic compounds (McClellan 1996; Kittelson et al. 2002; Bunn et al. 2004; Hesterberg et al. 2006).

By contrast, the studies in mice have yielded less consistent results. Some showed an increase in the incidence of lung neoplasms relative to the control animals (Pepelko and Peirano 1983; Heinrich et al. 1986; Takemoto et al. 1986), while some did not (Heinrich et al. 1995; Mauderly et al. 1996). In the study by Pepelko and Peirano (1983), Sencar mice were exposed from conception; in the study by Takemoto and colleagues (1986), ICR and C57BL mice were exposed as newborns; in the study by Heinrich and colleagues (1986) in NMRI mice, the spontaneous lung tumor rate of the control groups was unusually low compared with historical controls at the same institute (Heinrich et al. 1995). The negative studies were conducted in NMRI and C57BL mice (Heinrich et al. 1995) and in CD-1 mice (Mauderly et al. 1996). The EPA (2002a) concluded that although "earlier studies provided some evidence for tumorigenic response in diesel-exposed mice, no increases were reported in the two most recent studies (Heinrich et al. 1995; Mauderly et al. 1996) which utilized large group sizes and were well designed and conducted. Overall the results in mice must therefore be considered as unequivocal."

The two studies conducted in hamsters (Heinrich et al. 1986; Brightwell et al. 1989), using concentrations of DPM ranging from 4 to 6.6 mg/m^3 and numbers of animals similar to those in the rat studies, did not show any increases in benign or malignant lung tumors.

Several studies evaluated the carcinogenicity of filtered DE (i.e., with the same concentrations of gaseous components but without the particulate phase) in rats. All of the studies reported no increase in lung tumors in the animals exposed to filtered exhaust relative to the control animals, and all reported increases in the rats exposed to whole DE (Heinrich et al. 1986; Iwai et al. 1986, 1997; Brightwell et al. 1989). In their first study Iwai and colleagues (1986) found an increase in splenic malignant lymphomas in animals exposed to either filtered or unfiltered DE. The EPA assessment (2002a) noted that "this is the only report to date of tumor induction at an extrarespiratory site by inhaled DE in animals."

Only two studies evaluated the carcinogenicity of filtered exhaust in mice (Heinrich et al. 1986, 1995). In the 1986 study, which showed an increased incidence of lung tumors (from 13% to 32%) in the animals exposed to whole DE, a similar increase was also noted with filtered DE. However, the incidence of multifocal bronchoalveolar hyperplasia, interstitial fibrosis, and alveolar lipoproteinosis was greater in animals exposed to whole DE than in animals exposed to filtered DE. Studies conducted by the same group in the 1990s in two species did not find any significant tumor incidence after exposure to whole DE or filtered DE relative to animals exposed to clear air.

The EPA (2002a) concluded that "little direct evidence exists for carcinogenicity of the vapor phase of DE in laboratory animals at the concentrations tested."

Epidemiology

Among the more significant epidemiologic studies, only two have reported quantitative exposure data and been used for risk assessment: a series of U.S.-railroad-worker studies (Garshick et al. 1987, 1988, 2004, 2006; Woskie et al. 1988a,b; Larkin et al. 2000; Laden et al. 2006) and a U.S.-teamster study (Steenland et al. 1990, 1992; Zaebst et al. 1991). Although exposure data were collected from current workers, the studies were not designed to include the development of comprehensive exposure models nor to extrapolate from historical exposures.

The U.S. railroad industry converted from coal- to diesel-powered locomotives after World War II and during the 1950s. By 1959, 95% of the locomotives in service were diesel-powered. Garshick and colleagues (1987) conducted a case–control study of lung cancer deaths (with

data collected for 12 months in 1981 and 1982) in railroad workers who had had at least 10 years of service and were eligible for retirement benefits. There was a significant odds ratio (OR) of 1.41 (CI, 1.06–1.88) for lung-cancer death, controlling for smoking (including next-of-kin smoking history) and for asbestos exposure, among men 64 years of age or younger with 20 years of service in jobs associated with DE exposure starting in 1959. Garshick and colleagues (1988) also conducted a retrospective cohort study of workers aged 40 to 64 who were employed in 1959 in one of 39 jobs surveyed in an industrial-hygiene study (Woskie et al. 1988a,b). The cohort was followed up through 1980, and exposure was assessed as the cumulative years in jobs associated with DE exposure (assuming, again, that exposure started in 1959). The highest relative risk (RR) was observed for those workers who were 40 to 44 years of age in 1959, the group with the longest possible duration of exposure (RR =1.45; CI, 1.11–1.89). The same investigators performed additional analyses controlling for smoking, using indirect methods, of the follow-up data through 1976 (Larkin et al. 2000). The smoking-adjusted RR for lung cancer was 1.44 (CI, 1.01–2.05) compared with 1.58 (CI, 1.14–2.20) unadjusted.

In 1999, HEI critically evaluated the results of the studies of the railroad-worker cohort and determined if the data from them were adequate for quantitative risk assessment (HEI Diesel Epidemiology Expert Panel 1999). Both the HEI expert panel (1999) and an EPA consultant (Crump 1999) obtained the raw data and independently replotted the RR of lung cancer and different estimates of cumulative actual months exposure. Crump (1999) found a decreasing RR of lung cancer with cumulative exposure; the HEI panel (1999) found a similar decreasing RR with duration of employment for the main job categories (train workers, shop workers, and clerks) yet found that train workers had a higher risk than shop workers or clerks. The HEI panel concluded that "the railroad cohort study…has very limited utility for quantitative risk assessment of lifetime cancer risk from exposure to ambient levels of diesel exhaust" (HEI Diesel Epidemiology Expert Panel 1999).

The cohort was further evaluated by including deaths from 1981 to 1996 (Watanabe and Ohsawa 2002). Workers operating trains (engineers and conductors) who were between 40 and 44 years of age in 1959 had an RR of lung-cancer mortality of 1.49 (CI, 1.30–1.70). This elevated lung-cancer risk persisted after adjustment for smoking, as derived from the 1987 case–control study (Garshick et al. 2006). The risk of lung cancer, however, did not increase with increasing years of work in these jobs, confirming the findings of the earlier Crump (1999) and HEI (HEI Diesel Epidemiology Expert Panel 1999) analyses. Garshick and colleagues argued that the lack of dose–response was caused by a healthy-worker survivor effect and might also arise from exposure to coal-combustion products before 1959 and improvements in diesel-engine efficiency with reduced emissions over time. However, in a later analysis in which the years of exposure were weighted using estimates of the rate at which each railroad converted from coal to diesel (Laden et al. 2006), there was an increasing risk with increasing years of work in diesel-exposed jobs for workers who started work in 1945 or later as diesel locomotives were introduced.

The strengths of the railroad-worker studies were the very large cohort, extensive follow-up, and timing in relation to the conversion from coal to diesel; the strengths of the case–control study were ascertainment of smoking, asbestos exposure, and other potential confounders.

The National Institute of Occupational Safety and Health conducted a large case–control study of lung cancer in retired trucking-company teamsters whose deaths occurred between 1982 and 1983 (Steenland et al. 1990, 1992, 1998). An industrial-hygiene survey of PM and elemental carbon exposures in the trucking industry accompanied the epidemiologic study, thereby validating exposure assignments (Zaebst et al. 1991). The OR for lung cancer, controlling for smoking, was 1.69 (CI, 0.92–3.09) for mechanics, who had the highest exposure to elemental carbon. The ORs for short-haul (city) and long-haul (highway) drivers were 1.31 (CI, 0.81–2.11) and 1.27 (CI, 0.83–1.93), respectively (Steenland et al. 1990). The authors observed positive trends in lung-cancer risk with duration of employment for long-haul drivers after 1959, when long-haul trucks had generally converted to diesel. However, lung cancer risk was similarly elevated in short-haul drivers, whose trucks were still primarily gasoline-powered and who drove in urban settings, suggesting a contribution of traffic emissions not limited to diesel. In its 1999 review, HEI noted that "the investigators' analyses of the teamster data reported an exposure–response relationship that may be useful for quantitative risk assessment" (HEI Diesel Epidemiology Expert Panel 1999), but that further exploration of uncertainties and assumptions was needed.

Critiques of the studies of Garshick and colleagues and Steenland and colleagues for use in quantitative risk assessment cited the lack of concurrent exposure data, lack of dose–response relationship, possible misclassification of smoking habits and DE exposure, and, for the teamster study, a possibly insufficient latency period (because of uncertainties about the conversion to diesel in the trucking industry) (Hesterberg et al. 2006).

The increase in lung-cancer mortality observed in railroad workers and teamsters is consistent with findings in a large number of studies of a weak association between

work in a job associated with diesel exposure and death from lung cancer (Cohen and Higgins 1995).

Regulatory Summary

Because of the potential health effects of exposure to DE, the EPA (1999a) has included both DPM and diesel organic gases in its list of MSATs whose emissions might be further regulated. It has also completed its *Health Assessment Document for Diesel Engine Exhaust* (EPA 2002a) to "provide information about the potential for diesel engine exhaust to pose environmental health hazards." Other agencies, such as the National Institute for Occupational Safety and Health (1988), the International Agency for Research on Cancer (1989), the World Health Organization (1996), and the National Toxicology Program (2005), have reviewed the literature on the health effects of DE exposure and evaluated the human carcinogenic potential of DE. Based on the epidemiologic data and supporting evidence from animal and in vitro studies of DE, all of these agencies have classified DE as a probable human carcinogen. Based on a review of the health risk of exposure to DE conducted by the California EPA (1998), the California Air Resources Board (ARB) has designated DPM as a toxic air contaminant for which additional control measures might be needed (ARB 1999). A summary of these evaluations is shown in Table 10.

The EPA emphasized that "while EPA believes that the assessment conclusions apply to the general use of diesel engines today, as cleaner diesel engines replace a substantial number of existing engines, the general applicability of the conclusions in this health assessment document will need to be reevaluated" (Foreword by Paul Gilman, EPA 2002a).

CHRONIC NONCANCER HEALTH EFFECTS

Regulatory Summary

In addition to evaluating the potential cancer hazard associated with DE, the EPA conducted an assessment of potential chronic noncancer health effects to derive an inhalation reference concentration (RfC), an estimate of a daily inhalation exposure of the human population (including sensitive subgroups) that is "likely to be without an appreciable risk of deleterious effects during a lifetime" (EPA 2003c). For this assessment, the EPA used the information gathered in its 2002 DE health assessment. The evidence in support of the RfC was derived mainly from high-exposure long-term animal inhalation studies showing "consistent findings of inflammatory, histopathological (including fibrosis), and functional changes in the pulmonary and tracheobronchial regions of laboratory animals, including the rat, mouse, hamster, guinea pig, monkey, and cat," with some corroborative evidence from occupational studies suggesting the occurrence of mostly transient respiratory symptoms and impairment of lung function. Based on these studies, the EPA concluded that "chronic respiratory effects are the principal noncancer hazard to humans from long-term environmental exposure to DE." The RfC of 5 $\mu g/m^3$ for chronic noncancer respiratory effects of exposure to DPM was calculated from dose–response data on inflammatory and histopathological changes in the lung from chronic-inhalation studies in rats. The EPA commented that "other effects—such as neurological, growth and survival, lowered resistance to respiratory infections, liver effects—are observed in animal studies at higher concentrations than those producing the respiratory effects." The California EPA's *Health Risk Assessment of Diesel Exhaust* reached similar conclusions (California EPA 1998).

SHORT-TERM NONCANCER HEALTH EFFECTS

Inflammation and Allergic Responses

Asthma and allergies have emerged as important public health issues, and many investigations are underway to examine the broad variety of factors that might cause or exacerbate them. In this context, epidemiologic studies in adults and children have raised concerns that exposure to traffic-related air pollution (though not specifically DE) might be associated with the exacerbation of asthma and allergy symptoms (Duhme et al. 1996; English et al. 1999; Brauer et al. 2002; Janssen et al. 2003; Nicolai et al. 2003; Ryan et al. 2005). Because of these concerns, a number of studies have been conducted in which healthy and asthmatic participants have been exposed to DE or DPM to evaluate effects on allergic responses and the respiratory system. These studies showed that DE can cause some short-term effects on the airways under some experimental conditions. The results are summarized here.

Controlled exposures of healthy human participants to relatively high concentrations of fresh DE (300 $\mu g/m^3$ for 1 hour) from a 1990 diesel engine revealed modest changes in some inflammatory markers in lung sputum, lung biopsies, and blood but no changes in lung function (Salvi et al. 1999, 2000; Nordenhall et al. 2000). Similar studies in participants with mild asthma showed increases in airway reactivity, lung resistance, and markers of mild inflammation in sputum (no measures were taken in tissue biopsies or blood) (Nordenhall et al. 2001). In subsequent studies by the same research group involving exposure of healthy and asthmatic participants to DE containing 100 $\mu g/m^3$ DPM for 2 hours, both healthy and asthmatic participants

Table 10. Summary of Diesel Hazard Assessments[a]

Agency and Year	Findings
National Institute of Occupational Safety and Health 1988	Animal evidence "confirmatory" for carcinogenesis Human evidence "limited" DE classified as "potential occupational carcinogen" No quantitative risk assessment
International Agency for Research on Cancer 1989	"Sufficient evidence" for carcinogenicity in experimental animals Epidemiology data provide "limited evidence" for carcinogenicity DE considered a "probable" human carcinogen. No quantitative risk assessment
World Health Organization 1996	Rat data support carcinogenicity Human epidemiology data suggest "probably carcinogenic" Epidemiology studies considered "inadequate for a quantitative estimate of human risk" Rat data used for quantitative risk assessment
California Environmental Protection Agency 1998	Rat data "have demonstrated" carcinogenicity of DPM Causal association of DE and lung cancer in epidemiology studies is a "reasonable and likely explanation" Human epidemiology data used for quantitative risk assessment because of uncertainties in extrapolation from animals to humans DPM designated a "toxic air contaminant" (by California Air Resources Board)
National Toxicology Program 2005	DPM listed as "reasonably anticipated to be a human carcinogen" based on findings of elevated lung cancer in occupational groups exposed to DE and supporting animal and mechanistic studies No quantitative risk assessment
Environmental Protection Agency 2002a	Diesel emissions considered "likely to be carcinogenic to humans" No quantitative risk assessment Perspective of the range of possible lung-cancer risk was developed on the basis of occupational epidemiologic studies Evidence considered: • Strong but less-than-sufficient epidemiologic evidence • Rat lung tumor response (occurring only at high doses that cause inhibition of particle clearance, resulting in lung particle overload) not considered relevant to effects in humans exposed to low ambient concentrations • Results in mice considered equivocal; hamster results considered negative • Evidence of carcinogenicity of DPM in rats and mice when exposed by non-inhalation routes • Extensive supportive data include mutagenic or chromosomal effects of DE and its organic constituents

[a] Abbreviations: DE = diesel exhaust; DPM = diesel-exhaust particles.

showed a small increase in airway resistance, but most changes in inflammatory parameters in bronchial alveolar lavage (BAL) or lung tissue were observed only in healthy participants (Holgate et al. 2003). Participants with asthma, however, had higher baseline inflammation than healthy participants (Holgate et al. 2003). A separate study at the same DE concentration reported an increase in subjective symptoms and mild bronchoconstriction in healthy exercising participants but no changes in airway inflammation (Mudway et al. 2004). Overall, these studies suggested that the responses of healthy and asthmatic participants to DE are variable and that the baseline level of inflammation might influence the outcome.

The question of whether DE increases the specific allergic response to an allergen, which involves different inflammatory mediators from those involved in a nonspecific inflammatory response, has been addressed experimentally using an allergen challenge combined with exposure to DPM. Healthy and asthmatic volunteers were exposed to 300 µg of resuspended DPM (collected from

emissions generated by a 1980 diesel car engine and archived) via nasal spray (a physiologically nonrelevant method of exposure). Both groups of volunteers had enhanced production of total immunoglobulin E (IgE) in the nose (Diaz-Sanchez et al. 1994) and increased production of cytokines characteristic of both the T_H1 and T_H2 subsets of CD4+ T lymphocytes in the nasal mucosa (Diaz-Sanchez et al. 1996). These two subtypes of cells play distinct roles in the immune response. T_H1 cytokines are involved in cell-mediated immunity; T_H2 cytokines trigger IgE production by B lymphocytes and recruitment of eosinophils, which are indicators of allergic asthma. Intranasal challenge with DPM and ragweed allergen in human participants who were allergic to ragweed markedly enhanced the production of ragweed-specific IgE, but not total IgE, compared with a challenge with ragweed allergen alone, and resulted in decreased production of T_H1 cytokines and increased production of T_H2 and other cytokines (such as interleukin-6 (IL-6) (Diaz-Sanchez et al. 1997). However, these studies focused only on the nasal response and involved a bolus exposure to resuspended DPM, which might have different physicochemical properties from fresh aerosolized DPM.

Studies of allergic response in mice and rats (generally sensitized and challenged with ovalbumin as the allergen) have used different protocols for administering the allergen, different timing of the diesel exposure relative to the administration of the allergen, and different route of exposure. Because of these, the results obtained are not entirely consistent. Several studies have found evidence of adjuvant effects of DPM or DE on the production of allergen-specific IgE antibodies and inflammation (Takafuji et al. 1987; Fujimaki et al. 1997; Takano et al. 1997; Steerenberg et al. 2003; Dong et al. 2005). Steerenberg and colleagues (2003) found that the effect of DPM on ovalbumin-specific IgE production was dependent on the timing of the exposure relative to the timing of the ovalbumin administration. Some studies reported an effect of DPM on allergen-induced airway responsiveness (Hao et al. 2003; Dong et al. 2005; Matsumoto et al. 2006). In the Hao and colleagues study, which also measured ovalbumin-specific IgE production, there was no adjuvant effect of DPM.

Taken together, human and animal studies suggest that, under certain experimental conditions, DPM (from older engines) might induce markers of nonspecific inflammation in healthy and asthmatic participants, might cause changes in respiratory function, and might act as an adjuvant to increase the specific immune response to an allergen. Findings of adjuvant effects in humans, however, need to be validated in studies with more relevant exposure conditions. Also, there is some evidence in animals that other particles, such as Kanto loam dust, fly ash, carbon black, and alum (Maejima et al. 1997) or residual-oil fly ash (Lambert et al. 1999), can induce similar responses, raising the question of whether this is a DE-specific response or one induced by exposure to particles in general. However, conclusions about the studies in animals are difficult to generalize to humans because different effects can be observed when different animal species or study protocols are used.

Regulatory Summary

The EPA (2002a) concluded that "as with humans, there are animal data suggesting that DEP [DPM] is a possible factor in the increasing incidence of allergic hypersensitivity." The EPA concluded that "additional research is needed to further characterize the immunological effects of DE and to determine whether or not the immunological effects constitute a low-exposure hazard." In its determination of the inhalation RfC, the EPA (2003c) commented that the human and animal data for the immunological effects of DPM exposure (i.e., exacerbation of allergenicity, and asthma symptoms) are currently inadequate for dose–response evaluation and these data did not support further adjustment of the RfC. The California EPA *Health Risk Assessment* (1998) also concluded that the available information could not be used to develop quantitative estimates for determining the RfC but noted that "the potential relevance of these immunological endpoints to public health is very high, due to reports of large numbers of individuals with respiratory allergies and asthma in urban areas."

EFFECTS ON RESPIRATORY INFECTIONS

Animal Studies

A few studies have been conducted in mice and rats to evaluate the effects of inhaled DE on host defense against bacterial or viral agents. In these studies, mice or rats were exposed by inhalation to DE with high concentrations of DPM (generally greater than 2 mg/m^3; one study used 20 mg/m^3) or to clean air for 5 days or longer and then infected with a respiratory bacterium (*Listeria*) or virus (influenza) (Hahon et al. 1985; Castranova et al. 2001; Yin et al. 2004). The studies found increased lung injury, inflammatory response, and bacterial or viral loads in the animals exposed to DE compared with the animals exposed to clean air. Harrod and colleagues (2003) exposed mice to a high (1 mg/m^3) or low (0.03 mg/m^3) concentration of DPM, followed by infection with respiratory syncytial virus. They found a dose-related increase in the expression of viral mRNA, inflammatory mediators, and

interferon levels (a response that was the opposite of that reported in the Yin et al. [2004] study using exposures of 20 mg/m^3 DPM). Other changes included a dose-related increase in mucus-cell metaplasia and lung inflammation. A more recent study demonstrated that the use of low-sulfur fuel and a catalyzed trap completely, or almost completely, eliminated lung inflammation, oxidative stress, and the responses to viral infection induced after exposure to whole DE, compared with values observed in this and previous studies at the same exhaust dilution (McDonald et al. 2004). Overall, these studies suggested that DE might lower resistance to respiratory infections under certain conditions; these results have yet to be replicated.

Regulatory Summary

Based on two early studies in which mice were exposed to 2 to 8 mg/m^3 DPM (Campbell et al. 1981; Hahon et al. 1985), the EPA concluded that "exposure to DPM can reduce an animal's resistance to respiratory infection" but noted that these effects were observed only at very high concentrations (EPA 2002a). The California EPA *Health Risk Assessment* (1998) also stated that "inhalation or direct application of diesel into the respiratory tract of animals…increased susceptibility of exposed animals to lung infections." Because these effects were observed at exposure concentrations higher than those associated with other effects (such as lung inflammation and histopathological changes), the reduced response to respiratory infections was not used by the EPA in its determination of the RfC for DE.

EFFECTS ON REPRODUCTIVE FUNCTION AND FETAL DEVELOPMENT

Animal Studies

Although there is no evidence that maternal exposure to DE is associated with fetal malformation (EPA 2002a; Tsukue et al. 2002), some studies using a variety of exposure protocols and animal models and examining different endpoints suggested that exposure of pregnant rodents might cause subtle changes in both the mothers and their offspring. Maternal changes included alterations of hormonal balance after exposure during pregnancy to DE with 5.6 mg/m^3 DPM (Watanabe and Kurita 2001) and, after giving birth, a lower rate of nest construction after exposure during pregnancy to a DPM concentration of 3 mg/m^3 (though not at lower concentrations) (Tsukue et al. 2002). The effects reported in offspring exposed in utero included delayed or disturbed differentiation of the testis, ovary, and thymus (Watanabe and Kurita 2001) and delayed gonadal maturation and lower weight gain in the group exposed in utero to 3 mg/m^3 (Tsukue et al. 2002).

Some studies appear to suggest effects on the male reproductive system. Changes in endocrine function, decreased sperm production, and changes in hyaluronidase activity in growing male rats exposed from birth to 3 months of age to DE at a concentration of 5.6 mg/m^3 were also reported (Watanabe and Oonuki 1999). However, a study in which male rats were exposed to DE at concentrations of 0.3, 1.0, or 3.0 mg/m^3 for 8 months beginning at 6 weeks of age did not show changes in sperm counts (Tsukue et al. 2001, 2002). Possible reasons for the difference between the findings of this study and the one by Watanabe and Oonuki (1999) were the higher DPM concentrations and the younger age of the animals in the latter study. In both studies, the authors observed increased levels of serum testosterone. Mice seemed to be more sensitive than rats, based on a study by Yoshida and colleagues (1999), who reported a dose-dependent decrease in daily sperm production in mice exposed to DE at DPM concentrations of 0.3, 1.0, or 3.0 mg/m^3. No effects on the weight of the testis, epididymis, or adrenal glands were observed. Ultrastructural changes in Leydig cells (which are involved in spermatogenesis) were observed even at the lowest DPM concentration.

A recent study evaluated the effect of in utero exposure to whole DE on sperm counts and Sertoli cells in the adults rats. Pregnant mice were exposed to DE at 0.17 or 1.7 mg/m^3 DPM concentrations or filtered DE with similar levels of NO_2 (Watanabe 2005). The author reported that there were fewer Sertoli cells and sperm cells in the rats exposed in utero to both high and low concentrations of whole DE or filtered DE. Daily sperm production was also decreased, but no dose–response relationship was observed for any of these effects.

Regulatory Summary

The EPA (2002a) concluded that "DE is not likely to pose reproductive or developmental hazard to humans." The agency (2002a) also noted that "no teratogenic, embryotoxic, fetotoxic, or female reproductive effects were observed in mice, rats, or rabbits at exposure levels up to 12 mg/m^3 DPM." Although "effects on sperm morphology and number were reported in hamsters and mice exposed to high levels of DPM…no adverse effects were observed in sperm obtained from monkeys exposed at 12 mg/m^3 for 7 hours/day, 5 days/week for 104 weeks" (EPA 2002a). The California EPA *Health Risk Assessment* (1998) concluded that "the available literature does not provide sufficient information to determine whether or not diesel exhaust exposure induces reproductive, developmental, or teratogenic effects in humans." Because a number of studies have been published since the EPA and ARB assessments, this evaluation might need to be updated.

EFFECTS ON THE CARDIOVASCULAR SYSTEM

Animal and Human Studies

DPM contributes to the mixture of PM in ambient air, especially in urban environments, and it is likely that it contributes to some of the health effects associated with ambient PM. Epidemiologic studies in many places have shown that there is an association between short-term increases in PM concentrations and mortality and morbidity (and that people with cardiovascular or pulmonary disease seem to be most susceptible; see Pope and Dockery 2006 for a recent review).

Recent findings suggest some plausible mechanisms for how exposure to low concentrations of ambient or laboratory-generated PM might initiate a sequence of events that affect the cardiovascular or pulmonary systems: (1) induction of oxidative stress and inflammatory responses in the airways (such as increases in neutrophil number and levels of cytokines and chemokines); (2) induction of systemic inflammatory and other vascular responses (e.g., changes in blood pressure; levels of fibrinogen, C-reactive protein, and endothelins; plasma viscosity; and platelet numbers—several of which are associated with the risk of cardiovascular disease); and (3) dysfunction of the autonomic nervous system, leading to cardiac electrophysiologic changes and possibly to cardiac events, such as myocardial infarction or arrhythmias (Brook et al. 2004). Some of these effects have been observed, although not consistently, in experimental studies using a variety of animal models and types of PM (including concentrated ambient PM; laboratory-generated PM, such as metal-oxide PM; and source-specific PM, such as diesel, coal fly ash, and residual-oil fly ash).

Because DPM has some characteristics that have been hypothesized to be potentially associated with cardiovascular changes, including small particles with high surface area and adsorbed metals and organic components, some studies have been conducted recently to begin to evaluate the effects of DPM on the cardiovascular system. DE also contains a number of oxidant gases that are irritants and can cause oxidative stress.

One study in animals has shown that exposure of healthy F344 rats to DE for 6 months at 1 mg/m^3 PM (6 hours/day, 7 days/week) caused a small decrease in blood coagulation factor VII in both males (12%) and females (27%) (Reed et al. 2004). Spontaneously hypertensive rats exposed to the same concentration of DPM for 1 week had elevated heart rates throughout the exposure and significantly prolonged PQ intervals in their electrocardiograms, which might indicate a risk of arrhythmia (Campen et al. 2003). More recently, the same group of investigators reported that both the gaseous components of DE (i.e., filtered exhaust) and whole exhaust (with 3 mg/m^3 DPM) induced a decrease in heart rate and electrocardiogram changes consistent with myocardial ischemia in a mouse strain that spontaneously develops atherosclerosis (Campen et al. 2005). Whole DE induced airway inflammation, and filtered exhaust did not, suggesting different roles for the particulate and gaseous exhaust components. Recently, Mills and colleagues (2005) reported that exposure of human volunteers to DE (with 300 µg/m^3 DPM for 1 hour) impaired the regulation of vascular tone and fibrinolysis. These changes might be involved in the pathway to thrombosis and myocardial infarction. The studies appeared to suggest effects of DE on the cardiovascular system that are consistent with those attributed to PM as a whole.

Regulatory Summary

Because of a lack of data at the time, neither the EPA nor the California EPA considered these outcomes in their assessments.

SUMMARY

The results of studies investigating exposure to DE from older and more current engines indicate effects on the respiratory, reproductive, and cardiovascular systems. Extrapolation of these findings to people exposed to much lower concentrations of DE components than those used in experimental studies or in epidemiologic studies of occupationally exposed workers can be challenging.

Despite these challenges, many agencies have determined that DE is of sufficient concern to merit action to reduce emissions. New diesel engines with control systems meeting 2007 emission standards for heavy-duty on-highway vehicles are now on the market. Emissions from four such engines will be characterized in detail in the Advanced Collaborative Emissions Study (ACES), which is a joint effort of the Coordinating Research Council and HEI; chronic and acute health endpoints will be assessed for one of the engines. Although durable older engines with higher emissions will continue to be used, these new engines, and those designed to meet the more stringent 2010 standards, will gradually become more common, with substantial replacement expected by 2030.

DIESEL EXHAUST REFERENCES

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Summary and Conclusions

Air toxics are emitted into ambient air from many different sources. They comprise a diverse group of air pollutants that, with sufficient exposure, are known or suspected to cause adverse effects on human health, including cancer, effects on the development of organs or tissues, and damage to the immune, neurologic, reproductive, or respiratory systems. Tools and techniques for assessing project-specific health effects of MSATs are very limited. Indeed, there are substantial uncertainties about the health effects of air toxics in general, irrespective of their source allocation. While acknowledging these uncertainties, the U.S. EPA in its 1999 National Air Toxics Assessment (NATA) estimated that 92% of the U.S. population is at some increased risk for adverse effects on the respiratory system (including irritation and other effects) because of exposure to air toxics from outdoor sources (EPA 2006b). The NATA also estimated that in most of the U.S. people have a slightly increased lifetime risk of cancer from air toxics (between 1 and 25 in a million) if they were exposed to 1999 concentrations of these pollutants over the course of their lifetimes. Comparisons of total air toxics emissions by state indicated that heavily industrialized urban areas have the highest emissions.

MSATs are a subset of these air toxics. They are compounds that are emitted by on-road vehicles and non-road equipment and that are known or suspected to cause cancer or other serious health and environmental effects (*http://epa.gov/otaq/toxics.htm*). In its 2001 rule, the EPA lists 21 compounds or compound classes as MSATs. In the more recent 2007 rule, the EPA expanded this list and highlighted eight MSATs as "key": benzene; 1,3-butadiene; formaldehyde; acetaldehyde; acrolein; polycyclic organic matter (POM); naphthalene; and diesel exhaust (DE) (EPA 2007). Mobile sources are the principal sources of exposure for only a few of these MSATs, because many are also emitted by non-mobile sources. The EPA estimates that mobile sources are responsible for about 44% of estimated outdoor air toxics emissions, almost 50% of the estimated risk of cancer from air pollution, and 74% of the estimated noncancer risk. In addition to being a broad public health issue, the effects of MSATs on health influence the development of transportation projects at the federal, state, and local levels.

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

In creating this review of the literature on MSATs, the panel elected to focus on a subset of MSATs for which mobile sources are the principal sources of human exposure and for which existing data suggested that health effects might be observed at concentrations approaching those found in ambient exposures. The panel elected not to focus on a critical review of diesel particulate matter (DPM) and organic gases, which may substantially contribute to human exposure and health risks in the overall context of MSATs, because HEI and others have recently reviewed these issues in depth. Instead, the panel has provided an expanded summary of these reviews. The seven priority MSATs selected for detailed review by the panel were acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, naphthalene, and POM. For each of these, the panel asked three questions: (1) To what extent are mobile sources an important source of exposure to this MSAT? (2) Does this MSAT affect human health? and (3) Does this MSAT affect human health at environmental concentrations? The panel then reviewed the peer-reviewed literature, reached key conclusions, and made recommendations for future research.

SUMMARY

Ambient MSATs usually occur as part of complex mixtures. They often originate from sources in addition to air. MSATs can exist in the gas phase as well as in association with PM. Moreover, after emission, some MSATs can undergo atmospheric transformations that produce other known MSATs, products of unknown chemistry and toxicity, and nontoxic degradation products. In this report, the panel focused on the sources of MSATs—motor vehicles, particularly on-road motor vehicles—for which the broadest evidence exists. Non-road sources, such as trains, planes, and marine vessels, which are important but less studied, were not considered. Substantial exposures to many MSATs also come from sources other than motor vehicles.

Source attribution suggested that the contribution of mobile sources to overall emissions is greatest for 1,3-butadiene, followed by benzene, formaldehyde, acetaldehyde, and acrolein (of the priority MSATs reviewed here). Acrolein and the other aldehydes can be emitted directly

from mobile sources or be produced by atmospheric transformation of 1,3-butadiene and other volatile organic compounds (VOCs). Mobile source contributions to overall POM exposure vary depending on the POM species; however, it is clear that mobile sources are contributors to POM associated with PM. There are insufficient data on mobile-source contributions to naphthalene exposure, but it appears likely that the contributions of mobile sources to exposures are limited. Given that substantial exposures to certain MSATs can arise from non-mobile sources (e.g., smoking, food, and indoor environments) and can occur through air, water, food, and soil, coordinated efforts of regulatory authorities beyond those specified in the Clean Air Act would be required to substantially reduce overall human exposure to these air toxic agents.

Because exposures to MSATs occur as part of complex mixtures (which can also include non-MSAT compounds), it is especially difficult to deconvolute the contributions of any given compound to human health risks. Animal toxicology studies, typically concerning exposure to single compounds, provide insights into targets and the underlying mechanisms of toxicity and dose–response relationships. But they are constrained by uncertainties about extrapolations from high to low doses and about interspecies comparisons. Because relatively high levels of exposure are found in occupational settings, studies of occupational cohorts provide opportunities for understanding associations between exposure to individual MSATs and health effects. Epidemiologic studies in occupational cohorts have accordingly served to define risks associated with exposures to several MSATs. Identifying effects in community studies, however, is more challenging, because of low ambient exposure concentrations, exposures to multiple possible toxicants, and other confounders. Nonetheless, newer studies incorporating biomarkers that directly reflect individual exposure and early biologic consequences can reduce confounding due to misclassification errors in exposure and provide important insights into possible health effects of certain MSATs. This may be especially useful in occupational studies with low exposure concentrations and, to a more limited extent, in community settings.

The panel did not undertake quantitative risk analyses for the MSATs under consideration. Nonetheless, it was evident that the risks to human health associated with exposures to various ambient MSATs are not the same. Of the seven MSATs considered in depth by the panel, benzene is of primary concern because of its established human carcinogenicity as well as recent findings suggesting that hematologic effects can be observed in humans in occupational settings at concentrations that begin to approach those found in ambient air. 1,3-Butadiene is of concern, too, because of its well-documented, well-characterized carcinogenicity in animals and because of suggestive evidence for its carcinogenicity in humans. Mobile sources are thought to be significant contributors to ambient exposures for both of these air toxics. Mobile sources are not dominant sources for exposures to the aldehydes, acetaldehyde, acrolein, and formaldehyde. Nonetheless, their genotoxicity and carcinogenicity in studies in animals (as well as human carcinogenicity in the case of formaldehyde) make them of concern. Emerging issues concerning the possible increase in aldehyde exposures with changing composition of fuels used in mobile sources also highlight the need for further consideration of these aldehydes. They are highly reactive irritants that, individually and perhaps collectively, can affect pulmonary function. Although it is anticipated that overall MSAT emissions (at least per vehicle-mile, if not total emissions) will continue to decline in the future, utilization of alternative fuels is likely to lead to altered emission profiles. Emissions of certain MSATs, such as the aldehydes, will increase while others decline. POM is a broad class of carcinogenic and noncarcinogenic compounds, some of which have high toxic potencies, and undoubtedly contributes to the overall hazard associated with diesel exhaust. Naphthalene is an irritant and carcinogen in the nasal tract of rodents, but mobile sources are not the principal sources of exposures in humans.

It is important to read the statements in this report about the relative importance of MSATs in the context of the fact that DPM and organic gases (other than POM), especially from older engines, were not included in the panel's critical review yet contribute in substantive ways to mobile-source air pollution and its health effects.

To help the panel in its evaluations of each MSAT, the panel members considered three key questions: (1) To what extent are mobile sources an important source of exposure to this MSAT? (2) Does this MSAT affect human health? and (3) Does this MSAT affect human health at environmental concentrations? The panel then reviewed the peer-reviewed literature to answer these questions, reached conclusions, and made key recommendations. The aldehydes are discussed both individually and as a group.

BENZENE

1. To what extent are mobile sources an important source of exposure to benzene?

There are more air-monitoring data for benzene than for any other MSAT considered in this report. The highest concentrations have been found at urban roadside and urban in-vehicle locations. Mobile sources are an important component of overall exposure to benzene. Consistent

with this observation, levels of personal exposure to benzene appeared to be in the same range as those found in ambient settings.

2. Does benzene affect human health?

There is clear and widely accepted evidence from a variety of occupational epidemiologic studies that exposure to benzene increased the risk of acute myeloid leukemia; there is less certainty about other lymphohematopoietic cancers. Extended follow-up of an existing cohort further confirmed this association. Moreover, data from several new cohorts (petroleum workers and gas and electric utility workers) demonstrated increased leukemia risks at lower estimated exposures than previously observed.

3. Does benzene affect human health at environmental concentrations?

Some studies have indicated that an increased risk of childhood leukemia was associated with proximity to petrochemical works and gasoline stations, although identifying such effects in community studies is challenging. Studies have yielded mixed results with regard to associations between traffic and childhood leukemia. There has been substantial progress in the development of biomarkers for benzene. Studies using biomarkers have indicated a relationship between benzene concentrations in urine and the presence of cytogenetic abnormalities in community studies (e.g., in street vendors, gasoline-service-station attendants, and children attending schools near major roads). Variations in the enzymes involved in the metabolism of benzene have been identified and linked to increased sensitivity to benzene hematotoxicity. Several newer studies have revealed effects on hematologic indices at lower exposure concentrations than those reported before. However, there remains considerable uncertainty as to the lowest concentration that might be associated with adverse hematologic effects.

Key recommendations for benzene are the following:

- Continue the development of sensitive analytical techniques for measuring biomarkers of exposure, effect, and susceptibility.
- Validate the sensitive biomarkers used as predictors of adverse health effects in workers exposed to benzene.
- Use the sensitive, validated biomarkers to better characterize the shape of the benzene exposure–response curve at low ambient concentrations.

1,3-BUTADIENE

1. To what extent are mobile sources an important source of exposure to 1,3-butadiene?

Mobile sources are the most important contributors to 1,3-butadiene concentrations in ambient air in most locales. Because of 1,3-butadiene's short atmospheric lifetime, concentrations are highest near sources. However, its high reactivity results in the production of other MSATs, such as formaldehyde, acetaldehyde, and acrolein. Several recent studies indicated that indoor concentrations might be higher than outdoor ones—an effect not entirely accounted for by environmental tobacco smoke (a known source of indoor exposure). Thus, there might be other important sources of indoor exposure.

2. Does 1,3-butadiene affect human health?

The human evidence, though limited, is consistent with the possibility that 1,3-butadiene causes lymphohematopoietic cancers in high-exposure occupational settings. This is plausible, moreover, because there is good evidence that certain metabolites of 1,3-butadiene cause cancer and adverse reproductive effects in mice. In humans, however, the metabolism of 1,3-butadiene appears to be more like that of rats, a less susceptible species. At high exposure concentrations, such as those once found in the U.S. in certain industries, 1,3-butadiene is likely to be a human health hazard because of its carcinogenicity. The confounding of 1,3-butadiene's health effects by coexposure to styrene and dimethyldithiocarbamate cannot be ruled out. But on epidemiologic and toxicologic grounds, 1,3-butadiene seems likely to be the active agent. Biomarkers of exposure to 1,3-butadiene have been developed and validated. However, biomarkers of effect were identified inconsistently in exposed workers and are not correlated with biomarkers of exposure.

3. Does 1,3-butadiene affect human health at environmental concentrations?

In community studies, there is no direct evidence of health effects of exposure to 1,3-butadiene at ambient concentrations.

Key recommendations for 1,3-butadiene are the following:

- Identify the sources contributing to indoor concentrations of 1,3-butadiene and personal exposures to 1,3-butadiene.
- Undertake systematic analysis of trends in ambient concentrations of 1,3-butadiene at U.S. monitoring sites, especially high-traffic sites.
- Conduct well-controlled studies to understand more about species-specific differences in 1,3-butadiene metabolism.
- Pursue the development of specific, sensitive 1,3-butadiene biomarkers for use in community studies, recognizing that exposures in these populations come from multiple sources.

ACETALDEHYDE

1. To what extent are mobile sources an important source of exposure to acetaldehyde?

Mobile sources are a significant, but not the principal, source of exposure to acetaldehyde. Concentrations tend to be lowest outdoors; they are 2 to 10 times higher indoors and in vehicles. Acetaldehyde is also present in many foods.

2. Does acetaldehyde affect human health?

Like all aldehydes, acetaldehyde is chemically reactive. It causes irritation to the eyes, skin, and respiratory tract and induces cellular inflammation. Although acetaldehyde is a carcinogen in rodents, the data on the possibility of its carcinogenicity in humans are inadequate. Data on respiratory effects are limited mainly to small clinical studies of asthmatic patients that used exposure challenges with aerosols of acetaldehyde. The effects of exposures to multiple aldehydes, all of which can be irritants to the respiratory tract, are not known.

3. Does acetaldehyde affect human health at environmental concentrations?

There has been only one epidemiologic study of environmental exposure to acetaldehyde. This was a small study of children with asthma, which was unable to distinguish the effect of acetaldehyde from that of other pollutants. Inasmuch as indoor sources of acetaldehyde account for most personal exposure and ambient concentrations appear to be far below those producing irritation, it is doubtful that acetaldehyde in ambient air at concentrations observed in recent years has adversely affected human health. It is likely, however, that acetaldehyde emissions will increase with current requirements for increased use of ethanol, although the exact effect on future concentrations is not known.

Key recommendations for acetaldehyde are the following:

- Better characterize the sources of, and factors contributing to, higher acetaldehyde concentrations in urban vehicles, homes, schools, and personal exposures.
- Examine potentially sensitive subpopulations (e.g., asthmatic children), even though current acetaldehyde concentrations are lower than those causing health effects in the general population.

ACROLEIN

1. To what extent are mobile sources an important source of exposure to acrolein?

Because of the limited number of studies of acrolein, its highly reactive nature, and the limitations of sampling methods, the available environmental data for acrolein might not be sufficient to allow an assessment of ambient, indoor, or personal exposures. Additional limitations include the number and type of environments sampled, the number of samples collected, the lack of accounting for the presence or absence of sources, the absence of data on geographic and seasonal variability, the representativeness of residences and populations sampled, and the lack of sampling for sensitive or at-risk populations. Limited urban roadside and in-vehicle data do not suggest elevated exposures. Surprisingly low concentrations were observed in tunnel studies—a finding at odds with EPA estimates that overall contributions of acrolein from mobile sources are considerably higher. Substantial mobile-source contributions to exposure might result from the formation of acrolein from 1,3-butadiene in the air. Environmental tobacco smoke is a major indoor source of acrolein.

2. Does acrolein affect human health?

Acrolein is very irritating to the respiratory tract in humans and animals. Studies showed that chronic inhalation resulted in inflammation. Although acrolein might damage DNA, several animal bioassays have not provided substantive evidence of carcinogenicity. Because of its high chemical reactivity, acrolein is unlikely to be distributed throughout the body.

3. Does acrolein affect human health at environmental concentrations?

There are insufficient data to assess the effect of ambient exposures to acrolein on human health. However, it should be noted that measured environmental concentrations and personal exposures were only somewhat lower than concentrations shown to cause irritation.

A key recommendation for acrolein is the following:

- Develop and validate improved exposure monitors for acrolein, and collect more data on exposure.

FORMALDEHYDE

1. To what extent are mobile sources an important source of exposure to formaldehyde?

Indoor sources of formaldehyde appear to be the principal source of exposures. Indoor concentrations are three to five times higher than outdoor concentrations. However, mobile sources are an important source of ambient concentrations. The highest ambient concentrations were found at urban roadside sites. It appears that summer photochemical activity contributes more formaldehyde to ambient air than do direct vehicle emissions, as strong seasonal effects are observed. It is important to note that in Brazil, ambient formaldehyde concentrations have increased fourfold over

the past few years, following the expansion of the fleet of vehicles using ethanol fuels and compressed natural gas.

2. Does formaldehyde affect human health?

Like the other aldehydes, formaldehyde is an irritant to the eyes, skin, and respiratory tract in humans. It has recently been classified as a human carcinogen, in part because of evidence of nasopharyngeal cancer at concentrations historically encountered in industrial settings. The underlying mechanisms of this carcinogenicity are not fully understood but include DNA–protein crosslinking and increased cell proliferation.

3. Does formaldehyde affect human health at environmental concentrations?

There is limited and inconclusive evidence that indoor exposures to formaldehyde increase the occurrence of asthma in children. There is no evidence about health effects of outdoor exposures to ambient concentrations of formaldehyde, but given the likelihood of the expanded use of alternative fuels in the U.S. and the probable resulting increases in formaldehyde emissions, some attention should be paid to possible effects of increased emissions from mobile sources in the future.

A key recommendation for formaldehyde is the following:

- Identify formaldehyde exposure pathways and patterns of personal exposure to formaldehyde in cities and rural areas, including diurnal and seasonal variations.

KEY RECOMMENDATIONS FOR ALDEHYDES IN GENERAL

Key recommendations for aldehydes in general are the following:

- Continue to update the NATA models, critically evaluating and comparing them to actual measurements, to improve their usefulness in predicting the effects of increased use of alcohols and other alternative fuels.
- Establish a monitoring network capable of tracking long-term aldehyde concentrations.
- Elucidate the mechanism of tumor induction by aldehydes, particularly in relation to DNA–protein crosslinks, and pursue the development of biomarkers of exposure.
- Focus more on noncancer endpoints such as cough, irritation, and asthma in experimental and human studies, particularly in relation to long-term, low-dose exposures to aldehydes.
- Consider the combinatorial effect of exposures to multiple aldehydes on human health: Are the effects additive or synergistic?
- Identify and assess susceptible subpopulations.

POM

1. To what extent are mobile sources an important source of exposure to POM?

POM is a term commonly used to describe a mixture of hundreds of chemicals, including PAHs, their oxygenated products, and their nitrogen analogs. Some POM species are found in the gas phase, some in the particle phase, and some in both. Different measurement studies have looked at different POM mixtures; there is no standard exposure- or health-based definition of POM. There is a lack of consistency in PAH groupings and indicator compounds for POM. Mobile sources might be significant contributors to ambient concentrations of POM in urban settings. However, other combustion processes, such as wood burning, cigarette smoking, road paving, and roof tarring, as well as charbroiling foods, might lead to substantial additional exposures. Diesel vehicles emit more PAHs than gasoline-fueled vehicles; "cold starts" account for up to 50% of their PAH emissions.

2. Does POM affect human health?

A few PAH components of POM are potent animal carcinogens. Some of these (e.g., benzo[*a*]pyrene) are classified as human carcinogens. At high occupational exposures, there is sufficient evidence for an increased risk of lung cancer in coke-oven workers and possibly in asphalt-industry workers. An association between lung cancer and the use of "smoky" coal in China has also been observed. Health effects have been reported in highly polluted industrial sites for reproductive (lower birth weights), respiratory (obstructive lung disease), cardiovascular (ischemic heart disease), and immune (enhanced allergic inflammation) systems, but the linkages to POM are not firm.

3. Does POM affect human health at environmental concentrations?

While there is evidence that air pollution containing PAHs is genotoxic and has effects on reproductive health, there is no direct evidence from community studies that POM specifically, at ambient exposure concentrations, causes health effects. Because community studies involve exposures to complex mixtures, they have limited ability to address the effects of POM alone. Additional identification of relevant biomarkers of exposure is needed.

Key recommendations for POM are the following:

- Identify a core set of high-priority POM for further studies and identify POM indicator compounds to facilitate consistent research approaches.
- Determine ambient concentrations of PAH atmospheric transformation products, and conduct toxicology studies of these products and their mixtures.
- Identify "hot spots" of human exposure.

NAPHTHALENE

1. To what extent are mobile sources an important source of exposure to naphthalene?

Naphthalene is the most abundant polycyclic aromatic hydrocarbon (PAH) found in ambient air. Mobile sources (from both fuel combustion and evaporation) are an important, but not the primary, source of naphthalene. There is limited evidence to suggest that concentrations of naphthalene are higher at roadside sites and in vehicles. Indoor concentrations are typically 5 to 10 times higher than ambient concentrations and may be derived from environmental tobacco smoke and moth repellents. However, trends toward the reduction of these indoor sources might lead to the increased importance of outdoor sources as determinants of exposure.

2. Does naphthalene affect human health?

There is evidence in rodents that exposure to naphthalene leads to inflammation of the nasal tract and tumors of the nasal epithelium and olfactory epithelium. However, there are no data on carcinogenicity in humans. Several case reports, which were deficient in quantitative exposure assessments, suggest that single or repeated exposures can cause adverse effects in blood cells, such as hemolysis and hemolytic anemia.

3. Does naphthalene affect human health at environmental concentrations?

There are no epidemiologic or other studies that assess the health effects of exposure to naphthalene at ambient concentrations.

Key recommendations for naphthalene are the following:

- Identify naphthalene exposure pathways and patterns of personal exposure to naphthalene and its atmospheric transformation products.
- Undertake comparative studies of naphthalene's toxicokinetics in various species in order to decrease the uncertainty in extrapolating data across species.
- Undertake studies of the mechanisms of tumor induction by naphthalene and its atmospheric transformation products, including the role of direct genotoxicity and cytotoxicity by reactive oxygen species.

RESEARCH GAPS AND OVERARCHING RECOMMENDATIONS FOR FUTURE RESEARCH

Several common themes emerged when the panel considered the gaps in current research on exposure to MSATs and their health effects. It is evident that exposure to many MSATs comes from sources other than vehicles. Indeed, mobile sources are the primary sources of exposure for only a few of the 21 MSATs listed by the EPA in the its 2001 mobile source rule (EPA 2001b). There is a clear need for better attribution of the sources of these MSATs by, for example, measuring concentrations at roadsides and in vehicles. There is also a need for better attribution of the other sources of MSATs, as well as better characterization of concentrations in microenvironments, such as homes and workplaces, and of factors that affect these concentrations.

In addition, there is a need for better characterization of the contributions of outdoor concentrations to indoor concentrations and personal exposures. The atmospheric transformation products of some MSATs and the factors regulating their production need to be identified and characterized.

Efforts should also be made to collect existing MSAT data from local and state monitoring networks into useable, readily accessible databases to support further analyses.

Improved analytical-chemistry methodologies are needed to better understand exposure measures. For example, measured concentrations of acrolein appear to be lower than the actual ambient concentrations. This discrepancy might reflect technical limitations of conventional measurement techniques. There is a strong need to compile spatial and trend data on MSATs in the U.S. Very limited information on these topics is available in the peer-reviewed literature.

There is also a need to continue improving the NATA modeling estimates of exposures to MSATs. While in many instances the NATA estimates were similar to exposure concentrations reported in the literature, there were some instances, particularly among aldehydes, in which the NATA modeling appeared to substantially underestimate measured exposure concentrations. Improved modeling and better characterization of spatial and temporal trends are vital to assessing the effect of regulatory changes on the emissions of MSATs. They are also needed for the assessment of anticipated changes in MSAT emissions arising from increased utilization of alternative fuels. Indeed, the

widespread introduction of ethanol and compressed natural gas as vehicle fuels in some regions of the world that have less advanced engine and emission control technologies has already led to increases in ambient concentrations of aldehydes in these regions. Whether or not the same increases will be seen in the U.S. as alternative-fuel use increases is unknown but should be documented.

The risk of cancer has dominated health concerns about the MSATs. The panel concluded the following:

- Quantitative estimates of the relationship between cancer risk and exposure concentrations have been derived largely from studies of occupational cohorts in which exposure to high concentrations of one or more MSATs could be documented. Data from these occupational cohorts might be of limited utility in the evaluation of health effects at ambient concentrations because of the magnitude of the exposure differences. At this point, the panel does not recommend initiating new cohort studies in areas where exposures come from ambient settings to improve quantitative estimates of the cancer-causing potential of MSATs. Moreover, the cost, methodologic difficulties, and data challenges make it unlikely that there are feasible epidemiologic approaches capable of addressing the risks associated with ambient exposures on a compound-by-compound basis. Substantial improvements in the analytical sensitivity and specificity of biomarkers for key MSATs might provide firmer linkages between exposures and health effects; however, it will be important to validate these biomarkers first. Epidemiologic studies coupled with the use of such biomarkers will be of value in investigating the health effects of mobile-source emissions as a whole—for example, looking at populations living or working in proximity to roadways. Research opportunities for use of biomarkers might also arise in connection with emerging "hot spots."
- Some quantitative cancer-potency estimates for MSATs have been derived from animal models. However, extrapolating from these results to humans remains troublesome. A better understanding of the toxicokinetics (including biotransformation pathways) of MSATs in both animals and humans, particularly at ambient concentrations, might provide clearer perspectives on the similarities and dissimilarities between animal and human metabolism. However, the issue of potential species differences in toxicodynamics will remain.
- Animal studies and especially epidemiologic studies have tended not to focus on noncancer endpoints in investigating the toxicity of MSATs. It remains an open question whether developmental, reproductive, and neurologic effects result from mobile-source exposures and to what extent the MSAT aldehydes, singly and collectively, contribute to pulmonary irritation, cough, and asthma. Subpopulations susceptible to the health effects of MSATs also need to be better defined.

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APPENDIX A. NONPRIORITY MOBILE-SOURCE AIR TOXICS

As described earlier in this report, the Air Toxics Review Panel focused on the 21 mobile-source air toxics (MSATs) listed by the EPA in its 2001 rule (EPA 2001b): acetaldehyde; acrolein; arsenic compounds; benzene; 1,3-butadiene; chromium compounds; diesel exhaust (particulate matter and organic compounds); dioxin and furan compounds; ethylbenzene; formaldehyde; *n*-hexane; lead compounds; manganese compounds; mercury compounds; methyl *tert*-butyl ether (MTBE); naphthalene; nickel compounds; polycyclic organic matter (POM); styrene; toluene; and xylene. Criteria related to exposure and the contribution of mobile sources were then applied to narrow down this list to seven MSATs that the panel critically reviewed. These priority MSATs—acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, naphthalene, and POM—are discussed in detail in the body of this report, which also includes a summary of studies of diesel exhaust.

The panel used three principal criteria for the exclusion of an MSAT from the priority list: (1) exposure to concentrations of the MSAT was low, both in absolute terms and as a proportion derived from mobile sources (e.g., for arsenic compounds, chromium compounds, dioxins and furans, *n*-hexane, manganese compounds, mercury compounds, and nickel compounds); (2) trends indicated that substantial declines in exposure to the MSAT could be expected in the years ahead (e.g., for lead and MTBE); and (3) concentrations of the MSAT in ambient air were low relative to indices of toxicity (e.g., for ethylbenzene, styrene, toluene, and xylene).

Brief summaries of exposure and health information for the following nonpriority MSATs are presented in this appendix:

- arsenic compounds
- chromium compounds
- dioxin and furan compounds
- ethylbenzene
- *n*-hexane
- lead compounds
- manganese compounds
- mercury compounds
- MTBE
- nickel compounds
- styrene
- toluene
- xylene

ARSENIC COMPOUNDS

INTRODUCTION

Arsenic (As) is a naturally occurring semimetallic element found in soil and in many kinds of rock, especially in minerals and ores that contain copper or lead (Agency for Toxic Substances and Disease Registry [ATSDR] 2005g). In humans, food is the principal source of arsenic exposure (EPA 2000h). However, drinking water can also be a significant source of exposure if naturally occurring levels of arsenic are high. Exposure to arsenic by inhalation is generally less important. Arsenic can be released into ambient air by the combustion of fuel in power plants or vehicles. It can exist in a number of different valence states and in inorganic and organic forms. Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate (ATSDR 2005g). They also cannot be detected by odor or taste. The common forms of inorganic arsenic are arsenite (As[III]) and arsenate (As[V]). An organic form of arsenic known as arsenobetaine is commonly found in fish and shellfish. Organic arsenic is substantially less toxic than inorganic arsenic (ATSDR 2005g). Inorganic arsenic has an atomic weight of 74.92 g/mol. Its vapor pressure is 7.5×10^{-3} mm Hg at 280°C, and 1 ppm of inorganic arsenic in air is equal to 3.06 mg/m^3 (EPA 2000h; ATSDR 2005g).

Arsine is an inorganic gaseous form of arsenic that is colorless, has a garlic-like odor, and is highly toxic to animals and humans (EPA 2000h). Within a few hours of exposure in humans, headaches, vomiting, and abdominal pain can

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

result (EPA 2000h). The chemical formula for arsine gas is AsH_3. It has a molecular weight of 77.95 g/mol, and 1 ppm is equal to 3.19 mg/m^3 (EPA 2000h).

EXPOSURE

Arsenic in ambient air is usually a mixture of particulate arsenite and arsenate (ATSDR 2005g). Mean concentrations in ambient air in the U.S. have been reported to range from less than 1 to 3 ng/m^3 in remote areas and from 20 to 30 ng/m^3 in urban areas (ATSDR 2005g). Indoor concentrations of arsenic might be similar. Indoor concentrations ranging from 3.4 to 22.3 ng/m^3, for example, were measured as part of the U.S. National Human Exposure Assessment Survey (NHEAS) in Arizona (ATSDR 2005g). Because arsenic occurs naturally in the environment and is not broken down, everyone is exposed to some amount of it through ingestion of food and drinking water and by inhalation (ATSDR 2005g). Arsenic can enter the atmosphere during the mining of ores for metals and smelting. It can also enter the atmosphere during volcanic eruptions. In addition, small amounts of arsenic can be released into air from coal-fired power plants and incinerators, because the materials burned often contain some arsenic. Until recently, the most common use of arsenic was for the production of wood preservatives. In 2003, the wood-preservative industry voluntarily began a phase-out of this preservative, known as chromated copper arsenic, for residential uses, such as play structures, decks, and fencing. However, existing uses remain and the treated wood poses a potential health threat in the form of sawdust or fumes when burned. In the past, inorganic arsenic compounds were predominantly used as pesticides. Although these compounds are prohibited for use in agriculture today, soil contamination remains and represents a potential source of exposure via ingestion of soil or inhalation of dust. Table A.1 is a summary of exposure data for arsenic.

TOXICITY AND HEALTH

Metabolism

In humans, most of the arsenic that enters the body is excreted in the urine within a few days of exposure. It is excreted in urine whether exposure occurs by way of inhalation or ingestion (skin exposure is not usually significant). Inorganic arsenic can be excreted in urine directly or be converted to less toxic, organic forms of arsenic that are excreted more rapidly (National Library of Medicine 2003; ATSDR 2005g).

Toxicity and Health Criteria

Summaries of the toxicity of chronic arsenic exposure and regulatory criteria are presented in Table A.2.

Table A.1. Summary of Exposure Data for Arsenic[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (ng/m^3)	Citations
Urban	3,300	1.0–2.4	EPA 2004d; California Air Resources Board 2003; Riediker et al. 2003; Kinney et al. 2002; EPA 2002d; South Coast Air Quality Management District 2000
In-vehicle	50	1.5	Riediker et al. 2003
Roadside	50	1.0	Riediker et al. 2003
Tunnel	6	1.2	Chellam et al. 2005
Rural	—	0.058	EPA 2002d
Urban–Suburban–Rural Combined	15,000	1.7–2.0	EPA 2004a,d; Pratt et al. 2000

[a] Taken from Appendix Table B.5.

Table A.2. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Arsenic[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	Not available			EPA 1998e
California REL	0.03 μg/m^3	LOAEL (HEC) = 3 μg/m^3 (uncertainty factor 1,000)	Reduction in fetal weight; increased incidences of intrauterine growth retardation and skeletal malformations in mice	California EPA 2000a; Nagymajtenyi et al. 1985
Cancer				
EPA cancer classification	Inorganic arsenic Group A; "known human carcinogen"	4.3×10^{-3} per μg/m^3		EPA 1998e; Brown and Chu 1983a,b,c Lee-Feldstein 1983; Higgins 1982; Enterline and Marsh 1982
IARC classification	Group 1; "carcinogenic to humans"			IARC 2004b
NTP *Report on Carcinogens*	Inorganic arsenic compounds, "known to be human carcinogens"			NTP 2005
California EPA	Inorganic arsenic	3.3×10^{-3} per μg/m^3	Human occupational exposure; lung tumor incidence	California EPA 2005c; Enterline et al. 1987

[a] Taken from Appendix Tables C.1—C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; LOAEL = lowest observed adverse effect level; HEC = human equivalent concentration.

CHROMIUM COMPOUNDS

INTRODUCTION

Chromium (Cr) is a naturally occurring transition metal element found in rocks, soil, animals, plants, and volcanic dusts and gases (ATSDR 2000a). It can exist in several valence states, ranging from Cr(−II) to Cr(+VI) (EPA 2000p). Chromium in the environment is primarily present in the Cr(III) and Cr(IV) valence states. In its biologically active trivalent form, Cr(III), it is an essential nutrient and is involved in glucose, fat, and protein metabolism (EPA 1998g). The hexavalent form, Cr(VI), is considerably more toxic than other valence states of Cr. However, there are several mechanisms in the human body for converting Cr(VI) to Cr(III). Metallic chromium, Cr(0), is less common.

Cr(VI) in the atmosphere results from chromate chemicals used as rust inhibitors and emitted as mists in cooling towers, from particulate matter emitted during the manufacture and use of metal chromates, and from chromic-acid mist in the plating industry (ATSDR 2000a; National Library of Medicine 2005a). Cr(VI) tends to react in the atmosphere with other air contaminants to form Cr(III) or to settle with dust (ATSDR 2000a). Chromium persists longer in water and soil than in air. Chromium compounds, in either the Cr(III) or Cr(VI) forms, are used for chrome plating, in the dye and pigment industry, as leather and wood preservatives, and as toner in copying machines (ATSDR 2000a). Chromium emissions from coal and oil combustion and steel production consist principally of Cr(III) (ATSDR 2000a).

EXPOSURE

Atmospheric chromium concentrations are generally less than 10 ng/m^3 in rural areas and 10 to 30 ng/m^3 in urban areas; indoor concentrations are generally half of the ambient concentrations (ATSDR 2000a). Although wear in asbestos brake linings that contain chromium accounts for a small amount of the chromium in ambient air, vehicles are not the source of most atmospheric chromium (ATSDR 2000a). Chromium in the atmosphere is generally in the form of Cr(III) (EPA 2000p). Table A.3 is a summary of exposure data on chromium.

Because of the high boiling point of chromium, it is usually present in the solid state. Chromium in air is therefore usually found bound to particles or dissolved in droplets.

TOXICITY AND HEALTH

Metabolism

Humans can metabolize inhaled Cr(VI) to Cr(III). Reduction occurs in the lung, liver, stomach, and red blood cells (ATSDR 2000a). Many of the laboratory tests used to measure

Table A.3. Summary of Exposure Data for Chromium[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (ng/m^3)	Citations
Urban	3,400	0.0–6.5	EPA 2004d; California Air Resources Board 2003; Riediker et al. 2003; Kinney et al. 2002; EPA 2002d; South Coast Air Quality Management District 2000; Rodes et al. 1998
In-vehicle	110	1.9–40	Rodes et al. 1998
Roadside	90	1.1–30	Riediker et al. 2003; Rodes et al. 1998
Rural	—	0.65	EPA 2002d
Urban–Suburban–Rural Combined	14,000	1.8	EPA 2004a

[a] Taken from Appendix Table B.8.

chromium in the body cannot differentiate between the valence states (ATSDR 2000a).

The toxicity of chromium depends on the oxidation state of the chromium atom; Cr(VI) is the most toxic form.

Toxicity and Health Criteria

Summaries of the toxicity of chronic chromium exposure and regulatory criteria are presented in Table A.4.

Table A.4. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Chromium[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	Cr(III): RfD 1.5 mg/kg-day Cr(VI): aerosols RfC = 8×10^{-3} µg/m^3; particulates RfC = 0.1 µg/m^3	Cr(VI): aerosols: LOAEL (ADJ) = 0.714 µg/m^3 (uncertainty 90) Cr(VI): particulates: BMD (ADJ) = 34 µg/m^3 (uncertainty 300)	Nasal septum atrophy in occupationally exposed humans; Lactate dehydrogenase in bronchoalveolar lavage fluid in rats	EPA 1998f; Lindberg and Hedenstierna 1983; Glaser et al. 1990; Malsch et al. 1994
California REL	0.2 µg/m^3 (excluding chromium trioxide)	Cr(III); LOAEL (HEC) = 0.68 µg/m^3 (uncertainty 300) Cr(VI): LOAEL (HEC) = 24.5 µg/m^3 (uncertainty 100)	Nasal atrophy, nasal mucosal ulcerations, nasal septal perforations, transient pulmonary function changes in occupationally exposed humans; bronchoalveolar hyperplasia in rats	California EPA 2000b; Lindberg and Hedenstierna 1983; Glaser et al. 1990
Cancer				
EPA cancer classification	Cr(VI): Group A; "known human carcinogen"	1.2×10^{-2} per µg/m^3		Crump et al. 2003; EPA 1998f,g
IARC classification	Cr(VI): Group 1; "carcinogenic to humans" Cr(II) and Metallic Cr: Group 3; "not classifiable as to their carcinogenicity to humans"			IARC 1990
NTP *Report on Carcinogens*	Cr(VI): "Known to be human carcinogens"			NTP 2005
California EPA		Cr(VI): 0.15 µg/m^3		California EPA 2005c Mancuso 1975

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; RfD = reference dose; LOAEL = lowest observed adverse effect level; ADJ = adjusted; BMD = benchmark dose; HEC = human equivalent concentration.

DIOXIN AND FURAN COMPOUNDS

INTRODUCTION

Chlorinated dioxins and dibenzofurans are a family of compounds derived from dibenzo-*p*-dioxin and dibenzofuran (Figure A.1). The basic structure of dioxins consists of two benzene rings joined to each other by two oxygen atoms, with chlorine substitutions on the benzene rings. The basic structure of dibenzofurans consists of two benzene rings joined to each other by a single oxygen atom and a carbon–carbon bond. Chlorinated dibenzofurans have chlorine substitutions on the benzene rings. There are 75 dioxins and 135 dibenzofurans, differing from each other in the number and location of their chlorine atoms (ASTDR 1998). 2,3,7,8-Tetra-chlorodibenzo-*p*-dioxin (TCDD) is the most toxic and widely studied compound in the family (ATSDR 1998).

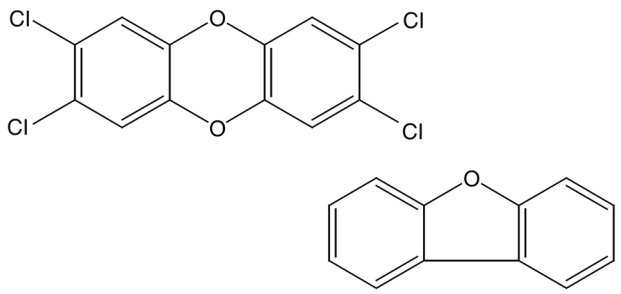

Figure A.1. Structure of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and dibenzofuran.

Dioxins and dibenzofurans are a product of incomplete combustion and are ubiquitous in the environment (ATSDR 1998). They are colorless, odorless solids (EPA 2000l). Dioxins and dibenzofurans are produced in trace amounts from the combustion of fossil fuels, including motor-vehicle fuels (ATSDR 1998). The EPA estimates that 80% of dioxin emissions originate from trash-burn barrels, land application of sewage sludge, coal-fired utilities, residential wood burning, metal smelting, and diesel trucks (ATSDR 1998; EPA 2000l). Dioxins can also be found in smoke from cigarettes and in herbicides and pesticides (ATSDR 1998). Notable noncombustion sources of dioxins include the bleaching of wood fibers in the manufacture of paper (ATSDR 1998). Some evidence suggests that natural combustion processes, such as forest fires and volcanic activity, might also be sources of dioxins and dibenzofurans, though to a much more limited extent (ATSDR 1998).

The vapor pressure of TCDD is 7.4×10^{-10} mm Hg at 25°C (EPA 2000l). At 1 atmosphere and 25°C, 1 ppm of TCDD is equal to 13.2 mg/m^3 (EPA 2000l).

EXPOSURE

Dioxins and dibenzofurans are often measured in toxic equivalence quotient (TEQ) units, a scale that expresses the toxicity of a given mixture of dioxin-like compounds (including furans and polychlorinated biphenyls) in terms of the toxicity of TCDD. Dioxins and dibenzofurans are generally found at very low concentrations in urban air, and their detection is often limited by analytical methods. Typical urban air concentrations range from less than 0.005 to 0.120 pg/m^3 (1 pg = 10^{-6} µg) (National Library of Medicine 2004). A general survey of the literature found that mean concentrations of dioxins and dibenzofurans in urban air were very low, ranging from 0.013 to 0.081 pg/m^3 TEQ (Table A.5).

TOXICITY AND HEALTH

Metabolism

Dioxins and dibenzofurans are metabolized primarily by the cytochrome-P450 family of enzymes—enzymes that are also involved in the metabolism of other air toxics, such as 1,3-butadiene, benzene, and polycyclic organic matter (POM). Dioxins and dibenzofurans are slowly metabolized in the liver to a variety of polar metabolites, which are then excreted in the bile and the urine. The major metabolite of TCDD is 1,3,7,8-tetrachloro-2-hydroxydibenzo-*p*-dioxin. Dihydroxy and monoethoxy derivatives are also formed. In addition to being metabolized by P450 enzymes, dioxins and dibenzofurans are potent inducers of these enzymes. They bind to the aryl hydrocarbon hydroxylase receptor and cause induction of the enzymes even at very low concentrations (National Library of Medicine 2004; International Agency for Research on Cancer [IARC] 1997c). Rats exposed to a series of four 20-µg/kg doses of TCDD, for example, exhibited two- to threefold increases in concentrations of P450 enzymes, resulting in increased metabolism of other compounds by this system (National Library of Medicine 2004).

Toxicity and Health Criteria

Summaries of the toxicity of chronic exposure to dioxins and furans, as well as regulatory criteria, are presented in Table A.6.

Table A.5. Summary of Exposure Data for Dioxins and Furans[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (pg/m^3)	Citations
Urban	135	0.013–0.081	California Air Resources Board 2004a,b; EPA 2003d; Hunt et al. 1997
Tunnel	15	0.039–0.076	Gertler et al. 2002; Gertler et al. 1998
Suburban	8	0.016	Cleverly et al. 2002

[a] Taken from Appendix Table B.9.

Table A.6. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Chlorinated Dibenzodioxins and Dibenzofurans[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency/ Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	Not calculated because RfC < average exposure of U.S. population; MOE ranges from < 1 to 4			EPA 2003d
California REL	0.00004 $\mu g/m^3$ (40 pg/m^3)		Alimentary system (liver); reproductive system; development; endocrine system; respiratory system; hematopoietic system	California EPA 2005d; Kociba et al. 1978
Cancer				
EPA cancer classification	Group B2; "Likely to be carcinogenic to humans"	Upper bound slope factor: 1×10^{-3} per pg per TEQ/kg-day	Carcinogenicity (all cancer sites combined in humans)	EPA 2003d; Steenland et al. 1999; Becher et al. 1998
IARC classification	TCDD: Group 1; "carcinogenic to humans" Assorted other chlorinated dibenzo-*p*-dioxins: Group 3; "not classifiable as to their carcinogenicity to humans" Chlorinated dibenzofurans: Group 3; "not classifiable as to their carcinogenicity to humans"			IARC 1997c
NTP *Report on Carcinogens*	TCDD: "known to be a human carcinogen"			NTP 2005
California EPA		38 per $\mu g/m^3$		California EPA 2005c

[a] Taken from Appendix Tables C.1—C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; MOE = margin of exposure based on NOAEL or BMD; TCDD = tetrachlorodibenzo-*p*-dioxin; BMD = benchmark dose; TEQ = toxic equivalence.

ETHYLBENZENE

INTRODUCTION

Ethylbenzene (CAS Registry Number 100-41-4) (Figure A.2) is a volatile aromatic hydrocarbon that exists at room temperature as a clear, flammable liquid and smells much like gasoline. It is used primarily in the production of styrene but can also be used as a solvent, in fuels, and to make other chemicals (ATSDR 1999b; EPA 2002f). At 1 atmosphere and 25°C, 1 ppm of ethylbenzene is equal to 4.34 mg/m^3 (EPA 2002f).

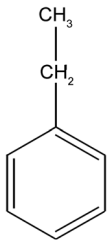

Figure A.2. Structure of ethylbenzene.

EXPOSURE

For the general population, the principal indoor sources of exposure to ethylbenzene are consumer products, carpet glues, varnishes, paints, and tobacco smoke (ATSDR 1999b). Outdoor sources include gasoline (2% ethylbenzene by weight is added to gasoline as an antiknock agent), automobile emissions, pesticides, and hot asphalt.

In indoor air, ethylbenzene is typically present at low concentrations (median, 4.3 µg/m^3) (ATSDR 1999b). In ambient air, it is widely present at low concentrations in urban, suburban, and rural locations. The highest concentrations are generally found near gasoline stations, tunnels, highways, and parking lots. Concentrations tend to be much lower in rural areas than in urban areas, where vehicle emissions are thought to be a major contributor (ATSDR 1999b). Ethylbenzene concentrations range from below detection limits in rural areas to approximately 1 µg/m^3 in urban settings and up to 100 µg/m^3 on busy urban streets (ATSDR 1999b). A general survey of the literature found mean urban measurements in the range of 0.6 to 2 µg/m^3, with higher concentrations at urban roadside (0.6 to 5.6 µg/m^3) and in-vehicle (0.6 to 9.7 µg/m^3) locations (Table A.7).

Table A.7. Summary of Exposure Data for Ethylbenzene[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (µg/m^3)	Citations
Urban	800	0.1–1.9	Adgate et al. 2004a; Sexton et al. 2004; Payne-Sturges et al. 2004; Kinney et al. 2002; California Air Resources Board 2003; Riediker et al. 2003; Mohamed et al. 2002; South Coast Air Quality Management District 2000; Rodes et al. 1998; Zielinska et al. 1998
Roadside	90	0.6–5.6	Riediker et al. 2003; Rodes et al. 1998
Urban–Suburban			
In-vehicle	220	0.6–9.7	Fitz et al 2003; Fedoruk and Kerger 2003; Riediker et al. 2003; Batterman et al. 2002; Rodes et al. 1998
Urban–Suburban–Rural Combined	117,000	0.54–1.0	EPA 2004a,d; Pratt et al. 2000; Zielinska et al. 1998

[a] Taken from Appendix Table B.11.

TOXICITY AND HEALTH

Metabolism

Ethylbenzene is metabolized quickly in humans to mandelic acid and phenylglyoxylic acid (89%) and excreted in the urine (National Library of Medicine 2005b). Urinary concentrations of mandelic acid can be used as an indicator of exposure to ethylbenzene (National Library of Medicine 2005b). In rats and rabbits, ethylbenzene is metabolized differently, and mandelic acid and phenylglyoxylic acid are only minor metabolites (EPA 2002f).

Toxicity and Health Criteria

Summaries of the toxicity of chronic ethylbenzene exposure and regulatory criteria are presented in Table A.8.

Table A.8. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Ethylbenzene[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	1,000 μg/m^3	NOAEL (HEC) = 4.34×10^5 μg/m^3; (uncertainty factor 300)	Developmental toxicity in rabbits	EPA 1991; Andrew et al. 1981; Hardin et al. 1981
California REL	2,000 μg/m^3	NOAEL (HEC) = 6.5×10^4 μg/m^3; LOAEL = 1.250×10^6 μg/m^3	Nephrotoxicity, body weight reduction (in rats), hyperplasia of the pituitary gland; liver cellular alterations and necrosis (in mice)	California EPA 2005e; Chan et al. 1998 NTP 1999
Cancer				
EPA cancer classification	"Not classifiable as to human carcinogenicity"			EPA 1991
IARC classification	Group 2B; "possibly carcinogenic to humans"			IARC 2000
NTP *Report on Carcinogens*	Not listed			NTP 2005
California EPA	Not listed			California EPA 2005c

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; HEC = human equivalent concentration.

n-HEXANE

INTRODUCTION

n-Hexane (CAS 110-54-3) (Figure A.3) is an alkane hydrocarbon that exists at room temperature as a colorless, highly flammable liquid with a slightly disagreeable odor. It is primarily used as a solvent, both for food products and for glues, varnishes, and inks. It can also be found in gasoline, where it makes up as much as 3% of the fuel for modern vehicles (ATSDR 1999c; EPA 2000i; National Library of Medicine 2005c). The vapor pressure of *n*-hexane is 153 mm Hg at 25°C, indicating that *n*-hexane exists as a gas in the atmosphere (National Library of Medicine 2005c). At 1 atmosphere and 25°C, 1 ppm of *n*-hexane is equal to 3.53 mg/m^3 (EPA 2000i).

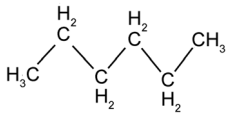

Figure A.3. Structure of *n*-hexane.

EXPOSURE

n-Hexane can be found at low concentrations (generally below 176 µg/m^3) in both urban and rural air (National Library of Medicine 2005c). Because of progressive improvements in emission controls, the concentrations of *n*-hexane in urban areas have decreased in recent times. A recent study showed the following average concentrations of *n*-hexane in the ambient air of several large cities: Vienna, 7.8 µg/m^3; Hamburg, 13 µg/m^3; Sydney, 4.4 µg/m^3; Chicago, 7.1 µg/m^3; Osaka, 19 µg/m^3; and Athens, 5.6 µg/m^3 (ATSDR 1999c). A general survey of the literature found mean *n*-hexane concentrations ranging from 1 to 25 µg/m^3, with higher in-vehicle values because close proximity to the exhaust systems of gasoline-fueled vehicles can lead to exposure to higher concentrations of *n*-hexane (ATSDR 1999c). Table A.9 is a summary of exposure data for *n*-hexane.

Table A.9. Summary of Exposure Data for *n*-Hexane[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (µg/m^3)	Citations
Urban	70	1.6–1,900	Zielinska et al. 1998
Urban–Suburban			
In-vehicle	130	1.8–24	Riediker et al. 2003; Fedoruk and Kerger 2003; Batterman et al. 2002
Urban–Rural	300	0.35–7.5	Zielinska et al. 1998
Urban–Suburban–Rural Combined	108,000	1.2	EPA 2004a

[a] Taken from Appendix Table B.13.

TOXICITY AND HEALTH

Metabolism

n-Hexane is metabolized primarily to 2,5-hexanedione in humans and in animals (National Library of Medicine 2005c). In rats, the principal urinary metabolite of *n*-hexane is 1-hexanol, but 2,5-hexanedione can also be found in rat urine at significant concentrations (National Library of Medicine 2005c).

Toxicity and Health Criteria

Summaries of the toxicity of chronic *n*-hexane exposure and regulatory criteria are presented in Table A.10.

Table A.10. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for *n*-Hexane[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	700 μg/m^3	7.3×10^4 μg/m^3 (uncertainty factor 300)	Peripheral neuropathy in rats	EPA 2005b; Huang et al. 1989
California REL	7,000 μg/m^3	LOAEL = 8.83×10^5 μg/m^3; NOAEL (HEC) = 2.04×10^5 μg/m^3 (uncertainty factor 30)	Peripheral neuropathy (electromyographic alterations; dose-related abnormal posture and muscle atrophy) in mice	California EPA 2005f; Miyagaki 1967
Cancer				
EPA cancer classification	Inadequate information to assess the carcinogenicity			EPA 2005b
IARC classification	Not evaluated			
NTP *Report on Carcinogens*	Not listed			NTP 2005
California EPA	Not listed			California EPA 2005c

[a] Taken from Appendix Tables C.1—C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; LOAEL = lowest observed adverse effect level; NOAEL = no observed adverse effect level; HEC = human equivalent concentration.

LEAD COMPOUNDS

INTRODUCTION

Lead (Pb) is a bluish-gray metallic element that occurs naturally in the earth's crust. Lead alloys are soft and malleable and have long been used to make a number of consumer products, including pipes, batteries, weights, shot, and ammunition. The principal use of lead is in the manufacture of batteries (EPA 2000j,q). Lead compounds were also used in paints, ceramic glazes, and dyes, but their use is being phased out globally because of public health concerns. Tetraethyl lead was used as an octane booster in gasoline and was phased out in the U.S. in the 1980s and now is being phased out in most other nations. Most lead is obtained from mines, recycled scrap metal, or batteries (ATSDR 2005h). Lead has a molecular weight of 207.2 g/mol. Its vapor pressure is 1.0 mm Hg at 980°C, and 1 ppm of lead is equal to 8.5 mg/m^3 (EPA 2000j,q).

EXPOSURE

Ambient concentrations of lead result from emissions from both mobile and stationary sources and were estimated to average 5.8 ng/m^3 in 1996 (ATSDR 2005h). The concentration of lead attributed to mobile sources alone was estimated to be 3.5 ng/m^3 (ATSDR 2005h). In the 1980s, by contrast, when leaded gasoline was being phased out, maximum quarterly average concentrations of lead were estimated from monitoring data to be 360 ng/m^3 in urban air (ATSDR 2005h). Because lead has been used for so long in so many industrial applications, it is commonly found in the environment. Thus, individuals can be exposed by inhaling contaminated air, by ingesting contaminated foods or liquids, or by swallowing lead-contaminated dust or dirt. Despite its ban for use in house paint, lead from peeling paint or paint dust remains an important source of exposure for young children living in older homes. Table A.11 is a summary of exposure data for lead.

Table A.11. Summary of Exposure Data for Lead[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (ng/m^3)	Citations
Urban	3,400	2.0–27	EPA 2002d, 2004d; California Air Resources Board 2003; Riediker et al. 2003; Kinney et al. 2002; South Coast Air Quality Management District 2000; Rodes et al. 1998;
Roadside	300	1.8–28	Martuzevicius et al. 2004; Riediker et al. 2003; Rodes et al. 1998
In-vehicle	100	0.0–30	Riediker et al. 2003; Rodes et al. 1998
Tunnel	6	—	Chellam et al. 2005
Rural	—	0.97	EPA 2002d
Urban–Suburban–Rural Combined	15,000	4.8–5.0	EPA 2004a; Pratt et al. 2000

[a] Taken from Appendix Table B.14.

TOXICITY AND HEALTH

Metabolism

Lead can enter the body by the inhalation of contaminated air or ingestion of contaminated foods or liquids. In general, skin absorption of lead is not an important route unless the skin is damaged. Inhaled lead can readily pass from the lungs into the bloodstream. Ingested lead does not readily pass from the stomach, though this varies with such factors as diet and age. Once in the body, lead is transported to the liver, kidneys, lungs, brain, spleen, muscles, and heart. After several weeks, most of it is transported to the bones and teeth. The lead that is not transported to bones or teeth is excreted in the urine or feces (ATSDR 2005h). Adults are able to eliminate lead better than children. In adults most of the lead is eliminated within a couple of weeks, whereas in children a larger percentage of lead is contained in bones and teeth (ATSDR 2005h). Lead continues to accumulate in bone if exposure continues.

Toxicity and Health Criteria

Summaries of the toxicity of chronic lead exposure and regulatory criteria are presented in Table A.12.

Table A.12. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Lead[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	No data for RfC; discussion for RfD			EPA 2004e
Cancer				
EPA cancer classification	Group B2; "probable human carcinogen"	Not available		EPA 2004e
IARC classification	Inorganic lead compounds: Group 2A; "probably carcinogenic to humans" Organic lead compounds: Group 3; "not classifiable as to their carcinogenicity to humans"			IARC 2006
NTP *Report on Carcinogens*	"Reasonably anticipated to be human carcinogens"			NTP 2005
California EPA		1.2×10^{-5} per µg/m^3		California EPA 2005c; Azar et al. 1973

[a] Taken from Appendix Tables C.1—C.3.

[b] Abbreviations: RfC = reference concentration; RfD = reference dose.

MANGANESE COMPOUNDS

INTRODUCTION

Manganese (Mn) is a silver-colored transition metal element that occurs naturally and forms compounds with chemicals such as oxygen, sulfur, and chlorine. It is ubiquitous in the environment; small amounts are found in air, water, soil, and food. Manganese in trace amounts is considered an essential nutrient for humans. Metallic manganese is used primarily in steel production to improve hardness and strength. Various manganese compounds are used to make consumer products, such as batteries, matches, animal feed, fertilizers, and ceramic glazes. In other countries, manganese has been present in fuels as a component of the additive MMT. Human exposure is most likely to occur in occupational settings where manganese is used. Elemental manganese has a molecular weight of 54.94 g/mol. Its vapor pressure is 1 mm Hg at 1292°C, and 1 ppm is equal to 2.25 mg/m^3 (ATSDR 2000b; EPA 2000r).

EXPOSURE

The general population is exposed to manganese in food, water, and air. The amounts from these sources are generally low. However, they can be higher near hazardous-waste sites or industrial facilities that use manganese. Manganese from contaminated soil or water does not readily pass through the skin. If manganese-contaminated dust is inhaled, some of the manganese can enter the bloodstream though the lungs (ATSDR 2000b). Annual average concentrations of manganese in urban and rural areas without significant manganese pollution are in the range of 0.01 to 0.07 µg/m^3 (ATSDR 2000b). Table A.13 is a summary of exposure data for manganese.

Table A.13. Summary of Exposure Data for Manganese[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (µg/m^3)	Citations
Urban	3,400	0.002–0.038	EPA 2004d; California Air Resources Board 2003; Riediker et al. 2003; Kinney et al. 2002; Rodes et al. 1998
Roadside	310	0.0016–0.010	Martuzevicius et al. 2004; Riediker et al. 2003; Rodes et al. 1998
In-vehicle	110	0.0042–0.030	Riediker et al. 2003; Rodes et al. 1998
Tunnel	6	—	Chellam et al. 2005
Rural	—	0.0019	EPA 2002d
Urban–Suburban–Rural Combined	15,000	0.0031–0.007	EPA 2004a; Pratt et al. 2000

[a] Taken from Appendix Table B.15.

TOXICITY AND HEALTH

Metabolism

A certain amount of manganese is essential to the normal functioning of the body. Humans excrete excess manganese largely in the feces (ATSDR 2000b).

Toxicity and Health Criteria

Summaries of the toxicity of chronic manganese exposure and regulatory criteria are presented in Table A.14.

Table A.14. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Manganese[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	0.05 µg/m^3	MnO_2: LOAEL (HEC) = 50 µg/m^3 (uncertainty factor 1,000)	Impairment of neurobehavioral function in occupationally exposed humans	EPA 1996a; Roels et al. 1987; Roels et al. 1992
California REL	0.2 µg/m^3	MnO_2: LOAEL (HEC) = 54 µg/m^3 (uncertainty factor 300)	Impairment of neurobehavioral function in occupationally exposed humans	California EPA 2005g; Roels et al. 1992
Cancer				
EPA cancer classification	Group D; "not classifiable as to human carcinogenicity"			EPA 1996a
IARC classification	Not evaluated			IARC 2005a
NTP *Report on Carcinogens*	Not listed			NTP 2005
California EPA	Not listed			California EPA 2005c

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; LOAEL = lowest observed adverse effect level; HEC = human equivalent concentration.

MERCURY COMPOUNDS

INTRODUCTION

Mercury (Hg) is a naturally occurring transition metal element that exists in several forms. The three major forms are metallic or elemental mercury, inorganic mercury, and organic mercury. The metallic or elemental form is pure mercury, a silvery liquid at room temperature. It is used in thermometers, barometers, and dental amalgams (EPA 2000s). It can volatilize, and the vapors are colorless and odorless (ATSDR 1999d). Inorganic mercury compounds, or mercury salts, include compounds in which mercury is combined with chlorine, sulfur, or oxygen. These compounds exist as white powders or crystals, except for mercuric sulfide (or cinnabar), which is red and turns black when exposed to light. In the past, inorganic mercury was used in laxatives, cosmetics, and latex paint (EPA 2000s). Organic mercury is mercury combined with carbon. There are many different organic mercury compounds. Methyl mercury is the most common form found in the environment; it accumulates in certain species of fish (ATSDR 1999d). It is formed from the methylation of the inorganic mercurial ion and has no industrial uses (EPA 2000s). Elemental mercury has a molecular weight of 200.5 g/mol. Its vapor pressure is 0.002 mm Hg at 25°C, and 1 ppm is equal to 8.2 mg/m^3 (EPA 2005d).

EXPOSURE

Average concentrations of mercury in ambient air range from approximately 10 to 20 ng/m^3, with higher concentrations in industrialized areas (ATSDR 1999d). Inhalation of elemental mercury in occupational settings is a major form of exposure. The general population can be exposed to low concentrations via dental amalgam (EPA 2000s). The general population is usually not exposed to inorganic mercury compounds, because their use has been discontinued in the manufacture of many products. In addition, the general population can be exposed to potentially high concentrations of methyl mercury through the consumption of fish. Table A.15 is a summary of exposure data for mercury.

TOXICITY AND HEALTH

Metabolism

Mercury can enter the body by inhalation of contaminated air, by ingestion of contaminated foods or liquids, or from skin contact (ATSDR 1999d). The three forms of mercury vary in how readily they enter the body. When inhaled, elemental mercury passes readily from the lungs into the bloodstream and is transported to the brain and kidneys, where it can persist for weeks or months (ATSDR 1999d). When ingested by a healthy individual, it does not pass from the stomach or intestines into the bloodstream. In pregnant women, it crosses the placental barrier and enters the fetus (ATSDR 1999d). Most elemental mercury in the body is eventually excreted in the urine or feces; smaller amounts are exhaled. When inhaled, inorganic mercury enters the body less readily than elemental mercury. When ingested, generally less than 10% of it is absorbed from the intestinal tract (ATSDR 1999d). Only small amounts of it have been reported to be absorbed from the skin. When inhaled, methyl mercury passes readily from the lungs into the bloodstream. When ingested, it is easily absorbed from the intestinal tract (about 95% of it is absorbed). Only small amounts can enter the bloodstream directly from the skin. Once in the bloodstream, mercury moves easily to most tissues and readily enters the brain. Like inorganic mercury, methyl mercury in the bloodstream of pregnant women can cross the placental barrier and enter the fetus. It can also be found (and passed on) in breast milk. Methyl mercury can persist in the body for many months. It is eliminated principally as inorganic mercury in the feces (ATSDR 1999d).

Toxicity and Health Criteria

Summaries of the toxicity of chronic mercury exposure and regulatory criteria are presented in Table A.16.

Table A.15. Summary of Exposure Data for Mercury[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration ($\mu g/m^3$)	Citations
Urban	330	0.002–0.0046	California Air Resources Board 2003; Riediker et al. 2003; Carpi and Chen 2002; EPA 2002d
Roadside	50	0.0038	Riediker et al. 2003
In-vehicle	50	0.0011	Riediker et al. 2003
Urban–Rural	780	0.00003–0.0024	Chen et al. 2004; EPA 2004f
Rural	—	0.0016	EPA 2002d
Urban–Suburban–Rural Combined	14,000	0.002	EPA 2004a; Pratt et al. 2000

[a] Taken from Appendix Table B.16.

Table A.16. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Mercury[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	Elemental mercury: 0.3 µg/m^3	LOAEL (ADJ) = 9 µg/m^3 (uncertainty factor 30)	Hand tremor, increases in memory disturbance; slight subjective and objective evidence of autonomic dysfunction in humans	EPA 2001c; EPA 1995; Fawer et al. 1983; Piikivi and Tolonen 1989; Piikivi and Hanninen 1989; Piikivi 1989; Ngim et al. 1992; Liang et al. 1993
California REL	Mercury salts, elemental mercury: 0.09 µg/m^3	LOAEL (HEC) = 8.9 µg/m^3 (uncertainty factor 100)	Hand tremor, memory and sleep disturbances; neurobehavioral and autonomic dysfunction in humans	California EPA 2005h; Fawer et al 1983; Piikivi 1989; Piikivi and Hanninen 1989; Piikivi and Tolonen 1989; Ngim et al. 1992; Liang et al. 1993
Cancer				
EPA cancer classification	Methyl mercury: "possible human carcinogen" Metallic and inorganic mercury: Group D; "not classifiable as to human carcinogenicity"	none		EPA 1995; EPA 2001c
IARC classification	Mercury compounds: Group 2B; Metallic mercury and inorganic mercury compounds: Group 3			IARC 1994
NTP *Report on Carcinogens*	Not listed			NTP 2005
California EPA	"Inadequate human and animal data"			California EPA 2005c

[a] Taken from Appendix Tables C.1—C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; LOAEL = lowest observed adverse effect level; ADJ = adjusted; HEC = human equivalent concentration.

METHYL *TERT*-BUTYL ETHER

INTRODUCTION

Methyl *tert*-butyl ether (MTBE) is a liquid organic compound manufactured by combining isobutylene and methanol (ATSDR 1996). MTBE was developed in the 1980s as a gasoline additive to enhance octane ratings. In the past, most exposures to MTBE were from fuel vapors or fuel exhaust, although gasoline leaks and spills have resulted in contamination of ground water and drinking water by MTBE. As a result primarily of concern about water contamination, in recent years MTBE has been removed from the gasoline supply in the U.S. MTBE has also been used as a laboratory chemical and in medicine to dissolve gallstones. It has a distinctive, disagreeable odor and is very volatile and water soluble. Gasoline leaks and spills have resulted in groundwater contamination by MTBE. MTBE has a molecular weight of 88.5 g/mol. Its vapor pressure is 245 mm Hg at 25°C (EPA 2000t), and 1 ppm of MTBE is equal to 3.61 mg/m^3 (EPA 2000t).

EXPOSURE

The general population can be exposed to MTBE by breathing air contaminated with vehicle exhaust or with gasoline fumes while refueling (EPA 2000t). Workers can be exposed by inhalation or skin contact (EPA 2000t). Table A.17 is a summary of air exposure data for MTBE.

Table A.17. Summary of Exposure Data for MTBE[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (µg/m^3)	Citations
Urban	660	1.1–60	Payne-Sturges et al. 2004; California Air Resources Board 2003; Kinney et al. 2002; Fedoruk and Kerger 2003; Rodes et al. 1998
Urban–Suburban–Rural Combined	9700	1.1–3.2	EPA 2004a,d

[a] Taken from Appendix Table B.17.

TOXICITY AND HEALTH

Metabolism

MTBE can readily enter the bloodstream via inhalation or ingestion; it enters the bloodstream more slowly through the skin. Most inhaled MTBE is exhaled. Some inhaled MTBE can be converted to other chemicals, but these also leave the body quickly. MTBE does not stay in any organ of the body for long; it is eliminated within one or two days (ATSDR 1996).

Toxicity and Health Criteria

Summaries of the toxicity of chronic MTBE exposure and regulatory criteria are presented in Table A.18.

Table A.18. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for MTBE[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	3,000 µg/m^3	NOAEL (HEC) = 2.5×10^5 µg/m^3; (uncertainty factor 100)	Increased absolute and relative weight in liver and kidney and increased severity of spontaneous renal lesions, increased prostration, and swollen periocular tissue in rats	EPA 1993c; Chun et al. 1992
California REL	8,000 µg/m^3	NOAEL (HEC) = 2.60×10^5 µg/m^3; (uncertainty factor 30)	Nephrotoxicity, prostration, periocular swelling in rats	California EPA 2005i; Chun et al. 1992; Bird et al. 1997
Cancer				
EPA cancer classification	Not available at this time			EPA 1993c
IARC classification	Group 3			IARC 1999b
NTP *Report on Carcinogens*	Not listed			NTP 2005
California EPA		2.6×10^{-7} µg/m^3		California EPA 2005c

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; NOAEL = no observed adverse effect level; HEC = human equivalent concentration.

NICKEL COMPOUNDS

INTRODUCTION

Nickel (Ni) is a hard, silvery-white transition metal element that occurs naturally in the earth's crust and is therefore found in food, water, soil, and air (EPA 2000u; ATSDR 2005i). It has no particular odor or taste. Food is the principal source of human exposure to nickel. However, exposure also occurs by breathing air, drinking water, or smoking tobacco containing nickel (ATSDR 2005i). Skin contact with soil, water, or metals containing nickel can also result in exposure. Because nickel is so tightly bound to dust and soil particles, it is not readily taken up by plants or animals. It is an essential nutrient in some mammalian species and might be an essential nutrient in humans (EPA 2000u). The principal use of nickel is in the production of stainless steel and other metal alloys (EPA 2005a). It is combined with other metals to increase hardness, strength, and corrosion resistance (ATSDR 2005i). In the environment, nickel is chiefly found combined with oxygen or sulfur (EPA 2000u). Certain nickel compounds, such as nickel chloride, nickel sulfate, and nickel nitrate, are water soluble and green in color (ATSDR 2005i). Nickel is released into the atmosphere during mining and by industrial processes that use nickel. It is also released into the atmosphere by power plants that burn oil or coal and by trash incinerators (ATSDR 2005i). Much of the nickel that is released ends up in soil and sediment, where it strongly attaches to particles containing iron or manganese (ATSDR 2005i). Nickel has a molecular weight of 58.71 g/mol. Its vapor pressure is 1 mm Hg at 1810°C, and 1 ppm is equal to 2.4 mg/m^3 (EPA 2000u; ATSDR 2005i).

EXPOSURE

Ambient-air data for the U.S. collected from 1977 to 1982 in both urban and rural areas showed concentrations of nickel ranging from 7 to 12 ng/m^3. Based on later data, from 1996, the EPA (ATSDR 2005i) estimated that the average nickel concentration in ambient air in the U.S. had decreased to 2.2 ng/m^3. Excluding the nickel in tobacco smoke, humans inhale 0.1 to 1 µg nickel/day (ATSDR 2005i). Table A.19 is a summary of exposure data for nickel.

Table A.19. Summary of Exposure Data for Nickel[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration ($\mu g/m^3$)	Citations
Urban	3,500	0.0087–0.032	Riediker et al. 2003; California Air Resources Board 2003; Manchester-Neesvig et al. 2003 Kinney et al. 2002; EPA 2002d Rodes et al. 1998;
Roadside	290	0.00023–0.0046	Martuzevicius et al. 2004; Riediker et al. 2003; Rodes et al. 1998; EPA 2002d
In-vehicle	100	< 0.0003–0.03	Riediker et al. 2003; Rodes et al. 1998
Tunnel	6	Individual measurements 0.001–0.084	Chellam et al. 2005
Urban–Suburban–Rural Combined	15, 000	0.0003–0.018	EPA 2004a; Pratt et al. 2000

[a] Taken from Appendix Table B.19.

TOXICITY AND HEALTH

Metabolism

Nickel can enter the body by inhalation of contaminated air, by ingestion of contaminated foods or liquids, or from skin contact (ATSDR 2005i). It can enter from the lungs or intestines, and small amounts can enter from the skin. It can be transported to all organs, but it accumulates mainly in the kidneys (ATSDR 2005i). Nickel is eliminated in the urine and feces.

Toxicity and Health Criteria

Summaries of the toxicity of chronic nickel exposure and regulatory criteria are presented in Table A.20.

Table A.20. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Nickel[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	Not available			EPA 1996b
EPA oral RfD	2×10^{-2} mg/kg/day	NOAEL= 100 ppm diet (5 mg/kg/day) (uncertainty factor 300)	Decreased body and organ weights in rats	Ambrose et al. 1976
California REL	0.05 µg/m^3	LOAEL = 60 µg/m^3 (as nickel sulfate hexahydrate) NOAEL (HEC) = 1.6 µg nickel/m^3 (uncertainty factor 30)	Respiratory and hematopoietic system: pathological changes in the lung, nasal epithelium, and lymph nodes in rats	California EPA 2005j; NTP 1996
Cancer				
EPA cancer classification	Nickel subsulfide: Group A; "known human carcinogen" Nickel carbonyl: Group B2; "probable human carcinogen"	Nickel subsulfide = 4.8×10^{-4} per µg/m^3		EPA 1996b
IARC classification	Nickel compounds: Group 1; "carcinogenic to humans" Metallic nickel: Group 2B; "possibly carcinogenic to humans"			IARC 2004b
NTP *Report on Carcinogens*	Nickel compounds: "known to be human carcinogens" Metallic nickel: "reasonably anticipated to be human carcinogen"			NTP 2005
California EPA		2.6×10^{-4} per µg/m^3	Cancer, based on nickel refinery workers	California EPA 2005c

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; RfD = reference dose; REL = reference exposure level; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; HEC = human equivalent concentration.

STYRENE

INTRODUCTION

Styrene (CAS Registry Number 100-42-5) (Figure A.4) is an organic compound that is a colorless liquid at room temperature. It evaporates easily and has a sweet odor. Years ago, styrene was used principally in the production of synthetic rubber. Today, it is used in making plastics, resins, coatings, and paints (ATSDR 1992; EPA 2000k). At 1 atmosphere and 25°C, 1 ppm of styrene is equal to 4.26 mg/m^3 (EPA 2000k).

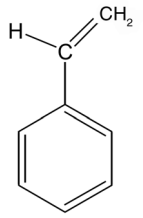

Figure A.4. Structure of styrene.

EXPOSURE

For the general population, the principal source of styrene exposure is emissions from building materials, consumer products, and tobacco smoke in indoor air. Average indoor concentrations are in the range of 1 to 9 µg/m^3 (EPA 2000k). Styrene can also be found in ambient air in urban areas at average concentrations ranging from 0.29 to 3.8 µg/m^3 (EPA 2000k) and in suburban and rural areas at average concentrations ranging from 0.28 to 0.34 µg/m^3 (EPA 2000k). A general survey of the literature found mean concentrations ranging from a low of 0.2 µg/m^3 in urban areas to a high of 190 µg/m^3 in vehicles (see Table B.21 in Appendix B). Table A.21 is a summary of exposure data for styrene.

Table A.21. Summary of Exposure Data for Styrene[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (µg/m^3)	Citations
Urban	800	0.1–24	Payne-Sturges et al. 2004; Adgate et al. 2004a; Sexton et al. 2004; California Air Resources Board 2003; Kinney et al. 2002; South Coast Air Quality Management District 2000; Zielinska et al. 1998
In-vehicle	80	1.1–190	Fedoruk and Kerger 2003; Batterman et al. 2002
Urban–Suburban–Rural Combined	111,000	0.10–1.2	EPA 2004a,d; Adgate et al. 2004b; Mohamed et al. 2002; Pratt et al. 2000; Zielinska et al. 1998

[a] Taken from Appendix Table B.21.

TOXICITY AND HEALTH

Metabolism

Styrene is metabolized to 7,8-styrene oxide via an epoxide intermediate (ATSDR 1992; EPA 2000k) and is excreted principally in the urine as mandelic acid and phenylglyoxylic acid (EPA 1993d; ATSDR 1992; National Library of Medicine 2005d).

Toxicity and Health Criteria

Summaries of the toxicity of chronic styrene exposure and regulatory criteria are presented in Table A.22.

Table A.22. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Styrene[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	1,000 μg/m^3	NOAEL (HEC) = 34,000 μg/m^3 (uncertainty factor 30)	Central nervous system effects in humans (occupational exposure)	EPA 1993d; Mutti et al. 1984
California REL	900 μg/m^3	BMC_{05} (HEC) = 2,600 μg/m^3 (uncertainty factor 3)	Neuropsychological deficits, as measured by memory and sensory motor function tests in humans (occupational exposure)	California EPA 2005k; Mutti et al. 1984
Cancer				
EPA cancer classification	None available	None available		EPA 1993d
IARC classification	Styrene-7,8-oxide, major metabolite: Group 2B; "possibly carcinogenic to humans"			IARC 2002
NTP *Report on Carcinogens*	Styrene-7,8-oxide, major metabolite: Group B; "reasonably anticipated"			NTP 2005
California EPA	Not listed	Cancer potency factor for styrene-7,8-oxide (major metabolite): 4.6×10^{-5} per μg/m^3		California EPA 2005c

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; NOAEL = no observed adverse effect level; BMC_{05} = benchmark concentration for 5% response incidence; HEC = human equivalent concentration.

TOLUENE

INTRODUCTION

Toluene (CAS Registry Number 108-88-3) (Figure A.5) is also known as methylbenzene or phenylmethane. It is an aromatic hydrocarbon that exists at room temperature as a clear, water-insoluble liquid. Toluene has a sweet odor that is similar to that of paint thinners. It is used in the production of polymers, as an organic solvent, as a solvent in paints and fingernail polish, and as an octane booster in gasoline (EPA 2000m, 2005c). At 1 atmosphere and 25°C, 1 ppm of toluene is equal to 3.77 mg/m^3 (EPA 2000m).

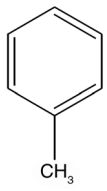

Figure A.5. Structure of toluene.

EXPOSURE

For the general population, the principal source of toluene exposure is emissions from common household products and cigarette smoke in indoor air. Average indoor concentrations are 31.5 µg/m^3 (ATSDR 2000c). Automobile emissions are the principal source of toluene in ambient air; concentrations of 10.8 µg/m^3 have been measured in urban areas, 0.7 µg/m^3 in suburban areas, and 1.3 µg/m^3 in rural areas (ATSDR 2000c). A general survey of the literature found mean concentrations ranging from a low of 2 µg/m^3 in urban areas to a high of 71 µg/m^3 in vehicles (see Appendix B). Table A.23 is a summary of exposure data for toluene.

Table A.23. Summary of Exposure Data for Toluene[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (µg/m^3)	Citations
Urban	960	2.0–45	EPA 2004a; Sexton et al. 2004; Payne-Sturges et al. 2004; California Air Resources Board 2003; Riediker et al. 2003; Kinney et al. 2002; South Coast Air Quality Management District 2000; Rodes et al. 1998; Zielinska et al. 1998
In-vehicle	200	10–67	Fitz et al. 2003; Riediker et al. 2003; Batterman et al. 2002; Rodes et al. 1998
Roadside	90	2.2–44	Riediker et al. 2003; Rodes et al. 1998
Urban–Suburban–Rural Combined	119,000	3.3–9.7	EPA 2004a,d; Adgate et al. 2004a; Pratt et al. 2000

[a] Taken from Appendix Table B.22.

TOXICITY AND HEALTH

Metabolism

Toluene is metabolized primarily to benzyl alcohol, but small amounts are oxidized to epoxide intermediates. Toluene is excreted in the urine as benzoic acid and hippuric acid, which are metabolites of benzyl alcohol (EPA 2000m). These metabolites are not specific to toluene, however.

Toxicity and Health Criteria

Summaries of the toxicity of chronic toluene exposure and regulatory criteria are presented in Table A.24.

Table A.24. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Toluene[a,b]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	5000 µg/m^3	NOAEL (ADJ) = 4.6×10^4 µg/m^3 (uncertainty factor 10)	Neurological effects in humans (occupational exposure)	EPA 1993e; Multiple human studies (listed in EPA 1993e)
California REL	300 µg/m^3	NOAEL (HEC) = 3×10^4 µg/m^3 (uncertainty factor 100)	Decreased brain (subcortical limbic area) weight, altered dopamine receptor (caudate-putamen) binding in rats	California EPA 2005l; Hillefors-Berglund et al. 1995 (with support from Orbaek and Nise 1989); Foo et al. 1990
Cancer				
EPA cancer classification	Group D; "not classifiable as to human carcinogenicity" (1986)	Not applicable		EPA 1993e
IARC classification	Group 3; "not classifiable as to their carcinogenicity to humans"			IARC 2000
NTP *Report on Carcinogens*	Not listed			NTP 2005
California EPA	Not listed			California EPA 2005c

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; LOAEL = lowest observed adverse effect level; HEC = human equivalent concentration; NOAEL = no observed adverse effect level; ADJ = adjusted.

XYLENE

INTRODUCTION

Xylenes (CAS Registry Number 1330-20-7) (Figure A.6) are a set of three benzene derivatives that have two methyl groups positioned *ortho*, *meta*, or *para* to each other. It is a colorless, sweet-smelling liquid that is very flammable, lighter than water, and has chemical properties that vary slightly among the isomers. Xylene is one of the top 30 chemicals (by volume) produced in the U.S. and is used as a solvent in the printing, rubber, and leather industries. It is also found in gasoline and airplane fuel (EPA 2000n; ATSDR 2005j). The vapor pressure of xylene is 7.99 mm Hg at 25°C, indicating that xylene exists as a gas in the atmosphere. It reacts quickly with photochemically produced hydroxyl radicals and degrades within a couple of days (National Library of Medicine 2005e). At 1 atmosphere at 25°C, 1 ppm of xylene is equal to 4.34 mg/m^3 (EPA 2000n).

EXPOSURE

Xylenes can be found at low concentrations, ranging from 3 to 380 µg/m^3 in ambient air in urban areas (EPA 2000n; ATSDR 2005j) and from 4.34 to 43.4 µg/m^3 in indoor air (ATSDR 2005j). Much of the release of xylene into the atmosphere is caused by the production, transportation, and processing of petroleum (ATSDR 2005j).

In a set of studies measuring xylenes in the air of tunnels, average concentrations of *o*-xylene and *m*,*p*-xylene were found to range from 17 to 20 µg/m^3 and 31 to 34 µg/m^3, respectively. Average concentrations of *o*-xylene and *m*,*p*-xylene near a busy highway were 12.5 µg/m^3 and 31.4 µg/m^3, respectively (ATSDR 2005j). A general survey of the literature found mean xylene concentrations ranging from 0.64 to 46 µg/m^3; higher values were measured on busy roadways and in vehicles (see Appendix B). Table A.25 is a summary of exposure data for xylene.

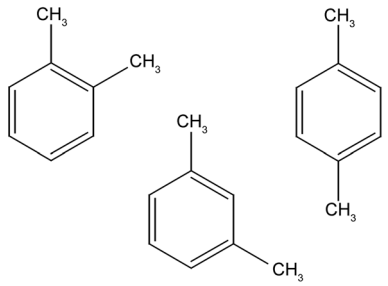

Figure A.6. Structure of three xylenes: *o*-xylene, *m*-xylene, and *p*-xylene.

TOXICITY AND HEALTH

Metabolism

In humans, xylene is metabolized and excreted primarily in the urine as either free *o*-, *m*-, or *p*-toluic acids or conjugated with glycine to form methyl hippuric acids; small amounts are excreted as corresponding xylenols (National Library of Medicine 2005e). These metabolites can be found in the urine within a few hours and are quickly eliminated (ATSDR 2005j). In rabbits and rodents, xylenes can be metabolized to the toxic aldehyde *p*-methylbenzaldehyde. This metabolite is not found in humans (National Library of Medicine 2005e).

Toxicity and Health Criteria

Summaries of the toxicity of chronic xylene exposure and regulatory criteria are presented in Table A.26.

Table A.25. Summary of Exposure Data for Xylene[a]

Type of Location	Approximate Number of Samples (*n*)	Mean Concentration (μg/m³)	Citations
***m- and p*-Xylene**			
Urban	700	1.3–10	Adgate et al. 2004a; Sexton et al. 2004; California Air Resources Board 2003; Kinney et al. 2002; Mohamed et al. 2002; Rodes et al. 1998
In-vehicle	160	3.8–46	Fedoruk and Kerger 2003; Batterman et al. 2002; Rodes et al. 1998
Roadside	40	9.9–20	Rodes et al. 1998
Urban–Suburban–Rural Combined	4,440	2.1–3.5	EPA 2004d; Pratt et al. 2000
***o*-Xylene**			
Urban	700	0.4–4.0	Adgate et al. 2004a; Fitz et al. 2003; Kinney et al. 2002
Roadside	18	0.8–8.0	Rodes et al. 1998
In-vehicle	80	0.7–6.2	Fedoruk and Kerger 2003; Batterman et al. 2002;
Urban–Suburban–Rural Combined	117,000	0.09–4.6	Adgate et al. 2004b; EPA 2004a,d; Sexton et al. 2004; Pratt et al. 2000; Zielinska et al. 1998
***m*-Xylene**			
Urban–Suburban–Rural Combined	3,000	1.0	EPA 2004a
***p*-Xylene**			
Urban–Suburban–Rural Combined	3,000	2.1	EPA 2004a
Total Xylenes			
Urban	130	4.3–4.7	Payne-Sturges et al. 2004; Riediker et al. 2003
In-vehicle	40	20	Riediker et al. 2003

[a] Taken from Appendix Table B.23.

Table A.26. Summary of Chronic Toxicity Evaluations and Regulatory Criteria for Xylene[a]

Regulatory Criteria	Regulatory Value or Classification	Underlying Value or Potency / Unit Risk	Endpoint	Citations for Toxicity Criteria and Underlying Study
Non-Cancer				
EPA inhalation RfC	100 μg/m^3	NOAEL (HEC) = 3.9×10^4 μg/m^3	Impaired motor coordination in rats	EPA 2003e; Korsak et al. 1994
California REL	700 μg/m^3		Central nervous system effects in humans; irritation of eyes, nose, and throat	California EPA 2005m; Uchida et al. 1993
Cancer				
EPA cancer classification	"Inadequate data, no evidence of carcinogenicity"	Not applicable		EPA 2003e
IARC classification	Group 3; "not classifiable as to their carcinogenicity to humans"			IARC 1999a
NTP *Report on Carcinogens*	Not listed			NTP 2005
California EPA	Not listed			California EPA 2005c

[a] Taken from Appendix Tables C.1–C.3.

[b] Abbreviations: RfC = reference concentration; REL = reference exposure level; NOAEL = no observed adverse effect level; HEC = human equivalent concentration.

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APPENDICES AVAILABLE ON THE WEB

Appendices B, C, D, and E contain supplemental material not included in the printed report. These appendices are available on the HEI Web site (*www.healtheffects.org*) and on a compact disk (CD) that accompanies the printed version.

In beginning its review of mobile-source air toxics (MSATs), the HEI Air Toxics Review Panel sought to identify the MSATs likely to pose the greatest risk to humans at ambient exposure concentrations. The panel elected to focus on the following 21 MSATs listed by the U.S. Environmental Protection Agency (EPA) in its 2001 rule:

- acetaldehyde
- acrolein
- arsenic compounds
- benzene
- 1,3-butadiene
- chromium compounds
- diesel exhaust (particulate matter and organic gases)
- dioxin and furan compounds
- ethylbenzene
- formaldehyde
- *n*-hexane
- lead compounds
- manganese compounds
- mercury compounds
- methyl *tert*-butyl ether
- naphthalene
- nickel compounds
- polycyclic organic matter
- styrene
- toluene compounds
- xylene

Gradient Corporation of Cambridge, Mass., was engaged to undertake a literature survey to identify and summarize published information on exposure and toxicity for these 21 MSATs. The information resulting from this survey was used by the panel in its evaluation of MSATs and is presented in Appendices B and C of this report. Appendix B consists of the tables summarizing information on exposure to the MSATs, and Appendix C the tables summarizing information on toxicity and health effects. (Shortly before publication of the report, Tables C.1 and C.2 were updated by HEI to reflect the current regulatory values.)

Further information was collected for six of the seven priority MSATs identified by the panel as meriting special attention (acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, and polycyclic organic matter). Additional information both on toxicity and health and on indoor exposures was collected. The toxicity and health information was incorporated into the tables in Appendix C; the information on indoor air concentrations is presented in Appendix D. Abbreviations and other terms used in the tables that make up Appendices B, C, and D are defined in Appendix E.

APPENDIX B. AMBIENT AND OUTDOOR EXPOSURE TABLES

Table B.1 is a summary of key information on the exposure studies for each MSAT, including brief descriptions of each study and details of time periods, locations, and types of location (i.e., urban, suburban, rural, in-vehicle, roadside, and tunnel).

Table B.2 is a matrix of data sources for exposure studies, showing the MSATs investigated in each study.

Tables B.3 through B.23 summarize the data for exposure information on each of the MSATs. Certain MSATs are represented by one or more surrogate compounds.

APPENDIX C. TOXICITY AND HEALTH EFFECTS TABLES

In the toxicity and health portions of the literature survey, information on acute, chronic, and subchronic health effects (including cancer and noncancer endpoints) was collected from peer-reviewed secondary sources, such as the EPA's Health Assessment Documents, U.S. Agency for Toxic Substances and Disease Registry (ATSDR) reports, and the International Agency for Research on Cancer (IARC) monographs. The primary sources that served as the basis for key toxicity criteria were also obtained. For the seven priority MSATs (acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde, naphthalene, and polycyclic organic matter), the survey was augmented with recent information from primary sources.

The survey was also augmented for the nonpriority MSATs in cases in which the secondary sources were out of date (i.e., 2001 or earlier).

Tables C.1 and C.2 summarize the toxicity criteria that were readily available in the secondary sources and online, showing whether a given MSAT is considered a carcinogen, how toxic or potent it is, and the date of the most recent evaluation. The principal focus is on inhalation, because this is the predominant route of exposure to MSATs. To facilitate the comparison of criteria, all cancer and noncancer toxicity criteria are expressed in units per $\mu g/m^3$ for the inhalation route and mg/kg-day for the oral route.

Table C.3 provides information on chronic noncancer health effects available at the time the literature survey was completed (winter 2004–2005). For each MSAT, the details of the key chronic-toxicology studies that formed the basis of the toxicity criteria are summarized, starting with the Integrated Risk Information System (IRIS) and adding other sources if they were more recent. In addition, the studies on which the toxicity criteria were based are listed in the last column of the table. Criteria based on oral-route studies are included in the table only when no toxicity criteria were identified for the inhalation route.

Table C.4 provides information on chronic cancer health effects available at the time the literature survey was completed. In addition, the studies on which the toxicity criteria were based are listed in the last column of the table. Criteria based on oral-route studies are included in the table only when the inhalation unit risk was not provided and the compound was classified as a carcinogen when inhaled; in these cases, the oral unit risk and associated critical study are provided.

Table C.5 summarizes the acute-toxicity criteria for each MSAT at the time the literature survey was completed. This report does did not include level 3 (in the acute exposure guideline levels and the *Emergency Response Planning Guidelines*), which pertains to life-threatening effects, because it was deemed too extreme to be useful in the report.

Table C.6 summarizes the studies that served as the basis for the acute-toxicity criteria for each MSAT at the time the literature survey was completed. The literature searches in this table were updated, like the literature searches in Tables C.3 and C.4, although to a lesser extent, because most of the exposure guidelines were of recent origin.

APPENDIX D. INDOOR EXPOSURE TABLES

The tables in Appendix D summarize information on indoor exposures for six of the seven priority MSATs (not including naphthalene).

Table D.1 is a summary of the sources of data on indoor exposure for each MSAT, including brief descriptions of each study and details of study time periods, locations, and types of location (e.g., residences, office buildings, and schools), as well as a description of each location and notes.

Table D.2 is a matrix of data sources showing the MSATs investigated in each exposure study.

Tables D.3 through D.8 are data summaries for each MSAT. Certain MSATs are represented by one or more surrogate compounds.

APPENDIX E. ABBREVIATIONS AND OTHER TERMS

This appendix defines abbreviations and other terms used in the tables in Appendices B, C, and D.

ABBREVIATIONS AND OTHER TERMS

ADH	alcohol dehydrogenase
AEGL	acute exposure guideline level
AIHA	American Industrial Hygiene Association
ALDH	aldehyde dehydrogenase
AML	acute myeloid leukemia (also referred to as acute myelogenous leukemia)
ARB	Air Resources Board (California)
ATSDR	Agency for Toxic Substances and Disease Registry (U.S.)
CI	confidence interval
DE	diesel exhaust
DMDTC	dimethyldithiocarbamate
DPM	diesel particulate matter
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency (U.S.)
EXPOLIS	Air Pollution Exposure Distributions of Adult Populations in Europe
FEV_1	forced expiratory volume in one second
HEC	human equivalent concentration
HEPA	high-efficiency particulate air
IARC	International Agency for Research on Cancer
IgE	immunoglobulin E
IL	interleukin
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
LOAEL	lowest observed adverse effect level
MATES	Multiple Air Toxics Exposure Study
mRR	meta rate ratio
MSAT	mobile-source air toxic
MTBE	methyl *tert*-butyl ether
NAD^+	nicotinamide adenine dinucleotide
NATA	National Air Toxics Assessment
NIOSH	National Institute of Occupational Safety and Health
NO_x	nitrogen oxides
NOAEL	no observed adverse effect level
NQO1	NAD(P) H: quinone oxidoreductase-1
NTP	National Toxicology Program (U.S.)
OEHHA	Office of Environmental Health Hazard Assessment (California)
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
PM	particulate matter
$PM_{2.5}$	particulate matter less than or equal to 2.5 µm in aerodynamic diameter
PM_{10}	particulate matter less than or equal to 10 µm in aerodynamic diameter
POM	polycyclic organic matter
PTEAM	Particle Total Exposure Assessment Methodology study
RfC	reference concentration
RfD	reference dose
RIOPA	Relationships of Indoor, Outdoor, and Personal Air study
RR	relative risk or rate ratio
SBR	styrene-butadiene synthetic rubber
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (European Commission)
SCE	sister-chromatid exchange
SD	standard deviation
SMR	standardized mortality ratio
SPIR	standardized proportionate incidence ratio
S-PMA	S-phenylmercapturic acid
TEAM	Total Exposure Assessment Methodology
t,t-MA	*t,t*-muconic acid
TWA	time-weighted average
VOC	volatile organic compound
WHO	World Health Organization

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