

HEI's Mobile Air Toxics Project

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A recent report of the Health Effects Institute (HEI), *Research Priorities for Mobile Air Toxics (1)*, provides information on research capable of narrowing uncertainties related to health effects of specific mobile-source air pollutants. The report, developed at a workshop in Monterey, California, 4–6 December 1992, provides research recommendations for four mobile-source toxic air pollutants specified in the Clean Air Act [formaldehyde, benzene, butadiene, and polycyclic organic matter (POM)], as well as for methanol, an important alternative fuel. HEI planned the workshop in collaboration with representatives of the U.S. EPA, California EPA, California Air Resources Board, and the automotive and petroleum industries. Scientists from academia, industry, and government participated in working groups on specific compounds. Although cancer was the primary health effect for most compounds, there was also much discussion of noncancer endpoints. HEI's report focuses on research needs related to understanding the effects of these agents at concentrations in the ambient air.

Section 202(l)(2) of the 1990 Clean Air Act Amendments deals with regulation of mobile-source air toxics. It specifies that within 54 months after the date of the enactment of the amendments of 1990, the EPA

Administrator shall promulgate (and from time to time revise) regulations. . . to control hazardous air pollutants from motor vehicles and motor vehicle fuels. The regulations shall contain standards for such fuels or vehicles, or both, which the Administrator determines reflect the greatest degree of emission reduction achievable through the application of technology which will be available. . . . The regulations shall, at a minimum, apply to emissions of benzene and formaldehyde.

The regulations are to be based on a study by EPA (2) also specified in the amendments [202(l)(1)]. "The study shall focus on those categories of emissions which pose the greatest risk to human health or about which significant uncertainties remain, including the emissions of benzene, formaldehyde, and 1,3-butadiene." In another part of the act [211(k)(10)],

toxic air pollutants are defined as benzene, 1,3-butadiene, POM, acetaldehyde, and formaldehyde. The HEI workshop focused on research that might decrease uncertainties in risk assessments for these pollutants before standards are set for them.

Research Recommendations

In this meeting report, we summarize the research that each working group decided was of the highest priority for providing information to decrease the uncertainty in risk assessments for these compounds. For four of the five working groups (all but methanol), cancer was the main health effect of concern.

Benzene

Human exposure to benzene causes aplastic anemia, chromosome aberrations, and acute nonlymphocytic leukemia (ANLL). These effects result from exposure to the high levels of benzene that were previously prevalent in the workplace. A critical question is whether any or all of these effects can also be produced at the low concentrations that occur in ambient air. In animals, benzene is a multisite carcinogen, but there is no useful animal model of benzene-induced leukemia. The benzene working group recommended the following research to reduce critical uncertainties in risk assessment for benzene:

Exposure Assessment

- Describe and characterize microenvironments that create substantial opportunities for benzene exposure.

Health Effects

- Conduct studies to determine whether benzene causes solid tumors and hematological malignancies other than ANLL in humans. This could be done by following up existing worker cohorts or by studying worker cohorts now being established in China.
- Develop specific markers of exposure to use in epidemiologic studies to clarify the shape of the dose–response curve in the low-dose region.
- Develop a suitable animal model to conduct mechanistic studies of benzene carcinogenesis. Questions to be ad-

ressed in animal models include the following: What is the mechanism by which combinations of benzene metabolites produce greater-than-additive cytogenetic and hematopoietic effects? What are the critical target genes and cells for benzene's effects? Is aplastic anemia an essential step in benzene-induced leukemia? What is the role of benzene-induced changes in cytokines and growth factor pathways relevant to leukemia?

1,3-Butadiene

Butadiene is used in production of synthetic rubber and is also a combustion product. It causes tumors in rats and mice, and there is highly suggestive evidence that it causes cancer in humans exposed occupationally. The EPA and the International Agency for Research on Cancer (IARC) have classified butadiene as a probable human carcinogen. Major uncertainties in the risk assessment are in extrapolation of potency from animals to humans. Human studies do not provide a sufficient basis for determining dose response. Extrapolation from animals is difficult because of differences in potency and a different spectrum of tumors in mice and rats. To address these uncertainties, the butadiene working group designated the following high-priority research recommendations:

Exposure Assessment

- Characterize emissions from both on-road and off-road vehicles and the effects of reformulated fuels.

Health Effects

- Determine rates of formation and metabolism of potentially toxic metabolites in target tissues (liver, heart, lung, bone marrow, lymphatic tissue) and nontarget tissue in humans, nonhuman primates, and rodents. Complete the development and validation of a physiologically based butadiene dosimetry model that predicts dose of butadiene and epoxides in target and nontarget tissues in rodents, nonhuman primates, and humans.
- Determine whether butadiene induces mutations and, if so, the frequency and mutational spectra in both laboratory animals and humans.

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- Identify the cancer-related DNA adducts produced by butadiene and its metabolites and develop sensitive methods for their detection in human body fluids and tissues. The goals are to develop biomarkers to assess uptake and metabolism of butadiene, provide mechanistic insights about butadiene carcinogenesis, and provide information on individual variability in butadiene metabolism.
- Develop a model of tumor development to elucidate mechanisms of chemical leukemogenesis in both humans and mice.
- Carry out epidemiology studies on new populations with higher exposures to expand and confirm findings from previous studies and to evaluate biomarkers and reproductive outcomes.

Formaldehyde and Other Aldehydes

Formaldehyde has been designated a probable human carcinogen by EPA and IARC. The major uncertainty in the unit cancer risk estimate, which is based on a study of nasal tumors (squamous cell carcinoma) in F344 rats, is due to the steep dose response observed in rats. Epidemiologic studies provide support for formaldehyde as a carcinogen, but these studies have not been used in quantitative risk assessments by the U.S. EPA or California EPA. Although formaldehyde risk assessments have focused only on cancer, the formaldehyde working group concluded that there is a need to understand better whether there are possible noncancer effects of exposure to formaldehyde at ambient exposures.

Exposure Assessment

- Conduct research to understand the total human exposure to aldehydes, including distribution of exposures to formaldehyde among various groups and the occurrence of peak exposures.

Cancer

- Investigate metaplasia in monkeys using existing tissue blocks from prior formaldehyde studies. This may enable development of dose-response information in a species more similar to humans than rodents for an endpoint that may be on the pathway to tumor formation.
- Undertake a meta-analysis of the best existing epidemiologic studies to develop a better estimate of the human dose-response relation for formaldehyde.
- DNA-protein crosslinks have been used as a measure of tissue dose of formaldehyde. Enhanced understanding of the reaction of formaldehyde with proteins and DNA is needed.

Noncancer Effects

- Investigate cellular and subcellular mechanisms of irritant effects to under-

HEI Mobile Air Toxics Workshop

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stand adaptation. Conduct dose-response studies of the effects of aldehydes in combination with other chemicals.

- Investigate the mechanisms associated with effects on pulmonary responses. This work should include efforts to develop animal models and human *in vitro* systems because human exposures to formaldehyde may not be possible.
- Investigate the molecular basis of increased aldehyde susceptibility due to polymorphisms in aldehyde dehydrogenase.

Methanol

The use of methanol as a fuel for motor vehicles would result in exposure to low concentrations of methanol via inhalation, dermally from spilling, and even possibly by ingestion. It is well known that high-level exposures to methanol can cause death from metabolic acidosis and damage to the visual system, including blindness. Formate is thought to be the metabolite responsible for such effects. Because of species differences in metabolism of methanol, rodent studies are not an adequate model for studying effects of methanol exposure at high levels. Animals with induced folate deficiency are more sensitive to methanol. Methanol research should investigate effects of potential human exposures and identify groups of the population that may be at greater risk.

Exposure Assessment

- Develop and validate exposure models to estimate exposure concentrations and routes of exposure in specific exposure scenarios. Conduct ambient and personal monitoring to determine the distribution of exposures.

Pharmacokinetics

- Determine the pharmacokinetics of methanol and formate during pregnancy in rats, mice, and nonhuman primates. Include animals with reduced levels of folate to determine whether exposure to methanol alters folate metabolism.

- Conduct human pharmacokinetic studies to develop a physiologically based pharmacokinetic model to quantify the disposition of methanol and formate in individuals with a range of folate levels.
- Investigate metabolism in target organs, including brain, testes, retina, and optic nerve.

Health Effects

- Conduct studies of developmental effects, including neurobehavioral endpoints, in rats and nonhuman primates with both normal and folate-deficient status.
- Carry out experimental human studies and epidemiologic studies to assess neurobehavioral and visual effects of short-term exposures.
- Conduct chronic animal studies of neurotoxic, visual, and neuroendocrine endpoints, using animals with normal and reduced folate levels.

Polycyclic Organic Matter

Polycyclic organic matter is a complex pollutant category. It is defined in Section 112, title II, of the Clean Air Act as a class of organic compounds with more than one benzene ring and a boiling point of 100°C or higher. POM includes polycyclic aromatic hydrocarbons, heterocyclics, and other subclasses like lactones. POMs with five or more rings are generally associated with particles, whereas those with four or fewer are semivolatile and partitioned between the particle and gas phases. Mobile sources contribute to human exposure to POM, but most compounds are not unique to mobile sources. Cancer is the potential health effect of concern for airborne exposures to POM, but the potential magnitude of health effects from environmental exposures is uncertain. There is evidence that some occupational exposures to POMs cause increased incidence of lung cancer.

Cancer

- Cross-validate different animal bioassay models for cancer in comparison with human data. Human epidemiological

data are available for a small number of POMs for which data from animal models are also available.

- Determine the potential role in lung cancer of ingested POMs (from the diet and from lung clearance of particles) compared to inhaled POMs.

Biomarkers

- Identify biomarkers of exposure to POMs and links to adverse health effects. Develop information to understand the relation between exposure and markers of dose and effects in target organs, such as protein and DNA adducts and genetic changes.

Risk Assessment Methods

- Evaluate various risk assessment methods that have been used for POMs (extrapolation from epidemiologic data, extrapolation from animal inhalation data, comparative potency using animal and human data, benzo[*a*]pyrene "toxics equivalence factor method") to determine the best approach.

Conclusions

The research recommendations summarized here, and the more extensive sets of recommendations presented in HEI's report (1), are aimed at all organizations funding research on the health effects of air pollutants and are not intended to be restricted to HEI's planning needs. As with any research, it is difficult to make predictions about where particular paths will lead, how many branches they may have, or how long it will take to reach their end. We can, in fact, only be certain that there will be major advances crucial to understanding the health impact of air toxics that were not predicted by anyone at HEI's workshop. Therefore, we stress the need for research organizations to maintain flexibility and to respond to rapid developments.

Specification of these compounds in HEI's report should not be interpreted as meaning that they are necessarily the compounds in motor vehicle emissions that

present the greatest risk to health. HEI and other organizations are assessing information on emissions, exposure, and toxicity of a large number of compounds derived from automotive emissions. This assessment must consider new emissions resulting from changes in fuels, additives, engines, and emissions-control technology, which must not cause an unreasonable health risk.

REFERENCES

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