

## **Air Pollutants from Fuel, Additives, and Combustion**

### **Introduction**

Air pollutants are chemical, physical, and biological agents that modify the natural characteristics of the atmosphere. Air pollution is generated by combustion of fossil fuels and other materials; industrial, agricultural, and residential activities, including chemical releases and use; and natural events, such as wildfires. Fuels such as gasoline, diesel, and coal are particularly of concern because of the vast quantities extracted, formulated, transported, and used in vehicles (on- and off-road) and by industry, particularly utilities.

A great deal of research has demonstrated the impact of air pollutants on respiratory health, including lung cancer, and cardiovascular disease. There is also evidence that ambient air pollutants affect birth outcomes, including the quality of fetal growth and development<sup>1</sup> which may affect susceptibility to adult diseases, including breast cancer.<sup>2</sup> The number of suspected mammary carcinogens that are air-borne makes air contaminants an intriguing area for breast cancer research.

Levels of these contaminants vary greatly in California, given the tremendous geographic and meteorologic diversity. The state is currently organized into 15 regional air basins to monitor and model air quality.<sup>3</sup> The South Coast air basin (which includes Orange county and parts of Los Angeles, Riverside and San Bernardino counties) historically has some of the highest air pollution levels due to the relatively high temperatures, concentration of population and industry, and

surrounding mountains that trap pollutants. The Great Basin Valleys (Alpine, Mono and Inyo counties) are more rural and very dry, with winds blowing over dried up lakes creating some of the highest particulate matter concentrations in the U.S. Wind and rainfall impact air conditions, such that pollution levels vary greatly across and even within these air basins.

This subsection will address air pollutants that may be measured individually and some that are constituents of particulate matter. For some, such as polycyclic aromatic hydrocarbons (PAHs), there has been a great deal of research, while fuels, including additives, are much less studied. Dioxins are another combustion by-product of concern. While dioxin exposure is mentioned here, this environmental pollutant is discussed in more detail in Section I, Chapter B.2, Persistent Organic Pollutants.

A number of other air pollutants may also be associated with breast cancer. Rudel et al. identified 35 pollutants of outdoor or indoor air that are possible animal mammary gland carcinogens, and listed several other chemicals that are known air toxics.<sup>4</sup> Several volatile organic compounds of concern for breast cancer risk are monitored by the California Air Resources Board (CARB) as hazardous air pollutants. Benzene, for example, is a natural constituent of crude oil and has been used in the past as an additive in gasoline, but much higher exposure is associated with its use as an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber, and dyes. Therefore, benzene is discussed in Section I, Chapter B.5, Solvents and Industrial Chemicals. Other combustion by-products and air

pollutants of concern covered in other chapters of this report include 1,3-butadiene, nitromethane, isoprene, styrene and ethylene oxide (also in Section I, Chapter B.5); DCBP, atrazine, chlordane, dichlorvos, and simazine (in Section I, Chapter B.4, Pesticides); and metals (in Section I, Chapter B.7).

## **PAHs**

Polycyclic aromatic hydrocarbons (PAHs) are a group of over 100 different chemicals that are formed by the incomplete combustion of coal, oil and gas, garbage, or other organic substances like tobacco or charbroiled meat. PAHs are usually found as a mixture of two or more of these compounds, such as soot. Some PAHs are manufactured. These pure PAHs are usually colorless, white, or pale green solids. PAHs are found in coal tar, crude oil, creosote, and roofing tar; a few are used in medicines, or to make dyes, plastics, and pesticides. Of the 15 PAHs listed as reasonably anticipated to be human carcinogens according to the 11<sup>th</sup> Report on Carcinogens (RoC),<sup>5</sup> six are monitored by CARB as part of CARB's ambient toxics data collection.

### **Concept/Exposure Definition**

Mixtures of PAHs are present in ambient air, tobacco smoke, and in foods that are grilled, smoked, or contaminated by air pollution. The primary route of exposure is inhalation of contaminated air, with some PAHs ingested in contaminated water and in foods. PAHs inhaled through the lungs can be carried through the bloodstream to the breast, where they can be stored, concentrated, and metabolized, and affect the types of cells where breast cancer arises.<sup>6</sup>

Benzo[a]pyrene is of particular concern because of its ubiquitous exposure pattern. It is found in gasoline and diesel exhaust, cigarette smoke, other types of smoke, soot, grilled foods, coal tar, petroleum asphalt, creosote, shale oil, and solvents.<sup>4</sup> The main sources of human exposure are tobacco smoke, ambient air pollution from exhaust and coal-fired power plants, and foods. Nitropolycyclic aromatic hydrocarbons (nitro-PAHs) are formed at high levels from diesel oil combustion.<sup>7</sup> In addition to exposure from ambient air, the general population may be exposed to nitro-PAHs via drinking water and dermal contact.

Background levels of PAHs are much higher in urban areas than rural. PAH emission levels and composition vary over time and geography, as do those of other air pollutants, which may influence their potential for affecting health, including carcinogenicity.<sup>8</sup>

### **Critical Review of Literature**

The International Agency for Research on Cancer (IARC) has listed soot and other PAH mixtures as known human carcinogens, and individual PAHs as probable human carcinogens.<sup>9</sup> PAHs are genotoxic and potentially carcinogenic to the human breast.<sup>7</sup> Nitro-PAHs and PAHs are both associated with increased mammary gland tumors in animals, with some, although not entirely consistent, evidence from studies in humans of an association with both male and female breast cancer.<sup>4,9</sup>

### ***In vitro***

Gilli et al. found that PAH concentrations extracted from the ambient air were statistically correlated with mutagenicity in Salmonella assays. This occurred both with and without metabolic activation, suggesting they are both direct mutagens and promoters.<sup>8</sup> They did not, however, observe a linear dose-response relationship with either benzo[a]pyrene or total PAHs, mutagenicity ratios were highly variable, and the levels of fine particles (PM<sub>2.5</sub>) and unsubstituted PAHs did not account for the total observed mutagenicity. The researchers noted that the role of other pollutants was not studied and should be investigated, as should nitro-PAHs and ultra-fine particulate matter.

### ***In vivo***

PAH mixtures and some individual PAHs are mammary carcinogens in animals. Five of eight studies on one nitro-PAH, 1-nitropyrene, reported increased benign and/or malignant mammary tumor development in exposed animals.<sup>4</sup> When administered by subcutaneous injections, 1-nitropyrene induced mammary tumors, including adenocarcinomas, in female rats.<sup>5</sup> One study in female rats injected intraperitoneally with 1-nitropyrene showed increased mammary tumors, while another found an increase that was not statistically significant. Mammary gland tumors were also increased following oral administration of 1-nitropyrene to female rats.<sup>5</sup> Further, benzo[a]pyrene, administered either by gavage or intraperitoneal injection, induced mammary tumors in female rats.<sup>4</sup>

### ***Human***

Brody et al.<sup>9</sup> identified seven case-control studies of the association between breast cancer risk and environmental exposure to PAHs, including several that evaluated air pollution in a limited geographic area. One study found an association between exposure to total suspended particles (TSP), a surrogate for PAH exposure, and breast cancer risk.<sup>10</sup> These investigators reported a statistically significant trend ( $p\text{-trend} < 0.05$ ) for higher breast cancer risk among women who lived at birth in areas with higher TSP levels. Among post-menopausal women, odds ratios were elevated but statistically unstable for higher TSP at birth, menarche, and first full-term pregnancy. The lack of an association at menarche and first full-term pregnancy for pre-menopausal women could be due to declining TSP levels in more recent years, shorter lag time (the time between a woman's exposure and when the researchers assessed the health effect), or other factors.

Another study used indicators of industrial and traffic density to estimate exposure to air pollution and PAHs. Lewis-Michl et al. reported a statistically significant higher risk associated with living near industrial air pollution sources in one county (OR = 1.61; 95% CI, 1.06-2.43), but not another county.<sup>11</sup> Results for living near high-density traffic were inconsistent.

A Belgian study found that exposure to PAHs from the ambient air was associated with a significant delay in breast development in a cohort of 200 adolescents (15.8–19.6 years old).<sup>12, 13</sup> The delay was also associated with a doubling of serum dioxin concentrations.

Many studies of breast cancer risk among women with work exposure to PAHs have been small and/or did not control for known breast cancer risk factors. Brody et al. identified two occupational studies of exposure to gasoline and vehicular exhaust that found elevated risk of breast cancer among females and males.<sup>9</sup> Men who worked for more than three months in an exposed job were particularly at risk if their first exposure was before 40 years of age (OR = 3.7; 95% CI, 1.7-7.9 with no lag time; OR = 5.4; 95% CI, 2.4-11.9 with 10 years lag time).<sup>14</sup> Women with occupational PAH and benzene exposure had higher breast cancer risk in a New York study (OR = 1.82; 95% CI, 1.02-3.16).<sup>15</sup>

The Long Island Breast Cancer Study assessed PAH exposure by measuring PAH-DNA adducts, a gauge of DNA damage caused by these compounds. This case-control study found the odds ratio for detectable versus non-detectable adducts was 1.32 (95% CI, 1.00-1.74).<sup>16</sup> Women with the highest compared to lowest PAH-DNA adducts had about 50 percent higher breast cancer risk, taking into account an extensive list of breast cancer risk factors. Results showing the strongest effects in premenopausal women are consistent with the Cal-EPA Report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant" that concluded tobacco smoke is associated with higher breast cancer risk in women under age 50.<sup>17</sup> The Long Island results did not show a dose-response relationship. However, dose may not be well-characterized in this study: measurements were taken after diagnosis and therefore represent exposure over the previous months to a few years, not consistent with the known latency of breast cancer; and they do not

consider the effects of DNA repair mechanisms. The study did not identify a relationship between grilled food or tobacco and PAH-DNA adducts, suggesting that other sources, perhaps air pollution, may be important or that women's recollections of diet and tobacco exposure are not relevant to recent blood measurements.<sup>9</sup> Additional analyses of the Long Island data suggest that certain genetic polymorphisms may influence the relationship between PAH exposure and breast cancer risk; and it will be informative to see whether these associations are observed in other studies as well.<sup>9</sup>

The small, hospital-based studies of PAH-DNA adducts in breast tissue are limited by low statistical power and lack of breast tissue samples from healthy controls for comparison.<sup>9, 18-21</sup>

### **Biological Mechanisms**

Combustion byproducts are well known for causing oxidative stress, which leads to respiratory and cardiovascular diseases. Oxidative stress can disturb redox homeostasis, resulting in OH-adducts in breast tissue, and distort the geometry of the DNA in measurable ways that are predictive of breast cancer.

PAHs are known to damage DNA and researchers are looking into the possible association between breast cancer, PAHs, and polymorphisms in carcinogen activation, detoxification, and DNA repair genes.<sup>9, 22</sup> Studies have investigated interactions with polymorphisms in XRCC1, XPD, SULT1A1, and GSTM1, yielding some positive and some null results.<sup>9</sup> It will be important to see whether consistent associations

emerge in multiple studies of these or other polymorphisms.

PAHs and their metabolites have been associated with mutations in the tumor suppressor gene p53, which are associated with poorer breast cancer outcomes.<sup>23, 24</sup>

Some studies have found p53 mutations to be more common among African American than white women or differences in the pattern of mutations between racial groups. A study found that African American women were significantly more likely than white women to have mammary tumors that over-express p53.<sup>25</sup> A previous study had not found a difference.<sup>26</sup> PAHs and their metabolites can also be agonists or antagonists in hormonal pathways.<sup>23</sup>

## **Dioxins**

Dioxins are organochlorine compounds, discussed in Section I, Chapter B.2, Persistent Organic Pollutants. However, because the primary source of dioxins is the combustion of organic material in the presence of chlorine, and they are commonly released into the air, some exposure issues are addressed here.

### **Concept/Exposure Definition**

Nearly 80 percent of dioxin emissions come from coal-fired utilities, metal smelting, diesel trucks and equipment (on- and off-road), land application of sewage sludge, and burning of treated wood and trash. After incineration, dioxins can reform in the atmosphere above the stack. With new emissions rules from 1995-97, the EPA estimated that incinerator emissions of dioxins would be reduced

by more than 95 percent, making it a minor contributor to atmospheric dioxin.<sup>27</sup> Dioxins are also present in smoke from typical cigarettes, particularly in those with chlorine-bleached paper and residues of chlorinated pesticides.

For the general population, most dioxin exposure occurs through the diet, with more than 95 percent of dioxins stemming from consumption of fats in milk, fish and meat. A much smaller proportion of exposure comes from inhalation of trace amounts of dioxins on particles in ambient air and in vapor form, from inadvertent ingestion of soil containing dioxins, and from absorption through the skin contacting air, soil, or water containing minute levels.<sup>28</sup> The ambient environmental contribution would be higher for people living near point sources where emissions are not adequately controlled. Workers may be exposed to dioxins in the chemical industry, or in the application of chemicals, notably herbicides.

Dioxins are commonly found in human adipose tissue, serum, and milk. Children are exposed to dioxins in utero and from breast-feeding. Animal experiments indicate the most sensitive stages to disruption of mammary gland development by dioxin occur in the womb and from infancy to sexual maturity<sup>12</sup>

### **Critical Review of Literature**

Evidence regarding dioxins is sparse and methodologically limited, but suggestive of an association with breast cancer. One dioxin congener, Tetrachlorodibenzo-p-dioxin (TCDD) is a known human carcinogen, based on an increase in all cancers.<sup>5</sup> TCDD binds strongly to the aryl hydrocarbon receptor (AhR), which is involved in

signaling and activating genes in mammary and other tissues. This binding can change gene expression, metabolism, and cell growth and differentiation, and can also disrupt hormone and growth factor pathways. The offspring of mice treated with TCDD during pregnancy had significant impairment of mammary gland differentiation, and slight impairment of hormone production.<sup>29</sup>

TCDD and other dioxins are also reported to have multiple endocrine effects, including estrogenic and anti-estrogenic activity;<sup>30</sup> although they cause cancer in animal models, they have been explored as possibly protective against breast cancer. Human evidence of the role of dioxins in breast cancer has come primarily from occupational studies and increasingly from the residents of Seveso, Italy, who were highly exposed from an industrial accident.<sup>9, 31</sup> The Belgian study cited above found that dioxins were also present in the ambient air, and that the significant delay in breast development in the adolescents was also associated with a doubling of serum dioxin concentrations.<sup>12</sup> Dioxins are discussed further in Section I, Chapter 2.2, Persistent Organic Pollutants.<sup>13</sup>

## Fuel Additives

With increases in fossil fuel prices and the stricter regulation of fuel economy and emissions, fuel formulations have been changing, particularly for motor vehicles. This leads to the production of different levels and mixtures of combustion byproducts. These changes are often made in response to economic, political and/or environmental concerns, before a thorough study

of potential long-term health effects has been conducted.

The main source of exposure to fuel additives among the general population is from inhalation while fueling at gasoline filling stations, driving, and in parking garages or homes with attached garages.<sup>32</sup> These products vary in solubility; some but not all may affect ground water quality.

**Fuel Oxygenates:** Under the 1990 Clean Air Act amendments, oxygenates must be added to gasoline to reduce carbon monoxide (CO) emissions. The oxygenate methyl tertiary-butyl ether (MTBE) reduces engine knocking and improves combustion, thereby minimizing CO and aromatic hydrocarbon emissions.<sup>33</sup> Nonetheless, MTBE is listed as a toxic in the volatile organic compounds monitored by the CARB, and combustion of MTBE results in increased formaldehyde, tertiary-butyl alcohol (TBA) and isobutene emissions. Due to concern for MTBE contamination of ground water and drinking water supplies, MTBE use in gasoline was discontinued at the end of 2002.<sup>34</sup>

MTBE is widely distributed in body tissues and can metabolize to formaldehyde, a genotoxic agent, within the body.<sup>35</sup> The weight of the evidence does not support a genotoxic mode of action for MTBE.<sup>33</sup> MTBE does not affect the estrogen receptor, but it increases estrogen catabolism. It has been associated with decreased incidence of endometrial hyperplasia and changes in other estrogen-sensitive organs, but serum estrogen levels and ER functions were not affected.<sup>36</sup>

MTBE is listed as unclassifiable as to its carcinogenicity to humans. Carcinogenicity by oral and inhalation routes has been observed in animals,<sup>34</sup> and as have weak tumorigenic responses,<sup>33</sup> but neither was observed specifically in breast tissue. No human cancer studies were identified. Some experts note that such actions either do not occur in humans, or that humans are less susceptible to these effects, concluding that it is unlikely that humans would be exposed to sufficient levels of MTBE to cause these tumorigenic responses.<sup>33</sup> One model predicted that the overall health effect of increased MTBE use would include a decrease in all cancers compared to gasoline that has not been reformulated, primarily due to the reduction of volatile organic compounds—specifically a decreased exposure to 1,3-butadiene and benzene.<sup>32</sup>

Ethyl tertiary-butyl ether (ETBE) and tertiary-amyl methyl ether (TAME) are alternative oxygenates used in gasoline. California limited the amount of these and other fuel additives shortly after the MTBE ban.<sup>37</sup> Data on ETBE and TAME are even more limited than MTBE, but the latter is considered more acutely toxic and from in vitro study, a dose-related chromosome aberration has been reported.<sup>32</sup> The single rat study of ETBE carcinogenicity found increased incidence of neoplasms at several sites, including malignant Schwannoma in the uterus.<sup>38</sup> The study design and interpretation have been questioned and it is not listed by IARC, National Toxicology Program, or other organizations classifying cancer risk. ETBE toxicity is sometimes inferred from data on MTBE. Computer modeling of the ETBE chemical structure has predicted that it is neither genotoxic nor carcinogenic.<sup>32</sup>

TBA, another oxygenate and a fairly persistent metabolite of both MTBE and ETBE, is not believed to be genotoxic.<sup>33</sup> TBA has not been classified as to its carcinogenicity by any major organization. One review found that while TBA exposure in drinking water was associated with adenomas and carcinomas at certain sites, it was associated with a decreased incidence of mammary adenomas, fibromas, and carcinomas in female rats.<sup>38</sup> At least one study found that there is great inter-individual variability in the metabolism of MTBE, ETBE and TAME, suggesting that the genetic polymorphism of a critical enzyme (CYP2A6) is important in determining individual sensitivity to these oxygenates.<sup>39</sup>

**Ethanol/Acetaldehyde:** The increasing use of ethanol as a substitute and oxygenate for gasoline will result in higher atmospheric concentrations of acetaldehyde (the first metabolite of ethanol oxidation) from motor vehicle exhaust, as well as peroxyacetylnitrate (PAN),<sup>35</sup> and ozone.<sup>40</sup> When unburned ethanol is released, it is also converted to acetaldehyde and eventually to PAN and formaldehyde.<sup>35</sup> Acetaldehyde is used in chemical production, including flavorings, fragrances, pesticides, disinfectants, drugs varnishes, and dyes, from which it is commonly released into the air.<sup>5</sup> It also occurs naturally in plant respiration and alcohol fermentation. Acetaldehyde is a Hazardous Air Pollutant listed as a Toxic Air Contaminant in California based on evidence of carcinogenicity (reasonably anticipated to be a human carcinogen per the 11<sup>th</sup> RoC<sup>5</sup>).

In addition to vehicle exhaust, the general public may be exposed to acetaldehyde in ambient and indoor air from cigarette smoke, wood burning

and other fuel combustion, and air deodorizers. It has been detected in breast milk.<sup>5</sup> Ethanol use in gasoline may increase the spread of benzene and other volatile organic chemicals (VOCs) in ground water.<sup>32</sup> While it has been assumed to pose a lower risk for ground water contamination than MTBE, the California Air Resources Board felt it would not affect the public health impact of air pollution.<sup>32</sup>

The vast majority of the research on acetaldehyde's role in cancer has focused on the direct consumption of alcohol, where it is suspected of co-carcinogenic effects, including dysregulation of proliferation and apoptosis.<sup>41</sup> Researchers have found that cancer risk related to acetaldehyde levels and metabolism is affected by genetics;<sup>41</sup> no literature on this genetic linkage was identified for inhalation exposure.

Among the limited inhalation research, some studies have found an association with other cancers,<sup>5,42</sup> but there is no evidence regarding mammary gland tumors. Acetaldehyde binds to proteins and DNA, resulting in impairment of cellular morphology and function, and which could provide a mechanism for replication errors and/or mutations in oncogenes or tumor suppressor genes.<sup>41</sup>

Research indicates that ethanol can also interact with cellular macromolecules and produce DNA damage through free radical mechanisms.<sup>35,41</sup> While this risk may be most significant for the increasing number of people working with ethanol, it remains to be seen whether this can occur with atmospheric ethanol. Exposure to peroxyacetylnitrate (PAN) is not well documented.<sup>43</sup> While PAN has not been tested for

carcinogenicity, it is reportedly genotoxic<sup>35</sup> and a weak point mutagen.<sup>32</sup> Further evaluation could also be directed at the potential impact of increased levels of acetaldehyde and PAN.

## Air Pollutants

**1,3-Butadiene:** Carcinogenicity Potency Database, National Toxicology Program and the National Library of Medicine Chemical Carcinogen Research Information System list 1,3-butadiene as a probable human carcinogen. 1,3-Butadiene is a component of gasoline, vehicle exhaust, and cigarette smoke. It is used to produce other compounds, including synthetic rubber, which also involves the use of styrene (see Section I, Chapter B.5, Solvents and Industrial Chemicals).

The most common route of exposure is inhalation. Air levels are higher near petrochemical facilities, while industrial releases have decreased.<sup>5</sup> Although some food packaging contains residual 1,3-butadiene, data suggest that it does not usually migrate to the food.<sup>4</sup> Certain cooking oils, such as rape oil (canola) release 1,3-butadiene when heated.

1,3-Butadiene metabolites are known to be mutagenic and carcinogenic and have been found in the urine of exposed workers. Metabolites appear to alter proto-oncogenes and/or tumor suppressor genes.<sup>5</sup> Three studies found increased levels of mammary tumors in mice and rats.<sup>4</sup> One of the rat studies found that mammary tumor formation involved the endocrine system.<sup>44</sup>

**Nitromethane:** This compound is primarily used to synthesize derivatives used as pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials, and is also addressed in Section I, Chapter B.5, Solvents and Industrial Chemicals. Moreover, nitromethane is used as a fuel or an additive with methanol in racing cars and boats, and in the production of explosives.<sup>5</sup> The most common nitromethane exposure sources are motor vehicle exhaust and tobacco smoke. However, people working with or near this hazardous substance may be exposed to higher levels through inhalation of fumes. Nitromethane is reasonably anticipated to be a human carcinogen. Administered by inhalation, it significantly increased benign and malignant tumors at multiple sites in both mice and rats, including mammary gland tumors in female F344/N rats. However, no human studies were found in the published literature and the mechanism by which nitromethane causes cancer is not known.<sup>5</sup>

## **Conclusions and Future Directions**

People are thinking about much too narrow a set of chemicals in relation to breast cancer, so it is important to think about all of the chemicals for which we have animal evidence that they are mammary carcinogens. With the advent of ethanol, continued use of oxygenates and other changes in fuel formulations, additional study of the impact of the parent compounds, metabolites and combustion byproducts is critical. Primary research into these issues is needed to identify possible links to breast cancer.

It is critical to study oxygenates, such as methyl tertiary hexyl ether and methyl tertiary octyl ether, before they are introduced.<sup>45</sup> Using these products

in fuel ensures their introduction into the environment and the potential for human exposure; therefore these compounds should be thoroughly tested.<sup>35</sup> Acetaldehyde and PAN are potentially significant carcinogens, indicating a need to better understand their health effects and the toxicokinetics of ethanol.

Methodological problems include inadequate dioxin and TCDD exposure assessment, lack of unexposed populations, and lack of preclinical markers to identify associations that may be obscured by disease latency. Work on identifying an appropriate biomarker is continuing.<sup>46</sup> It may also be important to study specific congeners, rather than look at total dioxins.

Perhaps most promising would be research into the polycyclic aromatic hydrocarbons (PAHs). Studies to date are suggestive of causal and promotional relationships between PAHs and breast cancer. It has been difficult to measure or estimate exposure to PAHs, since exposure occurs over a lifetime from multiple sources. Biological measurements in blood are intrusive and expensive, and would require repeated testing to represent long-term exposure. Ambient air monitoring and mapping of traffic and industrial sources to estimate exposures from outdoor pollution do not directly indicate exposure to individuals and do not account for time indoors.<sup>22,</sup><sup>47</sup> Self-reported exposures from tobacco smoke and diet involve errors and often bias in recall. Improvements in biomonitoring methods, additional ambient and personal air pollution monitoring, and refined modeling of relationships between environmental databases and individual

exposure will improve future epidemiologic studies.

Given the variety of PAHs and the mixtures encountered, further research needs to be carried out on nitro-PAHs and fine particles to understand the dose and mechanism for a mutagenic effect.<sup>8</sup> The relative contributions to adduct formation and breast cancer of the various PAH sources also need further study and may help distinguish between dietary and ambient air exposures. The development of new methods may help; for example, Binkova et al. reported that exposure to cigarette smoke and ambient air pollution, and a single polymorphism, were predictive of a PAH-DNA adduct specific to benzo[a]pyrene.<sup>22</sup>

While it is possible to directly measure the genotoxic effect (PAH-DNA adduct) in target tissue, this adduct is short-lived and it has been argued that higher levels may be “a biomarker of greater susceptibility.”<sup>23</sup> Better biological measures are needed and work is underway to develop new biomarkers.<sup>48</sup> To better understand the role of PAHs in breast cancer risk, epidemiologists could identify and monitor susceptible subpopulations or highly-exposed workers over time, improving the exposure estimates.

Other than PAHs, data on exposure to hazardous air pollutants, such as MTBE, acetaldehyde and 1,3-butadiene, are very limited. These exposures vary geographically in California. One attempt to model the cancer risk from volatile organic compounds (VOCs) in the ambient air in Los Angeles found levels from two to 100 times the U.S. EPA benchmark.<sup>49</sup>

Assessment of actual exposure to these pollutants has been challenging. Data from monitors is limited, so the CARB also uses emissions inventory and air quality models to evaluate air quality.<sup>50</sup> Their periodic air quality modeling may not be frequent enough or on a geographic scale that is useful for health studies, however they make an extensive collection of modeling software available to researchers and the public.

More robust, validated exposure assessment methods are needed to examine the relationship between various air pollutants and breast cancer, as well as other adverse health outcomes. Researchers at California universities and the California Department of Public Health’s Environmental Health Investigations Branch (EHIB) have been working on health effects associated with air pollution and evaluating models to estimate exposure for their usefulness in health studies.<sup>51-53</sup> It may be most useful to study air contaminants together, given that actual exposure is never limited to a single component. Future studies should also take into account that ambient concentrations of pollutants are not a good indicator of indoor where people spend most of their time.<sup>54</sup>

Finally, future research into the relationship between air pollutants and breast cancer should consider the significant potential confounding with neighborhood level disparities. Air pollution levels are often higher in lower income areas, given their proximity to traffic, industry and other sources of contamination. While the correlation is not perfect, racial and ethnic minorities are disproportionately exposed to air and other toxics, and associated health risks even across economic

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strata, but most pronounced in neighborhoods with high levels of poverty.<sup>55-59</sup> Recent research suggests that disparities associated with ambient air toxics are affected by segregation and that these exposures may have health significance for populations across racial lines.<sup>60</sup> These interactions between the physical environment and social disparities deserve additional research.

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