The Parallel Transformations of Polycyclic Aromatic Hydrocarbons in the Body and in the Atmosphere

Amy I.H. Hrdina, Ishwar N. Kohale, Simran Kaushal, Jamie Kelly, Noelle E. Selin, Bevin P. Engelward, and Jesse H. Kroll

1Department of Civil and Environmental Engineering, Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, USA
2Department of Biological Engineering, MIT, Cambridge, Massachusetts, USA
3Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
4Department of Geography, University College London, London, UK
5Institute for Data, Systems, and Society, MIT, Cambridge, Massachusetts, USA
6Department of Earth, Atmospheric, and Planetary Sciences, MIT, Cambridge, Massachusetts, USA

BACKGROUND. Polycyclic aromatic hydrocarbons (PAHs) emitted from combustion sources are known to be mutagenic, with more potent species also being carcinogenic. Previous studies show that PAHs can undergo complex transformations both in the body and in the atmosphere, yet these transformation processes are generally investigated separately.

OBJECTIVES. Drawing from the literature in atmospheric chemistry and toxicology, we highlight the parallel transformations of PAHs that occur in the atmosphere and the body and discuss implications for public health. We also examine key uncertainties related to the toxicity of atmospheric oxidation products of PAHs and explore critical areas for future research.

DISCUSSION. We focus on a key mode of toxicity for PAHs, in which metabolic processes (driven by cytochrome P450 enzymes), lead to the formation of oxidized PAHs that can damage DNA. Such species can also be formed abiotically in the atmosphere from natural oxidation processes, potentially augmenting PAH toxicity by skipping the necessary metabolic steps that activate their mutagenicity. Despite the large literature related to these two general pathways, the extent to which atmospheric oxidation affects PAH’s overall toxicity remains highly uncertain. Combining knowledge and promoting collaboration across both fields can help identify key oxidation pathways and the resulting products that impact public health.

CONCLUSIONS. Cross-disciplinary research in toxicology and atmospheric studies evaluate atmospheric oxidation products and their mixtures, and atmospheric measurements examine the formation of compounds that are known to be most toxic. Close collaboration between research communities can help narrow down which PAHs, and which PAH degradation products, should be targeted when assessing public health risks. https://doi.org/10.1289/EHP9984

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a broad class of environmental toxicants, known to lead to a number of negative effects in humans. They are introduced into the environment via incomplete combustion processes, such as fossil fuel combustion and biomass burning, and are found in all compartments of the environment—air, sediments, and natural waters—leading to their presence in food as an additional route of exposure. In general, PAHs in the air are more widely distributed and more bioavailable than PAHs bound to solid matrices, such as soil, making inhalation a major exposure route. In particular, fine particles, which may carry PAHs, are able to penetrate deep into the lungs. As a result, PAHs are a major subject of study in the fields of both toxicology and atmospheric chemistry. Their prevalence throughout the environment and their associated carcinogenic effects have prompted international regulations, such as those under the United Nations Economic Commission for Europe’s Convention on Long-Range Transboundary Air Pollution. In addition, the U.S. Environmental Protection Agency has developed a priority list of PAH compounds that are thought to be the most harmful.

Considerable work has gone into identifying the sources, transport, and fate of PAHs in the atmosphere. Atmospheric PAH sources can vary dramatically by region and include vehicle exhaust, forest fires, and wood and coal combustion. Another potentially important source is heavily polluted soil, in which the PAHs that have accumulated in the soil over time can volatilize back into the atmosphere. The mobility of PAHs through the atmosphere is governed by their water solubility and volatility and by atmospheric conditions. Ultimately their atmospheric lifetimes are determined by chemical processing (oxidation) and physical removal (deposition) during transport. Many PAHs are low in volatility and so will be present on (or in) fine particles, where they are relatively protected from oxidation. They can, therefore, have atmospheric lifetimes of up to weeks, during which time they can travel distances of up to tens of thousands of kilometers. The effects of PAH exposure on human health have also been a major area of research. This includes epidemiological studies on occupational exposure, as well as toxicological research centered on the metabolic pathways that drive PAH mutagenicity and carcinogenicity in humans. Several metabolic activation pathways of PAHs have been identified and they generally induce one of two predominant modes of toxicity: (a) mutagenicity, in which PAHs lead to the formation of DNA adducts, and (b) oxidative stress, in which the PAHs promote the formation of reactive oxygen species (ROS). The mutagenicity of PAHs generally increases with increased molecular weight; these larger PAHs are predominantly found in fine particulate matter [PM ≤2.5 μm in aerodynamic diameter (PM2.5)]. One such large PAH, benzo[a]pyrene [B[a]P], C20H12, has long been known to be a potent human carcinogen and is thus the focus of many toxicology studies and often serves as a model system for total PAH exposure.

A number of studies have examined the toxicity of the products of the atmospheric oxidation of PAHs. There has also been substantial work aimed at understanding the key metabolic transformations of PAHs. However, the two classes of...
Metabolic Activation of PAHs

Humans have evolved to detoxify and excrete xenobiotic chemicals. Nonpolar species, such as PAHs, must be transformed into more polar (water-soluble) metabolites to be effectively excreted from the body. In most cases, such metabolism of foreign chemicals in the body is driven by the cytochrome P450 superfamily of monooxygenase enzymes. The resulting oxidized (activated) metabolites are normally conjugated with polar moieties—such as glucorionate, glutathione, acetate, and sulfate—in a second stage of the removal process to make them water soluble.

The complex transformations that PAHs undergo within the body, using B[a]P as a model compound, are shown in Figure 1. The metabolism of B[a]P in the body can occur through three distinct pathways: (1) a radical-cation pathway, (2) a diol-epoxide pathway, and (3) a quinone pathway (Figure 1). These mechanisms are not mutually exclusive, and they likely all play a role in the overall carcinogenesis of B[a]P given that they all can lead to formation of toxic products.

In the radical-cation pathway (pathway 1), the one-electron oxidation of B[a]P by peroxidase enzymes forms a B[a]P radical cation that reacts with DNA to form depurinated adducts, inducing G → T transversions in DNA. In the diol-epoxide and quinone routes (pathways 2 and 3), the first step involves the P450-mediated formation of B[a]P-diol through an epoxide intermediate. The epoxide intermediate B[a]P-7,8-oxide is shown in Figure 1, although several others (the 2,3-, 4,5- and 9,10-oxides) are formed as well. B[a]P-4,5-oxide was originally thought to be the key toxic product that reacts with DNA, but it was later found to readily hydrolyze into B[a]P-4,5-diol, which is nonmutagenic.

Instead, it has been shown that the 7,8 regiosomer leads to the formation of toxic products. The initial B[a]P-7,8-oxide is less carcinogenic than B[a]P, which is likely due to its instability at physiological conditions. However, when it is hydrolyzed by epoxide hydrolase (EH), the epoxide ring opens to form B[a]P-7,8-diol, which is more carcinogenic than the parent. B[a]P-7,8-diol undergoes the epoxide route (pathway 2), another cycle of P450 and EH activation of B[a]P-7,8-diol leads to the formation of B[a]P-7,8-diol-9,10-epoxide (BPDE), which readily reacts with the guanine bases in DNA to form DNA adducts and is thus considered to be the ultimate carcinogen. In response to detecting moieties bound to DNA, the cell attempts to repair the adducts through the nucleotide excision repair (NER) pathway. In this process, a portion of the strand that has the DNA adduct is removed, and the resulting single-strand gap is then filled via repair synthesis. Although beneficial, NER does not always repair DNA damage fast enough to prevent the DNA adducts from interfering with the ability of the cell to accurately replicate the DNA. Unrepaired bulky lesions caused by BPDE are often read incorrectly by polymerases during DNA replication, leading to substitution mutations in the new copy of DNA. If the mutations occur in oncogenes or tumor suppressor genes, the alterations in gene function can potentially contribute to tumor formation.

First, the quinone pathway (pathway 3 in Figure 1) involves dehydrogenation of B[a]P-7,8-diol by aldo-keto reductase (AKR) enzymes, generating a catechol that enters a redox cycle with oxygen (O_{2}) to form B[a]P-7,8-quinone and ROS. In vitro assays show that B[a]P-7,8-quinone is capable of reacting with DNA (although it is less mutagenic than BPDE), and it can also generate ROS, resulting in extensive damage to DNA, proteins, and lipids.

Atmospheric Oxidation of PAHs

PAHs emitted into the air can undergo abiotic chemical processing via atmospheric photooxidation, sometimes referred to as atmospheric aging. Key atmospheric oxidants of PAHs include ozone (O_{3}), the hydroxyl (OH) radical, nitrogen dioxide (NO_{2}), and the nitrate (NO_{3}) radical. Oxidation can occur either in the gas phase or the condensed phase (i.e., in or on PM) and can form a number of products, including a range of oxidized PAH compounds.
Recent work has shown that mass-transfer limitations may slow heterogeneous oxidation. Particle coatings (formed either from heterogeneous oxidation or condensation of low-volatility species) can "shield" particulate PAHs, decreasing the rate of oxidation by gas-phase oxidants, thereby increasing their atmospheric lifetimes. Laboratory-derived chemical mechanisms are used to inform chemical transport models, which are used in assessments of atmospheric levels of PAHs and their associated human cancer risk. Across these modeling studies, the oxidation rate of particulate B[a]P is found to be a key driver of uncertainty in estimates of exposure, human cancer risk, and the importance of long-range atmospheric transport.

Examples of products formed by the heterogeneous oxidation of particulate PAHs (using B[a]P as a model compound) are shown in Figure 2. In most experimental studies of this system, products are generally detected using mass spectrometry, which provides information on chemical formulas but, typically, with no identification of specific regioisomers (in which the locations of the functional groups on the PAH skeleton are known). It is likely that regioisomers of B[a]P products other than those shown in Figure 2 are produced in atmospheric oxidation. Only a small handful of product studies have reported specific regioisomers. The formation of these general product classes are not specific to B[a]P: Heterogeneous oxidation also leads to the formation of similar oxidized products from other PAHs, such as phenanthrene, pyrene, and benz[a]anthracene. Similarly, the oxidation of PAHs within ambient aerosol particles with O3 and the OH radical also results in the formation of catechols/quinones and nitro products.

The further oxidation of oxidized PAH products likely leads to the formation of later-generation species that are even more functionalized than those shown in Figure 2. In addition, the PAH skeleton tends to break down as it undergoes further oxidation, and so such later-generation products may include more ring-opening species as well. However, because longer oxidation timescales are often not accessed in the laboratory and highly functionalized species tend to be challenging to detect, the identities of these later-generation products are generally not well understood at present.

**Discussion**

**Parallels between Atmospheric Oxidation and Metabolic Activation**

The pathways that activate PAHs in vivo (metabolically) or ex vivo (atmospherically) have notable parallels given that both processes involve the oxidation of PAHs to form a range of functionalized, polyaromatic species.
many of the known classes of products formed by atmospheric oxidation are similar to (and potentially the same as) metabolic mutagens formed in the body. This connection was first suggested by Pitts et al., who used the Ames Salmonella typhimurium bacterial assay to demonstrate the presence of active mutagens in ambient PM in Los Angeles; they suggested that oxy-PAHs, formed by atmospheric oxidation of PAHs, could be the underlying reason. In follow-up work, Pitts et al. observed that reaction of B[a]P with O3 led to the formation of B[a]P-4,5-oxide, a known metabolite of B[a]P that was originally thought to be highly mutagenic. The formation of this compound from PAH oxidation suggested that mutagenic PAH derivatives can be formed not only by metabolic activation but also abiotically in the atmosphere. This ”atmospheric activation” of PAHs could potentially bypass metabolic activation and directly form mutagens.

In the years since, a number of other classes of mutagenic metabolites (Figure 1), such as quinones and diols, have since been detected in PM and in controlled laboratory studies involving the oxidation of PAHs. Recently, it was even shown that B[a]P-diol-epoxides (a class of compounds that includes BDPE, a potent carcinogen) were formed by the atmospheric oxidation of B[a]P. Such studies affirm that atmospheric oxidation (Figure 2) can form species that are the same as (or regioisomers of) those generated throughout the metabolic activation chain (Figure 1).

Figure 3 shows the relationship between metabolic activation and atmospheric activation of PAHs (again using B[a]P as a model compound). The PAH emission sources introduce parent compounds into the atmosphere, with particle-bound PAHs able to undergo transport and aging over periods of several days. Atmospheric oxidation causes PAHs to become increasingly functionalized, with B[a]P oxidizing to form species such as B[a]P-oxides, B[a]P-catechol, B[a]P-diol-epoxides, and B[a]P-quinone products, all of which are formed in cell metabolism as well. These two systems are connected via inhalation, which can occur at any point along this time line, followed by transport through cell membranes, which is less understood (and discussed below). As a result, atmospheric oxy-PAHs are potentially delivered to the cells “preprocessed,” with no need for metabolic activation. A major implication of the atmospheric activation of PAHs is that the toxic effects of PAHs are not restricted to cell types that express P450, as is the case for metabolic activation.

There is substantial evidence that oxidized PAH species in PM can be important contributors to mutagenicity. Although earlier work tested for mutagenicity using bacterial assays (e.g., the Ames assay), more recent studies have shown the mutagenicity of oxy-PAHs and nitro-PAHs in various mammalian cells as well. Such studies find that these species contributed to the overall mutagenicity of sampled PM. However, there are also some instances where oxidized products have been found to be less toxic than their parent compounds; for example, a nitrated derivative of B[a]P, 6-nitro-B[a]P, appeared to be less toxic than B[a]P in several lung and liver carcinogenicity assays.

Implications and Uncertainties

Given that PAHs can undergo atmospheric activation in parallel to metabolic activation, atmospheric oxidation products need to be considered when assessing the health impacts of PAHs. However, there are also considerable differences between the two activation processes, which introduce a number of key uncertainties that limit our understanding of the role of atmospheric activation on human health. These include the identity of the oxidized...
PAH products formed by atmospheric aging, the role of the particle matrix in the toxicity of such species, and the bioavailability of such species. These three uncertainties are discussed below.

First, atmospheric measurements tend to be limited to measuring molecular formulas and not structures, so the exact oxy-PAH isomers formed during atmospheric aging is generally poorly constrained. Atmospheric processing is not as well regulated or selective as cell metabolism. Although metabolism generally leads to the formation of one isomer (or small handful of isomers) of a given reaction product (Figure 1), abiotic processing in the atmosphere can potentially form a wide range of oxidation products in each step (Figure 2). In particular, the regioisomers formed in atmospheric activation may differ from those formed in metabolic processes and may well exhibit different toxicity. For example, Zhou et al. observed the formation of B[a]P-diol-epoxides from the O3 oxidation of B[a]P but were unable to identify their exact structures owing to a lack of available standards; thus, the extent to which BDPE itself is formed in atmospheric oxidation remains unknown. This might have important implications for toxicity because there is evidence that even stereoisomers of BPDE, in which the locations of functional groups are the same but are spatially distinct, are not equally mutagenic. Similarly, Geier et al. have recently shown that the position of OH groups on naphthalene derivatives determined bioactivity and, in some cases, which tissue was targeted. Therefore, comprehensive studies of PAH oxidation products paired with toxicity studies of these products and product mixtures are needed to provide information on the toxicity of the full distribution of oxidized PAHs formed in the atmosphere.

Another challenge in determining the health impacts of PAHs is that oxidized PAHs (and their parent PAHs) are usually present within complex mixtures in atmospheric PM. Other chemical species co-present within the mixture may modify the toxicity and bioavailability of the oxy-PAHs, making it difficult to resolve the health impacts associated with these species alone. Recent work by Lammel et al. suggests the bioavailable fraction of oxy-PAH in PM is affected by the water solubility of the oxidized PAH and the lipophilicity of the particle matrix. Similarly, Dilger et al. demonstrated PAHs adsorbed to wood smoke particles were more potent in activating target gene expressions than pure B[a]P suspensions. Epidemiological studies have revealed that the effects of mixtures may be synergistic (enhanced cancer risk) or antagonistic (suppression of cancer risk) relative to the risks associated with PAH exposure alone. It seems likely that whether other compounds in PM enhance or suppress cancer risk is likely to be dependent on both the specific (oxy-)PAHs in question and the detailed composition of the mixture. Such effects can be quite complex: For example, a binary mixture of B[a]P and 1-methylphenanthrene (also a known carcinogen) can enhance DNA adduct formation while suppressing gene expression of metabolic enzymes. The fate and impacts of PAHs therefore cannot be fully resolved by only separating and identifying the specific oxidized derivatives formed in the atmosphere given that the role of interactions with the aerosol particle matrix and co-emitted pollutants must also be considered. We argue that such effects are an important area for further research.

Furthermore, the extent to which oxidized PAH products introduced into the body can enter cells and interact with DNA is poorly understood. Oxidized PAHs are more polar (less lipophilic) than the parent PAHs and thus may not easily cross the cell membrane. Therefore, even if oxy-PAHs known to be highly toxic are generated in the atmosphere and enter the body via inhalation, they may not enter the cells and undergo the same biochemical transformations of the parent PAH. Further, it is unclear whether oxidized PAHs bind to the AhR; as described above, binding to AhR activates a cell response that transports
the PAH into the nucleus. The extent to which oxidized PAHs can activate the same pathway is not fully known given that some oxidized PAHs might still require some level of metabolic activation to react with DNA. In a recent study, several oxy-PAHs (quinone and ketone derivatives) were found to induce P450 enzyme signals, suggesting activation of the AhR pathway. However, a few oxy-PAHs, such as benz[a]anthracene-7,12-quinone, showed both AhR activation and inhibition of P450 enzyme activity. The effect of oxidized PAHs on the metabolic pathway, and thus on mutagenicity, appears to vary with the identity of compounds. Geier et al. demonstrated that the relationship between structure and toxicity is complex and not predictable by generalized descriptors of physical properties, warranting further studies to understand the fate of oxidized PAHs in cells. Therefore, the degree to which atmospherically activated PAH products enter the cell, are metabolized, and/or ultimately interact with DNA, remains poorly understood. In addition, whether more heavily oxidized derivatives of PAHs (e.g., the later-generation products) are water soluble enough to be more easily excreted from the body is also essentially unknown.

These uncertainties add to the already substantial challenge in estimating the exposure and health effects of PAHs. In contrast to commonly regulated pollutants (e.g., O3, PM, NO2), measurements of PAHs and their derivatives are generally not monitored routinely and are thus extremely sparse. This increases reliance on the use of chemical transport models to predict ambient concentrations of parent PAHs across a wide range of temporal and spatial scales to assess their health effects. Such models must contend with uncertainties in emissions, transport, chemical degradation, and deposition; the need to track formation of toxic by-products (oxidized PAHs) adds still more complexity to such models. In fact, oxidized PAHs are very rarely represented in chemical transport models; this is in part due to a lack of detailed data on the products formed in atmospheric PAH oxidation. To our knowledge, only one global-modeling study has modeled the distributions and health impact of PAH degradation products (specifically nitro-PAHs). That study found that such products can represent a major contribution to the total health risk from PAHs, underscoring their potential importance and the need for more detailed studies of the identity and toxicity of PAH oxidation products.

Further, accurate modeling of exposure depends on individual behavior, as well as individual preexisting conditions that may make some members of the population more vulnerable. The biological response to PAH exposure varies from person to person, thereby affecting an individual’s genetic disposition and susceptibility. Given that metabolites of PAHs can induce various types of DNA damage, variations in DNA repair capacity can put certain populations at an increased risk of developing cancer, even at low-dose exposure. We highlight that further research is therefore needed to understand the mechanisms that influence an individual’s susceptibility to PAH-associated health impacts.

Conclusion

There is a growing body of research, both in toxicology and in atmospheric chemistry, dedicated to investigating the mechanisms and products of PAH oxidation. Cell metabolic processes that normally serve to help remove foreign chemicals can convert PAHs into metabolites that exhibit greater toxicities than the parent compound. In parallel, chemical reactions in the atmosphere can produce the same (or similar) breakdown products as those produced metabolically. As such, it is possible for the oxidation reactions that naturally occur in the atmosphere to activate certain PAHs ex vivo into their mutagenic and carcinogenic forms, thereby potentially bypassing the need for metabolism within the body to induce deleterious effects. Thus, we argue these two pathways should not be treated in isolation but, rather, ought to be considered as a whole when assessing the overall health risks associated with PAHs.

Such environmental formation of toxic species via atmospheric activation introduces substantial complexity to the question of the overall health impacts of atmospheric PAHs. In particular, toxic species may be introduced into the body at different points in the metabolic pathway (Figure 3); this suggests that the environmental concentrations of, and populations’ exposures to, these oxidized PAH products therefore need to be better understood. Further, as noted above, a number of major uncertainties remain, including the identities and toxicities of atmospheric activation products (which may be different from those formed in metabolic activation), the roles that other species within PM may have on PAH toxicity, and the ability of atmospherically activated oxidized PAH species to enter cells and interact with DNA. We propose that addressing these questions, which are located at the interface of fields of atmospheric chemistry and toxicology, will improve our understanding of the environmental risks that PAH oxidation products pose.

Despite several decades of research on the atmospheric and metabolic transformations of PAHs, the question of whether the products formed by atmospheric aging are more or less toxic than the parent PAH remains highly unclear. Answering this question, and therefore better understanding the detailed relationship between atmospheric PAH emissions and human health, requires closer collaboration between the atmospheric chemistry and toxicology communities. Atmospheric chemistry studies can identify the rates and products of atmospheric oxidation, as well as the distributions across scales (local, regional, global) of these product mixtures. In turn, toxicological studies can provide insight into the detailed health effects of those product mixtures. By refining our understanding of the parallel processes of atmospheric and metabolic activation (Figure 3), we believe both the atmospheric and toxicological fields can bring us closer to getting a fuller picture of the total risk that PAHs pose to the public. Furthermore, such discussions can help assess the efficacy of future control measures, and ultimately minimize their impacts on human health.

Acknowledgments

This work was supported by the National Institutes of Health/ National Institute of Environmental Health Sciences Superfund Basic Research Program (grant P42 ES027707, to B.P.E.).

References

1. Hecht SS. 2002. Tobacco smoke carcinogens and breast cancer. Environ Mol Mutagen 39(2–3):119–126, PMID: 11921179, https://doi.org/10.1002/em.10071.
2. Kim KH, Jahan SA, Kabir E, Brown RJC. 2013. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their health effects. Environ Int 60:71–80, PMID: 24013021, https://doi.org/10.1016/j.envint.2013.07.019.
3. Moorthy B, Chu C, Carlin DJ. 2015. Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. Toxicol Sci 145(1):5–15, PMID: 25911656, https://doi.org/10.1095/toxsci.kfx040.
4. Becker S, Halsall CJ, Tych W, Hung H, Attewell S, Blanchard P, et al. 2006. Resolving the long-term trends of polycyclic aromatic hydrocarbons in the Canadian Arctic atmosphere. Environ Sci Technol 40(10):3217–3222, PMID: 16534984, https://doi.org/10.1021/es052346l.
5. Durant JL, Thilly WG, Hemond HF, Lafleur AL. 1994. Identification of the principal human cell mutagen in an organic extract of a mutagenic sediment. Environ Sci Technol 28(12):2033–2044, PMID: 22191742, https://doi.org/10.1021/es00061a011.
6. Baker JE, Eisenreich SJ. 1990. Concentrations and fluxes of polycyclic aromatic hydrocarbons and polychlorinated biphenyls across the air-water interface of Lake Superior. Environ Sci Technol 24(3):342–352, https://doi.org/10.1021/es00073a009.
54. Adams JD Jr, Yagi H, Levin W, Jerina DM. 1995. Stereo-selectivity and regio-selectivity in the metabolism of 7,8-dihydrobenzo[a]pyrene [BaP] toward ozone. J Phys Chem A 116(26):7050–7056, PMID: 22676584, https://doi.org/10.1021/jp030870s.

55. Kapitulnik J, Levin W, Conney AH, Yagi H, Jerina DM. 1977. Benzo[a]pyrene-7,8-dihydriodiol is more carcinogenic than benzo[a]pyrene in newborn mice. Nature 266(5600):378–380, PMID: 859006, https://doi.org/10.1038/266378a0.

56. Gillet LCJ, Schärer OD. 2006. Molecular mechanisms of mammalian global genetic analysis of the association and substrate-specific activation of epoxide hydrolase function. Arch Biochem Biophys 402(2):275–286, PMID: 12051674, https://doi.org/10.1016/j.abb.2005.08.039.

57. Palackal NT, Burczynski ME, Harvey RG, Penning TM. 2001. The ubiquitous aldehyde reductase (AKR1A1) oxidizes proximate carcinogen benzo[a]pyrene [BaP] toward ozone. J Phys Chem A 116(26):7050–7056, PMID: 22676584, https://doi.org/10.1021/jp030870s.

58. Flowers L, Bleczinski WF, Burczynski ME, Harvey RG, Penning TM. 1996. Disposition and biological activity of benzo[a]pyrene-7,8-dione. A genotoxic metabolite generated by dihydrodiol dehydrogenase. Biochemistry 35(42):13664–13672, PMID: 888546, https://doi.org/10.1021/bi600760w.

59. Liu Y, Vinje C, Pacifico C, Natile G, Sletten E. 2002. Formation of adenine-N7/guanine-N3 cross-link in the reaction of platinum-orientated substrates with dinucleotides. J Am Chem Soc 124(13):12854–12862, PMID: 12392432, https://doi.org/10.1021/ja02725u.

60. Zhou S, Shiraiwa M, McWhinney RD, Pöschl U, Abbatt JPD. 2013. Kinetic limits of particle-borne benzo[a]pyrene (BaP) toward ozone. J Phys Chem A 117(26):7050–7056, PMID: 22676584, https://doi.org/10.1021/jp030870s.

61. Seinfeld JH, Pandis SN. 2006. Atmospheric Chemistry and Physics: From Air to Space. 2nd ed. Hoboken, NJ: Wiley.

62. Anderson JT, Achatz C. 2015. Time to say goodbye to the 16 EPA PAHs? Toward an up-to-date use of PAEs for environmental purposes. Polycycl Aromat Comp 35(2–4):330–354, https://doi.org/10.1080/10640363.2014.910142.

63. Estvez W, Buzdžinić H, Villenave E. 2004. Relative rate constants for the heterogeneous reactions of OH, NO, and NO2 radicals with polycyclic aromatic hydrocarbons adsorbed on carbonaceous particles. Part 1: PAHs adsorbed on 1–2 μm calibrated graphite particles. Atmos Environ 38(35):6063–6072, PMID: 15049071, https://doi.org/10.1016/j.atmosenv.2004.05.059.

64. Estvez W, Buzdžinić H, Villenave E. 2006. Relative rate constants for the heterogeneous reactions of OH, NO2, and O3 radicals with polycyclic aromatic hydrocarbons adsorbed on carbonaceous particles. Part 2: PAHs adsorbed on diesel particulate exhaust SRM 1650a. Atmos Environ 40(2):201–211, https://doi.org/10.1016/j.atmosenv.2005.07.053.

65. Kwamena NDA, Thorntom JA, Abbatt JP. 2004. Kinetics of surface-bound benzo[a]pyrene and ozone on solid organic and salt aerosols. J Phys Chem A 110(30):3638–3646, PMID: 15626646, https://doi.org/10.1021/jp051252d.

66. Butler JD, Crossley P. 1981. Reactivity of polycyclic aromatic hydrocarbons adsorbed on soot particles. Atmos Environ 15(1):51–94, https://doi.org/10.1016/0004-6981(81)90129-3.

67. Lu JW, Flores JM, Lavi A, Abo-Riziq A, Rudich Y. 2011. Changes in the optical properties of benzo[a]pyrene-coated aerosols upon heterogeneous reactions with NO3 and NO2. J Phys Chem A 114(14):4844–4849, PMID: 21378662, https://doi.org/10.1021/jp201144h.

68. Pitts Jr NJ, Van Cauwenberge KA, Grosjean D, Schmid JP, Fitz DR, Balzer WL, et al. 1978. Atmospheric reactions of polycyclic aromatic hydrocarbons: facile formation of mutagenic nitro derivatives. Science 202(4377):519–519, PMID: 12052341, https://doi.org/10.1126/science.202341.

69. Zimmermann K, Jariyasopit N, Massey Simonich SL, Tao S, Atkinson R, Arey J. 2013. Formation of nitro-PAHs from the heterogeneous reaction of ambient particle-bound PAHs with NO2/NO3. Environ Sci Technol 47(15):8434–8442, PMID: 23865889, https://doi.org/10.1021/es304789x.

70. Sánchez NM, de Klerk A. 2021. Heavy oil upgrading by oxidative ring-opening of polycyclic aromatic hydrocarbons. In: Catalytic and Noncatalytic Upgrading of Oils. Dalai AK, Daydburjir DB, Zhang Y, Duan A, Roberts WL, Nanda S, eds. Washington, DC: American Chemical Society, 189–209.
101. Dilger M, Mischke D, Grosjean TM, Simonov VF, Poole D. 1977. Mutagenic activity of airborne particulate organic pollutants. Toxicol Lett 1(2):65–70, https://doi.org/10.1016/0378-4177(77)90023-6.

102. Hermann M. 1981. Synergistic effects of individual polycyclic aromatic hydrocarbons on the mutagenicity of their mixtures. Mutat Res 90(4):399–409, PMID: 7038461, https://doi.org/10.1016/0165-2478(81)90062-8.

103. Gaskill SJ, Bruce ED. 2016. Binary mixtures of polycyclic aromatic hydrocarbons display nonadditive mixture interactions in an in vitro liver cell model. Risk Anal 36(5):968–991, PMID: 26356323, https://doi.org/10.1111/risa.12475.

104. Bocchieri, A, Magrino J, Fontana T, Pinto G, Cassoni F. 2017. Genotoxicity of airborne PM10, assessed by Salmonella and comet assays in five cities of the Emilia-Romagna (Italy) mutagenicity monitoring network. Environ Mol Mutagen 58(9):719–729, PMID: 28023966, https://doi.org/10.1002/em.22411.

105. LaVoie EJ, Tulley-Freiler L, Bedenko V, Hoffman D. 1981. Mutagenicity, tumor-initiating activity, and metabolism of methylphenanthrenes. Cancer Res 41(9):3441–3447, PMID: 7092972.

106. Kelly JM, Irving PD, Evans MJ, Kroll JH, Arin HA. 2011. Global cancer risk from unregulated polycyclic aromatic hydrocarbons. Geosheath 5(9):e2021GH000401, PMID: 24604840, https://doi.org/10.1029/2021GH000401.

107. Gaskill SJ, Bruce ED. 2016. Binary mixtures of polycyclic aromatic hydrocarbons display nonadditive mixture interactions in an in vitro liver cell model. Risk Anal 36(5):968–991, PMID: 26356323, https://doi.org/10.1111/risa.12475.

108. Gaskill SJ, Bruce ED. 2016. Binary mixtures of polycyclic aromatic hydrocarbons display nonadditive mixture interactions in an in vitro liver cell model. Risk Anal 36(5):968–991, PMID: 26356323, https://doi.org/10.1111/risa.12475.