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EDITORIAL

The overlooked toxicity of non-carcinogenic polycyclic aromatic hydrocarbons

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Recent climate change-induced wildfires and nuclear energy phasing-out policies have fostered atmospheric emissions of polycyclic aromatic hydrocarbons (PAHs). PAHs are pollutants produced by natural and anthropic processes under thermal treatment of organic matter, e.g. in fires and sedimentary rocks (Henner et al. 1997, Lichtfouse et al. 1997). They occur widely in the environment from trace levels, e.g. in polar ice, to high concentrations in oil spills. They have been found in aerosols, soils, sediments, waters, meterorites, coal, petroleum, bitumen and living organisms. Surprisingly, out of the 16 polycyclic aromatic hydrocarbons defined as 'priority' polluants for toxicity evaluation, ten light homologues have been poorly investigated because they did not show obvious carcinogenic effects.

Here, we argue that the toxicity of light PAHs has been overlooked (Fig. 1).

Fossil fuels are still major fuels globally

There is renewed interest in the study of PAHs in the context of the global pollution, energy crisis, wars and climate change. PAHs are environmental pollutants produced mainly by aromatization of various organic materials during thermal treatment, e.g. during incomplete combustion of wood, and during the formation of petroleum and coal during geological periods of time. In 2004, the worldwide emissions of the 16 US Environmental Protection Agency-listed PAHs amounted to 530,000 tons, including 114,000 tons in China, 90,000 tons in India and 32,000 tons in the USA (Zhang and Tao 2009). PAH research has been intensive from the 1970's, then declined after 2000. Now PAH studies are gaining renewed interest since about 2010 in the context of sharp policy changes by some countries, such as nuclear energy phasing-out, and rising PAH emissions (Shen et al. 2011). In 2022, fossil fuels are still the major contributor to electricity production worldwide with coal, gas and oil accounting for 35.6%, 22.5% and 3.2% of the total production, respectively, with only 38% produced from nuclear and renewable energy (Ritchie and Rosado 2020). This led the recent 28th conference of the parties (COP 28) in 2023 to mark the start of fossil fuel use decline in order to improve air quality and lower greenhouse gas emissions. However, while the use of fossil fuels should decline, another PAH source, wildfires, is now rising in the context of the global warming.

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Fig. 1 The neurotoxicity of light polycyclic aromatic hydrocarbons (PAHs) has been overlooked. Clockwise from left: acenaphthene, anthracene, flurorene, phenanthrene, fluoranthene, and pyrene

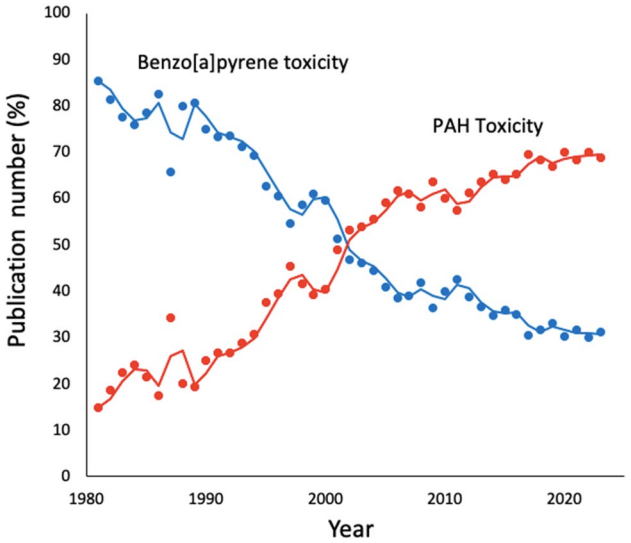

Fig. 2 The number of reports on PAH the toxicity of polycyclic aromatic hydrocarbons is dominated by investigations on the five-ring benzo[a]pyrene from 1980 to 2000. Data were obtained by searching PubMed for 'polycyclic aromatic hydrocarbons' or 'benzo[a]pyrene' associated with 'toxicity'

The rising contribution of wildfires

PAH emissions have recently accelerated by the rising contribution of wildfires worldwide in the context of global warming (Ghetu et al. 2022; Li and Banerjee 2021). For instance, New York was the fifth most polluted city worldwide during the East Canadian wild fires of 2023, and wildfire smoke is now considered as a major pollution source, even in remote areas from the fires (Ceamanos et al. 2023). Due to their low vapour pressure, some PAHs are rapidly emitted into the air or adsorbed onto particles, then transported into the atmosphere, where they can enter the food chain (Menzie et al. 1992). PAH pollution dominates in residential sectors, and eating food PAHs is considered as the major source of exposure in the average population, compared to inhalation and dermal absorption that are main routes of exposure for workers in cockery, steel plant electrometallurgy, low-pressure gas cementing, and asphalt and bituminous road surfacing work (Boffetta et al. 2003, Nikolova-Pavageau 2018). Depite their ubiquitous presence in ecosystems, only a minority of 'priority' PAHs have been in depth studied for their toxicity.

Numerous but understudied

Historically, studies on PAH toxicity have focused mainly on the carcinogenic effects of heavy PAHs such as the carcinogenic 5-ring benzo[a]pyrene (EFSA 2008). For instance, we found that publications on benzo[a]pyrene toxicity accounted for about 50–80% of publications on PAH toxicity during 1980–2000 (Fig. 2). After 2000, investigations on benzo[a]pyrene toxicity decreased, but still represent 30% of published reports in 2023. Since there is no evidence for the carcinogenicity of light PAHs, there has been few studies on their toxicological properties. In particular, the neurotoxicity of light PAHs has been underestimated. This is surprising because ten out of the 16 priority PAHs are considered as light compounds, namely naphthalene, acenaphthylene, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benzo[a]anthracene and chrysene. Nonetheless, recent studies show that light PAHs with four rings or less may induce more neurotoxicity than heavier PAHs (Abid et al. 2014; Cho et al. 2020, 2023; Kim et al. 2022; Nie et al. 2019; Wallace et al. 2022; Zhang et al. 2021). Moreover, light PAHs are widespread in the environment and occur mainly in gaseous form in the atmosphere, so they can be easily inhaled. For instance, fluoranthene is the most widely emitted PAH in France and Europe for all emission sectors, including the heavy industry, transport, the residential and tertiary sector, and agriculture (Citepa 2023). Overall, research has overloooked light PAHs despite several insights for their possible toxicity, as detailed below.

Crossing barriers to the brain

Several facts should have alerted scientists on the toxicity of light PAHs because they are more bioavailable than heavy PAHs due to their higher water solubility. Indeed, a phytotoxicity study showed that only light 1–2 rings PAHs induced reduced plant germination, compared to 3–5 rings PAHs (Henner et al. 1999). Light PAHs are also able to cross the pulmonary and intestinal barriers to be ultimately either metabolised in the liver or to accumulate in fat tissues (Cavret et al. 2005; Luo et al. 2021; Moon et al. 2012; Wang et al. 2022). The transfer of a light PAH to the brain was firstly suggested by the exposure of rats to high levels of 2–15 mg of ^{14}C-pyrene and pyrene per kg of body weight (Withey et al. 1991). Exposure of rodents to a mixture of the 16 priority PAHs at 0.01–1 mg/kg each during one week further showed that acenaphthylene and anthracene accumulated in the brain (Grova et al. 2011). The results also showed the accumulation of the metabolites of six light PAHs. On the contrary, for the six heavy PAHs, only two metabolites were detected. Fluorene and its metabolites were observed in rat brains after nose inhalation or oral ingestion (Peiffer et al. 2013). Phenanthrene and pyrene were also detected in the brain of the atherosclerosis mice model ApoE-KO fed with a high fat diet (Jin et al. 2021). Overall, the transfer of light PAHs into the brain of model animals suggests toxicity for the human brain, which is supported by epidemilogical studies below.

Neuropsychological symptoms

Few human investigations have studied the effects of PAH exposure on the brain during development, adulthood and ageing. The Taiyuan mother and child cohort study showed a dose–response relationship between the levels of 2-OH-fluorene and 2-OH-phenanthrene in maternal urine, telomere length in cord blood and decrease in infant's behavioural test scores at 3 days old (Nie et al. 2019). Similarly, another cohort work suggested a relationship between 1-OH-pyrene urinary concentrations and neurological development (Wallace et al. 2022). In older children, a report suggested a link between hydroxylated flurorene urinary concentrations, learning disability and attention deficit hyperactivity disorder; with a possible gender-specific effect, boys being more widely affected than girls (Abid et al. 2014).

In the adult population, a correlation between depressive symptoms and urinary concentrations of hydroxynaphthalenes was found in women, thus strenghthening the gender effect (Zhang et al. 2021). Alteration of brain regions was correlated with levels of 1-OH-phenanthrene and 2-OH-fluorene in urine of male firefighters (Kim et al. 2022), while no relationship was drawn between 1-OH-phenanthrene and brain atrophy in the general population (Cho et al. 2020). In the healthy elderly adult population, a study showed correlations between urinary concentrations of 2-OH-naphthol and 1-OH-pyrene and specific thinning of the cortex in men and women (Cho et al. 2020). Concerning neuropsychological tests, increased 1-OH-pyrene levels are associated with decreased memory and verbal learning scores, regardless of gender (Cho et al. 2020). 1-OH-pyrene and 2-OH-fluorene in urine were also linked to a marker of the Alzheimer's disease (Cho et al. 2023).

Neurodevelopmental studies of rockfish embryo and pufferfish larvae suggest that pyrene induces behavioural and neurodevelopmental toxicity (He et al. 2012; Sugahara et al. 2014). In adults, strong behavioural disturbances linked to a reduced acetylacholine esterase activity were observed in *Hyallela azteca*, an aquatic amphipod, exposed to a sublethal dose of phenanthrene (Gauthier et al. 2016). In mammals, the neurotoxicity of fluoranthene was observed in adult rats orally exposed to single doses ranging from 100 to 500 mg per kg of body weight, displaying locomotor deficits associated with muscle weakness and stereotypies (Saunders et al. 2003). Male rats exposed to fluorene by inhalation, or intraperitoneal or per os showed anxiety disorders compared to controls (Peiffer et al. 2013, 2016). Nonetheless, experimental studies carried out so far have used doses that are much higher than average exposure levels of the population.

DNA adducts

The mechanisms ruling PAH neurotoxicity are still debated, but a consensus suggest the interaction of PAHs with the aryl hydrocarbon receptor (AhR) (Chepelev et al. 2015; Tartaglione et al. 2023). However, this process is mainly activated by heavy PAHs such as benzo[a]pyrene, and expressed in the liver and brain (Kuban and Daniel 2021). For light PAHs, the mode of action and the pathways leading to neurotoxicity remain unclear. There are some insights such as the different effects of benzo[a]pyrene versus PAHs mixture on neuronal progenitors in cell cultures and differentiation profiles, suggesting another mode of action for the mixture (Slotkin et al. 2017). The role of the constitutive androstane receptor (CAR), another xenobiotic receptor expressed in the brain, is particularly questioned (Goedtke et al. 2021; Kajta et al. 2019; Oliviero et al. 2020). Indeed, this receptor was recently found to be expressed in endothelial cells of the blood–brain barrier and in cortical,

cerebellar and hippocampal cells, as reviewed by Torres-Vergara et al. (2020).

Another insight is the fact that some light and heavy PAHs can form DNA adducts that may interfere with normal cellular functions, and thus potentially lead to adverse effects, including neurotoxicity (Grova et al. 2017). For instance, PAHs have been shown to be chemically bound to DNA to form adducts in umbilical cord blood in a birth cohort in China, and adducts levels were positively correlated with neurodevelopmental disorders at the age of 36 months (Liu et al. 2019). PAH exposure may also induce methylation changes that are observed in neurodevelopmetal disorders, neural stem cell differentiation, brain development, and cognitive function (Grova et al. 2019). Overall, there is growing evidence for the neurotoxicity of light PAHs, and more investigations are needed to better understand underlying mechanisms.

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Declarations

Conflict of interest N. G. and E.L. declare that they are Editors of Environmental Chemistry Letters.

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