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Review

Neurotoxicity may be an overlooked consequence of benzo[*a*]pyrene exposure that is relevant to human health risk assessment

Nikolai L. Chepelev [a,*], Ivy D. Moffat [a,b], Wayne J. Bowers [a], Carole L. Yauk [a]

[a] Environmental Health Science and Research Bureau, Health Canada, Tunney's Pasture, 0803A, Ottawa, ON K1A 0K9, Canada
[b] Water and Air Quality Bureau, Health Canada, 269 Laurier Avenue W, Ottawa, ON K1A 0K9, Canada

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ABSTRACT

Benzo[*a*]pyrene (BaP) is a well-studied environmental compound that requires metabolic activation to have a carcinogenic effect. The neurotoxicity of BaP has received considerably less attention than its carcinogenicity. Environmental exposure to BaP correlates with impaired learning and memory in adults, and poor neurodevelopment in children. We carried out a comprehensive literature review to examine the neurotoxicity of BaP. The data were used to identify potential point of departure (POD) values for cancer and neurotoxicity endpoints using benchmark dose (BMD) modelling to compare the utility of both endpoints in the risk assessment of BaP. The POD for neurotoxicity in rodents, based on a standard behavioural test (Morris water maze), was 0.025 mg BaP/kg-bw-day compared to 0.54 mg BaP/kg-bw-day for rodent forestomach carcinogenicity, suggesting that neurotoxic endpoints are more sensitive than cancer endpoints for health risks associated with BaP exposure. Using the limited number of published studies on this topic, we propose a preliminary mode of action (MOA) to explain BaP-induced neurotoxicity in rodents. The MOA includes: (1) BaP binding to the aryl hydrocarbon receptor (AHR); (2) AHR-dependent modulation of the transcription of N-methyl-D-aspartate glutamate receptor (NMDAR) subunits; (3) NMDAR-mediated loss of neuronal activity and decreased long-term potentiation; and (4) compromised learning and memory. More data are needed to explore the proposed neurotoxic MOA. In addition, we consider alternative MOAs, including the hypothesis that BaP-mediated DNA damage may lead to either carcinogenicity or neurotoxicity, depending on the tissue. Our proposed MOA is intended to serve as a basis for hypothesis testing in future studies. We emphasise that further studies are needed to validate the proposed MOA, to evaluate its human relevance, and to explore other potential mechanisms of BaP neurotoxicity.

Contents

* Corresponding author. Tel.: +1 613 941 4773; fax: +1 613 941 8530.
E-mail addresses: nikolai.chepelev@gmail.com (N.L. Chepelev), Ivy.Moffat@hc-sc.gc.ca (I.D. Moffat), Wayne.J.Bowers@hc-sc.gc.ca (W.J. Bowers), Carole.Yauk@hc-sc.gc.ca (C.L. Yauk).

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1. Introduction

Benzo[*a*]pyrene (BaP) has received significant scientific attention since the origin of research in chemical carcinogenesis. In pioneering work, Yamagiwa and Ichikawa [1] described tumorigenesis in rabbit ears following dermal application of coal tar as a progressive process, consisting of four "periods". This was followed by the discovery that the chemical constituents of coal tar that are responsible for carcinomas in mice were polycyclic aromatic hydrocarbons (PAHs) by Cook, Hewett, and Hieger in 1933 [2]. The carcinogenic PAHs identified were dibenz[*a,h*]anthracene and BaP (reviewed in [3]). Subsequent experiments have shown that BaP causes carcinomas in different organs, in a diverse array of laboratory animals, and by various routes of exposure (reviewed in [4]). By the end of the last century, BaP had become an archetypal carcinogen and one of the most extensively studied chemicals [5]. Indeed, the International Agency for Research on Cancer (IARC) has deemed the overall weight of evidence sufficient to declare BaP a group 1 human carcinogen [4,6] and regulatory guidelines for BaP are based on its carcinogenicity.

Recently, we compared standard and toxicogenomics-based approaches for quantitative human health risk assessment, using BaP as an example. As part of this study, a catalogue of the diverse adverse effects of BaP in animal models and humans was created. A number of studies demonstrate that exposure to BaP has adverse effects across various systems including endocrine, reproductive, immunological, and nervous systems [4]. Neurotoxicity is defined as "an adverse change in the structure or function of the nervous system that results from exposure to a chemical, biological or physical agent" [7]. It is important to note that "neurotoxicity" is a broad term describing a multitude of effects triggered by chemicals acting (i) directly on the central nervous system (brain, spinal cord, optic nerves), (ii) and/or directly on the peripheral nervous system (motor, sensory and/or autonomic components and end organs), (iii) and/or indirectly via a peripheral organ such as the liver, where abnormal function can trigger abnormal brain activity (e.g., hepatic encephalopathy).

During our review it became apparent that neurotoxicity has been largely overlooked in the risk assessments of BaP. However, the available literature suggests that BaP-induced neurotoxicity may occur at lower doses and at earlier times than BaP-induced carcinogenicity, the primary endpoint that is generally used in the risk assessment of PAHs [8]. The nervous system has functional dominance in the entire operation of the human organism and its components. On the other hand, the nervous system may itself be influenced by numerous organs and systems; therefore, the impact of a toxicant on a diverse array of organs may impact neurobehavioral output [9]. Therefore, it is widely acknowledged that consideration of the adverse non-cancer effects of a compound, including its potential to induce neurotoxicity, is important in health risk assessment.

Current regulatory guidelines for BaP have been established primarily based on its carcinogenic potential. A comprehensive survey of the scientific literature on BaP indicates neurotoxicity reports represent a very small fraction of all BaP publications compared to cancer-related endpoints such as genotoxicity (Fig. 1). We anticipate that neurotoxicity will be considered in detail in upcoming re-evaluations of BaP, based on the emerging literature reviewed here.

To date (and to our knowledge), only one example applying a non-cancer endpoint (renal toxicity) exists for the BaP risk assessment conducted by the California Environmental Protection Agency (Cal/EPA) [10]. Although neurotoxic effects were considered in this risk assessment, the evaluation was based on data

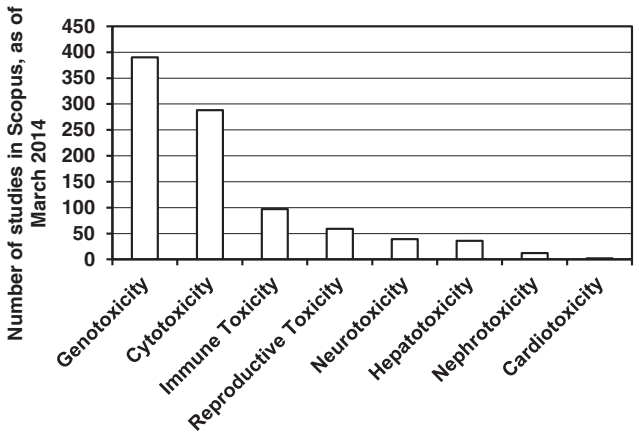

Fig. 1. Overview of the adverse effects of BaP exposure reported in human, animal and in vitro studies. The number of studies pertaining to different adverse effects of BaP exposure was estimated by literature searches in Scopus (http://www.scopus.com/home.url) using (January 01, 1965 to March, 2014): (CASREGNUMBER(50-32-8)) AND (TITLE-ABS-KEY((mouse OR mice OR rat) AND (RELEVANT KEYWORD*))) AND (EXCLUDE(DOCTYPE,"re") OR EXCLUDE(DOCTYPE,"cp") OR EXCLUDE(DOCTYPE,"ed") OR EXCLUDE(DOCTYPE,"le")), where relevant keyword was genotox*, cytotox*, "neurotox* OR "neurological effect"", hepatotox*, or cardiotox* (searched separately).