Version 2 PAH with BaP

Short report from Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: Polycyclic aromatic hydrocarbons containing benzo[a]pyrene. Scientific basis for setting a health-based occupational exposure limit

Members of the quality committee: Nellie Anne Martin (Miljøstyrelsen); Anoop Kumar Sharma (DTU Fødevareinstituttet); Mette Lausten Hansen, (Arbejdsmedicin AUH); Jesper Bo Nielsen (Institut for Sundhedstjenesteforskning, SDU); Vivi Schlünssen (NFA)

This report is based on a meeting 4th March 2022 headed by AT, where the results from the report were discussed after the authors presented the content of the report. The members of the quality committee had the chance to ask questions to the authors.

The Report: Sarah Søs Poulsen, Nicklas Raun Jacobsen, Anne Thoustrup Saber, Pernille Danielsen, Niels Hadrup, Karin Sørig Hougaard and Ulla Vogel. Polycyclic aromatic hydrocarbons containing benzo[a]pyrene. Scientific basis for setting a health-based occupational exposure limit. The National Research Centre for the Working Environment (NFA), Copenhagen 2021. 978-87-7904-383-1

Erratum:
Page 14, literature search: The searched database is not stated.
Page 50: "… risk of one cancer death per 250,000……" should be … "risk of one cancer death per 25,000……".
Page 50: (22.04 ug/40 years) should be (22.03 ug/40 years)

Response: Thank you, the database have been inserted and the errors have been corrected.

Overall evaluation of the report
This well written report reviews data relevant for assessing the hazards of polycyclic aromatic hydrocarbons (PAH) containing benzo[a]pyren (BaP) in humans and in animals. Furthermore, toxicokinetics and mechanisms of (geno)toxicity are reviewed, and previous risk assessments of BaP are summarized. The scientific basis for setting an occupational exposure limit (OEL) for BaP are presented including both a non-threshold effect (lung cancer)) and threshold effects (reproductive toxicity and developmental effects).
For non-threshold effect the authors assess an excess cancer risk from a meta-analysis to be 1:1,000 at 0.24 ug//m3, 1:10,000 at 0.024 ug//m3 and 1: 100,000 at 0.0024 ug//m3 BaP.
For threshold effects the authors, based on two F344 rat studies, suggest a DNEL (Derived No-Effect Level) equal to 0.335 ug/m3 (male and female reproductive toxicity) and 0.223 ug/m3 (developmental toxicity).

For comparisons reasons the committee suggest to adjust the assessments from DECOS and AGS to 1 per 1000/10,000/100,000 in order to be able directly to compare with the Danish assessment (page 8 and 12).

Response: We have expanded the tables to also include health-based OELs from previous assessments at levels 1 per 1000/10,000/100,000.

The literature search resulted in 332 publications, narrowed down to 54 references of potential relevance for the report, and eventually three were selected for descriptive review in the report. The committee acknowledge the description of the new data, but suggest a discussion section where differences between the new data and the old data (used for setting the OEL) are discussed.
Especially the study by Petit et al 2018 is well powered and comprehensive with numerous measurements. For Petit it is stated as a limitation only inhalation exposure is assessed. Is this also the case for the 39 studies included in the meta-analysis by Armstrong 2003?
In order to make a comprehensive search, the authors could have considered broaden the search to more databases.

Response: Thank you for highlighting this aspect, which we agree could need more emphasis. We have therefore added a paragraph in the summary section of the "Epidemiological cancer studies" section discussing new vs older data.
- We agree that the study by Petit et al. 2019 is comprehensive and well-performed. However, the output produced is not suited for calculating OELs. This is the main reason that we use this study for a supportive function in regards to the Armstrong et al. study. We can see that this point has not been conveyed properly, and we have therefore added a sentence addressing this in the "Petit et al. 2019" section.
- We agree that searching additional databases would broaden the search and potentially increase literature findings. We will consider this in our future reports, however, the choices of databases will depend on the institutional availability at NFA.

Table 3 (page 27) suggest major difference in unit relative risk (URR) for lung cancer by industry. Do the authors have any possible explanation for this?

Response: The report included an explanation for industry variation in the summary for epidemiological cancer studies. However, we understand both the curiosity and the need for reasoning immediately after table 3. We have therefore inserted a paragraph addressing this issue in the Armstrong et al. 2003/2004 section.

The committee suggest to include information about exposure routes in table 6 (page 36).

Response: Thank you for the comment. Exposure routes for each cancer type have been added in the table text.

The authors widely rely on existing previous risk assessments of BaP supplemented with a new search from 1978 - 2020. This approach is clearly stated in the introduction and the committee agrees with the approach but suggests to add a statement (disclaimer) about the implications of this choice (use of conclusions from existing sources, critical appraisal limited). Specifically, the authors decide to use BaP as an indicator for PAH exposure similar to existing previous risk assessments (e.g. DECOS 2006, AGS 2011). The committee would recommend to include a through discussion section where advantages and drawbacks using this approach (using a single chemical as indicator substance) is discussed. A table with published ratios between PAH and BaP would be helpful (and not only referring to the original material). As the authors also highlight BaP is probably not the most potent PAH (fig 7, page 44).

Response: Thank you for the comment. Advantages and drawbacks or each measurement approach is described in the "measurement" section. However, we acknowledge that this could be elaborated and we have therefore expanded the section. As PAH profiles vary tremendously between and within industries and are highly situational, we are therefore reluctant to include tables on this in the report. For the Sanderson et al., 2005 paper, the take home message is that BaP levels correlate with those of other PAH and total PAH in these industrial processes, and we think this is conveyed without the extra table.

There is no information about BaP levels in the Danish working population. We assume this is because no measurements from Denmark is available. It would be of relevance to include an estimate of numbers of exposed workers in Denmark, e.g. based on numbers of persons employed in relevant industries stated on page 6 in the report.

Response: Yes, we agree. This will be very relevant in the feasibility evaluation. However, it is not within the scope of this report.

There are important non-occupational sources for PAH/BaP exposure, including from diet, ambient air pollution, consumer products and smoking. In order to evaluate the occupational exposure level, a section on levels for the non-occupational sources would be helpful.

Response: We agree and have provided a section giving an overview of exposure in the general population in the "Human exposure" section.

Based on the literature lung cancer and bladder cancer is regarded as the critical effects for non-threshold effect, and the committee agree on this conclusion. Why the authors decide to use lung cancer only in the final assessment is not entirely clear.

Response: Thank you for the comment. The data foundation is unfortunately not strong enough to calculate OELs for bladder cancer. We acknowledge that this is not clear in the report and we have added a sentence in the "Health-based exposure limit based on epidemiological cancer data" section to state this.

The authors focus on studies dealing with occupational exposure by inhalation, and the committee support that decision, as inhalation is probably the major route of exposure for PAH/BaP for most workers. But as the authors correctly state, airborne PAH can, apart from inhalation, also reflect exposure in workers via ingestion and skin contact.

Response:
We agree. This is the reason we recommend a skin notation for BaP and other PAH. However, we have chosen to use inhalation as proxy for the entire exposure. A short sentence have been included in the section "Health-based exposure limit based on epidemiological cancer data" to clarify this.

The committee agree with the authors that the main mechanism of action for cancer is metabolism of PAH and BaP, which leads to bio-activated DNA-reactive metabolites through the diol epoxide pathway, the radical cation pathway, and the o-quinone and reactive oxygen species (ROS) pathways. The committee also agree on the suggested mechanisms for reproductive and developmental effects (genotoxicity, altered Leydig cell function, oxidative stress, stimulation of apoptosis, alterations in the estrous cycle, hormone imbalance, and mutagenicity). Are the authors aware whether the mechanism is primary or secondary apoptosis (page 45)?

Response: The source material did not investigate the pathway of apoptosis. However, we consider it the intrinsic pathway of apoptosis driven by primary genotoxicity.

Regarding animal studies, the two inhalation studies used for setting the non-threshold OEL use Fischer 344 rats, known to be very sensitive for various exposures in relation to outcomes, including the outcomes of interest in this report. The committee recommend to include a section discussing the implications of this.

Response: Thank you for the comment. All non-threshold OELs are calculated based on epidemiological data. DNELs are calculated based on Fischer 344 rats for reproductive and developmental effects. We agree that there are controversy regarding the use of Fischer 344 rats as a cancer bioassay model due to their sensitivity. We have included a paragraph in the section: "Health-based exposure limit based on reproductive toxicology and developmental data in animals" discussing this matter.

Scientific bases for an occupational exposure limit for RCS

The scientific basis for setting an occupational exposure limit (OEL) for BaP are presented including both a non-threshold effect (lung cancer)) and threshold effects (reproductive toxicity (lowered sperm quality, hormonal disturbed menstrual cycle) and developmental effects (decreased litter size, pop survival rate)). The assessment is based on a work life of 45 years and 40 hours/week for 48 weeks/year.

Of note, the data used to assess cancer risk is based on relative risk of lung cancer for males in Denmark. The committee support this as we anticipate most exposed workers are males, and the available data included in (Armstrong 2003) is mostly from males.

For non-threshold effect the authors assess an excess cancer risk (based on morbidity and mortality lung cancer data) from a meta-analysis including 39 studies to be 1:1,000 at 0.24 ug//m3, 1:10,000 at 0.024 ug//m3 and 1: 100,000 at 0.0024 ug//m3 BaP.

For threshold effects the authors, based on two F344 rat studies, suggest a DNEL (Derived No-Effect Level) equal to 0.335 ug/m3 (male and female reproductive toxicity) and 0.223 ug/m3 (developmental toxicity). In addition, the authors present data applying a lager correction factor for LOAEL (10 instead of 3). The committee support to use 3, in light of the very sensitive rat model (Ficher 344) used for setting the DNEL

For non-threshold effects the quality committee support the suggested risk estimate for cancer (lung cancer morbidity)): 1:1,000 at 0.24 ug//m3, 1:10,000 at 0.024 ug//m3 and 1: 100,000 at 0.0024 ug//m3 BaP.

For threshold effects the quality committee agree with the suggested DNEL (Derived No-Effect Level) equal to 0.335 ug/m3 (male and female reproductive toxicity) and 0.223 ug/m3 (developmental toxicity)

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