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, Karin Sørig Hougaard, Niels Hadrup 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)

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).

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.

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?

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

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).

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.

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.

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.

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.

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)?

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.

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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