

o Could the SAB clarify whether they are suggesting that the cervical hyperplasia and inflammation observed in the single study by Gao et al. (2011) are more appropriate endpoints for the basis of a reproductive RfD (instead of decreased ovary weight) or the overall RfD (instead of neurodevelopmental effects)?

The Gao study is compelling in establishing a relationship amongst BaP exposure, cervical hyperplasia and inflammation. Moreover, the apparent effect on ovary weight report by Xu (2010) is inconsistent with the results reported by Knuckles (2001) and Kroese (2001). Therefore, it is unclear as to why EPA would base an RfD on an apical, apparently inconsistent, response as compared to a single study comparing multiple endpoints and routes of administration.

Appropriate justification for not using these non-cancer endpoints from the Gao study for RfD determination was absent from the draft document. The SAB asks that EPA consider including their rationale for exclusion/inclusion to increase clarity and transparency, or include the Gao study and provide further perspective as to why it is relevant for risk assessment.

o Could the SAB expand on whether they consider cervical hyperplasia or inflammation to be directly related to impaired reproductive function?

Hyperplasia often precedes a tumor response. As EPA stated, cervical tumors were not observed in animal studies, but this tissue was not examined for histopathological changes. Therefore, microscopic changes may have gone unnoticed. A mass of sufficient size would be expected to complicate parturition. However, cervical hyperplasia and its impact on fertility and fecundity are unclear (human literature appears to focus on human papilloma virus, which causes proliferative lesions, and fecundity).

Dysregulation of anti-inflammatory cytokines has been suggested to be involved with cervical ripening/preterm labor (MacIntyre et al) and sufficient perturbation would be expected to impact birth outcome. Since BaP exposure was associated with alterations in inflammatory processes, this suggests that a potential link amongst BaP exposure, alterations cytokine signaling and preterm labor. Therefore this potential relationship, albeit speculative, is potentially relevant for risk assessment. The SAB recommends that EPA conduct the appropriate literature reviews to support either inclusion or exclusion of this endpoint for RfD determination.

MacIntyre DA¹, Sykes L, Teoh TG, Bennett PR. Prevention of preterm labour via the modulation of inflammatory pathways. Matern Fetal Neonatal Med. 2012 Apr;25 Suppl 1:17-20. doi: 10.3109/14767058.2012.666114. Epub 2012 Mar 13.

With respect to developmental toxicity as the most appropriate category of non-cancer effects, the SAB suggests that EPA give more consideration to the available reproductive outcomes, including cervical hyperplasia and cervical inflammation in Gao et al. (2011), ~~and at least~~ or provide a firmer justification for not selecting these as critical endpoints. *The Gao study is compelling in establishing a relationship amongst BaP exposure, cervical hyperplasia and inflammation. Moreover, the apparent effect on ovary weight report by Xu (2010) is inconsistent with the results reported by Knuckles (2001) and Kroese (2001). Therefore, EPA should clearly articulate the rationale for selecting an RfD based on an apical, apparently inconsistent ovarian response as compared to a single study that characterizes multiple cervical responses resulting from BaP exposure.*

Although cervical hyperplasia and its impact on fertility and fecundity are unclear (human literature appears to focus on human papilloma virus, which causes proliferative lesions and decreased fecundity), hyperplasia often precedes a tumor response. Nevertheless, disruption of cervical elasticity or a mass of sufficient size would be expected to complicate parturition. As EPA stated, cervical tumors were not observed in animal studies, but this tissue was not examined for histopathological changes. Therefore, microscopic changes may have gone unnoticed.

Dysregulation of anti-inflammatory cytokines has been suggested to be involved with cervical ripening/preterm labor (MacIntyre et al) and sufficient perturbation would be expected to impact birth outcome. Since BaP exposure was associated with alterations in inflammatory processes, this suggests that a potential link amongst BaP exposure, alterations cytokine signaling and preterm labor. Therefore this potential relationship, albeit speculative, is potentially relevant for risk assessment.

The SAB further recommends that 1) EPA consider including their rationale for either exclusion or inclusion to increase clarity and transparency 2) EPA conduct the appropriate literature reviews (as necessary) to support either inclusion or exclusion of this endpoint for RfD determination.

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