Short report from Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: 1,3-butadiene: 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 an online meeting 17th December 2021 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: Pernille Høgh Danielsen, Anne Thoustrup Saber, Niels Hadrup, Nicklas Raun Jacobsen, Sarah Søs Poulsen, Karin Sørig Hougaard, Ulla Vogel. Evaluation of the report: 1,3-butadiene: Scientific basis for setting a health-based occupational exposure limit. The National Research Centre for the Working Environment (NFA), Copenhagen 2021. ISBN 978-87-7904-377-0

Erratum: The heading for table 5 should be corrected to: “Relative risk of mortality”.
An overview of abbreviations would be helpful
Table 11. It is unexpected $BMDL_{10}$ is lower (1) than $BMCL_{05}$ (2.2). What is the difference between BMDL and BMCL?
Page 32, last line. Atophy should be corrected to atrophy.

Overall evaluation of the report

This well written report reviews data relevant to assessing the hazards of 1,3-butadiene in humans and in animals. Furthermore, toxicokinetics and mechanisms of (geno)toxicity are briefly reviewed, and previous risk assessments of 1,3-butadiene are summarized. The scientific basis for setting an occupational exposure limit (OEL) are presented including both non-threshold effects (cancer (leukaemia)) and threshold effects (reproductive toxicity (ovarian atrophy)).

For non-threshold effect the authors assess an excess cancer risk (based on mortality data (leukaemia) from one recently updated cohort) to be 1:1,000 at 3.1 mg/m3, 1:10,000 at 0.31 mg/m3 and 1: 100,000 at 0.031mg/m3 1,3-butadiene. The authors also assessed excess cancer risk based on incident mice data (lymphoma), and found a similar excess cancer risk (e.g. 1:1,000 at 1.556 mg/m3).

For threshold effects the authors, based on one mice study, suggest a DNEL (Derived No-Effect Level) equal to 0.138 mg/m3.

The authors widely rely on existing previous risk assessments of 1,3-butadiene updated with a new Pubmed search from 2010 - 2020. This 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).

The search resulted in 831 publications, narrowed down to 92 references of potential relevance for the report. It is stated: "*Of these, only some were relevant for inclusion in the report*". The committee suggest to include the exact number in the report.

There is no information about the search string in the report. In order to make a comprehensive search, the authors could have considered broaden the search to other databases, for example Scifinder.

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 1,3-butadiene due to the low boiling point..

There is no information about 1,3-butadiene 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. The authors could consider to include information provided in "Proposal for a Directive of the European Parliament and of the Council amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work" (page 148).

On page 17 (Toxicokinetics) there is a section on genetic variation. Does the statement "*The specific impact of these polymorphisms is not completely known, but it likely involves complex interactions. In vitro studies and in vivo molecular epidemiological studies indicate the range of increased sensitivity that may be attributed to some human genetic polymerphisms is approximately 2- to 3.5-fold in humans as a worst-case scenario*" refer to 1,3-butadiene – or is it a more overall statement?

Regarding animal studies it seem to be justified that mice produce significantly more epoxide metabolites – 2 orders of magnitude is mentioned (page 18, Kirman et al 2010), and therefore

potentially are more susceptible to 1,3-butadiene exposure compared to humans, which challenges the validity of animal models based on mice for the study of 1,3-butadiene. Still, mice studies are used in the present report to evaluate both non-threshold and threshold effects in animals. The committee are aware most data originate from mice studies (though, in contrary to mice, rats did not develop ovarian atrophy after exposure to comparable levels in (Doerr et al 1996). We suggest the authors to include a section in the report where they more explicitly touch upon this limitation in the animal (mice) studies.

Page 22, mechanisms of toxicity. Mutagenicity and genotoxicity are described as quotes from IARC 2008, 2012 and Kirman et al 2010. In order to evaluate the results the committee request more detailed information, including a brief summary of types of media (e.g. blood, urine), type of test (e.g. DNA adducts, comet assay, clastogenicity etc). What is the evidence in animals, e.g. some details about metabolites assessed in animals would be helpful (for instance studies that have tested both 1,3 butadiene and metabolites/DEB).

Page 23, epigenetic changes. Is there any information about 1,3-butadiene metabolites (most importantly DEB), or does the epigenetic papers only investigate 1,3-butadiene as such?

Page 25, DECOS (2013). The authors cite DECOS's reflections about leaving DMDTC out of the models used to assess dose-response relations (risk for over-adjustment) which is a valid argument. But why are the other covariates not taken into consideration in the models used in (Chen et al. 2007; Sathiakumar et al. 2015) e.g. ethnicity, plant, year since hire etc.)

Scientific bases for an occupational exposure limit for RCS

For non-threshold effect the authors assess an excess cancer risk (based on mortality data (leukaemia) from one recently updated cohort) to be 1:1,000 at 3.1 mg/m3, 1:10,000 at 0.31 mg/m3 and 1: 100,000 at 0.031mg/m3 1,3-butadiene. The authors also assessed excess cancer risk based on incident mice data (lymphoma), and found a similar excess cancer risk (e.g. 1:1,000 at 1.556 mg/m3).
The authors suggest to use the human data, and the committee agree on this decision.
Of note, the data used to assess cancer risk is only based on 1,3-butadiene exposed males, and similar dose-response relations for males and females are assumed. Furthermore linear models are used despite data might be better explained with other functions (figure 2 and figure 3)

For threshold effects, the authors, based on mice data, suggest a DNEL (Derived No-Effect Level) equal to 0.138 mg/m3. Based on the uncertainty for the animal results, most importantly the use of mice with a significant different metabolism of 1,3-butadiene and the uncertainty in the inter-species and intra-species factors, the Committee suggest to put less emphasis on the estimated threshold effects when deciding on the OEL.

The quality committee suggest to use the suggested risk estimate for cancer (leukaemia mortality): 1:1,000 at 3.1 mg/m3, 1:10,000 at 0.31 mg/m3 and 1: 100,000 at 0.031mg/m3 1,3-butadiene.
The quality committee suggest NOT to use the suggested DNEL (Derived No-Effect Level) equal to 0.138 mg/m3 1,3-butadiene.

References

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