Short report from Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: Zinc oxide: 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 23th April 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: Niels Hadrup, Anne Thoustrup Saber, Nicklas Raun Jacobsen, Pernille Danielsen, Sarah Søs Poulsen, Karin Sørig Hougaard and Ulla Vogel. Zinc oxide: Scientific basis for setting a health-based occupational exposure limit. The National Research Centre for the Working Environment (NFA), Copenhagen 2021. ISBN 978-87-7904-378-7

Erratum: Page 18, Figure 1. No explanation for the star symbol – significance level? The resolution of Figure 1 figure (and also Figure 2 and 3) could be improved.
Page 17: Consider to remove “other metal oxides” from the subheading – the section is only dealing with papers on CU and Zn.

Overall evaluation of the report

The report reviews data relevant to assessing the hazards of ZnO particles in humans and animals. Furthermore, toxico-kinetics and mechanisms of toxicity are reviewed, and previous risk assessments of ZnO are summarized. The scientific basis for setting an occupational exposure limit (OEL) are presented and based on this, the authors suggest a health based OEL for ZnO.

In general, the report is well written with a clear structure and easy to follow. The Committee recommend more consistency with regards to evidence level. It is of importance to know whereas "no or limited evidence" is due to missing data or due to studies indicating no effect. As an example it is stated page 30, last line: "No evidence of mutagenicity was found".

The literature search was performed by a research librarian, and details of searched databases and the search strings are included as an appendix in the report.

The vast majority of the included papers deals with welders, and barely any data for other working groups (e.g. workers producing ZnO containing products) is included. If this evidence is not available it would be helpful if this is explicitly stated.

If there is any available literature on the origin of SAA and CRP (e.g. from the liver) it would be relevant information to include in the report.

We anticipate a large within day and day – to day variability for ZnO (both for ZnO fume and dust), but information about this is not covered in the report. In order to be able to set an evidence based short-term OEL, literature with this information is needed. Probably many of the papers included in the reference (EU, 2004) and summarised in Table 3 contain information about exposure variability. This information is not included in Table 3. Furthermore, it would be helpful if it was clear from Table 3 whether the documentation is based on measurements or other kinds of exposure information. With regard to existing OELs, Belgium and Finland have a factor 5 between the short term and the 8 hours OEL, and Switzerland and Germany a factor 4. For Denmark a factor 2 is present.

On page 16 (Epidemiological studies of welders). It would be helpful with inclusion of more information on 1) exposure levels and 2) how smoking is taken into consideration (Ibfelt et al., 2010 and Mocevic et al., 2015).

The authors regard acute phase response as the critical adverse effects and argue for a causal association to cardiac disease. The committee agree on this decision, but it is a new approach to use a normal physiological response reaction as the critical effect, as opposed to earlier settings where abnormal physiological responses or disease (e.g. carcinogenicity) has been the critical endpoint. The committee therefore recommend to include a few lines about this new approach in the report.

On page 16 the authors summarise the epidemiological evidence for an association between acute phase response (especially CRP and SAA) and cardiovascular disease. The committee recommend to be less firm in the conclusions on causality. The epidemiological studies with the strongest design using Mendelian Randomisation to adjust for confounding find that CRP is not causally related to cardiovascular disease. No Mendelian Randomisation studies are available for SAA and cardiovascular disease. The committee agree

there is strong mechanistic evidence supporting that the underlying mechanism of action is a SAA-mediated effect on cholesterol transport, but until now this is not convincingly confirmed in the epidemiological literature.

The authors chose to focus on studies dealing with occupational exposure by inhalation, and the committee support that decision, as inhalation is the major route of exposure for ZnO. We also agree with the notion that a joint OEL for all particle sizes is the adequate approach, as inhaled ZnO particles undergo rapid dissolution at the low pH in lysosomes after cellular uptake.

The authors based the suggested health-based OEL on data from a human experimental study (Monse et al 2018), and the Committee agree on this decision. The evidence from animal studies are quite limited, especially for CRP and SAA.

The authors state the risk assessment methodology follows the guidelines suggested by ECHA (ECHA 2019), and they adequately argue for a threshold level approach.

Setting an occupational exposure limit for ZnO

In setting an occupational exposure limit with acute phase response as the critical endpoint the authors used the NOAEC of 0.5 mg/m^3 for increase in SAA and CRP after exposure (Monsé et l 2018, Figure 2 in the report). They corrected this value to an 8 hours working day = NOAEC *4 hour/8 hour = 0.25 mg/m^3.
Due to a large inter-individual variation observed in the reviewed biomonitoring studies, the authors use the highest assessment factor for inter-individual variation suggested by ECHA, a factor of 5
This results in a suggested long-term threshold limit value of 0.25 mg/m^3/5 = 0.05 mg/m^3 ZnO

The quality committee agree on the suggested long-term OEL of 0.05 mg/m^3 ZnO.

However, due to the anticipated large within day variability we do not judge the AT default factor 2 for short term exposures to reflect the actual variability, and we therefore request more data on within day and day – to day variability for ZnO exposure in order to be able to suggest a short-term OEL for ZnO.

References

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EU. European Union Risk Assessment Report Zinc Oxide. 2004.

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Mocevic E, Kristiansen P, Bonde JP. Risk of ischemic heart disease following occupational exposure to welding fumes: a systematic review with meta-analysis. International Archives of Occupational and Environmental Health 2015;88:259–272. doi:10.1007/s00420-014-0965-2

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