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# Short report from the Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: Carbon nanotubes: Scientific basis for setting a health-based occupational exposure limit.

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This report is based on a meeting 14th November 2018 at 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 change to ask questions to the authors.

The Report: Sarah Søs Poulsen, Nicklas Raun Jacobsen, Niels Hadrup, Karin Sørig Hougaard, Anne Thoustrup Saber and Ulla Vogel. Carbon nanotubes: Scientific basis for setting a health-based occupational exposure limit. The National Research Centre for the Working Environment (NFA) September 2018. ISBN 978-87-7904-350-3

**Overall evaluation of the report**

The report reviews data relevant to assessing the hazard of Carbon Nanotubes (CNTs) in humans and animals. Furthermore, toxicokinetics and mechanisms of toxicity are reviewed, and core previous risk assessments of CNTs 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 CNTs.

In general, the report is well written with a clear structure and easy to follow. More tables displaying the articles dealt with in each section would have increased the overview even more.

The committee judge the included literature in general to be sufficient and covering. The literature search was performed by a research librarian, and we recommend including details of searched databases and the search strings including dates for covering of the search as an appendix in the report.

Carbon nanotubes are a diverse class of nanomaterials with large variation in physical-chemical properties. Variation in toxicity potential based on different physical-chemical properties has been reported, but the relationship between physical-chemical properties of CNTs and their inhalation toxicity is not fully clarified. Furthermore, most commercially available CNT preparations are very heterogeneous. Therefore, the authors consider toxicity data from all types of CNTs. This decision is supported by the committee.

The authors chose to focus on studies dealing with occupational exposure by inhalation, and the committee supports that decision, as inhalation probably is the major route of exposure for CNT´s. Besides that, knowledge on other exposure routes are missing.

The authors based the suggested health-based OEL on data from experimental animal studies due to a lack of epidemiological studies, and the committee supports this decision.

The authors regard inflammation and carcinogenicity as the critical adverse effects, and the committee agree on this decision. It is noted however, that the authors in the risk assessment uses a measure where they include both benign and malign tumors in the evaluation of cancer risk, which tends to overestimate the carcinogenic effects of CNT.

With regard to inflammation, the report would benefit from a more detailed discussion and description of inflammatory effects, more specifically whether it is persistent or transients effects.

The authors states correctly secondary genotoxicity due to fibre-induced inflammation to be an important and well documented mechanism of action for the development of lung cancer. The committee supports to consider carcinogenicity as a non-threshold effect as the available data did not allow ruling out that CNTs could also induce cancer through a direct genotoxic mechanism.

The committee agrees on the REACH approach used in the report where both benign (adenomas) and malign (carcinomas) tumors are evaluated, but the committee have performed additional analysis based on the benchmark approach By a benchmark approach the available data are used more efficiently compared to the NOAEL approach used by REACH. A NOAEL value is very dependent of study design, number of exposure groups and the exposure contrast between exposure groups compared to the benchmark approach. Table 1 shows the results of the benchmark dose modelling:

Table 1. Benchmark dose modelling compared to NOAEL values

| Kasai et al. 2016 , Table 3. (PAGE 7) | BMDL 10 value EFSA Software ** | NOAEL value (REACH approach) |
|---|---|---|
| Male rats total adenomas and carcinomas | 0.01 mg/m3 | 0.02 mg/m3 |
| Kasai et al. Male rats total adenomas and carcinomas (with 15 responses in dose 0.2) * | 0.02 mg/m3 | 0.02 mg/m3 |
| Female rats total adenomas and carcinomas | 0.32 mg/m3 | 0.2 mg/m3 |
| Male rats total carcinomas | 0.06 mg/m3 | 0.02 mg/m3 |
| Female rats total carcinomas | 1.2 mg/m3 | 0.2 mg/m3 |

* In table 3 in Kasai et al 2016 there is a mistake (total number of tumors 15 and not 13).

** Benchmark response is set to 10% increase in tumors, which is the default value for animal cancer studies in benchmark dose modelling.

For total adenomas and carcinomas, the BMDL10 values and the NOAEL values are similar, whereas for carcinoma the BMDL values are 3-10 fold higher compared to the NOAEL approach. For non-threshold effects, two approaches are used in the report, namely measured lung burden in rats exposed by inhalation, and air concentrations directly. The authors suggest using the first approach.

A section discussing challenges with possible overload of exposure in the animal models due to the high exposure doses used in the models would be helpful to interpret the experimental results.

The authors identified four sub-chronic and one chronic inhalation study in rats as suitable for determining a DNEL for pulmonary inflammation. They used a conservative approach and calculated the DNEL based on the study using the CNT with the largest specific surface area and reporting the lowest NOAEC estimate (Pothmann et al 2015). This decision was supported by the committee, although it was not entirely clear what data was used from Pothmann et al 2015.

For cancer a 2 year inhalation study in rats was identified as suitable (Kasai et al 2016), and also this was supported by the committee.

**Setting an occupational exposure limit for CNT**

*Inflammation*

In setting an occupational exposure limit with inflammation as the critical endpoint the authors used the (NOAECPothmann) of 0.05 mg/m3 for pulmonary influx of neutrophils immediately after end of exposure (table 2). They corrected this value to an 8 hours working day and also took into account the breathing rate for workers at light work: NOAECCorrected = NOAECPothmann *6 hour/8 hour * 6.7 m3/10 m3 = 0.0251 mg/m3. They decided on the following default assessment factors:

Interspecies extrapolation 2.5; Intraspecies interpolation 5; Extrapolation from sub-chronic to chronic: 2

This results in a DNEL for chronic inhalation for pulmonary inflammation of: 1µg/m3.

The quality committee judge this DNEL to be adequate based on default assessment factors used in previous risk assessments of CNT.

***We therefore support a DNEL for pulmonary inflammation of: 1 µg/m3****

** The committee wants to express one reservation. The inflammatory outcomes can be reversible which is not clear from the report. As a consequence information on the nature of the exposure (continuous or short term intermittent with large non-exposed intervals) is of importance to emphasise in the final risk assessment.*

*Cancer*

About cancer, the quality committee recommend using the DNEL based on air concentrations directly. This decision is primarily based on the uncertainty with overloading of exposure, which is an issue with the alternative method using lung burden. Otherwise, we agree with the calculations performed

***Thus, the expected excess lung cancer risk in relation to occupational exposure to CNTs is 1:1 000 at 0.043 µg/m3, 1:10 000 at 0.0043 µg/m3 and 1:100 000 at 0.00043 µg/m3.***

**References**

Committee for Risk Assessment (RAC). Opinion proposing harmonised classification and labelling at EU level of Titanium dioxide. ECHA 2017

Kasai T, Umeda Y, Ohnishi M, Mine T, Kondo H, Takeuchi T, Matsumoto M, Fukushima S. Lung carcinogenicity of inhaled multiwalled carbon nanotube in rats. Part Fibre Toxicol 2016;13:53.

Pothmann D, Simar S, Schuler D, Dony E, Gaering S, Le Net JL, Okazaki Y, Chabagno JM, Bessibes C, Beausoleil J, Nesslany F, Régnier JF. Lung inflammation and lack of genotoxicity in the comet and micronucleus assays of industrial multiwalled carbon nanotubes Graphistrength© C100 after a 90-day nose-only inhalation exposure of rats. Part Fibre Toxicol 2015;12:21.