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Short report from the Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: Titanium dioxide nanomaterials: 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 chance to ask questions to the authors.

The Report: Anne Thoustrup Saber, Sarah Søs Poulsen, Niels Hadrup, Karin Sørig Hougaard, Nicklas Raun Jacobsen and Ulla Vogel. Titanium dioxide nanomaterials: Scientific basis for setting a health-based occupational exposure limit The National Research Centre for the Working Environment (NFA) September 2018. 978-87-7904-351-0

Erratum: Page 27, table 3 in the report. In column 3, third section: 4/100 Adenocarcinoma should be 4/100 adenoma

Overall evaluation of the report

The report reviews data relevant to assessing the hazards of TiO2 nanomaterials (TiO2 NMs) in humans and animals. Furthermore, toxicokinetics and mechanisms of toxicity are reviewed, and core previous risk assessments of TiO2 NMs 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 TiO2 NM.

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 to including details of searched databases and the search strings including dates for covering of the search as an appendix in the report. Recently ECHA´s committee for Risk Assessment (RAC) published an Opinion proposing harmonized classification and labelling at EU level of Titanium dioxide (: https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e18075daff). It is relevant also to include the RAC evaluation in the section where previous risk assessments of TiO2 NMs are summarized.

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 TiO2 NMs.

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 regards 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 TiO2 NM.

The authors states correctly secondary genotoxicity due to particle-induced inflammation to be an important and well documented mechanism of action for the development of lung cancer**.** Apart from this oxidative stress is a key mechanism for secondary genotoxicity (ECHA 2017). The committee supports to consider carcinogenicity as a non-threshold effect as the available data did not allow ruling out that TiO2 NM could also induce cancer through a direct genotoxic mechanism, although the evidence for a direct mechanism is sparse (Shi et al 2013).

The committee agree on the REACH approach used in the report, despite the overestimation of cancer due to inclusion of both benign and malign tumors in REACH. The authors have used the data from Heinrich et al. 1995, a chronic inhalation study of mice and rats and the only study where ultrafine particles were used. The limitation in the study is that only one dose (about 10 mg/m^3) was applied. In rats, a significant increase in total number of tumor bearing animals with all types of lung tumors was observed compared to the control dose group. No statistically significantly increase was observed in lung tumors in mice.

The committee aimed at performing 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. Due to few data including only one exposure level in Heinrich et al 1995, it was not possible actually to successfully complete the modelling.

NIOSH performed an analysis from three different studies (Lee at al. 1985, Muhle et al. 1991 and Heinrich et al. 1995). In these studies different particle sizes were used (ultrafine and fine). NIOSH concluded that they fit on the same dose response curve in a benchmark dose modelling approach when the dose was expressed as total particle surface area in the lungs (NIOSH 2011). NIOSH calculated the excess risk of lung cancer tumors based on benchmark dose modelling including data from the above mentioned three studies. Based on the analysis by NIOSH, it is indicated that a dose response relationship exists for TiO_2 particles including ultrafine particles and lung tumors. The committee agrees on this assumption.

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. TiO2 RAC has made an estimation of the level of lung overload in the studies conducted via inhalation or intra-tracheal administration of TiO2 in rats and/or mice and concluded that lung tumours were reported in rats in an overload context defined by an impairment of normal pulmonary clearance due to high accumulation of particles. The level of lung overload in the Heinrich et al 1995 study was described as ‘not yet excessive conditions of particle loading of lung macrophages’.

RAC further noted that although the evidence presented indicates a lower sensitivity of non-human primates and humans to PSLT induced lung inflammation (including alveolar inflammation) the observed lung adenocarcinomas are considered relevant to humans and TiO2 warrants a Category 2 classification for carcinogenicity.

The committee agree on the decision to include data from two rat inhalation studies as the basis for the risk assessment (for Inflammation Bermudez et al 2004; for cancer Heinrich et al 1995). The committee also considers Ferin et al 1992, but due to only one exposure level in Ferin et al, the data from Bermudez et al was considered more useful. Muhle et al 1991 and Lee et al 1985 was not considered due to the dust fraction (fine, not ultrafine) and due to the extraordinary high dust levels in Lee et al 1985 (10, 50, 250 mg/m3).

Both studies used for the risk assessment P25 TiO2 NM (15-40 nm diameter, 80% anatase/20% rutile). Which is the most commonly studied TiO2 NMs. Whether this reflect the actual use of TiO2 NMs is not clear from the report, but apparently, this knowledge is not available.

Setting an occupational exposure limit for TiO2

Inflammation

In setting an occupational exposure limit with inflammation as the critical endpoint the authors used the (NOAECBermudez) of 0.5 mg/m3 for pulmonary influx of neutrophils immediately after end of exposure (table 2 in the report). They corrected this value to an 8 hours working day and also took into account the breathing rate for workers at light work: NOAECCorrected = NOAECBermudez *6 hour/8 hour * 6.7 m3/10 m3 = 0.25 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: 10 µg/m3.

The quality committee judge this DNEL to be too low based on the evidence and based on default assessment factors used in previous risk assessments of TiO2.

We support to adjust for number of hours exposed as well as the breathing rate for workers at light work, but recommend to use the NOAECBermudez) of 2 mg/m3 for pulmonary influx of neutrophils seen after 4-52 weeks of exposure, as we judge this to be the most relevant exposure window for inflammation related to health. Furthermore we suggest to use the following default assessment factors: Interspecies extrapolation 2.5; Intraspecies interpolation 2.5; Extrapolation from sub-chronic to chronic: 2. Both interspecies and intraspecies assessment factors include variation in metabolism of the substance of interest. As TiO2 is not metabolised we find it most correct to use an intraspecies assessment factor of 2.5.

We therefore suggest a DNEL for pulmonary inflammation of: 2.00 mg/m3*6 hour/8 hour * 6.7 m3/10 m3 / 12.5 = 0.08 mg/m3 = 80 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 to use 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. Of note, the calculations are based on both benign and malign tumors and included benign tumors cystic keratinizing squamous cell tumors, a benign tumor of unknown human relevance. The suggested OEL is therefore based on an overestimation of the risk

The expected excess lung cancer risk in relation to occupational exposure to TiO2 NMs is 1:1 000 at 47 µg/m3, 1:10 000 at 4.7 µg/m3 and 1:100 000 at 0.47 µg/m3 TiO2 NM.

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