

Gezondheidsraad

Health Council of the Netherlands

Diane Miller, NIOSH Docket
Office, Robert A. Taft Laboratories,
Mail Stop C-34, 4676 Columbia
Parkway, Cincinnati, Ohio 45226
USA



Subject : comments NIOSH draft titaniumdioxide
Your reference : e mail 3 march 2006
Our reference : U523/DC/459-V51
Enclosure(s) : 2
Date : May 9, 2006

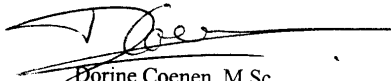
Dear dr Miller,

We highly appreciate that you gave us the opportunity to review the draft NIOSH document: 'NIOSH current intelligence bulletin: evaluation of health hazard and recommendations for occupational exposure to titanium dioxide'. The secretariat of DECOS received your request by e-mail on March 2, 2005.

As you might know, the members of DECOS do not belong to the scientific staff of the Health Council of the Netherlands but have busy jobs at other scientific organizations (e.g., universities) or chemical companies. Nevertheless, three DECOS members have given their comments on (parts) of the NIOSH document. Included are the comments of the members, Dr P(eter) Boogaard, Prof Dr P(aul) Borm, and Dr G(erard) Swaen. Please note that the comments are their personal views and not those of DECOS as a whole. Also, two publications that were referred to in the comments are included. We hope these comments are useful.

Please do not hesitate to contact us if you have additional questions.
We are looking forward to continue the fruitful cooperation with NIOSH.

Yours sincerely,



Dorine Coenen, M.Sc
Scientific Secretary

P.O. Box 16052
NL-2500 BB The Hague
Telephone +31 (70) 340 7473
Telefax +31 (70) 340 75 23
E-mail: d.coenen@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 VX The Hague
The Netherlands



Subject : comments NIOSH draft titaniumdioxide
Our reference : U523/DC/459-V51
Page : 2
Date : May 9, 2006

Comments of DECOS members on NIOSH draft on TiO₂-version November 22nd 2005.

Member 1

General

The NIOSH draft on TiO₂ (fine, ultrafine) is an innovative effort to link animal data to human epidemiological outcomes, in order to derive exposure standards to both fine and ultrafine TiO₂. As such this report is the first to classify ultrafine TiO₂ along with its fine counterpart. The report concludes that no clear evidence of elevated risks of lung cancer is found in production workers exposed to (fine) TiO₂ dust, and is conform the recent (February 2006) IARC evaluation. The authors then focussed on the animal responses induced by TiO₂, thereby focussing on inhalation studies and the most relevant metric of exposure. The gravimetric standards derived more or less reflect the surface driven inflammatory and carcinogenic animal response induced by both species of TiO₂. In its exercise NIOSH assumes that the tumourigenic effects of TiO₂ exposure in rats are not chemical specific but occur through inflammation as a secondary genotoxic mechanism. Lung tumour prevalence and lung inflammation in the rat are taken as crucial response to derive an equivalent dose in human to derive a recommended exposure limit in human (Figure 4-1). In its BMD model (Figure 4-4) to relate surface area dose to lung tumours, only inhalation studies were used (Lee et al, 1985; Heinrich et al, 1995).

Major comments:

- Later sub chronic studies by CIIT in 3 animal species (Bermudez et al, 2003) were not included although they would allow setting of a NOEL for non-carcinogenic endpoints also known to be associated to overload for both fine and ultrafine TiO₂ in rat (and hamster and mice). In this inhalation study (6 hrs/day, 5x per week, 3 months) the authors could show overload in rats with pigmentary TiO₂ at 50 mg/m³ and for ultrafine TiO₂ at 10 mg/m³. Indications for increased DNA synthesis in the centriacinar region were observed at 10 mg/m³ for fine TiO₂ and at 2 mg/m³ for ultrafine TiO₂. Similar findings were reported for inflammatory response based on neutrophils. These data suggest a 5-fold stronger action of ultrafine TiO₂ compared to fine, and contradicts the current

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 7473
Telefax +31 (070)340 75 23
E-mail: d.coenen@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.gr.nl



Subject : comments NIOSH draft titaniumdioxide
Our reference : U523/DC/459-V51
Page : 3
Date : May 9, 2006

conservative approach of the NIOSH draft leading to a 15-fold difference in REL. The latter factor (15) merely „ reflects NIOSH greater concern „ (page 96, line 1996) but is not quantitatively supported by research data

- Studies by intratracheal instillation of TiO₂ have not been included, although the NOEL when considering TiO₂ simply as one of the many poorly soluble low-toxicity particles is not that different from studies by inhalation (Borm et al, 2004). A recent follow-up of this so-called 19-dusts study (Morfeld et al, 2006) showed that PSP induced lung tumours in the rat is indeed best statistically described by a threshold, based on Cox-regression of all animals (n=750) in that study. Moreover, the study showed overall a factor 3 difference between ultrafine and fine particles as a whole. This again draws the attention for a better quantitative support of the difference between the RELs of ultrafine and fine TiO₂.
- Most (> 90 %) of the commercial (pigmentary) TiO₂ is available in a coated (silica) form and exposure of workers who handle or use TiO₂ would certainly be different qualitatively from production workers and a valuable asset to the set of epidemiological data. This may be added to the summary (2.3) on page 20.
- The potential effect of uF TiO₂ by uptake through the olfactory pathway should be included, as currently identified but not able to include in risk assessment.

Specific.

Table 1-1: MAK-value for TiO₂ currently under evaluation (footnote)

Member 2

NIOSH does not seem to agree with the authors that the 3 epidemiological studies are negative. From their studies, Fryzek and Boffetta concluded that they did not observe a carcinogenic effect. Nevertheless, the NIOSH report refers to a “negligible effect” (line 49) and “no clear evidence” (line 716) suggesting some kind of a small, but negligible effect. However, based on the aforementioned study, the conclusion should be that there is no evidence.

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 7473
Telefax +31 (070)340 75 23
E-mail: d.coenen@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.gr.nl

Gezondheidsraad

Health Council of the Netherlands



Subject : comments NIOSH draft titaniumdioxide
Our reference : U523/DC/459-V51
Page : 4
Date : May 9, 2006

Further, the statistical power to detect mortality from non-malignant respiratory tract diseases is questioned (line 721-724). Although these investigations do not statistically exclude a small effect, it is more important to conclude that they do not support a possible long-term effect.

The effects seen in experimental animals are due to overload. Considering this is the case, is it sound to perform a high dose-low dose extrapolation? And should it not be more appropriate to prevent overload and to chose a "non-overload" dose and calculate an exposure limit by applying assessment factors?

Member 3 (Only reviewed the sections on dose-response modelling)

The sections on dose-response modelling are not only very comprehensive but also very complex and not very transparent. Therefore, this section is not further reviewed because it requires much more time than the reviewer could afford.

P.O Box 16052
NL-2500 BB The Hague
Telephone +31 (70)340 7473
Telefax +31 (070)340 75 23
E-mail: d.coenen@gr.nl

Visiting Address
Parnassusplein 5
NL-2511 BX The Hague
The Netherlands
www.gr.nl