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) Swae. 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,

Dorien Coenen, M.Sc
Scientific Secretary
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
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 196) but is not quantitatively supported by research data.

- Studies by intratracheal instillation of TiO$_2$ have not been included, although the NOEL when considering TiO$_2$ 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 TiO$_2$.

- Most (> 90%) of the commercial (pigmentary) TiO$_2$ is available in a coated (silica) form and exposure of workers who handle or use TiO$_2$ 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 TiO$_2$ 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 TiO$_2$ 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.
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.