Gezondheidsraad
Health Council of the Netherlands

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Subject	: Review draft report on *Occupational exposure to carbon nanotubes and nanofibers*
Your reference	: E-mail, December 8, 2010
Our reference	: 6389/JR/fs/459-Q64
Enclosure(s)	: 1
Date	: February 16, 2011

Dear dr. Niemeier:

Thank you for the opportunity to review the draft document on Occupational exposure to carbon nanotubes and nanofibers, which was prepared by NIOSH. Enclosed are the comments of a subgroup of experts of the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands. The comments are limited to the establishment of the REL because the other aspects are not the expertise field of the DECOS.

If you have any questions regarding the comments, please contact me by E-mail jm.rijnkels@gr.nl, or telephone +31 703 406 631.

Sincerely yours,

Ms Jolanda M. Rijnkels, Ph.D
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DECOS peer review comments on *NIOSH Current Intelligence Bulletin: Occupational exposure to carbon nanotubes and nanofibers* by Prof. Dr. G.J. Mulder, Dr. R. Houba, Prof. Dr. I.M.C.M. Rietjens, Dr. T.M. Pal, and Prof. Dr. R.A. Woutersen.

General comments

1. The document is well written. NIOSH based its recommendation principally on animal data, but included technical feasibility issues related to measurable exposure levels as well. This resulted in a recommendation for a REL for carbon nanotubes and nanofibers of 7 $\mu g/m^3$ (respirable mass concentration of elemental carbon; 8h-TWA), based on the detection limit of NIOSH method 5040. DECOS understands that this approach, which includes technical feasibility of monitoring, is common practice in recommending RELs by NIOSH. This is different from the standard procedure that DECOS follows, which takes only health-based aspects into account, and, therefore, would have used the calculated working lifetime exposure levels of 0.2 – 2.0 $\mu g/m^3$ as point of departure in deriving an health-based recommended OEL. Additionally, DECOS would have taken into account uncertainties, such as inter-individual differences among exposed humans.
2. In the *Executive summary*, DECOS misses the result of the benchmark dose analyses, revealing working lifetime exposure levels for lung effects (BMDL10) of carbon nanotubes of between 0.2 and 2.0 $\mu g/m^3$, as shown in detail in Appendix A and Section 5. A somewhat more detailed information on results of the benchmark dose analyses in Section 5 would make the discussion and the flow of arguments more understandable. A summary of the information in annex A could be included in Section 5. The annex presents useful information for most readers.
3. DECOS notes that the document mainly focused on adverse health effects in the respiratory tract. In addition, DECOS notes that the available information on the adverse health effects of carbon nanotubes and nanofibers mainly showed effects in the respiratory tract. DECOS also expects that lung effects will most likely be the most relevant by inhalation of carbon nanotubes and nanofibers. However, the committee feels that other relevant, (systemic) adverse health effects may occur, such as cardiovascular diseases, and diseases related to the

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immune system. Although no data are yet available on whether or not carbon nanotubes and nanofibers could cause effects, data obtained from exposure to ultrafine particles may be taken to indicate a hazard. Therefore, DECOS would recommend to add a paragraph in Section 4, in which attention is given to this matter, including the state-of-the-art on this matter.

4. A major issue for DECOS is whether or not inhaled carbon nanotubes and nanofibers can induce cancer, such as mesotheliomas and lung tumors, like in case of asbestos fibers. Although evidence-based animal and human data are still lacking, early indications found in subchronic animal studies, and physicochemical comparisons, do suggest that certain carbon nanotubes and nanofibers may act similarly to asbestos fibers. DECOS recommends to discuss that in detail in Section 4 and/or 5. The discussion should include a state-of-the-art on this matter, and a rationale for not taking the possible carcinogenic effects into account as starting point in deriving a REL as a worst-case scenario. Did NIOSH consider to use the occupational exposure limit for asbestos fibers for carbon nanotubes and nanofibers?
5. NIOSH advises to use NIOSH method 5040 to measure airborne exposure levels of carbon nanotubes and nanofibers. The method uses the mass concentration of respirable elemental carbon as exposure parameter. DECOS understands that NIOSH prefers this method for pragmatic reasons; it is a relatively simple method with low costs, and no specialized expertise is needed. With NIOSH method 5040 high risk situations can be identified when the REL is exceeded. However, DECOS would like to emphasize that this method cannot lead to fully conclusive evaluations with regard to CNT and CNF exposure. It is not clear yet what the best and most relevant exposure measure(s) is (are) for nanoparticles and nanofibers. Therefore, DECOS recommends that efforts should be made by occupational hygienists, not only to measure mass concentration, but also to measure other possible parameters. In your document, examples of additional analytical techniques to better characterize exposures are given that could be used. DECOS believes that the same techniques could be valuable if a more detailed risk assessment is needed in specific situations. When using additional analytical techniques in specific working environments (*e.g.*, activities with the highest expected exposure potential) the risk assessment in workplaces can be performed in more detail. DECOS believes that this option could be made more explicit in the document.

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Specific and editorial comments

- *Page 18, third and fourth sentence*. A figure of nanotubes and nanofibers would more easily show the structural differences.
- *Page 21, second and third sentence*. Please explain what an agglomerate is (as compared to an aggregate).
- *Page 23, eleventh sentence*. Replace 'found particle concentrations' by 'contained particle concentrations'.
- *Page 27, last sentence of Section 2*. For clarification, please add units (mg/m^3) after mentioning particle mass concentrations.
- *Page 23, second paragraph, third sentence*. Define abbreviation CVD.
- *Page 29, third and fourth sentence*. Add whether or not the toxicity potential will be reduced or increased.
- *Page 29, second paragraph*. Is it not better to speak of nanomaterials, since, in general, nanoparticles are defined as having all its dimensions below 100 nm, and thus carbon nanotubes and nanofibers are – in the narrow sense of the word - not considered nanoparticles but a type of a nanomaterial?
- *Page 29-37, Sections 3.1 through 3.3*. Please specify correctly the units for exposure doses and concentrations (mg/animal, or mg/kg body weight). The same in the third paragraph on page 101 (mass dose).
- *Page 29-37, Sections 3.1 through 3.3*. A better separation should be made between the descriptions of the single and repeated exposure studies. This is to give more weight to the latter type of study, which resembles more the occupational situation than a single exposure study, and thus is of more relevance and interest in deriving a REL.
- *Page 36, tenth sentence from below*. 'The MWCNT sample used …' should be replaced by 'The MWCNT fibers in the sample used …'
- *Page 36, third sentence from below*. Replace 'peritoneal' by 'peritoneum'.
- *Page 37-38, Section 4*. It would be nice if NIOSH could describe in this section already more specifically which animal studies are of most relevance in deriving a REL, and which ones were used for benchmark dose analysis.

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- *Page 38, 'Results from cellular studies ...[Shvedova et al. 2003]'.* These (genotoxicity) studies are described for the first time in this concluding section. Should that not be done, and in more detail, in an earlier section, for instance in Section 3?
- *Page 40-41, Section 5.1.* Since Appendix A is very comprehensive, it would be helpful for the reader to summarize in more detail the most important and relevant data, considerations, and findings of the BMD analysis in this section.
- *Page 43, end of first paragraph.* Nanocyl used an overall assessment factor of 40. Is it known for what separate factors exactly was assessed for?
- *Page 44, First paragraph (Pauluhn 2010b).* In the final sentence is written that no uncertainty factors were used in deriving the estimate. However, in the previous sentences adjustments were made for human and rat differences, resulting in a final factor 2, by which the rat NOAEL was divided. Is this not considered an uncertainty factor?
- *Page 45, second paragraph.* In the last sentence it is written that "According to BMD-based estimates, excess risks of greater than 10% of early stage adverse lung effects would be expected at the OELs based on the NOAEL approaches". Please explain this view.
- *Page 106, 'In this analysis ... in the unexposed mice'.* Please rephrase the sentences as their meaning is not clear to DECOS.
- *Page 117, end of first paragraph.* Does the human equivalent BMD(L) lung dose concern deposited or retained dose?
- *Page 120-121, A.5 Conclusion.* The sentences 'These values are below … for CNT (Section 5).' appears here out of place, since Appendix A concerns quantitative risk assessment based on health effects only, and not on technically feasibility.

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