Development of prognostic occupational air standards for nanoparticles

Andrey S Radilov, Anzhela V Glushkova, Sergej A Dulov and Nataliya S Khlebnikova
Research Institute of Hygiene, Occupational Pathology and Human Ecology Federal State Unitary Enterprise, Federal Medical Biological Agency, Kuz’molovsky g/p, Vsevolozhsky District, Leningrad Region, 188663 Russia
E-mail: aglushkova_rihope@hotmail.com, radilov@rihophe.ru

Abstract. The intensive progress of nanoindustry in the Russian Federation makes quite urgent the problem of development and especially express development of occupational exposure standards for nanoparticles and nanoaerosols in the workplace air. We developed an approach to comparative toxicity assessment and express calculation of occupational exposure standards for nanoaerosols, based on criteria for the development of maximum allowable concentrations (MACs) of aerosols in the workplace air. The developed approach was used to obtain prognostic MACs of certain aerosols in the workplace air, mg/m³: nano-Ag 0.08, nano-TiO₂ 0.19, and C₆₀ 0.08.

1. Introduction
In view of the rapidly increasing industrial application of nanoparticles and, consequently, their possible health impact on workers and population, the problem of development of tentative occupational exposure standards for nanoparticles and, especially, nanoaerosols in the workplace air seems to be quite urgent (Nowack, B., Bucheli, T.D., 2007). Therewith, of particular importance is to assess the health impact of exposure to nanoaerosols at workplace. A key facet of this problem is express development of occupational exposure standards for nanoparticles and nanoaerosols, which may cardinaly improve the situation with hazard prognosis and introduction of nanotechnologies.

2. Methods
We developed a scale of safety factors depending on the routes of entry (intragastric, intraperitoneal, intratracheal, or inhalational) (Table 1). These safety factors can be used in calculation and substantiation of hygienic standards and also in the assessment of impact of nanoaerosols on workers’ health. If the TI at some route of entry is impossible to calculate, the worst scenario should be taken into account.

Depending on the exposure mode (acute, chronic) at the corresponding route of entry, the following safety factors are suggested. The suggested safety factors are based on the idea of NP bioavailability depending on the route of entry. Therewith, it should be taken into account that at the identical toxicity parameters for intragastric and intraperitoneal routes of entry the substance, independently of its hazard class, will possess a low bioavailability, and, therefore, its safety factor will equal 1.
Table 1. Determination of safety factors depending on the route of entry.

| Variant no. | Relative toxicities of nano- and microparticles at the corresponding routes of entry | Safety factor |
|-------------|----------------------------------------------------------------------------------|---------------|
| 1.  | $T_n > T_m$  | $T_n > T_m$  | 1-3 |
| 2.  | $T_n < T_m$  | $T_n < T_m$  | 4-9 |
| 3.  | $T_n = T_m$  | $T_n = T_m$  | 10-30 |
| 4.  | $T_n = T_m$  | $T_n = T_m$  | >30 |

Notes. *Here and hereinafter, $T_n$ and $T_m$ stand for the toxicity of nano- and microparticles of the same substance, respectively.

We suggest to calculate a toxicity index (TI) to relate the toxicity of microparticles of a substance to that of nanoparticles:

$TI = \frac{\text{toxicity parameters of microparticles}}{\text{toxicity parameters of nanoparticles}}$

The above formula can be used to estimate:

- $TI$ for acute exposure $LD_{50}(LC_{50})_{MPs}/LD_{50}(LC_{50})_{NPs}$; $\lim_{ac} MPs/\lim_{ac} NPs$;
- $TI$ for chronic exposure = $\lim_{ch} MPs/\lim_{ch} NPs$.

The safety factors for different routes of entry and comparative toxicity classification are presented in Table 2.

Table 2. Safety factors variants depending on the route of entry and classification comparative toxicity

| No. | TI i.g. | TI i.p. | TI i.t. or i.h. | Safety factor |
|-----|---------|---------|----------------|---------------|
| 1   | 1       | 1       | 1              | 3             |
| 2   | 1-3     | 1-3     | 1-3            | 3-9           |
| 3   | 3-10    | 3-10    | 3-10           | 9-30          |
| 4   | >10     | >10     | >10            | >30           |

The safety factors are calculated by the following formula:

$SF = TI \text{ i.g.} + TI \text{ i.p.} + TI \text{ i.t or i.h.}$

The MAC values for nanoparticles are calculated by the following scheme:

1. Determination of $LD_{50}$ or $LC_{50}$ for substances in the nano and macro forms;
2. Methods for calculation of occupational exposure standards for aerosols of metals, metal oxides, and other metal compounds in the workplace air, accepted in the Russian Federation, were used (MU 4000-85, Council for Mutual Economic Aid, 1982).

The MACs for metal aerosols were calculated by the formula:

$MAC_{wa} = 0.0008 \times LD_{50}$  \hspace{1cm} (1)

and for aerosols of metal oxides and other metal compounds, by the formula:

$\log MAC_{wa} = 0.85 \log LD_{50} - 3.0 + \log M - \log N$  \hspace{1cm} (2)

where $LD_{50}$ is intraperitoneal $LD_{50}$ for mice after a week observation period, milliatoms per kg body weight; $N$, number of metal atoms in the molecule; and $M$, molecular weight.

3. Determination of safety factors including the toxicity parameters for substances in the nano and macro forms (Table 2);

4. Estimation of MAC values for nanoparticles with the safety factors in Table 1, by the following formula:

$MAC_{wa \ NP} = MAC_{wa \ MP} / SF$
Below we present a calculation of a tentative hygienic standard for copper nanoparticles using the above equations for calculation of hygienic standards for metal aerosols in the workplace air, as well as toxicity of copper nanoparticles and the corresponding safety factor:

$$LD_{50} (\text{copper NPs}) = 413 \text{ mg/kg}$$

Safety factor for copper nanoparticles is equal 30.

(IT i.g. NPs more that MPs in 10 times, IT i.p. NPs more that MPs in 10 times and IT i.t. NPs more that MPs in 10 times),

$$\text{MACwa (copper NPs)} = (0.0008 \times 413) / 30 = 0.01 \text{ mg/m}^3$$

### 3. Results

The probability of a negative impact of NPs on the environment and population health is known to the determined of a potential hazard which is characterized, among other factors, by the toxicity of one or several components of a material contacting with live organisms (Nowack B., Mueller N.C., 2008).

Nanoparticles are not infrequently much more toxic than macro- and microparticles of the same substances. Table 3 compares the toxicities of selected nano- and microparticles (MPs).

| No. | Substance | Test object / Route of entry | LD_{50} / LC_{50} |
|-----|-----------|-----------------------------|-------------------|
|     | NPs       | MPs                         |                   |
| 1   | Cu        | rats/i.g.                  | 413 mg/kg [8]     | 5000 mg/kg [8] |
| 2   | Fe_{2}O_{3}| rats/i.g.                  | > 310 mg/kg [2]   | 98.6 g/kg [2] |
| 3   | Zn        | daphnias (Daphnia magna)   | 3.2 mg/l [19]     | 8.8 mg/l [19] |
|     |           | bacteria (Vibrio fischeri) | 1.9 mg/l [19]     | 1.8 mg/l [19] |

The prognostic MACs for selected nanoaerosols in the workplace air, calculated by the suggested approaches, are listed in Table 4.

| Substance       | Test object / Route of entry | LD_{50}, mg/kg NPs | LD_{50c}, mg/kg MPs | MAC_{wa}, mg/m$^3$ MPs | Prognostic MAC_{wa}, mg/m$^3$ NPs |
|-----------------|-----------------------------|---------------------|---------------------|------------------------|---------------------------------|
| Ag              | rats/i.p.                  | 5000 [3]            | not attained        | 1 [1]                  | 0.13                             |
| Cu              | rats/ i.p.                 | 413 [8]             | 5000 [10]           | 1 [1]                  | 0.01                             |
| TiO_{2}         | rats/i.p.                 | 12000 [14]          | not attained        | 10 [1]                 | 0.32                             |
| Fe_{2}O_{3}     | rats/i.g.                 | 310 [2]             | 98.6 g/kg [2]       | 6 [1]                  | 0.008                            |
| C_{60}          | rats/i.p.                 | 5000 [16]           | not attained        | 4 [1]                  | 0.13                             |
| Soots, black, industrial, benz(a)pyrene content ≤35 mg/kg |                             |                     |                      |                                   |                                 |

### 4. Discussion

Developing the set of safety factors, we based on the idea that the bioavailability of a substance depends on the route of entry. We suggest that the safety factor for NPs will depend primarily of the route they enter the body. For example, whatever the hazard class, if a substance has similar (or equal) toxicity parameters for the oral and intraperitoneal routes of entry, it will possess a low bioavailability and, consequently, we assign to this substance the safety factor 1. In cases where the intraperitoneal toxicity of a substance is higher than intragastric or inhalational, we assign to this substance the safety factor 10. And, finally, if the toxicity of a substance in the nano form is higher than the toxicity of the same substance in the micro form at the intragastric, intraperitoneal, and inhalational routes of entry,
we assign to this substance the safety factor 50. We would like to mention that the suggested safety factors are estimated and subject to discussion. It is known that if experimentally substantiated LD$_{50}$ for a substance at different routes of entry are available, the lowest (as a rule intragastric) of the available LD$_{50}$ values are used in the calculations, relying of the worst prognosis and the corresponding safety factor.

5. Conclusion
The suggested approaches to calculation of tentative occupational exposure standards for nanoaerosols in the workplace air make it possible to estimate hazard parameters for NPs and base on these data to assess, in the look-ahead manner, health risks to workers occupied in nanoindustrial enterprises.

Thus, the algorithm for express development of occupational exposure standards for NPs and nanoaerosols in the workplace air involves the following steps:
1. Comparison of the toxicities of nano- and microparticles.
2. Choice of safety factor, based on available comparative experimental toxicity data for nano- and microparticles.
3. Calculation of a tentative MAC$_{wa}$ value for nanoparticles by the standard formula, including the chosen safety factor.

References
[1] Predel'no dopustimye kontsentratssii (PDK) vrednykh veshchestv v vozduke rabochei zony: GN 2.2.5.1313-03 (Maximum Allowable Concentrations (MAC) of Hazardous Substances in the Workplace Air, Hygienic Standard 2.2.5.1313-03), Moscow, 2003.
[2] Ermakov, A.E., Poluchenie biosovmestimykh netoksichnykh nanoporoshkov dlya dostavki lekarstvennykh preparatov, diagnostiki i terapii novooobrazovaniy (Preparation of Biocompatible Nontoxic Nanopowders for Drug Delivery and Diagnostics and Therapy of Neoplasms), Abstracts of papers, 1$^{st}$ Int. Summer School “Nanomaterials and Nanotechnologies in Live Systems,” Moscow, June 29-July 4, 2009, p. 90.
[3] Kinzirskii, A.S., Bovina, E.V., Klochkov, S.G., etc., Novye dannye o toksikologii i bioraspredelenii typovykh nanochastits v organizme gryzunov (New Data on the Toxicology and Biodistribution of Typical Nanoparticles in Rodent’s Body), Abstracts of papers, 1$^{st}$ Int. Summer School “Nanomaterials and Nanotechnologies in Live Systems,” Moscow, June 29-July 4, 2009, p. 162.
[4] Metodicheskie ukazaniya po ustanovleniyu orientirovochnykh bezopasnykh urovnei vrednykh veshchestv v vozduke rabochei zony: MU 4000-85 (Methodical Guidelines on the Establishment of Tentative Safe Exposure Levels of Hazardous Substances in the Workplace Air: Methodical Guidelines 4000-85), Moscow, 1985.
[5] Postoyannaya komissiya po sotrudnichestvu v oblasti zdravoookhraneniya (Standing Commission on Collaboration in Public Health Portection), Kaloyanova-Simeonova, F. and Sanotskii, I.V., Eds., Moscow: Council for Mutual Economic Aid, 1982.
[6] Guidelines on Human Health Risk Assessment from Environmental Chemicals (P 2.1.10.1920-04), Moscow, May 5, 2004.
[7] Brown C.L., Whitehouse M.W., Tiekink E.R., Bushell G.R., Inflammopharmacology. 2008, 16(3), P. 133-137.
[8] Chen Z., Meng H., Xing G. et al. // The journal of physical chemistry. Toxicology letters. 2006 163,109-120.
[9] ECB. Technical Guidance Document on Risk Assessment; European Chemicals Bureau, 2003.
[10] Elder, A.C.P. The Toxicology of Nanomaterials. – Univ.of Rochester, 2007. – 37 p.
[11] Gurgueira S. A., Lawrence J., Coull B., Environ. Health Perspect. 2002 110(7) 749-755.
[12] Holsapple M.P., Farland W. H., Landry T. D. et al., *Toxicol. Sci.* 2005 88(1) 12-17.
[13] Nowack, B., Bucheli, T.D., *Environ. Pollut.* 2007 150 5–22.
[14] Nowack B., Mueller N.C., *Environ. Sci. Technol.* 2008 42 4447–4453.
[15] Oberdorster G., Oberdorster E., Oberdorster J., *Environ. Health Perspect.* 2005 113 823–839.
[16] Oberdorster G., Stone V., Donaldson K., *Nanotoxicology* 2007 1(1) 2-25.
[17] Ouellette J., *The Industrial Physicist.* 2003 8 18.
[18] Warheit D.B., Laurence B.R., Reed K.L. et al., *Toxicol. Science* 2004 77(1) 117-125.
[19] Wigginton N.S., Haus K.L., Hochella M.F., *J. Environ. Monit.* 2007 9 1306–1316.