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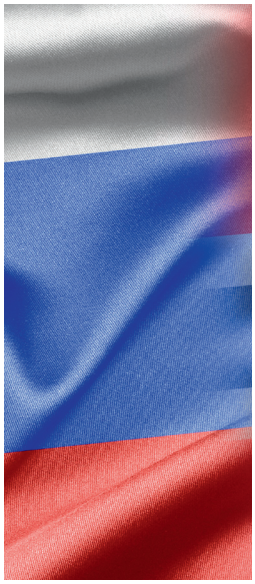

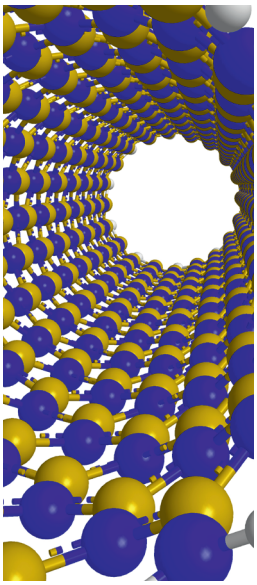

Norwegian - Russian Project Report

Risk Assessment and Regulations of Nanomaterials in Norway and Russia

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Contents

Summary

In both EU/Norway and Russia the risk assessment of engineered nanomaterials (ENMs) is in principle similar with respect to hazard identification and characterization, exposure assessment and risk assessment. No procedures specific to working with ENMs are used. They are based on the same methods and techniques as for substances in the micro- or macroforms. Furthermore, the regulatory policies both in EU/Norway and Russia presently seem to use the legal framework as for chemicals in general, and are based on ENM mass (with an exception for numbers of nanofibers). There are, however, differences:

EU/EEA/Norway

EU, and Norway as an EEA member, have adopted the REACH agreement, and the regulatory procedure for "Classification, Labelling and Packaging" (CLP) of chemicals. REACH is the EU regulation on chemicals and their safe use, and deals with the registration, evaluation, authorization and restriction of chemicals. REACH provides increased protection of human health and the environment posed by chemicals through identification of their hazardous properties, and by providing legislation and guidance for safe handling of chemicals, giving the industry the responsibility to manage the risks. The CLP regulation requires companies to appropriately classify, label and package their substances and mixtures before placing them on the market. Furthermore, both for workers and consumers the European Chemicals Agency (ECHA) is the driving force among regulatory authorities in implementing EU's ground-breaking chemicals legislation for the benefit of human health and the environment as well as for innovation and competitiveness. ECHA has appointed subgroups working on regulatory issues and guidance for ENMs. In Norway, the Norwegian Environment Agency (under the Ministry of Climate and Environment), is the REACH Competent Authority, and is responsible for enforcing REACH. The Labour Inspectorate enforces the law on chemical regulation in the work environment. For chemicals in food, including ENMs, the Scientific Committee and the Advisory Forum of EFSA (European Food Safety Authority) have established a Scientific Network for Risk Assessment of Nanotechnologies in Food and Feed. In Norway, there is an equivalent organisation under the Norwegian Ministry of Health and Care Services, the Scientific Committee of Food Safety (VKM), which carries out independent risk assessments of contaminants in food for the Norwegian Food Safety Authority. The Norwegian Institute of Occupational Health (STAMI) and the Norwegian Institute of Public Health (NIPH) perform health and safety research on ENMs and have an advisory role towards the authorities, in the work environment and for the general public, respectively.

Russian Federation

The Russian Federation Federal Service on Surveillance for Consumer Rights Protection and Human Well-being (ROSPOTREBNADZOR) is a branch of the Health Ministry and the main regulatory agency responsible for the health safety of the population and approval of standards for chemical substances. One important task for ROSPOTREBNADZOR is to evaluate the toxicity of ENMs and to perform subsequent safety regulation in water, atmospheric air, workplace air, soil, and environmental compartments. Several institutes carry out studies for determining exposure and toxic potential to chemicals (including ENMs), and are specially accredited by the Federal Service. There are no standard

regulatory procedures for working with ENMs. In these cases, methods and techniques for working with substances in micro- or macroforms are used. The Research Institute of Hygiene, Occupational Pathology and Human Ecology (RIHOPHE) (Saint Petersburg), the Institute of Nutrition (Moscow) or the State Center of Hygiene and Epidemiology (Moscow) may carry out risk assessment with ENMs. RUSNANO is a private company, also operating in the ENM field. RUSNANO receives expert opinions from competent scientific organizations on the level of danger or safety of products from nanotechnology industry. Within RUSNANO, the Department of Metrology measures nanoparticles (NPs), but otherwise RUSNANO does not specifically work with ENMs, and does not issue expert opinions for ENM. The main RUSNANO mission nowadays is to classify the ENMs based on hazard levels and to support profitable industries and enterprises based on using ENMs.

Comparison of risk assessment and regulatory policies

In principle, the risk assessment in EEU/Norway and Russia, seems similar, and is based on the relationship between mass and response, as for chemicals in general. In both EU/Norway and the Russian Federation no specific regulatory procedures for working with ENMs are obtained, and methods and techniques for working with substances in micro- or macroforms are used. With respect to regulatory policies there are differences, as Russia follows their federal legislation, in contrast to the EU- and EEA-countries (including Norway) that are bound by the legislation within the REACH/CLP framework. One important difference is that ROSPOTREBNADZOR has a regulatory role with chemicals, including ENMs, in different settings, both in water, atmospheric air, soil, workplace air, and consumer's goods. This gives a harmonized and coordinated approach in their regulatory policies. In comparison, in EU/EEA/Norway, this role is less centralized, and more institutions and ministries are involved, both internationally and at the national level.

Scope of the report

The European Parliament described in 2009 how the knowledge about potential health and environmental impacts of ENMs lagged significantly behind the rapid pace of market developments in the field of nanomaterial technology. Furthermore, this was raising fundamental questions about the ability of the current regulations to deal with emerging technologies such as ENMs. In the last years, a lot of research has focused on these questions, trying to reduce the knowledge gap. Also in Russia, important steps have been taken to increase the knowledge about such health and environmental issues.

The emerging use of nanotechnology in consumer products, industrial applications and in nanomedicine represents a breakthrough technology with foreseen great economic benefits. However, NPs released from ENMs to the work environment and consumer products may potentially induce adverse health effects both in workers and consumers. Thus, the technology needs to be developed in a sustainable manner, including a proper health risk assessment for the production and use of ENMs. In this risk assessment both particle characterization, estimation/measurements of exposures and determination of the health hazard linked to the production and use of different ENMs, are required. The NPs may be released from handling of ENMs or during production, in small amounts by mass, but still in great numbers and corresponding large surface areas. Furthermore, extensive variations in chemical composition might be of importance for health hazard assessment. This report sheds light on similarities and differences in regulatory policies between Russia and Norway towards ENMs in occupational settings and for the consumers.

The Norwegian approach and perspective: A summary of the current status

The regulatory policy in EU/EEA/Norway for chemicals, including ENMs, is based on the same procedures for risk assessment, risk management and risk communication[1]. Norway has adopted EUs regulations on chemicals, including ENM via the European Economic Area (EEA) agreement. EEA was established 01.01.1994 when EFTA (European Free Trade Association) states, not being EU members, joined the EU´s single internal market, adopting all relevant EU legislation other than regarding agriculture and fisheries.

Risk assessment, risk management and risk communication in EU/EEA/Norway

Risk assessment: The risk assessment of chemicals, including ENMs, is based on hazard identification, hazard characterization and exposure assessment, which is involved in the risk characterization. Subsequently, the potential health risk is estimated/calculated based on combining hazard data from experimental animal studies and emerging human studies and exposure data. Presently, the hazard characterization is based on animal and human clinical studies. However, there is a strong attempt to reduce animal experiments for such testing in EU. Thus, there is a lot of ongoing research to replace animal studies with advanced cell cultures combined with *in silico* modelling. This could be especially relevant for the large variety of NPs.

- **Hazard identification:** Does the agent cause adverse health effects?
- **Hazard characterization:** What is the relationship between dose and response?
- **Exposure assessment:** What types, levels and duration of exposures are experienced or anticipated?
- **Risk management:** Procedures to establish acceptable risks, such as by the hierarchy of controls, and other risk management procedures
- **Risk communication:** Interactive process between risk assessors and stakeholders

A stepwise approach to risk assessment:

- Step 1. Identifying hazards and those at risk
- Step 2. Evaluating and prioritizing risks
- Step 3. Deciding on preventive actions
- Step 4. Taking action
- Step 5. Monitoring and reviewing

For a more exact description, see: https://osha.europa.eu/en/topics/riskassessment

[1] http://ec.europa.eu/environment/chemicals/nanotech/pdf/jrc_report.pdf

Risk assessment of nanomaterials:

- Existing risk assessment methods are to a large extent applicable to ENMs
- No generalizations on the risk of ENMs are possible
- A case-by-case approach for the risk assessment is currently recommended

Nanomaterial definition:

EC recommendation of a definition (2011) for ENMs is described as follows: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF

Essentials of the definition:

- Material containing particles
- The origin may be natural, incidental or manufactured
- The particles may be in an unbound state, aggregated or agglomerated
- For 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm
- In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%
- From the definition above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as ENMs

The common regulatory framework in EU and Norway via the EEA agreement

Although many ENMs have novel or improved properties compared to their larger counterparts, no nano-specific regulation has been decided for use in occupational settings or in the environment by any country until now, although some experimental studies have been conducted and published with proposed occupational limit values for some ENMs. ENMs in occupational settings/consumer products/environment in EU member states are covered by the existing chemical regulation in REACH[2] (**R**egistration **E**valuation **A**uthorization and **R**estriction of **Ch**emicals) and the CLP (**C**lassification, **L**abelling and **P**ackaging) legislation. Possible risks are related to intrinsic properties of each ENM and their exposures. Therefore, according to EU legislation, and as for other chemicals, ENMs require a risk assessment, on a case-by case basis, starting with the EU definition on ENM and using available information.

[2] http://ec.europa.eu/growth/sectors/chemicals/reach/index_en.html

REACH see footnote 2

REACH is the EU regulation on chemicals and their safe use, and deals with the registration, evaluation, authorization and restriction of chemicals. REACH entered into force 1st June 2007 and placed greater responsibility on industry to manage the risks that chemicals may pose to the health and environment. The REACH regulations provide increased protection of human health and the environment from the risks that can be posed by chemicals, by identification of the hazardous properties of chemicals, and further by providing legislation and guidance for safe handling of chemicals. REACH was adopted to improve the protection of human health and the environment, and has replaced legislative framework for chemicals in the EU, prior to 2007. REACH applies to all chemicals, not only chemicals used in industrial processes, but also in our day-to-day life.

Furthermore, REACH has been implemented to enhance the competitiveness of the EU chemicals industry. REACH also promotes alternative methods for the hazard assessment of substances in order to reduce the number of animals used. ENMs are chemicals and comprised in the REACH regulation. Although there are no specific requirements for ENMs in REACH today, they should be assessed from a regulatory point of view according to the criteria used for other chemicals in occupational settings, consumer products and environment. There are, however, challenges for the registrants of ENMs to clearly identify the ENMs in the REACH registrations dossiers.

Classification, Labelling and Packaging (CLP)

The CLP Regulation is a regulation which aligns the EU system to the Globally Harmonised System. The regulation requires companies to appropriately classify, label and package their substances and mixtures before placing them on the market. CMR substances are substances with (C) carcinogenic effects, (M) mutagenic effects in germ cells and/or (R) reproductive effects. The CMR-substances are divided into categories dependent on the quality of the data supporting the endpoint. Category 1A requires human data, while category 2B is based on animal data. Category 2 is based on more equivocal data, both from human and animal studies. REACH focuses on regulation of these substances.

Substances that may have serious and often irreversible effects on human health and the environment, can be identified as substances of very high concern. Such substances have to meet the criteria for classification as CMR category 1A or 1B or they have to be persistent, bioaccumulative and toxic or very persistent and very bioaccumulative according to REACH. Substances with scientific evidence of probable serious effects as encompassed by these criteria, are classified to be of concern. Substances are identified on a case-by-case basis. If a substance is identified as one of very high concern, it will be added to the Candidate List for eventual inclusion in the Authorisation List.

As previously described, ENMs are considered as covered by the substance definition under REACH (Commission 2nd regulatory review on ENMs). ENM can be either substances on their own or nanoforms of a substance. ENMs that fulfil the criteria for classification as hazardous under Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures[3] must be classified, and the

[3] http://ec.europa.eu/environment/chemicals/nanotech/pdf/jrc_report.pdf

information on the nanoform must be included in the Materials data safety sheets (MSDS). Many of the related provisions, including safety data sheets and classification and labelling already apply today, independently of the tonnage in which the substances are manufactured or imported. Substances, including ENMs, meeting the classification criteria as hazardous and put on the market, must be notified to ECHA (see below). ENMs are specifically mentioned in CLP Article 9(5), which states that consideration should be made on the forms and physical state in which the substance or mixture is placed on the market, or in which form it can reasonably be expected to be used. These requirements are also included in the Norwegian CLP Regulation. Registrants need to demonstrate the safe use of their substances, whatever the form.

As many NPs are much more potent than larger particles when related to equal mass, it is questioned why there are no nano-specific regulations. The main issues are deficiencies in data and needs for refinement of methods for testing of ENMs. Thus, the scientific committees and agencies of the European Union point to major deficiencies not only in key data, but even in methods of obtaining such data; (Resolution by European Parliament (on Commission communication (2009)). More research is required before specific regulation of ENMs can be established. Such specific regulations includes characterization with definition of key properties, tools and protocols, sample preparation, measurement conditions and methods, standards, reference materials and knowledge on toxic properties.

The European Chemicals Agency (ECHA)

The European Chemicals Agency (ECHA) is EUs regulatory authority and driving force on the safety of chemicals, which also includes ENMs. ECHA administrative organ is located in Helsinki, Finland. ECHA aims at protecting human health and the environment by ensuring that chemicals are used safely and that the most hazardous ones are substituted by safer alternatives. ECHA has appointed subgroups working on regulatory issues and guidance for ENMs.

Any manufacturer or importer of a chemical substance or ENMs in quantities of one ton or more per year has to submit a registration to ECHA. A technical dossier (identity, manufacture and use, classification/labelling, guidance on safe use, study summaries of toxicity/ecotoxicity, testing proposals) and a chemical safety report need to be submitted. In the report a Chemical Safety Assessment is included. Roughly 20-30 ENMs have been registered. The information in the registration is based on the amount of substance that is manufactured or imported. The data requirement increases with increasing tonnage. How to evaluate data for different endpoints is thoroughly described in the guidance documents to REACH. Two concepts that are important in these guidance documents are integrated testing strategy and a weight of evidence approach. For substances with no or very few data, a sequential integrated testing strategy is recommended for developing adequate and scientifically sound data for assessment and classification. The objective of the testing strategies is to give guidance on a stepwise approach to hazard identification. The weight of evidence approach is an option to meet the information requirements by an evidence based expert judgment. The advantage is that this approach reduces the need for further testing.

[3] http://ec.europ

Extensive guidance and recommendations have also been provided by scientific institutions and national authorities in member states as well as in many countries outside Europe.

Regulations in EU and Norway

The Norwegian Environment Agency, NEA, (under the Ministry of Climate and Environment) is the REACH Competent Authority, and is partly responsible for enforcing REACH by establishing official controls and penalties for non-compliance. NEA exchange information and coordinate their enforcement activities through the Forum for Exchange of Information on Enforcement.

NEA is the main agency responsible for safety from chemicals, including ENMs with respect to chemicals in the environment, in consumer products and in occupational settings. With respect to ENM in food and feedings, the European Food Safety Authority (EFSA) and Norwegian Food Safety Authority (NSFA) are responsible for the Regulations and surveillance.

Regulations of ENMs in consumer products and the environment

Ministries and Directorates involved. The Ministry of Climate and Environment has the main responsibility for monitoring the exposure to chemicals in consumer products and the environment, but the Ministry of Health and Care Services (HOD) has also a role in assessment of health effects of some environmental pollutants. Notably, NEA is the REACH authorization agency and also the executing body in surveillance of compliances with the regulations of chemicals in consumer products and environment, including ENMs.

Norwegian Institute of Public Health (NIPH). NIPH is an institute governed by the Ministry of Health and Care Services (HOD).NIPH exerts research and delivers advice to the Ministry of Climate and Environment on health risk concerning consumer's exposure to chemicals in the environment. NIPH is doing research in the ENM field.

Specific regulations of ENMs in occupational settings

The EU directives on safety and health at work[4]. The REACH and CLP regulations are transposed into the Norwegian Working Environment Act and its regulations, REACH[5], CLP[6], as well as the EU directives on safety and health at work[7]. In addition to the REACH framework, also "The EU directives on safety and health at work" [8], (Directive 89/391 EEC) [9], Directive 98/24/EC - risks related to chemical agents at work[10] and Directive 2004/37/EC - carcinogens or mutagens at work [11] apply. The rational is that regarding safety aspects, ENMs are considered similar to chemicals in general, in that some may be hazardous, and some may not[12]. These directives are also valid for Norway and according to them, the EU Commission is under obligation to set occupational exposure limit values and biological limit values whenever feasible. The employers are obliged to assess the risks of hazardous chemical agents and to ensure that the risks from hazardous chemicals are eliminated or reduced to a minimum. This directive meets many of the challenges for assessment of ENMs, as described in REACH.

Regulations of ENMs at the workplace in Norway. Although Norwegian Environmental Agency is the REACH authorization agency also in occupational settings, the Norwegian Labour Inspection Authority, under the Ministry of Labour and Social Affairs, has a special role in surveillance of compliance with the regulations in occupational settings. The Norwegian Institute of occupational Health (STAMI), under the same Ministry, performs research in nanotoxicology, nanosafety and occupational hygiene at the worksite. STAMI has an important advisory task in updating regulators on scientific progresses in the field of nanosafety and on practical issues on safe handling of ENM to workers and employers.

Materials data safety sheets (MSDS). MSDS should give information on the nano-scale size of the substance if it is present. MSDS do not in general provide adequate and accurate information sufficient to perform an occupational risk assessment for nanomaterials contained in the product.

Occupational exposure limits for ENMs. No OELs are officially available for ENMs.

Regulations of ENMs in food and feeding settings

The European Food Safety Authority (EFSA). The use of nanotechnology in the food sector is mostly related to food additives and food contact materials, and these types of products/articles have to be authorised by EU in order to be put on the European market. Authorisation follows a thorough risk assessment performed by EFSA, the keystone of EU risk assessment regarding food and feed safety. In order to provide practical

[4] https://osha.europa.eu/en/legislation/directives
[5] https://lovdata.no/dokument/SF/forskrift/2008-05-30-516
[6] https://lovdata.no/dokument/SF/forskrift/2012-06-16-622?q=merking+klassifisering
[7] https://osha.europa.eu/en/legislation/directives
[8] https://osha.europa.eu/en/legislation/directives
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[11] https://osha.europa.eu/en/legislation/directives/exposure-to-chemical-agents-and-chemical-safety/osh-directives/directive-2004-37-ec-indicative-occupational-exposure-limit-values
[12] http://ec.europa.eu/growth/sectors/chemicals/reach/nanomaterials/index_en.htm

recommendations for the risk assessment of food related applications of nanotechnology, EFSA has published the "Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain" (EFSA, 2011). This guidance provides a practical approach for assessing potential risks arising from applications of nanoscience and nanotechnologies in the food and feed chain. Guidance is provided on: (i) the physico-chemical characterisation requirements of ENMs used; (ii) testing approaches to identify and characterise hazards arising from the nanoproperties.

The guidance allows for reduced information to be provided in two circumstances:

1. No exposure to ENMs is verified by data indicating no migration from food contact materials
2. Complete degradation/dissolution is demonstrated with no absorption of ENMs as such

The Scientific Committee and the Advisory Forum of EFSA established in 2010 the EFSA Scientific Network for Risk Assessment of Nanotechnologies in Food and Feed. The Network is composed of representatives from 21 member states and Norway, in addition to representation from the European Commission and observers from some non EU countries. The Network meets once a year, and the main overall goals are i) to facilitate harmonisation of assessment practices and methodologies; ii) enhance exchange of information and data between EFSA and member states of the EU.

Norwegian ministries and The Norwegian Food Safety Authority (NFSA). The Ministry of Agriculture and Food and the Ministry of Trade, Industry and Fisheries are responsible for regulation of chemicals (including NPs) in food and fish, respectively. However, NSFA ("Mattilsynet" in Norwegian) is the governmental body whose aim is to ensure that food and drinking water are as safe and healthy as possible for consumers. The majority of the regulations applicable in Norway are based on legislation acts, by which Norway is bound under the European Economic Area (EEA) Agreement and constitute common European rules. Thus, the majority of regulations within the food sector in Norway are the same as those in the European Union (EU).

The Norwegian Scientific Committee for Food Safety (VKM). VKM is an independent committee under the Norwegian Ministry of Health and Care Services, and carries out independent risk assessments for NFSA across the Authority's field of responsibility. One of its nine Panels is assigned responsibility for safety evaluations of nanotechnologies and ENMs in food. The organization of VKM with its various expert panels is very much the same as the organization of EFSA.

Norwegian Institute of Public Health (NIPH). NIPH has also a role with respect to risk assessment of residues in food and feeding. The Institute has an advisory role for NSFA, the Ministry of Agriculture and Food and the Ministry of Trade, Industry and Fisheries.

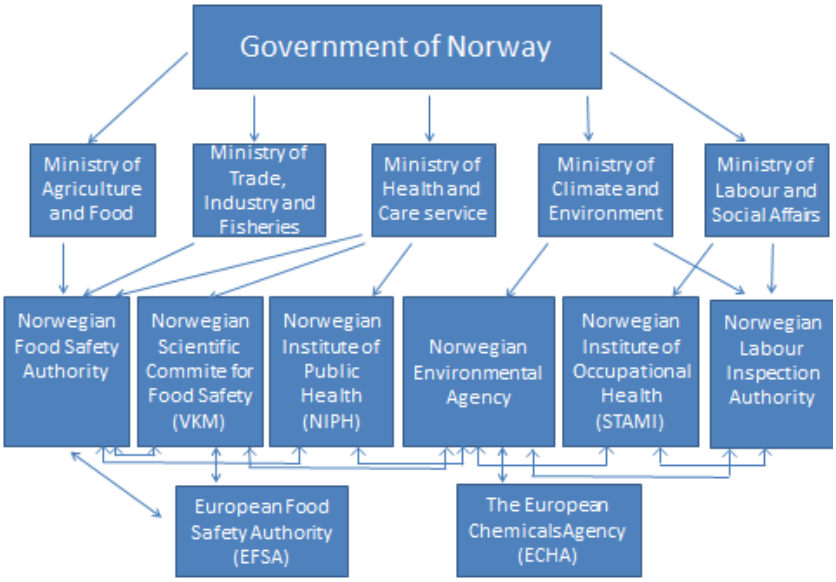

Figure 1. Schematic presentation of the Norwegian organization of the regulatory work with chemicals, including engineered nanomaterials (ENMs). The relationship to relevant organizations within EU, such as EFSA and ECHA, is also shown.

The Russian approach and perspective: A summary of the current status

General principles of risk characterization and management used in Russia

A traditional four-tier system of risk assessment is applicable that includes stage 1) identification of hazard 2) hazard characterization 3) exposure assessment and 4) risk characterization, by description of its quantitative expression, followed by scaling of risk; as negligible, moderate, high and very high.

Risk characterization. For this purpose the most commonly used model, which takes into account only deterministic effects, is based on the use of so-called "Hazard ratio" and "Hazard index». Presently, the risk characterization has a qualitative character, since all the current risks are associated with existing doses (measured or estimated) of NPs/ENMs at a level BELOW the reference values, and thus is considered insignificant. If you EXCEED the reference value there is a significant risk, but to clearly establish the quantitative relation of risk (probability of occurrence of adverse effects) with the degree of excess of reference dose value, is not currently possible.

Management of risk. This is based on 1) the assessment of the risks and 2) the presence of the legal framework at the state, local and corporate levels, allowing regulation of ENM production.

Regulation of nanotechnology which is now developing in most industrialized countries, is conventionally divided into the so-called "horizontal line" and "vertical line". The subject of "horizontal" regulation covers all kinds of products with a functional purpose, for example, all food, all cosmetics, medicines. Presently, the total amount of ENM products takes only a small part. In contrast, "vertical" legislation is specifically developed to regulate ENMs, and is applicable to them.

Organization of regulation of chemicals including ENMs in Russia

- **Federal Service on Surveillance for Consumer Rights Protection and Human Well-being** (ROSPOTREBNADZOR) is a branch of the Health Ministry and the main regulatory agency on the territory of the Russian Federation. ROSPOTREBNADZOR is responsible for the health safety of the population and approval of standards for chemicals substances. One important task is to evaluate the toxicity of ENMs and to perform subsequent safety regulation.
- **RUSNANO** is a private company. Their main focus is financial profit and to support successful industries which are using NPs for producing different types of products.

Federal Service on Surveillance for Consumer Rights Protection and Human Well-being (ROSPOTREBNADZOR). ROSPOTREBNADZOR is the main state organization which approves regulations concerning synthetic NPs in water, atmospheric air, workplace air, soil, and environmental compartments. ROSPOTREBNADZOR attaches great importance to the safety of working conditions in facilities that produce NPs and the security of products based on nanotechnology. ROSPOTREBNADZOR has created 50 regulatory and procedure documents for ENMs, including the subsequent functional blocks:

1. Prioritizing

Prioritizing is based on the assessment of the potential hazard of ENMs by the results of analysis of scientific sources. The operating research model "General keys", underlying the algorithm of ENM hazard assessment, includes all currently known properties of ENMs which can affect their potential hazard; geometric characteristics, physical and chemical properties, interaction with biomacromolecules, effects on cells and organisms, and environmental characteristics.

2. Methods for characterization of ENMs and determination of exposure levels

Methodological guidelines and recommendations describe the methods of detection, identification, and quantitation of engineered NPs and ENMs in environmental matrices and some kinds of food and packaging materials (a total of 12 regulatory and procedural documents).

3. Toxicological-hygienic and medical-biological safety assessment of ENMs

Methodological documents describing the methods of toxicological-hygienic and medical-biological safety assessment of NPs and NMs, using a multilevel test program:

- models of germ cell cultures
- model systems *in vivo*/laboratory animals
- special studies concerning long-term adverse effects

4. Regulatory documents for workers and consumer products

Documents establishing the procedures of expert examination of nanotechnology industry products (11 regulatory and methodological documents) have been developed. These documents are reflected in the Technical Regulations of the Customs Union TR TS 009/2011 "Safety of the perfumery and cosmetic products" (Section 9.3, article 5 and Section 4, article 6) and TR TC 0021/2011 "Food Safety" (articles 27-29)

5. Hygienic standards

In 2010 environmental standards for some NPs were approved for the first time (GN 1.2.2633-10). The tentative safe exposure levels (TSEL) in workplace air (shift average) were established for TiO_2 NPs (0.1 mg /m^3 at NP diameter 5–50 nm) and single-walled carbon nanotubes (0.01 fibre per 1 cm^3 at fibre length > 5 μm and fibre diameter 0.4–2.8 nm), as well as the tentative allowable level (TAL) for Ag NPs in drinking and surface water (0.05 mg/dm^3 at NP diameter 5–50 nm).

6. Risk Assessment and Risk Management

The Methodological Guidelines MG 1.2.0038-11 define the methods of risk assessment of the human health impact of NPs/NMs, and Methodological Guidelines MG 1.2.0041-11 define decision-making procedures in order to minimize adverse effects of NPs/ENMs.

All information on products containing NPs/ENMs is available on the Internet and is accessible to the public:

Unified computer platform of nanomaterials and nanotechnologies used by the Russian Federation (the Register)	http://web.ion.ru/GM_1/GM.asp
Register of the State-registered products in the Russian Federation and the Customs Union	http://fp.crc.ru/
Information on nanoproducts produced and sold in Russia	http://www.rusnanonet.ru/products/list/ http://www.rusnanonet.ru/goods/ http://www.portalnano.ru/

In establishing the maximum allowable concentrations (MACs) of hazardous chemicals (including NPs) in the environment, you need to comply with certain principles of hygienic regulation, which include:

1. "Look-ahead" principle. The principle claims that preventive measures are developed and introduced before a substance is started to be industrially produced and launched to the market.
2. Principle of a threshold. It means a principle of determining the thresholds of all types of effects of chemical compounds (including mutagenic and carcinogenic effects).
3. Principle of limiting nuisance. This principle sets the lowest concentration, of harmful chemicals.
4. Principle of evaluating/regulating each component in the different exposure settings separately. Hygienic standards for atmospheric air, workplace air, water, soil are installed separately, due to the specificity and variability of their physical and chemical properties.
5. Principle of standardizing the conditions and methods for risk assessment. Hygienic standards incur legal, medical and other functions that are required for strong regulation of the conditions of the measurement methods and assessment principles. Such standards in Russia are developed on the basis of the assessment of acute and chronic toxicity and long-term effects on both *in vitro* and *in vivo* models.

All institutions that develop regulatory standards for chemical substances (including NPs) should be certified by the Federal Accreditation Service and obtain a special license. No special certification for working with NPs is presently required. Furthermore, no standard operational procedures for NP assessment are presently available. Therefore, methods and techniques for micro- and macro-scale substances are used, however, some correction coefficients are introduced for NPs. Such correction coefficients are determined/-selected independently by each institution. To avoid great differences in the resulting values, it is advised that the standards for NPs differ not more than an order of magnitude from the respective values of the same substance in the macro- and microform.

Types of health risk advising institutes in the Russian Federation

Today, the Research Institute of Hygiene, Occupational Pathology and Human Ecology (RIHOPHE) (St. Petersburg), Institute for Nutrition of the Russian Academy of Medical

Sciences (RAMS) (Moscow), and State Center for Hygiene and Epidemiology (Moscow) may carry out this type of work with NPs. Surely, the list of institutions is not exhaustive.

Research Institute of Hygiene, Occupational Pathology and Human Ecology (RIHOPHE)

The main mission of RIHOPHE is to form the scientific basis for medical and hygienic support of work associated with the production, application, and handling of hazardous chemical substances and other hazardous factors.

The main focuses of RIHOPHE activity are:

- Toxicity and hazard assessment of highly toxic chemicals in *in vivo* and *in vitro* experiments
- Basic research into structure-toxicity relationships and mechanisms of toxic action and pathogenesis of acute and chronic intoxications
- Development of regulatory standards for hazardous chemicals at workplace and in the environment
- Development of medical and sanitary guidelines to ensure safety of people occupied in chemically hazardous industries and the population living in the vicinity of chemically hazardous industrial facilities
- Search for cause-effect correlations between workers' and population's health in relation to working and environmental conditions, respectively
- Studying long-term health effects of highly toxic chemicals
- Diagnosis and treatment of occupational diseases

RIHOPHE can do:

- Toxicity assessment and development of regulatory standards for chemical substances, including ENMs, by traditional toxicology methods and modern methods for the assessment of cytotoxic, embryotoxic, gonadotoxic, genotoxic (mutagenic), and immunotoxic effects, as well as pathomorphology.
- Exposure models: whole-body and nasal inhalation, oral, gavage, per- and subcutaneous, intraperitoneal, etc.

State Center for Hygiene and Epidemiology

This center uses the following test systems for hazard assessment of ENMs:

- Cultures of microorganisms
- Model systems *in vitro* (for toxicity and irritation action)
- Laboratory animals (model systems *in vivo* for toxicity and irritation tests)
- Special studies on adverse effects (animal chronic exposure experiments up to 6 months)

The Center supposes that the methods for assessing the toxicity of ENMs are based on the mass principles as used for risk assessment of traditional chemicals.

Institute for Nutrition RAMS

This institute has developed a procedure for ENM risk assessment, which is similar to that used for chemical substances in the micro- or macroforms. This was approved by ROSPOTREBNADZOR and put in force as "The concept of toxicological studies, risk assessment methodology, methods of identification and quantification of nanomaterials".

In addition to developing regulatory documents, the Institute also focuses on the registration and classification of NPs and ENMs. An information and analytical center for the safety of nanotechnology and ENMs has been established in connection with the Institute, and a single computer database on NPs and nanotechnology used in the Russian Federation was developed. To date, in the Russian Federation, a legislative, regulatory, and methodological framework is functioning, which regulates research and practical work with this type of products.

RUSNANO

RUSNANO receives an expert opinion on the level of danger or safety of the products from nanotechnology industry according to approved guidelines (MR 1.2.0016-2010) from competent scientific organizations (currently mainly from “State center of hygiene and epidemiology” of ROSPOTREBNADZOR). One of RUSNANO’s departments, the Department of Metrology (Metrology in Norwegian is “Justervesenet”) works and measures NPs, but otherwise RUSNANO does not specifically work with ENMs, and does not make expert conclusion for ENMs. The main RUSNANO mission nowadays is to support profitable industries and enterprises based on using ENM.

The expert conclusion on safety of ENMs provided for RUSNANO is based on approved methodology and algorithms of risk assessment/safety products of nanotechnology. Estimation of algorithm is based on mathematical models, using literature data about physico-chemical, biological and toxicological properties of ENMs.

Notably; RUSNANO separates ENMs in different categories; nanoobjects (for example, NPs TiO2 in paintings) and products of nanoindustry (for example, carbon nanotubes incorporated into tires). RUSNANO does not carry out any experiments *in vivo* or *in vitro*, and does not issue any recommendations about NP standards in water, atmospheric air, workplace air, soil, or environmental compartments.

However, RUSNANO is classifying the ENMs on different hazard levels, depending on 3 basic principles

- Safety of NP (toxicological, ecological, ecotoxicological safety)
- Technical regulations
- Sanitary and epidemiologic requirements

Methods of classifying are developed by RUSNANO and approved on state level by federal service on customers' rights protection and human well-being surveillance.

Classifications:

1. Nanoproducts and nanotechnologies, rated with low level of potential hazard:
    - additional research and examinations are not needed

- existing legislation is used for products circulating and entering into markets

2. Nanoproducts and nanotechnologies, rated with medium level of potential hazard:
   - a general toxicity assessment of products and ENMs contained in products and technological processes is recommended
3. Nanoproducts and nanotechnologies, rated with high level of potential hazard:
   - a full scope of toxicological and hygienic assessment including assessment of potential long-term adverse effects on health and special evaluation is recommended

For ENMs with medium and high levels of hazard the following actions/procedures are needed:

- set of actions aimed to minimize health and environmental risks (equipment sealing, mandatory ventilation, personal protection equipment, filtration of aerosol emissions, etc.)
- procedures of informing, including marking technologies of safe usage and disposal of products

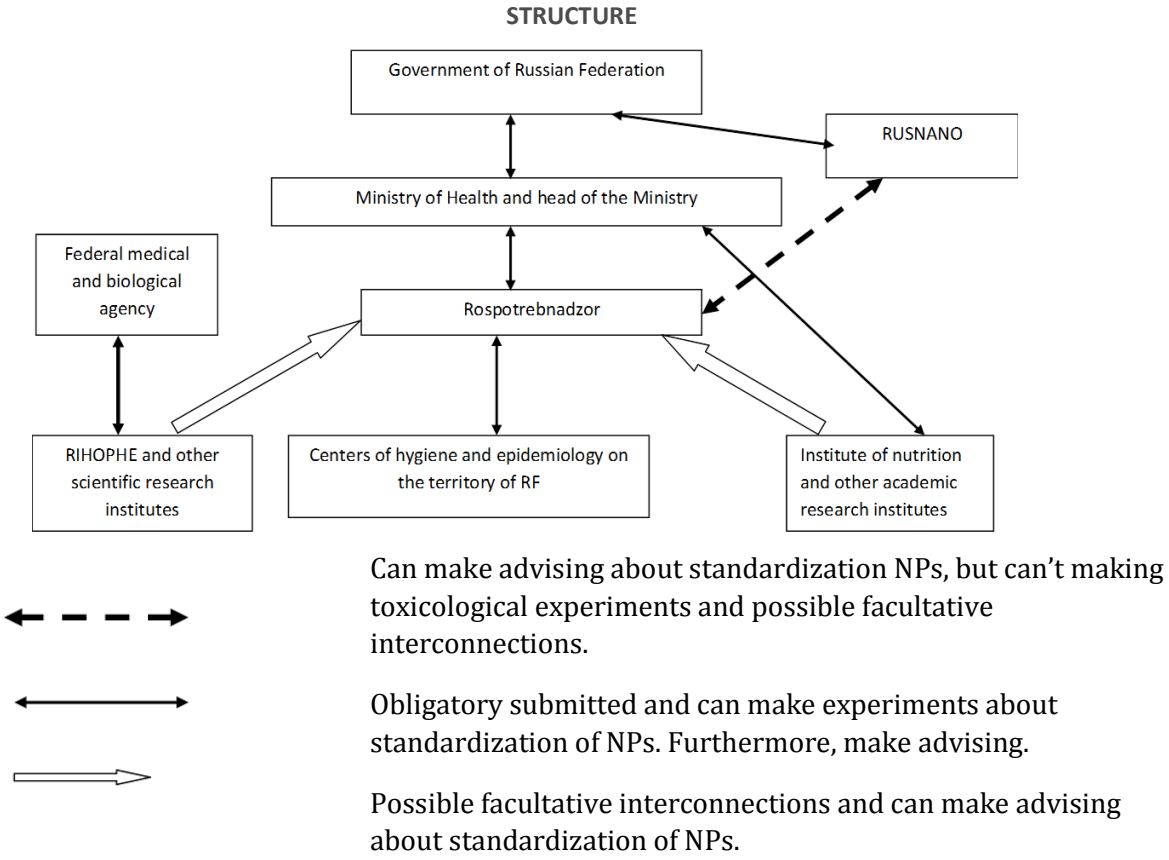

Figure 2. Schematic presentation of the Russian organization of the regulatory work with chemicals, including engineered nanomaterials (ENMs).

This is only a structure of possible interconnection between different organizations during the process of establishing hygienic and safety standards for NPs (organizations which can give recommendations about regulating standards for working with NPs in Russia).

Comparison between Russian and Norwegian regulatory policies on nanomaterials in chemicals, food and occupational settings

When comparing the risk assessment and regulatory policies in EU- and EEA-countries (including Norway) and the Russian Federation, the risk assessment is in principle similar, and is based on the relationship between the mass of ENM and response, as for chemicals in general. With respect to regulatory policies there are differences, as Russia follows their federal legislation, in contrast to the EU- and EEA-countries (including Norway) that are bound by the legislation within the REACH/CLP framework. One important difference is that the Federal Service on Surveillance for Consumer Rights Protection and Human Well-being (ROSPOTREBNADZOR) has a regulatory role with chemicals, including ENMs, in different settings, both in water, atmospheric air, soil, workplace air, and consumer's goods. This may be an advantage, giving a harmonized and coordinated approach in the regulatory policies. In comparison, in EU/EEA/Norway, the regulatory policies are less centralized, and more institutions and ministries are involved, both internationally and on the national level.

Conclusions

Risk assessment and risk management of engineered ENMs pose challenges for regulators, industry, workers and consumers both in EU/EEA (including Norway) and the Russian Federation. Due to lack of, or poor scientific data on, hazard and exposure characteristics, it is still very difficult for many ENMs to be fully evaluated as other chemicals. Notably, there are no toxic effects that seem unique to all ENMs. Furthermore, the nano-specific health effects, anticipated years ago, have not up to now been confirmed by research. Thus, presently current risk assessment methods seem applicable, although there are still challenges for the risk assessment and management of ENMs. From a regulatory point of view, it has been difficult to assess the importance of different dose metrics for ENMs (mass, size, surface area and chemical composition).

In both EU-and EEA countries (including Norway) and the Russian Federation, the risk assessment of NPs is in principle similar with respect to hazard identification and characterization, exposure assessment and risk assessment. Furthermore, the regulatory policies seem to use the legal framework as for chemicals in general, and based on particle mass.

EU, and Norway as an EEA member, strictly follow the REACH agreement, and a regulatory procedure for "Classification, Labelling and Packaging "(CLP). Furthermore, both for workers and consumers, the European Chemicals Agency (ECHA) is EUs regulatory authority on the safety of chemicals, which also includes ENMs. For chemicals in food, including ENMs, the Scientific Committee and the Advisory Forum of EFSA is responsible for risk assessment of nanotechnologies in food and feed.

In Norway, the Norwegian Environment Agency is the REACH Competent Authority. The Labour Inspectorate is responsible for the surveillance of chemicals, including ENMs, in occupational settings. There is an equivalent organisation under the Norwegian Ministry of Health and Care Services, The Scientific Committee for Food Safety (VKM), which carries out independent risk assessments of contaminants in food, including ENMs, for the Norwegian Food Safety Authority. The Norwegian Institute of Occupational Health (STAMI) and the Norwegian Institute of Public Health (NIPH) have research and advisory roles of ENMs for occupational settings and the general population, respectively.

In the Russian Federation "Federal Service on Surveillance for Consumer Rights Protection and Human Well-being" (ROSPOTREBNADZOR) is a branch of the Health Ministry and the main regulatory agency, which is responsible for evaluating the toxicity of chemicals (including ENMs), and approval of standards of the chemical substances. Several institutes accredited by the "Federal service on accreditation" carry out studies for determining exposure and toxic potential to chemicals (including ENMs). However, with respect to ENMs these institutes presently do not need additional accreditation for their work, since there are no specific regulatory procedures for working with NPs. Methods and techniques for working with substances in micro- or macroforms are used. The Research Institute of Hygiene, Occupational Pathology and Human Ecology (RIHOPHE) (Saint-Petersburg), the Institute of Nutrition (Moscow) or the State Center of Hygiene and Epidemiology (Moscow) may carry out these types of work with ENMs. RUSNANO is a private company, also operating in the ENM field. This institution receives expert opinions

from competent scientific organizations on the level of danger or safety of the products from nanotechnology industry, and makes a classification based on the hazard levels.

When comparing the risk assessment and regulatory policies in EU/EEA/Norway and Russia, the risk assessment in principle seems similar, and the risk assessment of ENMs is based on the relationship between mass and response, as for chemicals in general. In both EU/Norway and the Russian Federation, no specific regulatory procedures for working with ENMs are obtained. With respect to regulatory policies, there are also differences, as Russia follows their own federal legislation, in contrast to the EU- and EEA-countries (including Norway) that are bound by the legislation within the REACH/CLP framework. In EU/EEA/Norway, many institutions are involved, both at an international and national level, whereas in the Russian Federation ROSPOTREBNADZOR seems to have a regulatory role in issues regarding chemicals/ENMs in the environment, for consumers and in occupational settings.

Acknowledgements

This report comparing Risk assessment and Regulatory work in the Russian Federation and Norway is mainly built on the seminar " Risk Assessment of Engineered Nanoparticles" in St. Petersburg, Russia (see attached programme and list of participants). The report has been made by the authors, but with substantial input from Vidar Skaug, M.D, toxicologist, Norwegian Institute of Occupational Health and PhD, toxicologists Ragna Hetland and Christine Instanes, Norwegian Institute of Public Health.

Appendix

Seminar Programme and Abstracts

“Risk assessment of engineered nanoparticles”

19 May 2015; St. Petersburg, Russia

Seminar at Hotel Oktiabrskaya

Scope of the seminar: The emerging use of nanoparticles in consumer products and nanomedicine represent a breakthrough technology with great economic benefits. Simultaneously, the nanoparticles may potentially induce adverse health effects both in occupational settings and for the consumers. Thus, it is of uttermost importance to develop the technology in a sustainable manner by performing a proper health risk assessment for the use of nanoparticles. In this risk assessment, both particle characterization, estimation/measurements of potential exposure and determination of the health hazard linked to the use of different nanomaterials, are required. This seminar will deal with the methods and challenges for risk assessment of these particles. They may be emitted in small amounts, but still in great numbers and with large surface areas, and also with an extensive variation in chemical compositions. In addition, the seminar will shed light on similarities and differences in regulatory policies between Russia and Norway towards nanoparticles/materials in occupational settings and for the consumers, during inhalation, oral and dermal uptake.

Programme:

8.30- 9.00	Registration of participants
9.00-9.15	Welcome and introduction to the seminar, Prof. Andrey Radilov, Director Research Institute of Hygiene, Occupational Pathology and Human Ecology (RIHOPHE), St. Petersburg: and Per Schwarze, NIPH, Norway Seminar moderators: Per Schwarze and Andrey Radilov

9.15-9.50	The importance of characterization in risk assessment of nanoparticles. Anna Yu Godymchuk; Division of Nanomaterials and Nanotechnologies, Tomsk Polytechnic University, Tomsk, Russia
9.50-10.25	Risk assessment of inhaled engineered nanoparticles- lessions learned from studies of ultrafine ambient particle. Per Schwarze, NIPH, Norway
10.25-11.00	Inhalation system: nanoparticle technology for in-vivo research and risk assessment Lena Wenzler; TSE Systems, Germany
11.00-11.15	Coffee break
11.15-11.50	Risk assessment and regulations of inhaled engineered nanoparticles in occupational settings - the Norwegian and EU-perspective. Vidar Skaug, STAMI, Norway
11. 50-12.25	Methodological approaches to the hygienic regulations concerning engineered nanoparticles and nanomaterials in Russian Federation Oxana Guskova; Center for Hygiene and Epidemiology; Moscow, Russia
12.25-13.25	Lunch
13.25-14.00	Risk evaluation of nanomaterials used in consumer's goods. Ivan Gmoskinski, Research institute of nutrition; Russian academy of medical science, Moscow, Russia
14.00-14.35	Risk assessment of nanoparticles and regulations subsequent to oral administration-the Norwegian/EU/EFSA perspective Ragna Hetland, NIPH, Norway
14.35-14.50	Coffee break
14.50-15.25	Risk assessment and regulations of engineered nanoparticles with focus on public health: the Norwegian /EU and REACH perspective. Christine Instanes; NIPH; Norway

15.25-16.00	Methodology for assessing safety of nanotechnology products. Olga Makarova; RUSNANOTECH, Moscow
16.00-16.45	Discussions, and further work- Moderators Magne Refsnes and Marit Låg; NIPH, Norway

List of participants, St. Petersburg, Risk assessment of Nanoparticles; 19th May 2015

No.	Name / имя	Institution / учреждение	Title / должность
1	Fehmer, Jurgen / Юрген Фехмер	TSE Systems, Germany	Director
2	Glushkova, Anzhela / Анжела Глушкова	RIHOPHE, Saint-Petersburg	Senior Scientist
3	Gmoshinski, Ivan / Гмошинский Иван Всеволодович	Research Institute of Nutrition; Russian Academy of Medical Science, Moscow, / д. б. н., ведущий научный сотрудник лаборатории пищевой токсикологи и оценки безопасности нанотехнологий ФГБУ НИИ питания РАМН (Москва)	Senior Researcher, PhD. D.Sc.
4	Godymchuk, Anna Yu / Анна Годымчук	Division of Nanomaterials and Nanotechnologies, Tomsk Polytechnic University, Tomsk	PhD, Ass Professor
5	Guskova, Oxana / Оксана Гуськова	Center for Hygiene and Epidemiology in Moscow	Specialist of general hygiene department of preventive toxicology and sanitary-epidemiological expertise of non-food products
6	Hetland, Ragna / Рагна Хетланд	Department of Food, Water and Cosmetics, Norwegian institute of Public Health (NIPH), Oslo	Senior Scientist, PhD
7	Instanes, Christine / Крстин Инстансес	Department of Chemicals and Radiation, Norwegian institute of Public Health (NIPH), Oslo	Senior Scientist, PhD
8	Khlebnikova, Natalia / Наталия Хлебникова	RIHOPHE, Saint-Petersburg	Head of Foreign Relations, Senior Scientist

9	Kombarova, Maria / Комбарова Мария	Department of Hygienic Regulation RIHOPHE, Saint-Petersburg	PhD, Head of Department of Hygienic regulation
10	Låg, Marit / Марит Лаг	Department of Air Pollution and Noise, Norwegian institute of Public Health (NIPH), Oslo	Senior Scientist, PhD, Professor
11	Makorova, Olga / Ольга Макарова	RUSNANOTECH, Moscow	Head of Department Nanosafety Assessment Nanomaterials and Nanoparticles, PhD
12	Nikolaev, Anatoliy / Николаев Анатолий Иванович	Research Institute of Hygiene, Occupational Pathology and Human Ecology, (RIHOPHE), St. Petersburg	Senior Researcher, PhD / к.х.н., ст.н.сотр.
13	Nikolaev, Boris / Николаев Борис Петрович	Laboratory Nanotechnologies and Immune Genetics; Research Institute of Pure Biochemicals,Saint-Petersburg	PhD, Head of Laboratory Nanotechnologies and Immune Genetics / к.м.н., заведующий лабораторией нанотехнологий и иммунной генетикки
14	Prokofieva, Daria / Прокофьева Дарья Станиславовна	Research Institute of Hygiene, Occupational Pathology and Human Ecology, (RIHOPHE), St. Petersburg	Senior Researcher, PhD / к.б.н., старший научн.сотрудн
15	Radilov, Andrey / Андрей Радилов	RIHOPHE, Saint-Petersburg	Deputy Director RIHOPHE, Prof., PhD
16	Refsnes, Magne / Магне Рефснес	Department of Air Pollution and Noise, Norwegian institute of Public Health (NIPH), Oslo	Senior Scientist, PhD
17	Schwarze, Per / Пер Шварц	Department of Air Pollution and Noise, Norwegian institute of Public Health (NIPH), Oslo	Department Director, PhD
18	Skaug, Vidar / Видар Скауг	National Institute of Occupational Health, Oslo	Dr.Med
19	Torgersen, Elena/ Торгерсен, Елена	Department of International Public Health, Norwegian Institute of Public Health/ Норвежский институт общественного здравоохранения	Senior Adviser, / старший советник, отдел международного здравоохранения
20	Wenzler, Elena / Елена Венцлер	TSE Systems, Germany	Area Sales Manager North East Europe
21	Zvezdin, Vasilij / Звездин Василий	Laboratory of Biochemical and Nanosensory Diagnostics, Perm	PhD, Head of Laboratory Biochemical and Nanosensory Diagnostics

Abstracts from the Seminar on Risk assessment and Regulatory policies:

The importance of characterization in risk assessment of nanoparticles

Anna Godymchuk[1,2,a], *Denis Kuznetsov*[2], *Alexander Gusev*[2,3], *Elena Yunda*[1], *Elizaveta Karepina*[1], *Evgeny Kolesnikov*[2]

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[2]National University of Science and Technology "MISIS", Moscow, Russia
[3]Tambov State University named after G.R. Derzhavin, Tambov, Russia
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The demand and production of nanosized powders is growing due to a rapidly emerging use of nanomaterials on the global market. From this follows an increased need for an improved understanding of characteristics and potential toxicity of nanomaterials, essential data for classification and risk assessment.

Nanoparticles can be released into the ambient air of the working area during the production and due to its size (up to 100 nm) they can penetrate into the body mainly by respiratory route. Industrial aerosols, independent of the source, are extremely undesirable because they pose a threat to people's health and inflict damage on the environment. Several authors have repeatedly demonstrated that nanoparticles have a strong penetrating power, diffusive energy, and high toxicity when inhaled by a living organism into the respiratory system. Therefore, as far as the development of industrial production of nanomaterials is concerned, the struggle with such aerosols is becoming more and more relevant.

Although, it is clear *a priori*, that nanoparticles radically change their properties when entering the atmosphere and hydrosphere, nevertheless there is still lack of information about physicochemical behavior and fate of nanoparticles in liquid biological media (saliva, sweat, lung fluid, etc.). This does not so far allow predicting the behavior of nanoparticles and establish regular correlations between the physicochemical state of engineered nanoparticles and cytotoxic effects.

The lecture includes both the experimental research of the team and the survey on the physicochemical properties, fate, and toxicity of engineered nanoparticles in the environment including atmosphere and liquid surroundings.

First of all, we will present a dispersion and morphological analysis of a working site's air made in order to determine the active sources of particulate emission from the nano- and submicron range at various stages of particles production in a specialized research laboratory.

Then, the special attention will be given to the influence of abiotic parameters on nanoparticles migration in the environment and human body, uptake, translocation and clearance of inhaled nanoparticles, dermal uptake of nanoparticles. A mixed effect of nanoparticle physicochemical properties (size, dose- and concentration, surface charge, shape, surface-area, chemistry, dissolution, aggregation) on toxicological properties will

be presented by means of comparison studies of nanoparticles behavior in different environmental media.

The prognosis of the metal-containing nanoparticles accumulation in human lung based on metal particles solubility in simulated lysothomal liquids will be discussed.

On the one hand, nanoparticles released into the atmosphere do not undergo a crystalline modification and are able to maintain their morphology and crystalline structure. On the other side, nanomaterials released into the liquid environment may radically change their properties. We will show, that depending on particle reactivity and exposure conditions nanoparticles form aggregates of different size and stability in solution at the same time as different dissolution/metal release processes take place. We try to use obtained results to predict nanoparticles behavior in physiological and environmental solutions, while it may be highly difficult due to the wide range of nanopowders available and limited quantitative and mechanistic understanding of these processes (often both chemically and electrochemically induced).

From the point of toxicology it is highly essential to reveal what chemicals are formed during interaction of metal nanomaterials with the environment, since toxic effect caused by metal-containing materials may be comparative. Therefore, the high physicochemical activity of electroexplosive metal nanopowders will be shown in simulated physiological and environmental solutions.

Inhalation system: nanoparticle technology for in-vivo research and risk assessment

Lena Wenzler

Deputy Sales Director Eastern Europe & Middle East; TSE Systems, Germany

With the industrial production of nanomaterials, the health and environmental impact of nanoparticles is now at the focus of public concern. Risk assessment and Health effects – whether positive or negative – are of particular interest. Systems for accurate, repeatable and validated experimental studies on health effects provide a major challenge for nano research investigations. In this respect, in-vivo and in-vitro inhalation exposure studies are an essential instrument.

A wide range of technical tools and equipment is required for the experimental studies. Starting from established exposure systems for classical inhalation, the particular properties of nanoparticles and the challenges on the instrumentation associated with them must be taken into consideration.

- Nanoparticle generators and conditioning units
- Application units such as Whole Body, Head Nose Only and Cell Culture exposure chambers
- Sampling and analysis equipment for nanoparticles
- Control and regulation instrumentation and software for automatic experiment procedures
- Operational essentials and safety features such as air supply, filter systems, exhaust stations

Validated systems must satisfy high demands in order to ensure standardized and therefore reproducible test conditions and research results.

- Controlled nanomaterial production and conditioning
- Standardized experiment designs
- Robust and reliable exposure technology
- Precise and suitable analysis equipment
- Loss-free raw data management and fraud-resistant data recording

Regulations and guidelines (OECD, EPA, ISO) give the experiments a framework with respect to standardization and thus the assignment of test results in the overall context.

Risk assessment and regulations of inhaled engineered nanoparticles (ENM) in occupational settings - the Norwegian and EU-perspective.

Vidar Skaug; M.D, toxicologist ; STAMI, Norway

ENMs are designed and produced intentionally at the nanoscale (particles with at least one dimension < 100 nm), to utilize novel properties or improvements of already known inherent properties available for particles with larger sizes. In 2006 a definition of nanomaterials was recommended by the European commission[1].

Regulations

Although many ENMs have novel or improved properties compared to their larger counterparts, no nano-specific regulation has been decided by any country until now. Nanomaterials in occupational settings in EU member states are covered by the exciting chemical regulation in REACH[2] (**R**egistration **E**valuation **A**uthorization and **R**estriction of **Ch**emicals) and the CLP (**C**lassifiaction , **L**abelling and **P**ackaging) legislation. Also The EU directives on safety and health at work[3] also applies, such as the European Framework Directive on Safety and Health at Work (Directive 89/391 EEC)[4], the Directive 98/24/EC - risks related to chemical agents at work[5] and The Directive 2004/37/EC - carcinogens or mutagens at work [6]. The rational is that regarding safety aspects, they are considered similar to chemicals in general, in that some may hazardous, and some may be not[7]. Possible risks are related to intrinsic properties of each ENM and their exposures. Therefore, according to EU legislation, and as for other chemicals, ENM require a risk assessment, on a case-by case basis, starting with the EU definition on NM and using available information.

REACH *see footnote 2*

-2004-37-ec-indicative-occupational-exposure-limit-values
[1] http://ec.europa.eu/growth/sectors/chemicals/reach/nanomaterials/index_en.htm
sectors/chemicals/reach/nanomaterials/index_en.htm
[2] http://ec.europa.eu/environment/chemicals/nanotech/pdf/commission_recommendation.pdf
opa.eu/environment/chemicals/nanotech/pdf/commission_recommendation.pdf
n_recommendation.pdf
[4] http://ec.europa.eu/growth/sectors/chemicals/reach/index_en.htm
_en.htm
[5] https://osha.europa.eu/en/legislation/directives
[5] https://osha.europa.eu/en/legislation/directives/the-osh-framework-directive
-framework-directive
[6] https://osha.europa.eu/en/legislation/directives/exposure-to-chemical-agents-and-chemical-safety/osh-directives/75
[6] https://osha.europa.eu/en/legislation/directives/exposure-to-chemical-agents-and-chemical-safety/osh-directives/directive-2004-37-ec-indicative-occupational-exposure-limit-values
ectives/exposure-to-chemical-agents-and-chemical-safety/osh-directives/directive-2004-37-ec-indicative-occupational-exposure-limit-values

The REACH regulations provides increased protection of human health and the environment from the risks that can be posed by chemicals, by identification of the hazardous properties of chemicals, and further by providing legislation and guidance for safe handling of chemicals. REACH has replaced legislative framework for chemicals in the EU, prior to 2007.

ENMs are chemicals and comprised in the REACH regulation. Although there are no specific requirements for ENMs in REACH today, they should be assessed from a regulatory point of view according to the criteria used for other chemicals I the working environment. There are however challenges for the registrants of nanomaterials to clearly identify the NMs in the REACH registrations dossiers[8]

CLP:

Nanomaterials that fulfill the criteria for classification as hazardous under Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures[9] must be classified and labelled. Many of the related provisions, including safety data sheets and classification and labelling apply already today, independently of the tonnage in which the substances are manufactured or imported. Substances, including nanomaterials, meeting the classification criteria as hazardous and put on the market must be notified to ECHA. Nanomaterials are specifically mentioned in CLP Article 9(5): It states that consideration should be made on the forms and physical state in which the substance or mixture is placed on the market or in which it can reasonably be expected to be used. These requirements are also included in the Norwegian CLP Regulation.

The EU directives on safety and health at work[10].

The Council Directive 98/24/EC of 7th April 1998 on the protection of the health and safety of the workers from the risks related to chemical agents: This Directive is also valid for Norway and according to this Directive, The Commission has obligation to set occupational exposure limit values and biological limit values and the employers have obligations to assess the risks of hazardous chemical agents and to ensure that the risks from hazardous chemicals are eliminated or reduced to a minimum. This Directive meets many of the challenges for assessment of ENMs, as described in REACH.

Norway: Regulations of nanomaterials at the workplace.

Norway, as a member of EFTA (European Free Trade Association), and the European Economic Area (EEA), participates in EU´s single internal market, adopting all relevant EU legislation other than regarding agriculture and fisheries. The REACH and CLP regulations are transposed into the Norwegian Working Environment Act and its regulations, REACH[11], CLP[12], as well as the EU directives on safety and health at work[13].

-2004-37-ec-indicative-occupational-exposure-limit-values

[8] http://ec.europa.eu/growth/sectors/chemicals/reach/nanomaterials/index_en.htm
ropa.eu/growth/sectors/chemicals/reach/nanomaterials/index_en.htm

[9] http://ec.europa.eu/environment/chemicals/nanotech/pdf/jrc_report.pdf
/environment/chemicals/nanotech/pdf/jrc_report.pdf

[11] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF
:L:2008:353:0001:1355:EN:PDF

[12] https://osha.europa.eu/en/legislation/directives

Risk Assessment

Current risk assessment methods are applicable, even if work on particular aspects of risk assessment is still required**.**

Risk assessment and risk management of ENMs poses challenges for regulators, industry and workers. In REACH, CLP and the Directive 9824/EC there are challenges for the risk assessment (RA) and management of ENMs. Due to lack of or poor scientific data on hazard and exposure characteristics it is still very difficult for many ENMs to be fully evaluated as other chemicals in REACH and CLP. There are no toxic effects that are unique to all nanomaterials. In this sense, the nano-specific health effects anticipated years ago have not been confirmed by research.

Also others issues have been difficult to assess from a regulatory point of view, such as dose metrics, the great variability among ENMs in physical and chemical characteristics and in toxicities for others parameters than size distribution.

More work to be done on regulatory issues and safety of Nanomaterials.

ECHA (The European Chemical Agency; the administrative organ in REACH located in Helsinki, Finland) has appointed subgroups working on regulatory issues and guidance for ENMs. The REACH implementation guidance from ECHA informs on requirements on MN in REACH[14,15,16].

Extensive guidance's and recommendations have also been provided by scientific institutions and national authorities in member states as well as in many countries outside Europe.

Materials data safety sheets (MSDS)

In Norway MSDS should give information on the nano-scale size of the substance if it is present.

MSDS do not in general provide adequate and accurate information sufficient to inform an occupational risk assessment for nanomaterials contained in the product.

Occupational exposure limits for ENMs:

No OELs are available for nanomaterials

Registration of ENMs:

In Norway registrants should give information on the nano-scale size of the substance whenever present.

[12] https://lovdata.no/dokument/SF/forskrift/2008-05-30-516
ttps://lovdata.no/dokument/SF/forskrift/2008-05-30-516
516
[14] https://lovdata.no/dokument/SF/forskrift/2012-06-16-622?q=merking+klassifisering
ssifisering
[15] https://osha.europa.eu/en/legislation/directives
[15] http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon1.pd

europa.eu/environment/chemicals/nanotech/pdf/report_ripon1.pd

Methodological approaches to the hygienic regulations concerning engineered nanoparticles and nanomaterials in Russian Federation

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Taking into account that the use of nanotechnology and NM is one of the most promising areas of science and technology and taking into account the possibility of close human contact with the products of nanotechnologies in production and daily life, the study of the potential risks of their use seems paramount, both in Russia and abroad .

Federal Service for Supervision of Consumer Rights Protection and Human Welfare (Rospotrebnadzor) attaches great importance to the safety of working conditions at work with minorities and the security of products produced using nanotechnology. Created 50 regulatory and procedural documents including functional blocks:

1. Prioritizing
2. Methods for determining the NP and NM
3. Safety assessment NM
4. Sampling
5. Oversight
6. Risk Assessment and Risk Management

In addition to creating a regulatory basis is working on the registration and classification of nano (NP and NM). On the basis of FGBU Institute of Nutrition Academy of Sciences was established information-analytical center on the safety of nanotechnology and nanomaterials and developed a single computer database on minorities and nanotechnology used in the Russian Federation. To date, the Russian Federation, the legislative, regulatory and methodological framework, which regulates the research, sampling, identification and quantification of the procedure for the examination of this type of product.

It is paramount hygienic regulation - enactment harmless (safe) for human exposure levels of harmful environmental factors: the maximum permissible concentration (MPC) of chemicals. Methodology hygienic standardization quality of the environment has received wide application in Russia.

In establishing the MPC of harmful chemicals in the environment comply with certain principles of hygienic rationing, which include:

1. principle of timing
2. principle of standing
3. principle of a threshold
4. principle of limiting index
5. principle of the separation of objects valuation
6. principle standardize the conditions and methods

The established principles of valuation chemicals form the basis of the current sanitary legislation.

Currently in Russia there are hygienic standards (GN 1.2.2633-10) - NP titanium dioxide, and single-walled carbon nanotubes in the working area (0.1 mg / m3 and 0.01 fiber per 1 cm3 at a fiber length> 5 m, respectively) and NP silver in drinking water and water reservoirs - 0.05 mg / dm3. Hygienic standards allow content control and monitoring of harmful chemicals in the environment.

At the present stage by using a multi-level toxicity testing program, there is an accumulation of the experimental material in the toxicity of different HM as mammals, and in alternative models for further standardization in the sanitary environment.

Hygienic regulation NP - methodologically and technically complex process, since the degree of danger to human NP may vary greatly depending on their physical characteristics. At the same time the screening risk assessment, even at the low acute toxicity, and even more so in cell cultures or the simplest organisms does not provide sufficient reliable conclusions about human safety.

The presence of the NP and HM in the ambient air or water body - this is a serious problem that should be taken into account in the design and implementation of many industrial processes, to ensure the safety of the population. It is important to obtain data on the properties of HM, which would allow to assess, control and minimize the risks arising.

Risk evaluation of nanomaterials used in consumer's goods.

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There is currently a massive introduction of nanotechnology and engineered nanomaterials in manufacturing of cosmetic products, while their use in food industry, packaging materials, household chemicals etc. still includes a limited number of items and does not show a significant upward trend. However, due to higher production volumes of priority nanomaterials and their arrival in the environment, the problem of their exposure on the population and the associated risks is relevant. In accordance with the frequency of use in mass-produced consumer goods, leading priority nanomaterials are silver nanoparticles (NPs) and (by a wide margin) NPs of gold, platinum, and titanium dioxide. Frequency of nanosized silica introduction into food products as a food additive, at the moment, seems to be underestimated, since the use of this nanomaterial is not declared by manufacturers of products and objective control of its content is difficult. Analysis of literature data on toxicological properties of nanomaterials shows that currently accumulated amount of information is sufficient to establish the safe doses of nanosized silver, gold and titanium dioxide. In a series of studies data have provided concerning the effect of oral intake of nanosized silica on the condition of laboratory animals, including on the performance of the immune system. The article examines the existing approaches to the assessment of population exposure with priority nanomaterials, characteristics of existing problems and risk management.

Risk assessment of nanoparticles and regulations subsequent to oral administration - the Norwegian/EU/EFSA perspective

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The Norwegian Food Safety Authority (NFSA) is a governmental body whose aim is to ensure that food and drinking water are as safe and healthy as possible for consumers. The majority of the regulations applicable in Norway are based on legislation acts which Norway is bound by under the European Economic Area (EEA) Agreement and constitute common European rules. Thus, the majority of regulations within the food sector in Norway are the same as those in the European Union (EU).

The Norwegian Scientific Committee for Food Safety (VKM) is an independent committee under the Norwegian Ministry of Health and Care Services and carries out independent risk assessments for NFSA across the Authority's field of responsibility. One of the nine Panels is assigned responsibility for safety evaluations of nanotechnologies and nanomaterials in food. The organization of VKM with its various expert panels is very much the same as the organization of The European Food Safety Authority (EFSA).

The use of nanotechnology in the food sector is mostly about food additives and food contact materials, and these types of products/articles have to be authorised by EU in order to be put on the European market. Authorisation follows a thorough risk assessment performed by EFSA, the keystone of EU risk assessment regarding food and feed safety. In order to provide practical recommendations for the risk assessment of food related applications of nanotechnology, EFSA published the "Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain" (EFSA, 2011). This guidance provides a practical approach for assessing potential risks arising from applications of nanoscience and nanotechnologies in the food and feed chain. Guidance is provided on: (i) the physico-chemical characterisation requirements of engineered nanomaterials used; (ii) testing approaches to identify and characterise hazards arising from the nanoproperties, which, in general, should include information from *in vitro* genotoxicity, absorption, distribution, metabolism and excretion and repeated-dose 90-day oral toxicity studies in rodents. The guidance allows for reduced information to be provided when no exposure to the engineered nanomaterial is verified by data indicating no migration from food contact materials or when complete degradation/dissolution is demonstrated with no absorption of engineered nanomaterials as such.

The Scientific Committee and the Advisory Forum of EFSA established in 2010 the EFSA Scientific Network for Risk Assessment of Nanotechnologies in Food and Feed. The Network is composed of representatives from 21 Member States and Norway, in addition to representation from the European Commission and observers from some non EU countries. The Network meets once a year and the main overall goals are i) to facilitate harmonisation of assessment practices and methodologies; ii) enhance exchange of information and data between EFSA and Member States of the EU.

Risk assessment and regulations of engineered nanoparticles with focus on public health; Norwegian/EU and REACH perspective

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We are exposed to nanoparticles (NP) in our daily life through several different consumer products. The European Chemicals Agency (ECHA) is EUs regulatory authority on the safety of chemicals, which also includes NP. ECHA aims at protecting human health and the environment by ensuring that chemicals are used safely and that the most hazardous ones are substituted by safer alternatives. REACH is the EU regulation on chemicals and their safe use and deals with the Registration, Evaluation, Authorisation and restriction of Chemicals. REACH entered into force 1st June 2007 and placed greater responsibility on industry to manage the risks that chemicals may pose to the health and environment. REACH applies to all chemicals, not only chemicals used in industrial processes but also in our day-to-day life and REACH also regulate the use of nanomaterials. REACH was adopted to improve the protection of human health and the environment from the risks that can be posed by chemicals, and at the same time enhancing the competitiveness of the EU chemicals industry. It also promotes alternative methods for the hazard assessment of substances in order to reduce the number of animals used. Norway follows EUs regulations on NP.

Any manufacturer or importer of a chemical substance or nanomaterials in quantities of one ton or more per year has to submit a registration to the European Chemicals Agency (ECHA). A technical dossier (identity, manufacture and use, classification/labelling, guidance on safe use, study summaries of toxicity/ecotoxicity, testing proposals) and a chemical safety report (CSR) need to be submitted. In the CSR a Chemical Safety Assessment is included. This assessment needs to show the risks and demonstrate safe use concerning human health and the environment. Roughly 20-30 nanomaterials have been registered. The information in the registration is based on the amount of substance that is manufactured or imported. The data requirement increase with increasing tonnage. How to evaluate data for different endpoints are thoroughly described in the guidance documents to REACH. Two concepts that are important in these guidance documents are integrated testing strategy (ITS) and a weight of evidence approach (WoE). For substances with no or very few data, a sequential test strategy like ITS, is recommended for developing adequate and scientifically sound data for assessment and classification. For existing substances with insufficient data, this strategy can also be used to decide which additional data, beside those available, are needed. The objective of the testing strategies is to give guidance on a stepwise approach to hazard identification. WoE is an option to meet the information requirements by an evidence based expert judgment. The WoE makes use of all available data and assesses the relative weights of different pieces of the available information. The advantage is that this approach reduces the need for further testing.

The CLP Regulation is a regulation which aligns the European Union system to the Globally Harmonised System (GHS). The regulation requires companies to appropriately classify, label and package their substances and mixtures before placing them on the market. CMR substances are substances with (C) carcinogenic effects, (M) mutagenic effects in germ cells and/or (R) reproductive effects. The CMR-

substances are divided into categories dependent on the quality of the data supporting the endpoint. Category 1A requires human data, while category 2B is based on animal data. Category 2 is based on more equivocal data, both from human and animal studies. REACH focus on regulation of these substances.

Substances that may have serious and often irreversible effects on human health and the environment can be identified as substances of very high concern (SVHCs). SVHC substances have to meet the criteria for classification as CMR category 1A or 1B or they have to be persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) according to REACH. Substances where there is scientific evidence of probable serious effects that cause an equivalent level of concern as with CMR or PBT/vPvB substances, also meets the criteria as an SVHC-substance. Substances are identified on a case-by-case basis. If a substance is identified as an SVHC, it will be added to the Candidate List for eventual inclusion in the Authorisation List.

The next regulation step for the SVHC substances is authorisation. The aim of authorization is to ensure that the risks from SVHC are properly controlled and that these substances are progressively substituted by alternative substances or technologies. Substances included in the Authorisation List cannot be manufactured or imported in the EU except if the companies have obtained an authorisation for their specific use(s). This authorisation can either be granted because the risks are controlled or because the socioeconomic benefits outweigh the risks.

Restriction is a tool to protect human health or the environment from substance that poses an unacceptable risk. Restriction is based on SVHC-substances and unmanaged exposure, and a balanced view of the identified risks and the benefits and costs of the proposed restriction. Restricted is related to certain activities and it regulates both import and export.

Substance evaluation is a process based on initial grounds of concern and it is possible to claim additional data to clarify risk. In 2012 silicon dioxide (synthetic amorphous silica) was evaluated by the Netherland and in 2015 silver was evaluated by the Netherland and titanium dioxide was evaluated by France.

When REACH was developed there was no focus on NP. Hence, the challenges with NP were assessed by the RIP-oN2 (expert-group) for nanomaterials and recommendations for toxicological information requirements were included in annexes to the REACH guidelines later. In the appendix attached to the endpoint specific guidance R7a the expert group has given advice on the most important issues related to evaluations of NP regarding endpoint evaluation. Lung overload is an important issue and is related to inhalation of poorly soluble and low toxicity particles. When clearance of particles is lower than exposure the alveolar macrophages are overloaded and loses there mobility and the clearance is severely impaired. The result is particle accumulation and inflammation which may results in mutations and metaplasia and development of tumors (neoplasia). Hence, interpretation of data after high doses of PSLT particles should be approached with caution and if the mechanism is lung overload the relevance for humans should be evaluated. There are indications that rats are more sensitive to overload than humans and this should be taken into consideration when the results are evaluated. Another known challenge is that NP often interferes with commonly used assays. NP may contribute to the absorbance

or fluorescence of colometric or fluorometric assays, or may bind to assay components including the substrate or the biomarker being measured. Ames test is a common genotoxic *in vitro* test. Generally drawback with Ames test is that it generates false positive results. However, for NP predominantly negative results has been obtained and speculations concerning nanomaterials ability to cross the bacterial wall or kill the test organism has been raised.

Methodology for assessing safety of nanotechnology products. Experience of RUSNANO group of companies.

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Nanotechnologies make possible to create new environmentally friendly and energy efficient enterprises and products. Realizing that any new technologies can create the potential risks, "RUSNANO" defines and develops the basic legal and technical tools (standardization, technical regulations, safety assessment, certification, self-regulation) aimed at minimizing risks to the consumer, staff, population and environment and creation conditions for sustainable launch on to the market quality and safe (competitive) nanoproducts.

Tool of minimizing risks associated with the possible impact of nanomaterials on human health is a methods of classifying nanoindustry products and nanotechnologies by their potential hazard rate.

The Methods of classifying developed by RUSNANO and approved on state level of Russia.

This method is being used by RUSNANO for more than two years and showed positive results in easing the process of entering high-quality and safe products of nanotechnology into markets.

Classification is based on identifying and assessment of the following criteria:

- Presence of nanomaterials (nanoobjects and nanoparticles) in product or technology
- Level of energy connections of nanoobjects in nanomaterial
- The risk of human's exposure to nanoobjects in regular conditions and when the product is exposed to external forces
- Measure of a product's overall (but not only it's nanoscale component) proximity to human
- Possibility of occurrence of nanoscale aerosols during the manufacturing process
- Level of potential hazard of nanomaterial contained in products and\or technological processes.

The introduction of the Methods of classifying in Russia and Europe can be an important step to harmonization of Russian and European approaches to safety assessment of nanotechnologies and nanoindustry production and to removal from state special regulation in nanotechnology field of significant amount of nanotechnologies and nanomaterials.

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