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Working Party on Manufactured Nanomaterials

COMPILATION OF NANOMATERIAL EXPOSURE MITIGATION GUIDELINES RELATING TO LABORATORIES

7th Meeting of the Working Party on Manufactured Nanomaterials taking place at OECD Conference Centre in Paris, France on 7-9 July 2010, starting at 10h00 on the first day

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This is an accompanying document to the report of the document ENV/CHEM/NANO(2010)14. This document is the final draft of the project Compilation of Nanomaterial Exposure Mitigation Guidelines Relating to Laboratories. This project was leaded by Germany with support from the Steering Group 8 (SG8).

SG8 would like to invite the WPMN to agree that this document be forwarded to the Chemicals Committee with a request for its declassification. However, SG8 would like to emphasize that there is a potential opportunity for identifying additional bibliography relevant to the project during the Aerosol Symposium (30 June-2 July). If that is the case, SG8 will inform the WPMN during its 7th WPMN meeting and will amend the document as appropriate. This should ensure that the document be published as updated as possible.

Action Required: ***The Working Party is invited to agree this document be forwarded to the Chemicals Committee with a request for its declassification.***

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TABLE OF CONTENTS

COMPILATION OF NANOMATERIAL EXPOSURE MITIGATION GUIDELINES RELATING TO LABORATORIES

1 Introduction

1. Nanotechnology is regarded as a future technology with increasing social and economical importance. However, despite of the new chances this expanding technology brings, the toxicological assessment of nanomaterials risks has not been completed comprehensively and/or at all in all cases. Therefore, the mitigation of the exposure to nanomaterials has great importance. Even though adequate workplace controls for the use of nanomaterials in large-scale production plants are applied, common standards do not exist yet. In addition to the wide use of a low number of high volume nanomaterials produced in large-scale, a high quantity of different nanomaterials are applied in a laboratory scale such as during subsequent processing of nanomaterials into various products in many laboratories including the research level.

2. For this reason, a particular interest exists regarding assessment criteria for the handling of nanomaterials in laboratories. Institutions as well as companies entering the nano-sector in all countries are producing and utilizing nanomaterials in a laboratory scale. Several strategies for assessment and implementation of protection measures must have been developed in those areas.

3. In the framework of the objective Exposure Mitigation In Occupational Settings [ENV/CHEM/NANO(2007)24/ADD2], one prioritized scope of SG8 is the implementation of the project "Compare exposure mitigation guidance for laboratories". This document is the outcome of this SG8 project covering contributions of several OECD SG8 members based on their different activities.

4. The document was mainly developed within the Federal Institute for Occupational Safety and Health (BAuA) by Mrs Baron (BAuA), Mrs kleine Balderhaar (BAuA), and Dr Wolf (BAuA). Additionally, Dr Berges (BGIA, Germany), Dr Brock (BG Chemie, Germany), Mrs Grossi (Fundacentro, Brazil), Dr Engel (BASF, Germany), Mrs Plitzko (BAuA, Germany) and Dr Reuter (VCI, Germany) contributed to the precedent draft version of this document. Considering this background, this document is to be seen as one element within the frame of exposure mitigation in the handling of a wide range of nanomaterials with a large variety of production and manufacturing procedures.

5. Based on the fact that there is a large amount of literature available, this compilation is carefully focused on different available institutional guidelines. Such guidelines are compiled in a structured manner taken their nature (i.e. general, specific to certain manufactured nanomaterials and targeted to laboratories) into account.

2 Scope

6. This document aims to provide an overview over recently published guidelines regarding the usage of nanomaterials in a laboratory scale. It is intended to perform a compilation of exposure mitigation guidelines relating to laboratories that handle nanomaterials. This issue is of great importance since there are no globally standardized protection measures determined for nanomaterials. The insight in the state of the art of good practice for nanomaterials in laboratories may not only be important for research

laboratories, but it can furthermore be of great interest for small industrial enterprises, which produce or process nanomaterials in a laboratory scale. Since a compilation of guidelines with appropriate measures provides support for the exposure mitigation and therefore generally for the occupational safety and health, a positive international feedback is supposable.

7. This document focuses on both pointing out publications of primary importance and representing a general overview of the international spectrum of publications in that topic. The guidance reports were mostly gained by research via internet. Research criteria used in this internet research were relevant search terms like ‘guidance’, ‘nanomaterial’, ‘research’ and ‘laboratory’. Further publications were obtained by selection of available collections of the participating authors. The guidance documents were chosen particularly on the basis of their level of detail in the respective aspects of protection measures.

8. This compilation is categorized by 1) specific nanomaterial guidelines relating to laboratories (herein after referred to as category S(pecific)), 2) general nanomaterial guidelines with regards / applicable to laboratories (category G(eneral)), as well as 3) general laboratory guidelines with regards/applicable to nanomaterial (category L(aboratories)).

9. This aim was based on the assumption that only a very limited amount of specific nanomaterial guidelines relating to laboratories is published. However, an unexpectedly high number of specific guidelines were found. For this reason, this literature compilation focuses mainly on category S guidelines and is structured based on the different topics that are addressed. The statements of category S guidelines are supplemented by guidelines from category G and L, if indicated. Strictly speaking, guidelines of the categories G and L are only included if they provide additional information content in order to avoid a high degree of redundancy.

10. In this literature compilation, a range of different opinions shall be highlighted. These suggestions, which are mentioned in this compilation, reflect the respective positions of the authors. An overview over the specific aspects of these guidelines can be found attached to this document as an excel table.

3 Compilation of Guidelines for Safe Handling and Use of Nanomaterials Focusing on Laboratories

11. The compilation of guidelines is structured according to typical concepts of occupational safety. These concepts include the precautionary approach, risk assessment, categorization, safer manufacturing approaches, technical measures, organizational measures, personal protective equipment, medical surveillance, transport, waste disposal and documentation. The respective paragraphs are structured further according to the following three categories:

- Category S(pecific): specific nanomaterial guidelines relating to laboratories,
- Category G(eneral): general nanomaterial guidelines with regards / applicable to laboratories,
- Category L(aboratories): general laboratory guidelines with regards/applicable to nanomaterial.

3.1 Precautionary approach

12. Given the deficit of knowledge on the environmental and health impact of nanomaterials, the application of the precautionary approach to the handling of nanomaterials is recommended by a number of specific nanomaterial guidelines relating to laboratories (S: AIST; CHS; DOE-NRSC; EPFL; Georgia Tech; HSE-a; ISU; MIT; NASA-ARC; NSF; OUHSC-IBC; TU Delft; UCI; UCSB) and by general nanomaterial guidelines (G: MHLW; NIOSH).

13. In one general guideline for nanomaterials, it is recommended that a precautionary approach guided by reference to the ‘precautionary principle’ be adopted in order to limit workplace exposure (Safe Work Australia). However, the authors mention that, once data about the health and safety risks have been determined and defined, the principle of ‘As Low As Reasonably Practicable’ (ALARP) can be adopted (Safe Work Australia).

14. It is additionally mentioned in several specific guidelines that nanomaterials might be toxic (S: CHS; DOE-NRSC; ISU). In a detailed view, an acute toxicity in the short run and a chronic toxicity in the long run has to be considered and a carcinogenity of particles cannot be excluded (S: DOE-NRSC).

15. One guideline specifically supports the precautionary measures if the mass of the nanomaterial sample exceeds the milligram range (S: TU Delft). The used nanomaterial shall be regarded as potentially toxic, if the primary units of the particles are smaller than 100 nm, if they are water insoluble and/or if the macroscopic material is classified as toxic (S: TU Delft). In this context, the expression ‘nanotoxic’ is used to underline the difference of this possible property to the potential toxicity specification of larger size particles of the same material. It is further mentioned that oxidizable materials in a condition, which they define as nanopowder state, must be considered as potentially pyrophoric and explosive when in contact with air (S: TU Delft).

16. The risks of reproductive toxicity (G: OSHA-EUROPA), sensitization (G: OSHA-EUROPA), pulmonary inflammation, granulomas and fibrosis (G: Hallock et al., 2009) are also addressed in general nanomaterial guidelines which are also applicable for laboratories.

17. Additionally, it was recommended that the general precautionary measures for new substances with unknown hazardous properties should be also applied for unknown nanomaterials (L: AGS-BMAS; DGUV). New substances in laboratories, which are insufficiently examined for their properties, which includes acute and chronic toxicity and physico-chemical characteristics, shall be treated like not less than acute toxic, caustic, chronically toxic, flammable, pyrophoric and explosive (L: AGS-BMAS; DGUV).

3.2 Categorization

18. Extending the precautionary approach to treat the nanomaterials as potentially toxic due to some of their unknown properties, a number of proposals to grade the potential hazard exist (S: AIST; EPFL; DOE-NRSC; Georgia Tech; HSE-a; NASA-ARC; ORC Worldwide; Penn-EHRS; TU Delft, UCI; UCSB).

19. One aspect of categorization distinguishes the various physical conditions of the used nanomaterials (S: DOE-NRSC; EPFL; Georgia Tech; HSE-a; NASA-ARC; ORC Worldwide; Penn-EHRS; TU Delft; UCI; UCSB). Manufacturing and handling procedures, that involve dry, dispersible nanoparticles, nanoparticle agglomerates or nanoparticle aggregates, require more stringent risk management controls than those where nanoparticles are suspended in liquids where their exposure is substantially reduced (S: DOE-NRSC). The exposure can be minimized further by handling solid nanomaterials with nanostructures fixed to the material surface, or moreover solid materials with imbedded nanostructures (S: DOE-NRSC).

20. In one specific nanomaterial guideline for laboratories, five handling categories for nanomaterials are differentiated (S: AIST). The handling category 1 is related to samples embedded in a matrix since no potential for nanomaterial release can be expected. Handling category 2 refers to work which is operated in an enclosed system, a sealed reactor or glove box (S: AIST). Nanomaterials suspended in liquids are

categorized in handling category 3 (S: AIST). The handling categories 4 and 5 are directed to work in open environment, i.e. manufacturing, cleaning, transportation, pre-treatment for measurement and works which include unsealing of containers or packages (S: AIST). The categories 4 and 5 generally apply if a potential for nanomaterial release exists (S: AIST). Category 4 and 5 are distinguished concerning the quantity of nanomaterial, which is used in an experiment (S: AIST).

21. Factors, which can influence the risk of nanomaterials, are, amongst others, the number and mass of insoluble particles (S: HSE-a) as well as their size (S: Georgia Tech; TU Delft). One criterion of relevance for a possible exposure mitigation action threshold was referred to as a minimum amount of nanomaterial (S: TU Delft). Furthermore, a minimum amount of specifically 1 g insoluble carbon particles (S: NASA-ARC) and generally 1 g of a used nanomaterial quantity per experiment was mentioned as threshold criterion of relevance (S: AIST). This value was decided based on the evaluation result provided by the respective research institute (S: AIST)

22. Particles with a high surface reactivity were also considered to possess a higher toxicity risk (S: Georgia Tech).

23. Additional to the specific nanomaterial guidelines related to laboratory use, several recommendations are given by general nanomaterial guidelines also applicable to nanomaterials. Extending the correlation between size and toxicity potential, it is highlighted that certain small particles that are smaller than 10 nm reach the alveolar spaces in the lungs in case of inhalation and particles with a diameter of 1 µm or less are able to penetrate the human epidermis (G: Hallock et al., 2009).

24. The issue of hazard assessment has a high complexity and the toxicological profile of nanomaterials is supposed to be based on their morphology, size, surface, solubility, agglomeration/aggregation, mass, surface modifications, particle concentration and volume (G: IRSST; OSHA-EUROPA). The toxicity can be further influenced by crystalline structure and charge or even contaminants (G: IRSST; Schulte et al., 2008). Other factors with impact on toxicity can be the reactivity, redox potential, potential to generate free radicals, porosity, hydrophilicity/hydrophobicity, biopersistence, and the age of particles (G: IRSST). However, it was highlighted that it is currently still uncertain, which parameters represent the best predictive value for toxicity (OSHA-EUROPA). It was therefore suggested to elucidate, which of these properties represents the best predictive value for toxicity (G: OSHA-EUROPA). Another hazard assessment suggests, since it is not possible to test each particle type, to develop and validate strategies which involved testing to categorize nanoparticles by their possible toxicity (G: Schulte et al., 2008). Another guideline points out that this would facilitate development of new approaches like structure activity relationships or various end points of *in vitro* experiments, such as inflammatory markers or the generation of reactive oxygen species (ROS) (G: Schulte et al., 2008).

3.3 Risk assessment

25. Performing a risk assessment is generally supported by a high number of guidelines (S: DOE-NRSC; HSE-a; ORC Worldwide; UD; VCU). This risk assessment can be generated individually for all involved nanomaterials and processes (S: VCU). The requirements of scientific information, past experience and a regular review are regarded to be necessary for the reliability of the risk assessment (S: HSE-a). Even though the need of a risk assessment is generally accepted, the opinions of the essential contents are diverse.

26. It was mentioned that the risk assessment should both involve a well-defined description of the work, subject matter experts, hazards and uncertainties as well as specify hazard controls (S: DOE-NRSC).

The applied hazard controls shall include engineered controls, design reviews, formal procedures, usage of PPE, training, other administrative controls and defined criteria for work-change control (S: DOE-NRSC).

27. From the risk assessment, the need for and the specific type of health monitoring shall be deduced (S: HSE-a). This includes an evaluation of the potential for worker exposure to nanomaterials (S: DOE-NRSC).

28. In the area of work process procedures, the use of electrical and magnetic fields or temperature gradients as well as the possible risk of fire and explosion should be noted (S: ORC Worldwide). It was furthermore mentioned that the waste stream collection and disposal of materials containing nanoparticles in solid, liquid or air is also an important issue.

29. They also suggest considering the specific properties of the nanomaterials, which include the physical form, the nanoparticle size range and the toxicity (S: ORC Worldwide).

30. In one general guideline related to nanomaterials, it is mentioned that in later development/production activities, and once the toxicological and other relevant properties of the nanomaterial have been determined, the control measures should be reviewed through a thorough process-specific risk assessment and, if warranted, modified accordingly (G: Safe Work Australia). The authors recommend that a complete life-cycle analysis of the nanomaterial should always be made to identify potential ‘hotspots’ of worker exposure, including construction, packaging, manufacturing, handling, maintenance or cleaning work, and end-of-life and safe disposal issues (G: Safe Work Australia). It is highlighted that a whole range of jobs and tasks need to be considered (G: Safe Work Australia). Additionally, they recommend that existing ventilation systems that are effective for extracting ultrafine dusts in other industries should also be employed and optimally maintained where appropriate, in order to reduce exposure to engineered nanomaterials (G: Safe Work Australia).

31. The necessary information about the toxicity is specified further in several general guidelines related to nanomaterials. For the purpose of taking preventive measures against exposure, understanding the properties of nanomaterials is regarded as essential aspect (G: MHLW). One suggestion is a single case assessment according to the physico-chemical (G: IRSST; HMUELV; OSHA-EUROPA), toxicological and ecotoxicological properties (G: HMUELV). The knowledge on nanomaterial properties such as their particle size distribution, particle morphology, particle composition, particle surface area, particle number concentration, particle structure and reactivity in solution shall be used for the purpose of risk assessment (G: OSHA-EUROPA; Safe Work Australia). Also, it is pointed out that the presence of substances such as detergents, surfactants and other “surface active” chemicals are known to increase the absorption rate of some chemicals, which could include nanomaterials (G: Safe Work Australia).

32. The risk assessment shall be based on the most current toxicological data on the specific material as well as exposure assessments and exposure control information data (G: PENNSTATE).

33. These current data can be provided by the manufacturers of nanomaterials (G: MHLW) and gained for instance by web research (G: Hallock et al., 2009).

One guideline suggests for the case of no or insufficient data available for risk assessment to perform risk estimation either from existing data or determined by the judgment of experts (G: Safe Work Australia).

34. It is recommended that the efficiency of the preventive measures against exposure shall be confirmed by measurement of the concentration of nanomaterials (G: MHLW). Furthermore, it is stated that this measurement should be performed not only at regular intervals, but also at the time, when the

status of nanomaterial-related work changes (G: MHLW). Suggestions for measurement instruments are SMPS (Scanning Mobility Particle Sizer), CPC (Condensation Particle Counter) and DC (Diffusion Charger-based Surface-Area Monitor) etc. (G: MHLW).

35. In one guideline, the regular repetition and enhancements of the risk analysis is recommended in order to account for new scientific knowledge and practical conditions of the work environment (G: IRSST). Here, a case by case approach shall be preferred (G: IRSST). This guideline also suggests to apply a control banding approach for a qualitative risk assessment, which is based on the use of a limited number of factors for evaluating the risk level in order to reduce the complexibility and increase the applicability for non-experts (G: IRSST).

36. A control banding approach for research and early development activities involving nanomaterials is furthermore suggested in another general guideline, where similar control measures shall be used within categories of nanomaterials that have been grouped ("banded") according to their exposure potential and hazardous properties (G: Safe Work Australia). In this guideline, control banding is considered to be an appropriate method because of the current lack of data available for the risk assessment of individual nanomaterials, since there is some understanding of hazards posed by different groups of nanomaterials (G: Safe Work Australia).

37. For instance, if nanomaterials are classified as potential carcinogens on the macroscale, then specialist advice is recommended when handling these nanomaterials (G: Safe Work Australia).

38. It is regarded as an essential aspect that the risk assessment is in accordance with the existing regulations for individual settings and materials and does not have its own separate requirements (G: Safe Work Australia).

3.4 Physical hazards

39. In several specific nanomaterial guidelines for laboratories, physical hazards like catalytic effects, fire or explosion, which apply especially to nanopowders and nanofibers, are mentioned (S: AIST; DOE-NRSC; Georgia Tech; HSE-a; ISU; MIT; TU Delft; UC). It is also elucidated that nanoparticles might be pyrophoric (S: TU Delft).

40. Supplementary, in one general nanomaterial guideline applicable for laboratories, it is highlighted that, depending on the specific production methods being used, other hazards should be considered such as electrocution associated with the generation of a plasma via the use of high currents or asphyxiation hazards owing to possible leaks of inert protective gases during some processes (G: OSHA-EUROPA). In another guideline, it is mentioned that the ignition energy and the violence of an explosion are influenced by the particle size or area (G: IRSST).

41. Regarding the handling of new substances with unknown hazardous properties in laboratories, it is highlighted by a general laboratory guideline, which is also applicable to nanomaterials, that new substances shall be treated with high precaution since these new substances are insufficiently examined especially concerning their acute and chronic toxicity and physico-chemical characteristics (L: AGS-BMAS; DGUV). Hence, it is stated that they could be acute toxic, caustic, chronically toxic, flammable, pyrophoric and explosive (L: AGS-BMAS; DGUV). It is further specified that nanomaterials with insufficiently known properties shall be treated like such new substances (L: DGUV).

3.5 Safer manufacturing approaches

42. Safer manufacturing approaches are generally recommended by several reports regarding the handling of nanomaterials in laboratory scale (S: HSE-a; ORC Worldwide; UCI; UCSB; UD).

43. It is stated that a potential form of safer manufacturing approaches is a change of the physical condition of the used nanomaterial, i.e. replacing the powdered state by a liquid or macroscopic solid state in order to minimize the possible release of nanoparticles (S: CHS; DOE-NRSC; ORC Worldwide; UCI; UCSB; UD). Specifically it is suggested to consider applying wet method which treats nanomaterials as suspension liquids as an effective measure to prevent exposure (S: AIST). Furthermore, it is highlighted that the risk of exposure to the liquid dispersion itself and chemical reactions should always be kept in mind (S: AIST).

44. Several general reports related to nanomaterials state that hazardous substances shall be replaced with less hazardous substances in this risk mitigation approach if this is technically feasible and economically acceptable (G: HMUELV; Hoyt and Mason, 2008; IRSST; OSHA-EUROPA).

45. However, this principle does not specifically relate to nanomaterials since the properties of nanomaterials are not obligatory associated with a hazard assumption, but result in the application of the precautionary approach. Since the properties of the respective nanomaterial might be especially required, the safer manufacturing approaches apply preferably to the form of appearance of the respective nanomaterial.

46. Two general nanomaterial guidelines mention explicitly that a substitution of nanomaterials might not be a suitable hazard reduction method since the presupposed unique properties of nanomaterials include their production and use (G: NanoSafe Australia; Safe Work Australia).

47. However, the option to reduce the *in vitro* cytotoxicity of several nanomaterials, e.g. of fullerenes, carbon nanotubes, quantum dots and metal/metal oxides by modifications is pointed out (G: Safe Work Australia).

48. It is also suggested to modify the type of process, for example to replace a dry process with a wet process (G: IRSST). The handling of bound nanomaterials in dispersions, pastes, compounds or solid media is for instance favored over powder nanomaterials to minimize possible exposure (G: BAuA / VCI; HMUELV; Safe Work Australia).

49. A further guideline recommends measures of preventing fire and explosion depending on the property of the nanomaterials, for instance the reduction of dust concentration, prevention of static electricity generation and the reduction of oxygen concentration in manufacturing/handling experiments (G: MHLW).

3.6 Technical measures

50. The need for technical exposure mitigation has been accentuated by all specific nanomaterial guidelines which are related to laboratories (S: CHS; DOE-NRSC; EPFL; Georgia Tech; HSE-a; ISU; MIT; NASA-ARC; NSF; ORC Worldwide; OUHSC-IBC; Penn-EHRS; TU Delft; UBC; UC; UCI; UCSB; UD; VCU). Specifically it was recommended that procedures involving the handling of nanomaterials shall be performed in a closed system (S: AIST; DOE-NRSC; MIT; NASA-ARC; ORC Worldwide; TU Delft). A closed system is specifically required for activities like measuring raw or manufactured materials,

pouring (including mixing) into or collecting from the producing or processing equipment, cleaning the container, waste processing etc., unless there is no potential for exposure (S: AIST).

51. A ventilation and filtration of this enclosure is recommended especially if free or low level aggregated/agglomerated nanoparticles are handled (S: Penn-EHRS), but also for suspensions of nanoparticles or the cleaning of potentially contaminated parts of reactors or furnaces (S: MIT). It is further recommended that the enclosure shall feature a negative pressure differential compared to the worker's breathing zone (S: DOE-NRSC).

52. One example for a closed system is a fume hood or fume cupboard, respectively (S: CHS; ISU; MIT; NASA-ARC; Penn-EHRS; UCI; UCSB). It is mentioned that the exhaust air has to be passed through a HEPA filter, since at this time it is the only air pollution control device known to control nanoparticles with high efficiency (S: CHS). According to several specific nanomaterial guidelines relating to laboratories, a fume exhaust hood (S: Georgia Tech; NASA-ARC; TU-Delft; UC; UCI; UCSB) or ventilated hood with air flux (S: EPFL) is required especially to expel free of low level aggregated/agglomerated nanoparticles from tube furnaces or chemical reaction vessels.

53. It is recommended that, independently on the type of hood, the effectiveness of the air flow shall be tested before using it (S: ORC Worldwide). A nanoscale particle counter is suggested to determine if free or low level aggregated/agglomerated nanoparticles escape from the containment (S: ORC Worldwide).

54. In one general nanomaterial guideline, which can also be applicable for nanomaterials and relates to carbon nanotubes, it is mentioned that a good visualisation of the air flow can be provided by smoke tubes (G: Hoyt and Mason, 2008). This could help to detect leaks and find the optimal application of hoods, etc. for exposure mitigation.

55. It is distinguished in a general nanomaterial guideline, which can likewise be applied for laboratories, that working with nanomaterials shall either be performed under an ducted fume cupboard or a recirculating fume cupboard (G: HSE-b). In this case, the ducted and the recirculating fumehood shall be in accordance to BS 7989:2001 and BS EN 14175-4:2003 including HEPA filtration, respectively (G: HSE-b).

56. A further possibility for a closed system is a biological safety cabinet (S: CHS; DOE-NRSC; ISU; MIT; Penn-EHRS; OUHSC-IBC). Examples include class II (S: CHS; DOE-NRSC; MIT) cabinets type A2 (S: MIT), B1 (S: CHS; MIT) or B2 (S: CHS; MIT). It is mentioned that, since type A2 and B1 cabinets are only equipped by recirculation of air, processes involving higher amounts of dust shall be avoided as the internal fans of these cabinets are not explosion proof (S: MIT). For processes including higher amounts of free or low level aggregated/agglomerated nanoparticles and solvents, B2 cabinets with 100 % exhaustion are regarded as appropriate to avoid recirculation of nanoparticles and solvents into the room (S: MIT). Air from inside the cabinet shall not be recirculated within the laboratory except as provided for in ANSI Z9.7 (American National Standard for Recirculation of Air from Industrial Process Exhaust Systems) (S: DOE-NRSC).

57. The requirements for certification are explained in detail in a general nanomaterial guideline which can also be applied for laboratories. In this guideline, a certification by NATA (Australian National Association of Testing Authorities) and an annual testing of the efficiency are suggested (G: NanoSafe Australia).

58. The advantage of a laminar flow system in a cabinet has also been mentioned in specific nanomaterial guidelines related for laboratories (S: CHS; Georgia Tech; ORC Worldwide; TU Delft; UBC; UC). According to one guideline, the laminar flow hood, which has preferably low velocity such as the models provided by Flow Sciences (S: ORC Worldwide), shall be equipped with HEPA filtration (S: Georgia Tech; TU Delft, UBC; UC). In one guideline, it is specifically advised against horizontal laminar flow hoods, which direct a flow of HEPA-filtered air into the face of the operator, in case of free or low level aggregated/agglomerated nanoparticle handling (S: DOE-NRSC).

59. This opinion is shared by a general nanomaterial guideline, which can also be applied for laboratory scale, which does not recommend the usage of laminar flow cabinets, since they blow contaminated air towards the operator (G: NanoSafe Australia).

60. In one specific nanomaterial guideline related to laboratories, advice is given against handling engineered nanoparticles under a downflow booth, since the protection without additional respiratory protection is considered as not sufficient (S: ORC Worldwide).

61. Glove boxes (S: AIST; CHS; DOE-NRSC; ISU; MIT; ORC Worldwide; Penn-EHRS; TU Delft; UCI; UCSB) and glove bags (S: AIST; DOE-NRSC; MIT) have been likewise suggested as examples for a closed system. Processes where engineered nanoparticles are produced shall be generally conducted in glove boxes or bags with negative pressure differential compared to the workers breathing zone (S: DOE-NRSC). In one guideline, it is highlighted that the air reactivity of precursor materials may make it unsafe to operate in a negative pressure glove box and a positive pressure differential may be needed, which shall be assured with a helium leak test (S: DOE-NRSC).

62. It is recommended that reactors and furnaces, which are required for nanoparticle processing, are equipped with ventilation (S: MIT). Gasses should be run through a liquid bubbler system, if possible (S: MIT).

63. A general report regarding nanomaterials, which can also be applied for laboratories, highlights the university best practice in using reactors and furnaces in order to prevent inhalation exposure (G: Hallock et al., 2009). With regards to synthesis processes in reactors or furnaces, the exhaustion of reactor gases, the purging before opening, the providing local exhaust ventilation for emission points and the performing of part maintenance in fume hood are regarded as essential aspects which increase the safety level (G: Hallock et al., 2009).

64. The exposure can be decreased with local exhaust ventilation (LEV) (S: AIST; CHS; DOE-NRSC; HSE-a; MIT; NASA-ARC; ORC Worldwide; UCI; UCSB; UD). A LEV is recommended if the work processes make enclosure difficult (S: AIST). This LEV can be HEPA-filtered (S: UD) and associated with a reactor (S: NASA-ARC). It is stated that the LEV shall include a push-pull ventilation system (S: AIST). The use of an electric dust collector, etc. is regarded as reasonable if the targeted material can be collected properly (S: AIST). Another guideline suggests using additional respiratory protection and close localisation to the nanoparticle source if the LEV is open (S: ORC Worldwide). LEV can be applied for instance to clean parts of reactors or furnaces that are too large for a fume hood (S: MIT). In this case, a design of a special customised enclosure, which is evaluated by a health and safety office, can be reasonable (S: MIT). For handling of fumes and gases, a dedicated exhaust duct is suitable (S: ISU). It is suggested to periodically inspect the LEV to ensure the proper operation (S: AIST).

65. One general nanomaterial guideline, which is applicable to research in laboratory scale, highlights that moreover access opening for maintenance and inspection of enclosures shall be equipped by LEV (G: MHLW). In this guideline, it is suggested to direct the outlet of the LEV directly open to the

outside air or, if this would be difficult to achieve, to connect the LEV to the existing exhaust duct (G: MHLW). It is further proposed to select high performance filters, which are capable of collecting nanomaterials like HEPA-filters (G: MHLW).

66. Regular maintenance and annual testing of local exhaust ventilation are recommended by two general nanomaterial guidelines (G: HSE-b; MHLW).

67. A ventilation system in the working area, where nanomaterials are handled, is proposed by a number of specific nanomaterial guidelines for laboratories (S: CHS; DOE-NRSC; MIT; NASA-ARC; Penn-EHRS; TU Delft, UC; UCSB; UD). It is recommended that, considering the laboratory airflow, arrangement and separation of the equipment shall be carefully laid out corresponding to the level of exposure (S: AIST). The airflow control is regarded as an effective measure to prevent exposure because nanomaterials and their quantities are very small and their behaviour is similar to that of airflow (S: AIST). It is also mentioned that a stable lower air pressure equivalent to 6 mm water column shall be maintained in the laboratory area, where nanoparticles are handled (S: EPFL). Furthermore, the proposal is made to install a non-recirculating ventilation system with 6 to 12 air changes per hour and negative laboratory pressurization (S: Penn-EHRS). HEPA-filtration is recommended for passing the exhaust air (S: CHS).

68. The issue of ventilation is also addressed by some general nanomaterial guidelines, which can also be applied for laboratory scale. A regular maintenance and function testing is considered as mandatory (G: BAuA / VCI). According to EN 1822-1 to EN 1822-5, multistage filters with a HEPA- or ULPA-filter as final filter are regarded as reasonable (G: IRSST; OSHA-EUROPA; Safe Work Australia). Another mentioned extraction method for particles involves the use of electrostatic precipitation, which can remove nanoparticles (G: Safe Work Australia).

69. Further safety equipment like eyewash station according to ANSI and OSHA requirements (S: VCU), safety shower, first aid kit, fire extinguisher and emergency exits are mandatory in the laboratory area (S: UBC).

3.7 Organizational measures

70. The need for organizational measures is emphasized in a number of specific nanomaterial guidelines applicable for laboratories (S: CHS; DOE-NRSC; EPFL; Georgia Tech; HSE-a; NASA-ARC; ORC Worldwide; OUHSC-IBC; Penn-EHRS; TU Delft; UBC; UC; UCI; UCSB; UD).

71. The accountability for surveillance shall be placed at either a responsible person like a project manager (S: EPFL), a cleanroom manager (S: UBC), a security agent (S: EPFL) or a health and safety officer (S: CHS; Georgia Tech; ORC Worldwide; VCU).

72. One prominent organizational aspect refers to the access control to the working area (S: AIST; EPFL; UBC; UD). Possibilities to control the access can be a login (S: UBC), a control access zone (S: EPFL) and a user list at the entrance (S: EPFL; UBC). The signage “dangerous nanoparticles” prevents the unintentionally admittance of unauthorized persons (S: EPFL).

73. It is recommended that working outside the normal working hours should be avoided (S: UBC). A dangerous work shall be than only performed from two persons together (S: UBC), whereas it is sufficient for less-dangerous works if an informed person is present in the building (S: UBC). The cleanroom area, where nanoscaled particles are handled, may be closed at nights (S: UBC).

74. A general guideline for nanomaterials considers reducing the time spent in possible exposure areas (e.g. hot areas) and the number of potentially exposed personnel (G: Safe Work Australia).

75. It is also suggested by one specific guideline for nanomaterials in laboratories to separate the areas, where nanomaterial exposure can occur, from other areas (S: AIST). Firstly, it is recommended to separate the office from the laboratory area. Secondly, the laboratory shall be divided into the areas with potential for exposure and the areas not susceptible to exposure (S: AIST).

76. Special areas further recommended are facilities for changing clothes (S: CHS; DOE-NRSC; EPFL; UBC; UD) or, as mentioned in a single report, showering (S: UD). Also hand-washing facilities could be required (S: OUHSC-IBC; Penn-EHRS). Furthermore, an area, in which work clothing and protective wears/equipment can be stored, and a changing room are regarded as necessary (S: AIST). Nanomaterial adhered work clothing shall be treated appropriately to prevent the nanomaterials from spreading beyond the workplace (S: AIST). For this reason, it is suggested to separate work clothing together from other clothing by using separate lockers (S: AIST). A hand-wash and eye-wash station near the changing room shall be additionally installed (S: AIST). Furthermore, it is recommended to organize the installation and fixtures on the floor and wall in a way to facilitate cleaning up, for instance by water rinsing or vacuum cleaning of the floor (S: AIST).

77. In one general guideline, the installation of locker rooms to avoid mixing work and street clothes are likewise recommended (G: IRSST). Supplementary, it is suggested that a laundry service should be provided to the employees, so that they do not take clothing contaminated with nanomaterials to their home (G: NanoSafe Australia).

78. To promote good personal hygiene, washbasins and showers shall be installed to allow decontamination of workers (G: IRSST). Another general aspect on organization refers to the standardization of all work surfaces, which should be non-porous and easy to clean (G: IRSST).

79. A number of specific nanomaterial guidelines related to laboratories suggest minimizing the release of dust by mitigation of the exposure (S: CHS; DOE-NRSC; EPFL; Georgia Tech; HSE-a; TU Delft; VCU). Since the risk potential of possible fire and particle dust explosion increases due to the combustible particulate being nanosize, preventive measures shall be implemented, for example usage of explosion proved equipment in case of handling combustible gas or solution (S: AIST). The preparation of nanoparticles with minimal exposure can be ensured by the compliance with standard operating procedures (S: VCU) and the measurement of emissions to the air (S: DOE-NRSC).

80. One general nanomaterial guideline suggests the preparation of operation rules on working nanomaterials to the workers (G: MHLW). They specify that these operation rules shall contain information about the health effects of the nanomaterials regarding the working environment (G: MHLW). A general nanomaterial guideline proposes to generally minimize the time of exposure by organizing the timeline of working procedures (G: HMUELV).

81. Several specific nanomaterial guidelines for laboratories state that activities such as eating, drinking, chewing gum or smoking as well as the storage of food or cosmetic products shall be prohibited in the working area (S: EPFL; NASA-ARC; UBC; UC; UCI; UCSB; UD). Pipetting with the mouth is likewise not permitted (S: EPFL). According to these aspects, the storage of nanoparticles in non-working areas like offices or the hallway is not allowed (S: EPFL). An example for the correct storage of nanoparticles describes the storage of carbon nanopowder amount of more than 1 g in sealed metal containers (S: NASA-ARC). These metal containers are in this case recommended in order to avoid the generation of electrostatic activity (S: NASA-ARC).

82. In one guideline, it is suggested to enhance the safety in the laboratories, where nanoparticles are handled as well as in the entrance room, by fitting the working zone with a stable air depression (6 mm of water column) (S: EPFL). It is recommended to equip the cleanroom with a telephone for the case of emergency (S: UBC). A single guidance suggests that the air is monitored with a nanoparticle detector and if the quantity of nanoparticulate materials produced during gas phase work exceeds the limit of 1 µg/h (S: TU Delft). For this purpose, the instruments "Joint Length Monitor" and "DelfChemTech" are emphasized (S: TU Delft). One indirect opportunity to both determine the exposure of the workers and document the performed activities is by recording the equipment time usage (S: UBC).

83. An exceptional impact affects the usage of needles and syringes (S: OUHSC-IBC). It is highlighted that a safe needle device for administration and a needle-locking for disposable syringes are required in this case (S: OUHSC-IBC).

3.7.1 Labelling

84. It cannot be assumed that nanomaterials are all hazardous, but the precautionary approach may be applied. For this reason, labelling is required regarding the in-company handling of nanomaterials, which is described as following in the individual guidelines.

85. Safety and health signs and texts to inform occupational safety and health measures for nanomaterials such as appropriate hazard and exposure mitigation signs is regarded as necessary in several specific nanomaterial guidelines, which are related to nanomaterials and address this point (S: CHS; DOE-NRSC; MIT). Several suggestions for required labels have been reported.

86. It is recommended that areas, where easily dispersible nanomaterials are used, should be labelled with appropriate signs (S: DOE-NRSC; MIT). It is specified that these post signs should indicate the hazards, PPE requirements, and administrative control requirements (S: DOE-NRSC; MIT). Furthermore, it is mentioned that these signs should be placed at entry points into designated areas, where dispersible, engineered nanomaterials are handled (S: DOE-NRSC). A designated area may be an entire laboratory, an area of a laboratory or a containment device such as a laboratory hood or glove box (S: DOE-NRSC). It is mentioned that a "Designated Area" sign, which could be available from the EHS office, could be used, if indicated, to label the fume hood, laboratory bench, or laboratory itself (S: MIT). Equipment, which could be contaminated by nanoparticles can be separately labelled. For instance, one guideline recommends to label HEPA vacuum cleaner with the sign "For Use with Nanoparticles Only" (S: CHS).

87. In one guideline, the following labelling for containers containing nanomaterials is suggested: CAUTION - Nanomaterials Sample - Consisting of (technical description here) Contact: (POC) at (contact number) in Case of Container Breakage (S: CHS). However, details about the context are missing, i. e. it is not specified if these containers shall be dedicated for storage, transport or waste management.

88. However, other guidelines address this issue in more details. It is suggested that nanomaterial storage containers should be labelled for their contents in engineered nanomaterial (S: MIT) respectively nanoparticulate form (S: DOE-NRSC), such as "nanoscale zinc oxide particles" or other identifier instead of just "zinc oxide" (S: MIT).

89. One guideline recommends to internally transport nanomaterials in closed, labelled containers, e.g. marked "Zip-Lock" bags between work stations (S: CHS; DOE-NRSC). They suggest for nanomaterials, which are being moved outside, that the label text shall indicate that the particulates might be unusually reactive and vary in toxic potential, quantitatively and qualitatively, from normal size forms

of the same material (S: DOE-NRSC). Additionally, they make the statement that for external transport: nanomaterials with suspected or recognized hazardous properties (toxic, reactive flammable) must be packaged, marked, labelled and shipped in accordance with 49 CFR 100 to 185 and applicable DOE Orders with an accompanying properly prepared dangerous goods declaration and in accordance with the ICAO technical instructions (S: DOE-NRSC). Furthermore, they highlight that nanomaterials with unknown hazardous properties still may pose health and safety issues and that they shall therefore be consistently packaged and labelled using the equivalent of a DOT-certified Packing Group I (PG I) container (S: DOE-NRSC). For transport, the following explanatory notes are suggested: CAUTION - Nanomaterials Sample - Consisting of (technical description here) Contact: (POC) at (contact number) in Case of Container Breakage (S: DOE-NRSC).

90. Regarding waste management, labelling the waste container with a description of the waste and the words "contains nanomaterials" is recommended (S: DOE-NRSC; MIT). Available information characterizing known and suspected properties shall also be included (S: DOE-NRSC). Another suggestion refers to the addition of a hazardous red tag (S: MIT).

91. According to a general guideline for nanomaterials, necessary information to facilitate preventive exposure measure are the name and components of nanomaterials and precautions for handling such nanomaterials on the labelling of the container or package (G: MHLW). Supplementary, it is mentioned in general nanomaterial guidelines also related to laboratories that the consistency of the signs indicating hazards and exposure mitigation requirements on all containers containing nanomaterials with the laboratory requirements is a precondition (G: PENNSTATE).

92. It is also highlighted that a substance can have in principle different categorization and labelling depending on the specific properties and that the properties of a nanomaterial, which deviate from the bulk material, can be reflected by categorization and labelling (G: OSHA-EUROPA).

3.7.2 Personal training

93. One important point of organisational measures addresses a broad range of possibilities for information and training of the workers who are potentially exposed to nanomaterials (S: AIST; CHS; DOE-NRSC; EPFL; HSE-a; NASA-ARC; NSF; UBC; UCI; UCSB; UD; VCU). It is suggested to brief workers handling nanomaterials on the potential hazards of the research activity followed by a written report for the participants (S: UCI; UCSB). In some guidelines, a regular information (S: UD) or annual training (S: CHS) is suggested.

94. Several other reports explain the proposed training courses in more detail. In one guideline, regular workers attend to several courses such as a chemical and laboratory safety orientation course and a qualification course on individual equipment (S: UBC). Regarding access rules, it is mentioned that students need to be additionally chaperoned by a qualified user, whereas visitors need supplementary agreement with the cleanroom manager to access the nanomaterial working area (S: UBC).

95. It is also recommended that the training of the employees shall be performed in collaboration with the project managers (S: EPFL). It is further regarded to be reasonable to involve the employees in the design and implementation of control measures (S: HSE-a).

96. In one guideline, it is highlighted that training courses shall cover recommendations for using personal protective equipment, handling potentially contaminated clothes or surfaces and disposal of

spilled nanomaterials (S: DOE-NRSC). In another guideline, the importance of the education about the potential risks associated with the handlings of nanomaterials is highlighted (S: AIST).

97. The workers knowledge on the used nanomaterials can be expanded further by a provided lab safety plan, standard operating procedures (SOP), material safety data sheets (MSDS) and Job Hazard Analysis Worksheets (JHA) (S: NASA-ARC). It is furthermore mentioned that the education of the workers shall be based on an established manual for the handling procedures (S: AIST).

98. Also specific training courses regarding specific nanoparticle-related health and safety risks, laboratory safety training modules, special instructions for injections and needles and a respiratory protection program according to OSHA's 29 CFR 1910.134 and ANSI Z88.2 requirements are noted (S: VCU).

99. Beside the specific nanomaterial guidelines related to laboratories, the topic of personal training is mentioned in some general nanomaterial guidelines. A training and information of the employees on controlling the exposure to nanomaterials is recommended (G: HSE-b). The instructions of the chemical hygiene plan are regarded as generally applicable (G: Hallock et al., 2009). One general guideline for nanomaterials lists that the employees shall be educated on operation rules, physical and chemical properties of nanomaterials, health effects of nanomaterials, control measures for the work environment, preventive measures against exposure to nanomaterials such as the use of PPE and measures of preventing fire and explosion (G: MHLW). Especially for respiratory protection, the employees shall be instructed in detail about the following aspects of respiratory protection: 1) proper selection; 2) the method about pulling on; 3) measurement method of leakage test; 5) method of fit test and 6) storage and maintenance (G: MHLW).

3.7.3 Cleaning

100. The aspect of cleaning is an essential issue mentioned in the predominant number of specific nanomaterial guidelines for laboratories (S: CHS; DOE-NRSC; EPFL; Georgia Tech; ISU; MIT; NASA-ARC; ORC Worldwide; OUHSC-IBC; Penn-EHRS; TU Delft; UBC; UC; UCI; UCSB; UD; VCU). The cleaning shall be organised by the person in charge of cleaning in the laboratory (S: EPFL).

101. How frequently the cleaning ought to be carried out is differently regarded spanning a range from cleaning after each procedure (S: VCU), cleaning at the end of each shift (S: DOE-NRSC; UD), after a daily (S: CHS; EPFL; Penn-EHRS; UCI) or a weekly period (S: NASA-ARC).

102. It is recommended that the routine cleaning of potentially contaminated surfaces shall be performed either by using a HEPA filtered vacuum cleaner (S: AIST; CHS; DOE-NRSC; ISU; NASA-ARC; Penn-EHRS; TU Delft; UC; UCSB; UD), which is labelled “for use with nanomaterials only” (S: CHS), or by wet wiping (S: AIST; CHS; DOE-NRSC; ISU; NASA-ARC; OUHSC-IBC; Penn-EHRS; UBC; UCI; UCSB; UD).

103. The wet-wiping method can be accomplished using cleanroom or disposable wipes (S: DOE-NRSC; UBC) and spraybottles (S: NASA-ARC). Recommended agents taken for wet-wiping are iso-propanol (S: UBC), water (S: NASA-ARC) or cleaning agents compatible with the respective nanomaterial (S: ISU; OUHSC-IBC; Penn-EHRS). Possible complications due to chemical or physical properties of the agent ought to be considered (S: DOE-NRSC).

104. The application of solvents is regarded controversially since in one guidelines it is recommended to utilise them to clean lab equipment and exhaust systems (S: NASA-ARC), but another guideline advises against their use (S: ISU). Both guidelines provide no detailed reasons for their argumentation.

105. If HEPA-filtered vacuuming is carried out, the potential air-reactivity of nanoscaled powders shall be considered (S: DOE-NRSC). In accordance, several guidelines explicitly prohibit dry sweeping, the usage of compressed air (S: CHS; DOE-NRSC; NASA-ARC) respectively air spray (S: AIST) or vacuuming without HEPA filters (S: NASA-ARC). A single guideline addresses the importance of a half-face respirator with P100 filter during vacuuming (S: ISU).

106. A benchtop protective material (S: CHS; UCI; VCU), can likewise be chosen instead of vacuuming. This bench paper shall contain impervious backing to limit the potential for contamination of surfaces (S: VCU). Both recommendations for cleaning daily (S: CHS) or after each usage (S: VCU) exist.

107. It is highlighted in one guideline that water sensitive instrument surfaces shall be cleaned with electrostatic microfibers cleaning cloths (S: NASA-ARC).

108. A walk-off adhesive mat at the entry of the working area is assumed to minimize the spread of nanoscaled particles (S: DOE-NRSC; UBC; UCSB).

109. Regarding the wet wiping method, one general nanomaterial guidelines remarks that the water-solubility of the nanopowder has to be taken into account regarding the wet wiping method (G: MHLW). For this reason, cleaning operations shall be conducted in consideration of both the status of the workplace and the properties of nanomaterials (G: MHLW).

110. Special requirements for the vacuum cleaner are mentioned in one general nanomaterial guideline which is also applicable for laboratory use (G: NanoSafe Australia). Quality features are fulfilled if the vacuum cleaner complies with the Australian standards AS 3544-1988 and its HEPA filter with AS 4260-1997 (G: NanoSafe Australia). According to these quality characteristics, an industrial vacuum cleaner for particulates hazardous to health, i. e. not a household vacuum cleaner, is required (G: NanoSafe Australia). The need for explosion-proof cleaning equipment is highlighted in the case of explosive nanoparticles (G: IRSST). This vacuum cleaner can be designed with insulating materials, a ground or an explosion vent to prevent production of ignition sources, i.e. sparks or static electricity. Another option is to use an electrical mobile vacuum cleaning system with an induction motor to avoid sparks (G: IRSST).

111. In cases of spills, several specific nanomaterial guidelines for laboratories likewise recommend wet wiping (S: DOE-NRSC; TU Delft; UCI; UCSB), vacuuming with a HEPA-filtered vacuum cleaner (S: DOE-NRSC; Georgia Tech; Penn-EHRS; TU Delft; UC; UCI; UCSB) and walk-off mats (S: DOE-NRSC; UCI; UCSB). Absorbent materials or liquid traps can also be applied (S: TU Delft).

112. Potential pyrophoric hazards that are associated with vacuuming nanomaterials shall be considered (S: DOE-NRSC).

113. Dry sweeping (S: DOE-NRSC; Penn-EHRS; UCI; UCSB) and the use of compressed air shall be prohibited (S: DOE-NRSC).

114. One guideline states that extra cautious preventive measures against exposure should be taken since the potential risk for exposure is increased (S: AIST).

115. It is mentioned, that personal protective equipment may be required to avoid contact with nanoparticles and nanoparticle-containing solutions (S: TU Delft). This includes double nitrile

gloves and, in the case of particle powder, respiratory protection (S: UCI; UCSB). It is highlighted that potentially contaminated clothes and personal protective equipment shall be cleaned carefully and thoroughly according to laboratory procedures in order to avoid secondary contamination (S: AIST; DOE-NRSC). The cleaning procedures and the referred type of nanoparticles are not further specified in this context.

116. It is recommended to wet wipe the affected area three times with soap and water or an appropriative cleaning agent (S: VCU). Barriers that minimize the air currents might be required if a liquid contamination occurs (S: CHS).

117. All exposed reaction vessels shall be cleaned in a fume hood (S: MIT; TU Delft) or other type of exhausted enclosure (S: MIT) using wet wiping or HEPA-filtered vacuuming. Equipment which is too large to be enclosed in a fume hood has to be cleaned using specially designed local exhaust ventilation (S: MIT).

118. In case of nanoparticle overflow, it is recommended to close and decontaminate the contaminated zone (S: EPFL). It is mentioned that in this case, the project manager shall give instruction to the work place about the procedure to follow in case of accident or incident (S: EPFL). For this purpose, it is highlighted that it could also be necessary to demarcate this zone with barricade tape (S: CHS) and contact the health and safety office (S: CHS; Georgia Tech).

119. It is mentioned especially for carbon-based nanomaterials, a spill kit containing spray bottles with water and disposable wipes could be reasonable (S: NASA-ARC).

120. A nanomaterial spill kit, which consists of barricade tape (S: CHS; MIT), latex (S: CHS) or nitrile gloves (S: CHS; MIT), disposable N95 (S: CHS) or P100 (S: MIT) respirators, absorbent material (S: CHS; MIT), wipes (S: CHS; MIT), sealable plastic bags (S: CHS; MIT) and a walk-off mat (S: CHS; MIT), could assure that appropriate equipment is present in case of contamination.

121. Beside these general opinions reflecting a mixture of differently stringent measures, several guidelines differentiate the way of spill handling according to the contamination amount.

122. Small spills can be cleaned by trained personnel (S: CHS). Small spills of powder, for instance less than 5 mg (S: VCU), can be firstly sprayed with a water mist (S: NASA-ARC) and wiped clean (S: NASA-ARC) or wiped with a wet cloth (S: CHS; MIT; ORC Worldwide) or paper towel (S: ORC Worldwide) dampened in soaped water (S: VCU). Small spills of solution, for instance less than 5 ml (S: VCU), shall be cleaned with absorbent material (S: NASA-ARC; MIT; VCU) with cleaning cloths or paper towels (S: NASA-ARC). The solutions ought to be cleaned immediately before they dry (S: NASA-ARC).

123. A number of recommendations exist for larger spills. A single guideline defines these spills as spills where the cleaning will take more than 5 min (S: NASA-ARC). An exact definition is missing in the other available guidelines. A possibility is cleaning these spills with a HEPA-filtered vacuum cleaner (S: MIT; ORC Worldwide) followed by wet wiping of the surface (S: ORC Worldwide). It might be also necessary to demarcate the area with barricade tape (S: DOE-NRSC) and contact the health and safety office (S: CHS; Georgia Tech; UCSB; VCU). Further options are to either leave the area or use personal protective equipment (PPE), i.e. a respirator and disposable protective clothing, and comply with the requirements for emergency response by hazardous materials user (S: NASA-ARC). A restriction of the laboratory entry to a laboratory waste management crew is also thinkable (S: DOE-NRSC).

124. Suggestions of the guideline documents referring to the treatment of contaminated materials are addressed in section 3.11 "Waste disposal". Similarly, it is suggested to call an emergency telephone number and restrict the entrance to the affected area to a designated hazardous material emergency response team if the spill exceeds the capability of the laboratory (S: NASA-ARC).

125. In general nanomaterial guidelines which are also applicable for laboratories, special aspects of cleaning spills are highlighted further. An appropriate absorbent material is required for the wet wiping method (G: Hallock et al., 2009; Surrey-ATI). A previous collection of bulk material could be necessary in cases of larger spills (G: PENNSTATE). An essential issue is related to HEPA-filtered vacuum cleaners which have to avoid electrostatic charges by neutralising any charges (G: Surrey-ATI).

126. Beside the various aspects of regular cleaning and cleaning of contaminations, the cleaning hygiene of the employees is an essential issue which ensures a certain hygiene standard and consequently the safety of the employees.

127. The required hygiene can be achieved amongst others by washing hands before any procedure (S: EPFL) and after handling nanomaterials (S: ISU; MIT; Penn-EHRS), respectively before (S: VCU) and after (S: DOE-NRSC; VCU) wearing gloves. Hand washing shall also be performed before eating (S: UD), smoking (S: UD) or leaving the working area (S: Georgia Tech; UD). Soap and water can be sufficient to clean the hands (S: VCU). It might be necessary to include cleaning of the forearms (S: DOE-NRSC; MIT) depending on the area of contamination.

128. The working clothes shall be stored separately (S: UBC) whereas the laboratory coats shall be changed once in a work week (S: UBC).

129. Contaminated clothes are recommended to be changed promptly (S: VCU) with adjacent laundry (S: ISU) or to be disposed (S: DOE-NRSC; ISU). It could furthermore be necessary to wear disposable coveralls and boots if a certain probability for contamination exists (S: ISU).

3.8 Personal protective equipment

130. The general application of appropriate personal protective equipment (PPE) while handling nanomaterials, which supplements organizational and engineering measures, is recommended by a number of guidelines (S: AIST; CHS; DOE-NRSC; EPFL; Georgia Tech; HSE-a; ISU; MIT; NASA-ARC; NSF; ORC Worldwide; OUHSC-IBC; Penn-EHRS; TU Delft; UBC; UC; UCI; UCSB; UD; VCU).

131. The recommendations for respiratory protection range from the usage of disposable masks with type N95 filters (S: CHS; NASA-ARC) to half masks with type P100 cartridges (S: CHS; DOE-NRSC). In cases of high load, i.e. if the nanoparticle concentration is very high or information of the adequateness of the respirator to the specific type of nanoparticles are missing, the use of a breathing apparatus, which is provided with clean air from an independent source, is preferred (S: HSE-a). This breathing apparatus is composed of a full-face mask with a compressed air supply (S: HSE-a). Also the need of a powered air-purifying respirator (PAPR) in conjunction with either a flexible hood, which covers head, shoulders and upper torso, or a full-facepiece is stated (S: ORC Worldwide). Predominantly P100 filters are approved (S: CHS; DOE-NRSC; UCI; UCSB), but also type N95 (S: CHS; NASA-ARC), N-100 (S: UCI; UCSB) and R-100 filters (S: UCI; UCSB) are mentioned. Regarding respiratory protection, comparable European and Australian standards exist for filters, named P2 and P3 (G: BAuA / VCI; HMUELV; Safe Work Australia)

132. The range of respiratory protection described by specific nanomaterial guidelines related to laboratories is extended by several general nanomaterial guidelines. In two documents, the opinion is advanced that the usage of respiratory protection is only necessary for cleaning of large spills (G: Hallock et al., 2009; PENNSTATE). In contrast to this statement, a mask with an assigned protection factor (APF) 40 or higher is recommended as a minimum standard (G: HSE-b). It is suggested that the respirator shall be used with either a flexible screen that covers head, shoulders and the upper torso, or a properly adjusted full face shield (G: IRSST). Moreover, an expert opinion is recommended to ensure a sufficient protection level according to the respective risk (G: IRSST).

133. One general nanomaterial guideline suggests selecting respiratory protection according to a selection chart, which was provided by the guideline itself as following (G: MHLW):

1. Respiratory protection with APF (assigned protection factor) of 10 or higher is required for handling nanomaterials in a closed system, automation of manufacturing processes and the use of nanomaterials embedded in resins. This includes replaceable half-face type masks and disposable dust masks (G: MHLW).

2. Respiratory protection with APF of 50 or higher is needed if a LEV is utilized. Options for respiratory protection are for instance half facepiece, fan-assisted PAPR, supplied air-masks as well as replaceable full-face type dust masks.

3. In the case of specialized operations or high exposure concentrations, for instance occurring during cleaning operations or collecting and recycling products, respiratory protections with APF of 100 to 1,000 or even higher are suggested. These APF values can be provided by full facepiece and hood type fan-assisted PAPR, supplied-air respirator and pressure demand-type airline mask (G: MHLW). The fit of the used mask ought to be tested every time of wearing (G: MHLW).

134. The wearing of gloves is also regarded as necessary by all specific nanomaterial guidelines applicable for laboratories addressing this point (S: AIST; CHS; EPFL; Georgia Tech; ISU; MIT; NASA-ARC; NSF; ORC Worldwide; OUHSC-IBC; Penn-EHRS; TU Delft; UBC; UC; UCI; UCSB; UD; VCU). The gloves should be impermeable (S: AIST). The preferential material is nitrile (S: CHS; DOE-NRSC; ORC Worldwide; UBC; UD; VCU). Further recommended materials are latex (S: UBC; UD; VCU) or chemical resistant triple polymer (S: UBC). The glove material should be chosen according to the chemical compatibility to the respective nanomaterial (S: ORC Worldwide; UBC). In a number of reports, the wearing of a double pair of gloves is favored, which is graduated from a double glove wearing suggestion in cases of strong skin contact (S: MIT) to two sets of gloves as minimal requirement (S: TU Delft). The gloves should both cover the hands and overlap the sleeves of the lab coat (S: ISU; VCU). It is also recommended that the gloves should be removed inside the closed system, for instance the enclosing hood (S: ORC Worldwide).

135. Supplementary, in a general nanomaterial guideline, which is also applicable for laboratories, double gloves made from different materials with latex and nitrile or polypropylene are suggested (G: NanoSafe Australia). Another guideline presents a glove management system, whose key elements include maintenance, storage, removal, disposal, training, ergonomics, material selection and the exposure/task scenario (G: Safe Work Australia). When handling liquids, nitrile gloves with extended sleeves are regarded as a good option (G: Safe Work Australia). However, gloves shall be chosen after considering the resistance to chemical attack of both nanomaterial and liquid (G: Safe Work Australia).

136. Safety glasses or face shields are suggested for eye protection in the predominant number of specific nanomaterial guidelines for laboratories (S: AIST; CHS; DOE-NRSC; Georgia Tech; VCU; UBC;

UC). In two general nanomaterial guidelines, the need for protective googles with side-protection is highlighted (G: BAuA / VCI; Safe Work Australia).

137. Regarding footwear, the wearing of closed shoes is mostly recommended preferably from a non or low permeability material (S: AIST; CHS; DOE-NRSC). An additional coverage of the shoes with disposable boots (S: EPFL; UBC) may be used to prevent tracking nanomaterials from the laboratory area.

138. The recommendation for shoe material is specified in a general nanomaterial guideline also applicable for laboratories, in which shoes made of neoprene material are suggested (G: NanoSafe Australia).

139. As further protection measures, predominantly laboratory coats, disposable laboratory coats (S: MIT) or disposable overalls are listed (S: UD; VCU). It is recommended by one guideline, that the protective clothing should be impermeable (S: AIST). Another guideline suggests utilizing disposable overalls, which could be made up of tyvek textile (S: UD). However, one report controversially leaves the usage of a laboratory coat or a long sleeved shirt with buttons on the back to one's decision (S: EPFL).

140. It is pointed out in general nanomaterial guidelines also applicable for laboratories that the laboratory coats shall not consist of cotton, wool or knitted materials (G: HSE-b; MHLW; OSHA-EUROPA). In one guideline, it is suggested to enhance the protective effect by wearing double overalls from different materials, i.e. to wear a supplementary overall from tyvex or polypropylene over a fabric overall (G: NanoSafe Australia).

141. Further PPE may be hair and beard protection (S: UBC), long trousers without cuffs (S: CHS; DOE-NRSC), long sleeved shirts (S: CHS; DOE-NRSC; Penn-EHRS) or aprons (S: NSF).

142. In the general nanomaterial guidelines applicable also for the laboratory scale, it is generally mentioned that the protective clothing should cover the full body or, more precisely, all areas of skin (G: NanoSafe Australia; HMUELV).

143. One specific nanomaterial guideline for laboratories highlights that wounds or lesions on the skin as well as dermatological diseases shall be in each case covered.

3.9 Medical surveillance

144. In one general guideline for nanomaterials, several potential disease outcomes are named including the acute and chronic immune system responses of inflammation, allergy and autoimmunity to viral-sized monodispersed nanoparticles and their bacterial-sized aggregates, respiratory, skin and gastrointestinal related disorders (e.g. liver dysfunction following sequestration of circulating particulates), neurological disorders as well as the potential for cancer of several different types due to oxidative damage to DNA and the tumour promoting events of chronic inflammation and wound repair from ongoing tissue damage (G: Safe Work Australia).

145. The issue of health monitoring of the exposed workers was addressed in several specific nanomaterial guidelines for laboratories (S: CHS; DOE-NRSC; EPFL; Georgia Tech; HSE-a; UC; UD).

146. It is recommended that the potentially exposed employees pay especially attention to the onset of potentially chronic effects of the respective nanomaterial (S: Georgia Tech).A medical surveillance can be requested by a responsible person for example the manager of the project if necessary (S: EPFL).

147. It is also thinkable that the medical recording is performed by a medical director. The medical director takes care of a health monitoring program and performs a periodic medical surveillance of pulmonary, renal, liver and haematopoietic functions (S: DOE-NRSC).

148. It is stated that one can determine the need for and the specific type of health monitoring by performing a risk assessment (S: HSE-a). One guideline states that health monitoring can ensure the detection of any health effects at an early stage and consequently the reduction of the likelihood of long-term harm (S: HSE-a). However, the required parameters of this health monitoring are not addressed (S: HSE-a).

149. It is furthermore specifically recommended that the personnel should receive medical permission from a medical doctor before being fitted with a respirator (S: CHS). A differentiated view on the medical surveillance is presented in another guideline, which points out that the medical surveillance should be classified on basis of the potential exposure routes of the nanomaterials (S: UC). One guideline recommends that the special medical examination for the respective nanomaterial shall be received based on the substance category applicable to one of the existing special medical examinations (S: AIST). The employer shall implement regular health examinations under the Industrial Safety and Health Low or the Pneumoconiosis Law (in Japan), and recognize the latest health conditions of the worker (G MHLW).

150. It is mentioned that allergenic or carcinogenic particles should be screened specifically since even tiny quantities of these particles may be biologically significant (S: UC). It is added by way of explanation that skin contact can occur easily during the handling of suspension of nanoparticles or dry powders (S: UC). Furthermore, it is determined that pregnant workers are not allowed to work with nanomaterials (S: UC).

151. Regarding first aid, the following recommendations are given by one specific nanomaterial guideline for laboratories: 1) If nanomaterials get into the eye, they shall be flushed and rinsed with plenty of water; 2) and 3) In case of inhalation or ingestion, they suggest gargling, washing and rinsing the mouth thoroughly, whereby for 2) inhalation, the movement to a clean air area and for 3) ingestion, spitting out is expedient; 4) If nanomaterials are adhered to the skin, they ought to be washed with soap or wiped off with cleansing cream (S: AIST) (G: MHLW).

3.10 Transport

152. Several specific nanomaterial guidelines for laboratories agree in the opinion that nanoscaled materials shall be transported like normal chemicals (S: TU-Delft), i.e. in closed, labelled containers (S: CHS; ISU; MIT; Penn-EHRS). In one guideline, the requirements are explained explicitly (S: DOE-NRSC). Nanomaterials shall be transported according to 49 Code of Federal Regulations (CFR) 100-185 and, if shipped by air, also according to the International Civil Aviation Organizaton (ICAO) (S: DOE-NRSC). The respective nanomaterial shall be double packaged whereas the outer and inner package shall meet the definition of a Package Group (PG I) type package (S: DOE-NRSC). It is suggested to apply adequate safety measures equivalent to the measures for chemical materials in order to protect the container or package from damages due to earthquake and fire (S: AIST). One mentioned option refers to the outer package, which shall be filled with a shock and liquid absorbing material both to protect the inner container from damage and to absorb potential leakages (S: DOE-NRSC). This leakage shall be moreover prevented by a tight sealing of the innermost container (S: DOE-NRSC).

3.11 Waste disposal

153. Several specific nanomaterial guidelines for laboratories suggest the general disposal of nanomaterials as chemical or hazardous waste according to local legal requirements (S: CHS; Georgia Tech; ISU; NASA-ARC, NSF; Penn-EHRS; UC; UCI;, UD).

154. It is further recommended by one guideline to treat nanomaterial waste including dust filters, collected waste liquid and cloth, appropriately to prevent secondary contamination and to dispose this waste according to the waste separation method specified by the respective Institutes (S: AIST).

155. Several guidelines also highlight a gradation for disposal treatment. It is one option, to treat quantities of nanomaterials with low water solubility exceeding the milligram range as chemical waste (S: TU-Delft). Nanomaterials with high water solubility shall be treated according to the toxicity class of the macroscopic material (S: TU-Delft).

156. It is also suggested to dispose nanomaterials in solution according to the hazardous waste procedures for the solvent (S: UCI; UCSB).

157. Regarding the aspect that there are no specific regulations that apply to nanomaterial waste, one guideline suggests waste management of the following nanomaterial waste streams: a) pure nanomaterials, b) items contaminated with nanomaterials, c) liquid suspensions containing nanomaterials and d) solid matrixes with nanomaterials friable or attached to the surface (S: MIT). In this guideline, the treatment of nanomaterials as hazardous waste is generally recommended (S: MIT). The guideline does not apply to nanomaterials embedded in a solid matrix that cannot reasonably be expected to break free or leach out when they contact air or water (S: MIT).

158. The chemical properties of the respective nanomaterial can determine what kind of disposal approach is to be followed. It is suggested to characterize the nanomaterials according to their characteristics as either hazardous or nonhazardous waste based on the requirements in 40 CFR 261.10-38 or equivalent state regulations (S: DOE-NRSC).

159. Specifically, it is suggested to treat contaminated liquid and solid wastes in an appropriate way to inactivate the nanomaterial (S: EPFL). However, no details are provided about the way of inactivation and the type of nanomaterials addressed.

160. Similarly, it is recommended to dispose the nanomaterial as hazardous waste if the chemical or mixture is regulated as such by environmental regulations (S: ORC Worldwide). Otherwise, a disposal as special waste shall be chosen such as incineration, chemical treatment or immobilization (S: ORC Worldwide). A special consulting is required for a larger amount of waste (S: ORC Worldwide).

161. Several recommendations for the disposal of nanomaterial packaging and contaminated materials exist. One option is to collect these materials in a double bag or double container, label and seal these materials for disposal (S: CHS; DOE-NRSC; Georgia Tech; MIT). This double-bag can be for instance a 6 ml plastic bag (S: Georgia Tech). Another guideline describes a singular packing in a bag or bucket (S: ORC Worldwide). Contaminated nanomaterials shall be either disposed as hazardous waste (S: TU-Delft) or through incineration (S: VCU).

162. In a number of general nanomaterial guidelines also applicable to laboratories, the disposal of nanoscale materials as hazardous waste is likewise recommended (G: Hallock et al., 2009; HSE-b; NanoSafe Australia; Surrey-ATI).

163. A single guideline stated that the disposal ought to follow the requirements for the respective bulk material since they are still no specific guidelines for disposal of waste materials existing (G: PENNSTATE). However, the disposal shall be based on a previous consultation of the EHS office (G: PENNSTATE). Exceptions are nanomaterials which contain toxic metals or flammable carbon. These materials shall be treated as hazardous waste (G: PENNSTATE).

164. The disposal of nanomaterials with metal and metal oxide constituents, like quantum dots or zinc oxide, is for instance restricted in Australia since they are assumed to be potent biocides (G: NanoSafe Australia).

Nanomaterials can finally be bound within some matrix like concrete and be disposed in a licensed land-fill scape (G: NanoSafe Australia).

165. Another suggestion is related to carbon nanotubes which can be incinerated as hazardous waste in a high temperature incinerator since heating above 500 °C oxidizes these materials completely (G: HSE-b). The disposal conditions as well as the incineration temperature shall be documented thoroughly (G: HSE-b).

3.12 Documentation

166. Several recommendations regarding the correct documentation are provided by several specific nanomaterial guidelines for laboratory application. Documents, which shall be read by all employees working with nanomaterials and kept in the laboratory working areas permanently, can be the laboratory safety plan or manual (S: AIST; ISU; NASA-ARC), chemical hygiene plan (S: DOE-NRSC; VCU), standard operating procedures (SOP) (S: ISU; NASA-ARC; VCU; Surrey-ATI) and material safety data sheets (MSDS) (S: DOE-NRSC; Georgia Tech; MIT; NASA-ARC; UCI; UCSB).

167. Additionally, Job Hazard Analysis Worksheets (JHA) can be required for specific laboratory procedures (S: DOE-NRSC; NASA-ARC).

168. In order to better ensure understanding and competence, it is suggested that specific procedural requirements shall be incorporated into written procedures (S: DOE-NRSC). However, this recommendation is given on a general basis with no details indicating which work steps or manufacturing approaches are addressed.

169. It is further suggested to document not only incidents (S: NSF) but also the training (S: NSF) and the exposure of the nanoparticle-exposed employees (S: DOE-NRSC).

170. Protocols including the *in vivo* usage of nanoparticles shall suitably include completion of IACUC Hazardous Chemical Information Page (S: OUHSC-IBC; VCU). Furthermore, the approval through the Institutional Animal Care and Use Committee and the Institutional Biosafety Committee (IBC) is required (S: OUHSC-IBC; VCU). Protocols, which involve the administration of nanoparticles to humans, specifically require Institutional Review Board (IRB) approval (S: OUHSC-IBC).

171. Other aspects of documentation are mentioned in general nanomaterial guidelines also applicable for laboratory research. The compiled protocol shall include information on performed tests (G: HMUELV), protection measures (G: HMUELV; PENNSTATE) and nanomaterial properties like particle size distribution, composition and configuration (G: PENNSTATE). It is recommended that this protocol, which contains specific requirements addressing health and safety protection (G: PENNSTATE), shall be

either shown to the supervisor (G: Surrey-ATI) or the environmental health and safety office (G: PENNSTATE). Furthermore, the name of the worker, the engaged period of work and the general description of the nanomaterial-related work, shall be documented (G: MHLW). It is suggested to keep the documentation for a prolonged period (G: MHLW).

172. The generation of an internal database which contains a series of documents is reasonable (G: HMUELV). It is recommended to insert documents about the nanomaterial properties, toxicological and epidemiological data, safety tests and measures, measures for exposure mitigation, MSDS, product utility, the number of exposed employees, quality assurance and the question of liability in liability case (G: HMUELV).

173. In general nanomaterial guidelines, which are also applicable for laboratories, the quality of MSDS is regarded controversially. It is argued that MSDS may not contain accurate information (G: PENNSTATE). MSDS often refer to micron scale materials whereas the properties from microscale and nanoscale materials differ (G: Hallock et al., 2009; PENNSTATE). The composition of the micro- and nanoscale carbon materials is applied as comparison. In one commercially available carbon material, graphite is composed of coarse particle, whereas CNTs have a fiber shape (G: PENNSTATE). These forms also differ in their toxicity (G: PENNSTATE).

174. MSDS are on the one hand regarded as important sources of information (G: OSHA-EUROPA) and on the other hand considered critically since the MSDS at present only refer to the macroscale level of a substance and are not adapted to the unique properties of nanomaterials differing from the original substance (G: Hoyt and Mason, 2008).

4 Conclusion

175. A compilation of nanomaterial exposure mitigation guidelines relating to laboratories is presented in this document. It was of special interest to provide a broad overview of recently published literature referring to this topic since no globally standardized protection measures for handling nanomaterials are determined yet.

176. The content and structure of the analysed guidelines is primarily based on typical guideline concepts. The various aspects, which are mentioned in these guidelines, refer to the precautionary approach, categorization, assessment of nanospecific and physical hazards, measures according to the STOP principle (i.e. substitution (here, use of safer manufacturing approaches), technical measures, organizational measures and personal protective equipment), medical surveillance, transport, waste disposal and documentation of the taken measures.

177. The reported opinions on the majority of aspects agree on many points and exhibit basically only a minor deviation. As an example, it is generally regarded as essential to use precautionary measures to minimize risk in laboratories. Further aspects, which are regarded to be essential, refer to the general application of risk assessment, use of safer manufacturing approaches, technical and organizational measures and personal protective equipment. A consensus also exists on routine cleaning by vacuuming and wet wiping as well as on cleaning hygiene of the employees by regular hand washing. A disposal of nanomaterials as hazardous or chemical waste is likewise suggested by the majority of guidelines.

178. However, a large variation exists regarding several aspects. In the paragraph on categorization, the simplified view of an equal potential toxicity assumption of nanomaterials is extended to a distinction of defined risk levels considering the specific properties of the respective nanomaterial for instance size, chemical composition and surface area.

179. For risk assessment, a case by case approach is suggested. Furthermore the application of a control banding approach for a qualitative risk assessment is recommended, which is based on the use of a limited number of factors for evaluating the risk level in order to reduce the complexity and increase the applicability for non-experts.

180. Regarding the risk assessment, a high diversity of opinions on the necessary contents is mentioned. A large variation of recommendations is similarly given in respect to respiratory protection ranging from disposable masks with type N95 filters to half masks with type P100 cartridges.

181. Additionally, singular noticeable opinions on some aspects have been detected. For instance, one guideline only recommends precautionary measures if the mass of the nanomaterial sample exceeds the milligram range. Specific suggestions for technical measures are a stable depression of 6 mm water column in the laboratory area and a ventilation system with 6 to 12 air changes per hour. Regarding organizational measures, it is stated that carbon nanoparticles of more than 1 g shall be stored in sealed metal containers due to their electrostatic activity. Similarly, specific recommendation for the cleaning agent like iso-propanol, water, cleaning agents compatible to the respective material are given. The cleaning measures shall be different above a threshold of 5 mg nanopowder or 5 ml nanomaterial solution as well as at a cleaning time of more than 5 min. Specific personal protective equipment like neoprene shoes or disposable overalls from tyvex textile is likewise suggested.

182. One can conclude that the reviewed guidelines mainly agree in the basic issues of occupational safety with respect to nanomaterials in laboratory scale. These issues can therefore be regarded as a consolidated consensus.

183. In other aspects, a large range of different recommendations on health and safety measures can be found. The suggestions on the one side of the range, where lesser protection measures are mentioned, are possibly more suited to deal with low hazard nanomaterials.

184. Some very specific remarks appear only sporadically and hence should be regarded carefully. They provide very detailed information, which might be helpful to determine precise measures.

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