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Nanotechnologies — Overview of available frameworks for the development of occupational exposure limits and bands for nano-objects and their aggregates and agglomerates (NOAAs)

Nanotechnologies — Vue d'ensemble des cadres disponibles pour la définition de limites et bandes d'exposition professionnelle applicables aux nano-objets, à leurs agrégats et agglomérats (NOAA)

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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The committee responsible for this document is ISO/TC 229, *Nanotechnologies*.

Introduction

Nano-objects and their aggregates and agglomerates (NOAAs) represent a subset of particulate materials that can be dispersed in the air and can represent health risks via inhalation exposures. NOAAs include structures with one, two or three external dimensions in the nanoscale from approximately 1 nm to 100 nm, which may be spheres, fibres, tubes and others as primary structures. NOAAs can consist of individual primary structures in the nanoscale and aggregated or agglomerated structures, including those with sizes larger than 100 nm. An aggregate comprises strongly bonded or fused particles (structures). An agglomerate is a collection of weakly bound particles (structures)[1][2][3][4].

The purpose of this document is to describe a general framework for the development of occupational exposure limits (OELs) or occupational exposure bands (OEBs) for individual NOAAs or categories of NOAAs with different levels of available data. OELs and OEBs are important tools in the prevention of occupational illness. OELs have a long history in industrial hygiene and are based on observations of workers or studies of laboratory animals. OELs are established to minimize the likelihood of adverse effects from exposure to potentially hazardous substances in the workplace[5][6]. An OEL is generally substance-specific (although sometimes generically expressed, such as dust). Sufficient data to develop an OEL may not be available, especially for substances such as NOAAs used in emerging technologies. To aid in hazard communication and exposure control decisions for substances without OELs, hazard banding has been used for many years[7][8][9]. Substances are assigned to a hazard band based on limited toxicity data usually from animal studies. Hazard banding schemes typically consist of qualitative bands ranging from low to high severity of effects. Thus, a hazard band represents a range of potential toxicities for a particular substance or category of substances. Some hazard banding schemes include associated OEBs[10]. The term OEB is a general term for exposure concentration ranges used in some hazard banding schemes that are related to the ranges of hazard potentials. In contrast to an OEB, an exposure band is a range of potential concentrations of a substance (or category of substances) to which workers may be exposed in a defined occupational scenario and which is based on factors such as the amount of NOAA processed or used, the nature of the process, and the form of the NOAA including dustiness[3]. In control banding, the hazard band and the exposure band are combined to determine the control band for any particular occupational scenario (e.g. ISO/TS 12901-2).

OELs and OEBs are part of an overall occupational safety and health (OSH) program and are not intended to identify and address all safety and health risks associated with a specific process or task. OELs and OEBs are intended to provide occupational safety and health professionals with a health basis for assessing the effectiveness of exposure controls and other risk management practices. The exposure assessment of nanomaterials including carbon nanomaterials [such as fullerene, graphene, single-walled carbon nanotube (SWCNTs) and multi-walled carbon nanotube (MWCNTs)], metal oxides (TiO_2, SiO_2, zinc oxide, iron oxide), and metals (silver and gold nanoparticles) remains a challenge in the field of occupational hygiene, as there have been relatively few studies on the characterization of workplace exposures to NOAA. Sampling and analytical methods that have the capabilities to accurately measure nanomaterials are still under development. Most sampling devices that measure airborne particle count concentrations, such as condensation particle counters and optical particle counters, cannot differentiate ambient exposures to background nanoparticles from NOAA in the workplace environment. Airborne measurements of carbon nanotubes (CNTs) and carbon nanofibres (CNFs) using mobility particle sizers also sometimes could present a unique challenge due to the arcing caused by the charged airborne CNT and CNF agglomerates in the differential mobility analyser[11]. Although several groups have attempted to measure and count CNT structures using transmission electron microscopy or other microscopic methods[12][13], there are still no standard methods for measuring and counting CNT structures. In addition, determining the mass concentration of CNTs and CNFs based on measuring the elemental carbon (EC) remains a challenge due to other sources of elemental carbon in the workplace, such as organic composite materials and air and diesel pollution that could interfere in the determination of CNT and CNF exposures.

Scientific and technical methodologies used to set exposure limits may differ from one entity to another, which can lead to disparities in worker protection from country to country[14]. Therefore, harmonizing the scientific methodologies used in developing OELs, including using the best available evidence for interspecies extrapolation and specifying the type of data and uncertainties involved in the OEL determination is necessary for a robust health and safety evaluation framework for NOAAs.

This document provides a collaborative, science-based platform to describe and evaluate the state-of-the-art in such data and methods.

Current risk assessment methods are likely to apply to NOAAs[15], although the limited health hazard data for many NOAAs and the considerable variety in the types of manufactured NOAAs present a challenge to the efficient development of OELs for individual NOAAs. To date, few OELs and OEBs have been developed for specific NOAAs and none have been formally regulated by a government agency. Standard OEL and OEB methodologies for NOAAs are needed to evaluate the evidence on the hazard potential of NOAAs in the workplace to provide a health basis for risk management decisions, including selection and evaluation of engineering control options. One of the goals of this document is to identify both the similarities and differences in the methods used to develop OELs. This evaluation may lead to improvements in methods for setting exposure limits or bands.

This document presents an overview of the state-of-the-art in the development of OELs and OEBs for NOAAs. Current approaches for assigning default hazard bands in the absence of NOAA-specific toxicity data are described. These approaches build on current hazard and control banding strategies, such as those developed in ISO/TS 12901-2. The current state of the methods and data to develop OELs and OEBs for NOAAs is described in this document, along with an evaluation of those methods used in developing the current OELs for NOAAs. Categorical approaches to derive OEBs for NOAAs with limited data are also discussed, such as those based on biological mode-of-action (MOA) and physico-chemical (PC) properties. The basis for the framework described in this document is the U.S. NIOSH Current Intelligence Bulletin *Approaches to Developing Occupational Exposure Limits or Bands for Engineered Nanomaterials*[16]. This document also takes into consideration other state-of-the-science reports, including outputs of the workshop "Strategies for Setting Occupational Exposure Limits for Engineered Nanomaterials," which was held on September 10-11, 2012 in Washington, DC, USA[6] and the OECD Working Party on Manufactured Nanomaterials Expert Meeting on Categorization of Manufactured Nanomaterials, September 17-19, 2014[17].

The primary target audience of this document is occupational safety and health professionals in government, industry, and academia, who have the expertise to develop OELs or OEBs based on the guidance in this document. In addition, the evidence-based approach described in this document may be useful in the evaluation and/or verification of current hazard and control banding schemes and for identifying the key data gaps. Control banding requires information on both the applicable hazard category and exposure category. Appropriately verified control banding tools would be broadly useful, as these tools require less specialized expertise and resources (than for a comprehensive risk assessment) and are accessible to a wider group of individuals and small businesses. Therefore, this document can be considered complementary to ISO/TS 12901-2 on control banding for nanomaterials as it describes the state-of-the-art in the process of assigning nanomaterials to hazard bands/OEBs when the scientific evidence is not sufficient to develop an individual OEL.

Some of the cited methods lead to results that are not necessarily consistent and this may be due to method selection biases of the authors. In these cases, diverse results will also make it difficult to use information to confidently establish exposure and band levels. It is beyond the scope of this document to attempt to identify the methods which lead to both correct and consistent results. In the event that methods lead to diverse results, it is hoped that this report will lead to additional methods development that will lead to improvements and that these improvements can be relied on for setting exposure and banding levels.

The objectives of this document include

a) describing an evidence-based state-of-the-art framework to develop OELs or OEBs for manufactured NOAAs, and

b) examining the currently available data and other approaches and methods used (e.g. benchmark substances and benchmark exposure levels) in the occupational risk management decision-making for NOAAs.

It is anticipated that this document will contribute to the development of standard hazard and risk assessment methods and facilitate the systematic evaluation of the potential health risk of occupational exposure to NOAAs.

Nanotechnologies — Overview of available frameworks for the development of occupational exposure limits and bands for nano-objects and their aggregates and agglomerates (NOAAs)

1 Scope

This document provides an overview of available methods and procedures for the development of occupational exposure limits (OELs) and occupational exposure bands (OEBs) for manufactured nano-objects and their aggregates and agglomerates (NOAAs) for use in occupational health risk management decision-making.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/TS 80004-2 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org/obp

3.1
agglomerate
collection of weakly or medium strongly bound particles where the resulting external surface area is similar to the sum of the surface areas of the individual components

Note 1 to entry: The forces holding agglomerates together are weak forces, for example, van der Waals forces or simple physical entanglement.

Note 2 to entry: Agglomerates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO 26824:2013, 1.2]

3.2
aggregate
particle comprising strongly bonded or fused particles where the resulting external surface area is significantly smaller than the sum of surface areas of the individual components

Note 1 to entry: The forces holding an aggregate together are strong forces, for example, covalent or ionic bonds, or those resulting from sintering or complex physical entanglement, or otherwise combined former primary particles.

Note 2 to entry: Aggregates are also termed secondary particles and the original source particles are termed primary particles.

[SOURCE: ISO/TS 80004-2:2015, 3.5]

3.3
bulk material
material of the same chemical composition as the NOAA, at a scale greater than the nanoscale

3.4
exposure
contact with a chemical, physical or biological agent by swallowing, breathing, or touching the skin or eyes

Note 1 to entry: Exposure can be short-term (acute exposure), of intermediate duration, or long-term (chronic).

3.5
health hazard
potential source of harm to health

[SOURCE: ISO 10993-17:2002, 3.7]

3.6
health risk
combination of the likelihood of occurrence of harm to health and the severity of that harm

[SOURCE: ISO 10993-17:2002, 3.8]

3.7
nanofibre
nano-object with two external dimensions in the nanoscale and the third dimension significantly larger

Note 1 to entry: The largest external dimension is not necessarily in the nanoscale.

Note 2 to entry: The terms nanofibril and nanofilament can also be used.

Note 3 to entry: See 3.9 Note 1 to entry.

[SOURCE: ISO/TS 80004-2:2015, 4.5]

3.8
nano-object
discrete piece of material with one, two or three external dimensions in the nanoscale

Note 1 to entry: The second and third external dimensions are orthogonal to the first dimension and to each other.

[SOURCE: ISO/TS 80004-1:2010, 2.2]

3.9
nanoparticle
nano-object with all external dimensions in the nanoscale where the lengths of the longest and the shortest axes of the nano-object do not differ significantly

Note 1 to entry: If the dimensions differ significantly (typically by more than 3 times), terms such as nanofibre or nanoplate may be preferred to the term nanoparticle.

[SOURCE: ISO/TS 80004-2:2015, 4.4]

3.10
nanoscale
length range approximately from 1 nm to 100 nm

Note 1 to entry: Properties that are not extrapolations from a larger size are predominantly exhibited in this length range.

[SOURCE: ISO/TS 80004-1:2010, 2.1]

3.11
particle
minute piece of matter with defined physical boundaries

Note 1 to entry: A physical boundary can also be described as an interface.

Note 2 to entry: A particle can move as a unit.

Note 3 to entry: This general particle definition applies to nano-objects.

[SOURCE: ISO 26824:2013, 1.1]

3.12
solubility
maximum mass of a nanomaterial that is soluble in a given volume of a particular solvent under specified conditions

Note 1 to entry: Solubility is expressed in grams per litre of solvent.

[SOURCE: ISO/TR 13014:2012, 2.27]

3.13
occupational exposure limit
maximum concentration of airborne contaminants deemed to be acceptable, as defined by the authority having jurisdiction

[SOURCE: ISO 16972:2010, 3.133]

3.14
occupational exposure band
quantitative representation of hazard band which describes hazard potential of a particular material or class of materials in workplace air

3.15
breathing zone
space around the face of a worker from where he or she takes his or her breath

[SOURCE: ISO 24095:2009, 3.1.21]

4 Symbols and abbreviated terms

ACGIH	American Conference of Governmental Industrial Hygienists
AGS	Ausschuss für Gefahrstoffe (German Committee on Hazardous Substances)
AGW	Arbeitsplatzgrenzwert (occupational exposure limit)
AIST	Japanese National Institute of Advanced Industrial Science and Technology
BALF	bronchoalveolar lavage fluid
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Safety and Health)
BEI	biological exposure index
BEL	benchmark exposure level
BMD	benchmark dose
BMDL	benchmark dose estimate, 95 % lower confidence limit

BSI	British Standards Institution
CMAR	carcinogenic, mutagenic, asthmagenic, or reproductive toxicant
CNF	carbon nanofibre
CNT	carbon nanotube
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DMEL	derived minimum exposure level
DNEL	derived no-effect level
EPA	United States Environmental Protection Agency
EU	European Union
EU-OSHA	European Agency for Safety and Health at Work
GBP	granular biopersistent particle
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
IARC	International Agency for Research on Cancer
IFA	Institut für Arbeitsschutz (German Institute for Occupational Safety and Health)
ILV	indicative limit value
JSOH	Japan Society for Occupational Health
LC50	concentration associated with 50 % lethality
LOAEL	lowest observed adverse effect level
MAK	Maximale Arbeitsplatzkonzentration (maximum workplace concentration)
MOA	biological mode of action
MOEL	Korean Ministry of Employment and Labour
MSHA	United States Mine Safety and Health Administration
MWCNT	multi-walled carbon nanotube
NIOSH	United States National Institute for Occupational Safety and Health
NOAAs	nano-objects, and their aggregates and agglomerates including those larger than 100 nm
NOAEL	no observed adverse effect level
NRV	nano-reference value
OECD	Organization for Economic Cooperation and Development
OEB	occupational exposure band
OEL	occupational exposure limit
OEL (PL)	period-limited occupational exposure limit

OELV	occupational exposure limit value
OSH	occupational safety and health
OSHA	United States Occupational Safety and Health Administration
PC	physico-chemical
PCM	phase contrast microscopy
PEL	permissible exposure limit
QRA	quantitative risk assessment
REACH	Regulation, Evaluation, Authorization and Restriction of Chemicals
REL	recommended exposure limit
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCOEL	Scientific Committee on Occupational Exposure Limits
STEL	short-term exposure limit
STOT-SE	Specific target organ toxicity — single exposure
STOT-RE	Specific target organ toxicity — repeated exposure
SWCNT	single-walled carbon nanotube
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	ultrafine
VLEP	Valeur Limite d'Exposition Professionnelle (occupational exposure limit)
WHO	World Health Organization
WHS	Work Health and Safety

5 Description of available processes for setting OELs and OEBs

5.1 General considerations

Exposure to substances or mixtures in the workplace can occur through inhalation, absorption through the skin or ingestion. Most exposure occurs through the inhalation of vapours, dusts, fumes or gases. For some chemicals, absorption through the skin may also be a significant source of exposure.

The response of the body to exposure from substances and mixtures depends on the nature of the substance, the health effects it can cause and the amount of the substance or mixture absorbed by the body. Individuals also have differing abilities to metabolize chemicals which can cause considerable variation in the toxic effects between people. The extent to which a person is exposed mainly depends on the concentration of the substance or mixture in the air and the amount of time exposed and, of course, on the effectiveness of controls. Substances and mixtures may cause immediate acute health effects or it may be decades before effects on the body become evident.

Occupational exposure limits are intended to prevent adverse health effects in "nearly all workers"[18] even with repeated or daily exposures over a working lifetime. Some OELs are based on health effects data only (e.g. ACGIH TLV), and other OELs also include consideration of the technological feasibility (e.g. NIOSH RELs) or economic feasibility (e.g. OSHA PEL) of measuring and controlling exposures.

For a few substances, usually the more potent probable and established human carcinogens, it is not currently possible to assign an appropriate exposure limit. For these substances, exposure should be controlled to the lowest practicable level. Biological monitoring may provide a more reliable indication of workplace exposure for these substances.

The evaluation of hazards posed by atmospheric contaminants in the working environment is often a complex task, taking into account the potentially large variability of exposure at the workplace requiring sound occupational hygiene exposure assessment strategies. For this reason, it is essential that those persons responsible for such assessments are knowledgeable and experienced professionals, who are fully aware of all issues canvassed in this document and have appropriate qualifications and experience in occupational hygiene.

NOTE A knowledgeable and experienced professional is an individual who will properly perform a specific job. This person utilizes a combination of knowledge, skills and behaviour to improve performance. More generally, competence is the state or quality of being adequately or well qualified, having the ability to perform a specific role[3].

The relationship between various exposure limits should not be used as a general measure of their relative toxicity. This is because, among other things, the values for different substances are often established with regard to different biological effects, such as irritation or systemic toxicity. Similarly, the exposure limits should not be used as a basis for the evaluation of community air quality, or for long term, non-occupational exposures.

Most substances used in industry have not been assigned exposure limits. This does not imply that these substances are safe or non-hazardous. In many cases there is insufficient information on the health effects of these unlisted substances to allow national regulatory bodies to assign an exposure limit, even on a tentative basis. In other instances, the use of the substance does not lead to significant airborne levels of contaminant, or its use is so restricted that an exposure limit is not warranted.

It is a good general policy to keep the exposure to any substance as low as is practicable, irrespective of whether present information indicates it is hazardous or not. Some substances previously thought to be comparatively safe have subsequently been found to pose serious long term health risks.

There are three types of exposure limits:

— time-weighted average (TWA) limit;

— short term exposure limit (STEL);

— peak or ceiling limit.

These limits and other technical aspects of setting OELs are further described in A.1.2.

5.2 Description of evidence-based process

The methods for developing OELs depend on the available data. Schulte, et al.[5] describe three general scenarios for varying amounts of toxicological data. This framework was refined to describe linkages between the evidence basis for these general categories through benchmark substances. Benchmark substances are well-characterized materials (e.g. airborne particles or fibres) with sufficient dose-response data from animal and/or human studies to develop quantitative risk estimates and health-based OELs (Figure 1)[19][20]. Benchmark materials also provide a reference (e.g. as a positive or negative control) in comparative toxicity assays with new NOAAs that have limited toxicological data but similar physico-chemical properties and inferred biological mode-of-action (MOA)[19][20][21]. The focus of this document is on occupational airborne exposures to nanomaterials since inhalation is the major route of exposure to potentially hazardous substances, including NOAAs, in the workplace.

As shown in Figure 1, in the first case, if dose-response data are sufficient, an OEL for an individual NOAA can be developed using quantitative risk assessment (QRA). The definition of sufficient will ultimately be based on a judgment about the available data, and may include weight of evidence evaluations, including the availability of adequate data for benchmark dose modelling[22] or no observed adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAEL) from well-conducted studies. Second, if data are insufficient for QRA for a specific substance, but adequate information is available on a similar substance in the same mode-of-action category, then a categorical OEL may be assigned by qualitative or quantitative methods including read-across and structure-bioactivity modelling, with comparisons between NOAAs and benchmark substances. Third, if data are insufficient to develop a substance-specific or categorical OEL, then initial (default) hazard and control bands may be derived by comparing NOAA properties to that of similar materials in broad categories. The objective of this evidence-based approach is to facilitate decision-making about exposure control strategies for NOAAs in the workplace based on best available evidence. The framework allows for iteration and revision of an OEB or OEL as new data become available based on standard criteria for data and methods. At this time, more examples of OELs developed for NOAAs are available than of categorical OELs or OEBs for NOAAs.

The data available for developing OELs or OEBs for NOAAs may include

a) data from *in vivo* and *in vitro* testing of specific NOAAs (e.g. from the OECD testing program, manufacturers of NOAAs, and non-regulatory government agencies such as the NIOSH and the NTP in the US), and

b) existing toxicology or epidemiology studies of lung effects from inhaled particles and fibres for comparative toxicity analyses.

General chemical hazard databases (e.g. as used in GHS[23] hazard classification) are also available for some of the parent or bulk materials with similar chemical composition to the NOAA for use in hazard band/OEB allocation and control banding (e.g. see ISO/TS 12901-2). Table 1 summarizes the type of data and methods needed to develop OELs or OEBs.

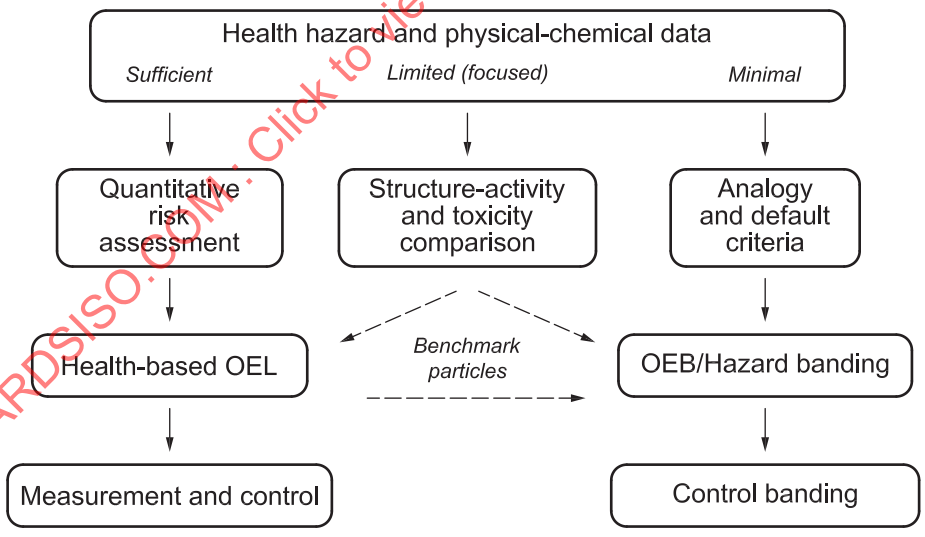


Figure 1 — Evidence-based strategy to develop exposure control limits and bands for NOAAs, based on level of evidence

Table 1 — Data and methods needed to develop exposure limits or bands

Guidance value	Level of evidence	Data, analysis tools and methods
Substance-specific OEL	Sufficient	Substance-specific dose-response data for quantitative risk assessment; availability of substance-specific sampling and analytical method
Categorical OEL	Limited (focused)	Comparative toxicity, clustering and categorization to estimate hazard or risk based on physico-chemical properties and biological mode-of-action data
OEB	Minimal or inadequate	Analogy; default hazard categories and exposure control options are applied.

5.3 Substance-specific OELs

The substance-specific OELs typically do not take separate account of the nanoparticle size, although some of these OELs do specify the particle size sampling criteria associated with regional respiratory tract deposition. These sampling criteria include inhalable (total), thoracic (airways), and respirable (pulmonary) size fractions. Nanoparticles are capable of depositing anywhere in the respiratory tract region, including the pulmonary region where gas exchange takes place. Some of the individual OELs are specific to the dust and/or fume forms, and fumes by nature consist of nanostructured particles. The OELs for fumes may be lower mass concentrations than the OELs for dust of the same chemical substance (e.g. the NIOSH REL and OSHA PEL for copper is 1 mg/m^3 for the dust and 0,1 mg/m^3 for the fume)[24]. In other cases the OEL applies to both the dust and fume (e.g. iron oxide, NIOSH REL is 5 mg/m^3 and OSHA PEL is 10 mg/m^3; cobalt metal dust and fume, NIOSH REL is 0,05 mg/m^3 and the OSHA PEL is 0,1 mg/m^3). It is relevant to note that those OELs vary at least as much by chemical composition as by descriptors of particle size (dust, solid particles generated by any mechanical processing of materials such as crushing, grinding, and handling or fume, airborne dispersion consisting of small solid particles created by condensation from the gaseous state).

Clause 6 and Table 2 provide a description and list of the OELs that have been developed for specific nanomaterials by non-regulatory government agencies, companies, and nongovernmental organizations. To date, no regulatory standards have been circulated for NOAAs.

5.4 Categorical OELs

Historically, many airborne particulate materials were regarded as a “nuisance” or as “low toxicity” dusts and categorical OELs, such as a generic inhalable OEL of 10 mg/m^3 and a respirable OEL of 4 mg/m^3 were set for many low-toxicity poorly-soluble dusts including aluminium oxides, graphite, titanium dioxide and others[25]. In Germany, the DFG MAK commission recently reduced the OEL for biopersistent granular particles from 3 mg/m^3 to 0,3 mg/m^3 (respirable fraction), reflecting concerns about a possible carcinogenic potential for this category of substances[26]. All these values, however, were not intended for particulate materials with specific known inhalation or systemic toxicity (e.g. asbestos and lead, respectively) for which substance-specific OELs were also determined.

Advantages of categorical approaches include:

— more efficient use of data;

— reduced costs;

— reduced animal use;

— increased sample size;

— greater robustness of results;

— increased biological plausibility for other materials in the same mode of action category[27].

Categorical approaches are compatible with hazard and risk assessment frameworks proposed for NOAAs (e.g. References [5], [20] and [28]) and with a standard risk assessment paradigm[29]. Methods

to derive OELs for NOAAs using categorical approaches may include quantitative or qualitative read-across[27]; comparative potency analyses of NOAAs to benchmark (reference) particles in the same mode-of-action (MOA) category[19][20], e.g. using a "parallelogram" approach[19][30][31][32]; and assigning an untested substance to the low end of the distribution of OELs for materials in the same hazard class[33].

Other risk analysis and categorization approaches include both occupational and environmental components, such as screening tools of potential risks over the NOAA lifecycle[34][35]. The multi-criteria decision analysis (MCDA) approach includes evaluation of the risks and benefits with weightings obtained through expert elicitation[28]. This process has been used to assign NOAAs to qualitative risk categories (low, medium, high)[36].

Clause 7 summarizes the categorical OELs that have been proposed by governmental and nongovernmental organizations. These categories are based on broad groups of physico-chemical properties that influence toxicity (soluble, biopersistent low toxicity, biopersistent high toxicity, and fibres). The BSI and IFA categories are provisional exposure limits based on existing OELs for particles and fibres in these categories, which includes in some cases a precautionary downward adjustment for the nanoscale form. The extent to which chemical substance-specific data are available would allow refinement of the categorical OELs to an individual OEL that may be more applicable to an individual substance.

5.5 Initial or default occupational exposure bands

When data are not sufficient to develop an individual OEL, hazard banding approaches are often used to facilitate decision-making among engineering control options[5]. Control banding typically utilizes a matrix approach to categorize substances according to their hazard and exposure potential[37][38][39][40][41][42] to determine an appropriate control technology (such as general ventilation, local exhaust, or containment)[39][41][42][43]. The combination of the selected hazard and exposure bands determines the control band and associated engineering control options. However, the utility of such an approach is frequently limited by the availability of adequate toxicological data for use in hazard assessment. The absence of such data makes workplace risk characterization and the subsequent selection of appropriate control measures problematic. Another suggested approach is the utilization of initial default hazard categories or OEBs for NOAAs based on the physico-chemical properties associated with point-of-entry or systemic toxicity, including particle surface chemistry and area, shape, diameter, and solubility, as well as any evidence on the mutagenicity, carcinogenicity, or reproductive toxicity of the nanomaterial or parent material[20][42][44][45][46].

ISO/TS 12901-2 also incorporates available toxicological information and physico-chemical properties to designate nanomaterials into hazard bands. In this method, nanomaterials are grouped into one of five inhalation hazard groups (A to E) according to increasing severity described in GHS hazard classification applicable to chemicals[23].

— Category A (no significant risk to health) corresponds to an OEB of 1 mg/m^3 to 10 mg/m^3 (as 8 h time-weighted average)

— Category B (slight hazard; slightly toxic) — 0,1 mg/m^3 to 1 mg/m^3

— Category C (moderate hazard) — 0,01 mg/m^3 to 0,1 mg/m^3

— Category D (serious hazard) — <0,01 mg/m^3

— Category E (severe hazard) has no concentration ranges provided in ISO/TS 12901-2 and other hazard allocation schemes (8.1)

The decision logic for assigning NOAAs into these hazard bands includes considerations of solubility, fibrous nature and hazardous properties of bulk and analogous materials[3].

Hazard and control banding approaches were developed to facilitate risk management decision-making in small business. A key research need for hazard and control banding strategies in general, and those specific to NOAAs, is evaluation and validation of the utility of these strategies to provide adequate

health protection to workers in a variety of jobs and workplaces. A study evaluating the general hazard and control banding strategies found little or no margin of safety between worker exposures and the effect levels in animal studies[47].

6 Substance-specific OELs for nanomaterials

6.1 General overview

Currently, there are no specific regulatory OELs established for manufactured NOAAs. Interim or draft OELs have been proposed for certain NOAAs, including "benchmark exposure levels" based on analogy with OELs for other particles or fibres[44]. Since no epidemiology data are available on adverse health effects of exposures to most manufactured NOAAs, dose-response data from animal studies are typically used to estimate risk in humans. Experimental studies in animals and *in vitro* studies are also used to evaluate hazard and understand mechanisms of toxicity.

More recently, non-regulatory OELs for some specific NOAAs have been developed (see Table 2). These include OELs proposed by governmental agencies, researchers, and producers of specific nanomaterials.

Table 2 — Examples of OELs proposed for NOAAs

Nanomaterial	OEL ($\mu g/m^3$, unless stated otherwise)	Reference
Titanium dioxide (ultrafine)	610[a]	Gamo 2011[48]; Nakanishi 2011[49]
	300	NIOSH 2011[50]; JSOH 2013[51]
	17	Aschberger, et al. 2011[52]
Fullerene (C_{60})	390[a]	Shinohara 2011[53]; Nakanishi 2011[49]
	7,4	Aschberger, et al. 2011[52]
MWCNT (Baytubes®)	50	Pauluhn 2010[54]
Carbon nanotubes	30[a]	Nakanishi 2011[55]
MWCNT Carbon nanotubes and nanofibres	1 to 2	Aschberger, et al. 2010, 2011[52][56], Nanocyl 2009[57]
	1	NIOSH 2013[58]
Carbon nanotubes and nanofibres	0,01 f/cm^3	SUVA 2015[59]
Silver (nanoparticles)	0,33 to 0,67	Aschberger, et al. 2011[52]

[a] Period-limited (15 years) OEL.

Differences among OELs for the same or similar NOAAs in Table 2 are due to differences in the data and/or risk assessment methods used to derive the OEL. Some differences could be related to differences in chemical compositions and physical dimensions of similar NOAAs. The proposed OELs vary by up to an order of magnitude or more for the same or similar type of NOAAs, indicating that differences in the data and/or methods used to derive the OEL can influence the basis for risk management decisions such as selection of engineering controls. This illustrates the critical need to develop standardized risk assessment procedures that are based on the best available scientific evidence and methodologies.

6.2 Available substance-specific OELs

6.2.1 Carbon nanotubes

Carbon nanotubes (CNTs) are an example of manufactured nanomaterials that have been the subject of several recent risk assessments producing interim and voluntary occupational exposure limits. CNTs can have wide variations in structure, size, shape and chemistry (including impurities) affecting their hazard properties, exposure potential and ultimately risk. CNT and CNF are in growing use in a lot

of industry sectors, including construction as concrete reinforcement, for medical treatments, as fuel additives, and so on.

To date, there was limited information regarding adverse health effects in workers using or producing CNT or CNF. Few epidemiological studies have shown that some detectable biomarkers were related to exposure to CNT or CNF or other nanoparticles[60][61][62][63]. However, there are studies of animals exposed to CNT and CNF that are informative in predicting potential human health effects consistent with ways in which scientists traditionally have used such data in recommending risk management strategies.

In 2013, NIOSH recommended a REL of 1 µg/m^3 (8 h TWA) for CNT and CNF. The NIOSH REL for CNT and CNF is based on preventing the development of earlier adverse lung responses of pulmonary inflammation and fibrosis over a 45-year working lifetime. The REL for CNT and CNF is based on animal data, although since no chronic studies were available, the dose-response data from short-term and subchronic studies in rats and mice were extrapolated to humans. Since the REL for CNT was set at the limit of quantification of the sampling and analytical method for measuring airborne elemental carbon in the workplace, the 45-year working lifetime excess risk estimates for developing early-stage pulmonary inflammation or fibrosis exceed 10 % for some end points and assumptions[58]. Methodology used to derive this exposure limit is described in Clause 5 and further details can be found in A.11.

In 2011, the Japanese National Institute of Advanced Industrial Science and Technology (AIST) published a series of reports containing risk assessments of several nanomaterials: carbon nanotubes[55], titanium dioxide[48] and fullerenes[53]. The reports put forward period-limited (PL) OELs for SWCNT set at 0,03 mg/m^3 and for MWCNT set at 0,08 mg/m^3. These OELs (PL) were derived using inflammation as an end point observed in sub-acute inhalation exposure tests. The working exposure period employed in OEL calculations was set at 15 years. Further details about derivation of these OELs can be found in A.7.

6.2.2 Nanoscale TiO_2

Titanium dioxide, TiO_2, is a noncombustible, white, crystalline, solid, odourless powder. It exists in several crystal forms of which anatase and rutile are commercially the most relevant. TiO_2 is used extensively in many commercial products, including paints and varnishes, cosmetics, plastics, paper, and food as an anticaking or whitening agent.

Titanium dioxide is produced and used in the workplace in varying particle size fractions including fine (which is defined as all particle sizes collected by respirable particle sampling) and ultrafine or nanoparticles (defined as the fraction of respirable particles with a primary particle diameter of <0,1 µm [<100 nm]).

In 2011, NIOSH recommended separate RELs for ultrafine (nanoscale) and fine (microscale) titanium dioxide (TiO_2), i.e. 0,3 mg/m^3 for ultrafine TiO_2 and a REL of 2,4 mg/m^3 for fine-sized TiO_2 (8 h TWA respirable concentrations)[50]. These RELs were set at the 45-year working lifetime exposure concentration associated with a 1/1 000 excess risk of lung cancer (95 % lower confidence limit) estimated from nonlinear models of dose-response data from animal chronic inhalation bioassays of fine or ultrafine TiO_2. The rat-based risk estimates were extrapolated to humans by estimating an equivalent retained lung burden after a 45-year working lifetime, with adjustment for the differences in alveolar surface area in rats and humans and the use of human lung dosimetry modelling to account for interspecies differences in the long term clearance and retention of respirable particles. For both lung cancer and inflammation responses, ultrafine (nanoscale) TiO_2 was more potent on a mass basis than fine (microscale) TiO_2, which is the reason for the lower mass-based REL for ultrafine TiO_2[50]. Methodology used to derive this exposure limit is described in Clause 5 and further details can be found in A.11.

In 2013, the Japan Society for Occupational Health (JSOH) newly set the provisional OEL-M, 0,3 mg/m^3, for nanoparticles of titanium dioxide[51]. In addition AIST conducted subchronic inhalation studies using rats and derived OELs based on pulmonary inflammation end point. The OEL (PL) was determined to be 0,6 mg/m^3 (respirable dust, 8 h TWA, 15-year working period)[48]. Further details about derivation of this OEL can be found in A.7.

6.2.3 Fullerenes

Fullerenes are a form of spherical carbon structures. The AIST report[53] focuses on one fullerene configuration composed of 60 carbon atoms, C_{60}. Diameter of C_{60} is approximately 1 nm. C_{60} is a solid under normal temperature and pressure, and is commonly sold as a black powder. C_{60} is insoluble in water and other polar solvents, but can be dispersed in the form of agglomerates between 25 nm and 500 nm. It is soluble in organic aromatic solvents.

In 2011, fullerenes were mostly used as additives for resins used in glassware, bowling balls, a metal additive, a lubricant additive, and in cosmetics. Future applications may include resin additives for solar cell electrodes and fuel cell electrodes as well as pharmaceutical-related raw material such as for drug delivery. Fullerenes are also generated as bi-products in any combustion process of carbon-containing material.

Similar to CNTs and TiO_2, the AIST study used the inflammation end point and subchronic inhalation animal data. After taking into account uncertainty factors, the occupational exposure limit (period-limited) was set at 0,39 mg/m^3. Further details about derivation of this OEL can be found in A.7.

6.3 Evaluation of OEL methods

6.3.1 Similarities and differences

Presently most OELs for manufactured NOAAs are developed using standard risk assessment methods involving five steps:

a) evaluating the available data;

b) selecting the adverse response (non-reversible, clinically significant);

c) determining the critical dose (e.g. NOAEL or BMDL);

d) calculating the human equivalent dose (accounting for species-specific differences that affect the target tissue dose, e.g. ventilation rates and particle deposition and clearance kinetics);

e) determining the working lifetime exposure concentration that would result in that dose (including consideration of deposition, uptake, and clearance)[5][64].

Use of uncertainty factors is a simple, default approach often used to derive an OEL from a NOAEL in the absence of sufficient resources (information or expertise) to perform quantitative risk assessment with dose-response modelling and dosimetry-based extrapolation methods. Since human health effects data for manufactured nanomaterials are not available for risk assessments at this time, dose-response data in animals are used in the risk assessment analyses reviewed in this report.

Without a globally harmonized approach to OEL setting process, OELs established by different groups for the same manufactured NOAAs using traditional QRA methods even for the same toxicity data can vary by orders of magnitude. For example, recommended OELs for nano-TiO_2 include 0,017 mg/m^3[65], 0,3 mg/m^3[50] and 0,6 mg/m^3[48][49]. Such differences arise from differences in the interpretation of the supporting toxicity data, selection of health end points, and use of uncertainty and modifying factors[6]. Table 3 summarizes these differences for recommended OELs for TiO_2.

Table 3 — Parameters and uncertainty factors used in developing OELs for nanoscale TiO_2

Parameter/ uncertainty factor	Analysis and reference		
	Stone, et al. 2010[65] Christensen, et al., 2011[66]	Gamo 2011[48] Nakanishi 2011[49]	NIOSH 2011[50]
Health end point	Pulmonary inflammation	Pulmonary inflammation	Lung tumours
Level of risk	NOAEL	NOAEL	1/1 000 excess risk
Study data reference	Bermudez, et al. 2004[67]	Bermudez, et al. 2004[67]	Lee, et al. 1985;[68] Muhle, et al. 1991;[69] Heinrich, et al. 1995[70]
Rat effect level	0,5 mg/m^3	2 mg/m^3	0,044 m^2/g of lung[d]
Human (occupational) adjustment of rat effect level	0,5[a]	0,91[b]	Internal dose estimation
Human-equivalent effect level	0,25	1,82 mg/m^3	17 m^2 (per lung) (0,35 g per lung)[e]
Interspecies extrapolation	1,5 (UF)	3 (UF)[c]	Pulmonary surface area adjustment: 102 m^2 human; 0,4 m^2 rat (no UF)
Interspecies variation	5 (UF)	1 (UF)	95 % lower confidence limit estimate (no UF)
Exposure duration (subchronic to chronic)	2 (UF)	1 (UF)	45-year working lifetime (no UF)[f]
OEL (8 h TWA)	0,017 mg/m^3	0,61 mg/m^3	0,3 mg/m^3

[a] Adjusts for daily exposure duration (rat/human) and for human ventilation (in 8 h) at rest vs. light activity (work): (6 h/8 h) × (6,7 m^3/10 m^3)[65], based on ECHA 2008[71].

[b] Adjusts for the pulmonary deposited dose in rats and humans, based on the respiratory minute volume (RMV), time (T), deposition fraction (DF), per unit body weight (BW), in each species[49].

[c] Reference [49].

[d] Table 4-5 of NIOSH 2011;[50] benchmark dose estimate, 95 % lower confidence limit (BMDL) associated with 1/1 000 excess risk of lung cancer in rats, based on the dose-response model average (MA).

NOTE The value of 0,029 in Table 4-5 of NIOSH 2011[50] is not the correct value that was used to derive the human BMDL estimate in Table 4-6. The correct value is 0,044, which is the accelerated bias-corrected bootstrap estimate.

[e] Table 4-6 of NIOSH 2011;[50] the human-equivalent lung dose to the rat BMDL MA estimate (see footnote [d]) is calculated as follows: 0,044 m^2 TiO_2/g rat lung × 1,5 g [reference rat lung weight] × (102 m^2/0,4 m^2) [human/rat pulmonary surface area] = 17 m^2 TiO_2/lung [humans] (as described in 4.2.3 and 4.3.2.3); to obtain the human lung mass dose of ultrafine TiO_2 of 0,35 g, the TiO_2 surface area dose (m^2) is divided by the specific surface area of ultrafine TiO_2 (48 m^2/g).

[f] Table 4-6 of NIOSH 2011;[50] the recommended exposure concentration (REL) of 0,29 (rounded to 0,3) mg/m^3 for ultrafine TiO_2 is the 45-year working lifetime mean airborne exposure (8 h TWA concentration) associated with the human-equivalent retained lung dose at a 1/1 000 excess risk of lung cancer (95 % LCL estimate). The mean airborne exposure was estimated using the Multiple-Path Particle Deposition (MPPD) human model;[72] details in Reference [50].

6.3.2 Influence of methods on derived OEL values for nanomaterials

As shown in Table 3, OEL derivation methods for TiO_2 include a simple uncertainty factor approach;[65] [66] a combined dosimetry-based and uncertainty factor approach[48][49]; and quantitative risk assessment and dosimetry modelling methods[50]. In the first two analyses, a NOAEL for pulmonary inflammation is selected as the critical health end point from a subchronic (13 weeks) inhalation study in rats; however, the interpretation of which dose is the NOAEL differed in the analyses in References [65] and [66] and References [48] and [49]. The third analysis[50] used lung tumours as the

critical health end point. The first two analyses estimated a human-equivalent NOAEL, while the third analysis derived a risk-based exposure concentration (associated with 1/1 000 excess risk).

The first analysis simply adjusts the rat NOAEL by the difference in the daily exposure duration in rats vs. workers (6 h vs. 8 h) and the difference in a human resting vs. light work ventilation rate (6,7 m^3/8 h-d vs. 10 m^3/8 h-d)[65][66]. No dosimetry adjustments are made, and uncertainty factors are used for interspecies, intra-species, and exposure duration[65][66]. The second analysis includes dosimetry adjustments to account for differences in rat and human ventilation rates and particle size specific pulmonary deposition fraction of the inhaled dose; this dose is normalized to body weight[48][49]. No dosimetry adjustments are made to account for differences in the rat and human clearance and retention kinetics of the inhaled dose; and an uncertainty factor is used for interspecies (toxicokinetic) extrapolation[48][49].

The third analysis[50] uses quantitative modelling methods to describe the dose-response relationship in rats and to estimate the human-equivalent working lifetime exposure concentration. The dose-response modelling approach used to derive the REL was a three-model average of nonlinear models including multistage, Weibull, and log-probit (fit to the rat nonlinear dose-response data for lung tumours). The variability in the rat dose-response data was taken into account in the confidence interval estimates of the critical dose. The dose metric used in these analyses was the retained particle surface area dose in the lungs (estimated from the measured mass of TiO_2 and particle specific surface area) following chronic inhalation exposure to either fine or ultrafine TiO_2. A human lung dosimetry model was used to estimate the working lifetime mean exposure concentration associated with the human retained lung dose that is equivalent to the critical lung dose in rats (BMDL estimate). An assumption in this analysis is that humans would be equally sensitive to the rat at an equivalent retained lung dose. No uncertainty factors were used in the derivation of this risk-based REL.

Interestingly, the NIOSH dose-response modelling also used the same rat pulmonary inflammation data (Reference [67]) as used in the first two analyses[48][49][66][73], but different estimates were derived, resulting in a human-equivalent mean exposure of approximately 0,1 mg/m^3, which is the dose associated with minimal pulmonary inflammation [4 % increase in polymorphonuclear leukocytes (Table 4-3 of NIOSH 2011[50])]. This working lifetime exposure associated with pulmonary inflammation is lower than that associated with the estimated 1/1 000 risk of lung cancer — which is consistent with the evidence that TiO_2 is an indirect carcinogen acting through persistent pulmonary inflammation. In the third analysis[50], a major difference in methods compared to the first and second analyses[48][49][66][73] in Table 3 is that NIOSH used dosimetry modelling to account for differences in the long term particle retention kinetics in the lungs of rats and humans. The NIOSH REL is intended to minimize the risk of lung cancer in workers exposed to TiO_2 over a full working lifetime.

Despite the differences in the health end points and methods and assumptions in these three risk assessments, two of the three OELs are within a factor of two (0,3 mg/m^3 and 0,61 mg/m^3). These OELs would fall within a 0,1 mg/m^3 to 1 mg/m^3 control band, and thus the selection of workplace exposure controls may be similar based on each of those analyses. The third OEL is more than an order of magnitude lower and would indicate the need to use tighter containment and control options.

6.3.3 State of the science in support of risk assessment methods for nanomaterials OELs

Ideally, the best available scientific evidence and methods should be used to derive OELs. However, resource limitations may preclude a full quantitative risk assessment in every case, even if sufficient data are available. More often, data are limited and so simple default risk assessment methods will be needed for many NOAAs. The development of a framework in which full quantitative risk assessments are performed for selected benchmark (reference) particles within biological mode-of-action (MOA) categories, combined with simplified risk assessments and comparative analyses with NOAAs in the same category, may facilitate OEL development for NOAAs. Such an approach is described further in this document. Conceptual categories have been proposed as described in Clause 7, although more analyses involving structure-activity relationships based on physico-chemical properties of NOAAs will be needed to develop a reliable and predictive risk assessment framework.

7 Categorical OELs for nanomaterials

7.1 Summary of options proposed

7.1.1 United Kingdom

The BSI "Guide to safe handling and disposal of manufactured nanomaterials"[44] provides simple precautionary risk guidance in the form of a Public Document for the development, manufacture, and use of nanomaterials. In this document, all nanomaterials are grouped into four hazard categories with assigned Benchmark Exposure Levels (BEL). Similar to the IFA recommendations, BELs are described as "pragmatic guidance levels only" and are derived from OELs for larger particle forms "on the assumption that the hazard potential of the nanoparticle form is greater than the large particle form." First, there is the "fibrous" category, defined as an insoluble nanomaterial with a high aspect ratio (ratio >3:1 and length >5 000 nm), which is assigned a BEL of 0,01 f/cm^3 (one tenth of the asbestos OEL prescribed in the US and elsewhere). Second, there is the "CMAR" category, defined as any nanomaterial which is already classified in its larger particle form as a Carcinogenic, Mutagenic, Asthmagenic, or Reproductive toxicant. Nanomaterials in the CMAR category are assigned BELs at one tenth of the mass-based OEL for its larger particle form. Third, there is the "insoluble" category, defined as insoluble or poorly soluble nanomaterials not in the fibrous or CMAR category. Nanoparticles in this category are assigned BELs at one fifteenth of the mass-based OEL for its larger particle form or 20 000 p/cm^3. Fourth, there is a "soluble" category, defined as a soluble nanomaterial not in fibrous or CMAR category, which is assigned a BEL at one half of the mass-based OEL for its larger particle form.

7.1.2 Germany

7.1.2.1 Federal Ministry of Labour and Social Affairs

In the Announcement on Hazardous Substances 527 "Manufactured Nanomaterials" from May 2013 by the Federal Ministry of Labour and Social Affairs[46] in Germany, nanomaterials are grouped into four categories:

a) soluble nanomaterials;

b) biopersistent nanomaterials without specific toxicity (granular biopersistent nano-particles – nano-GBP);

c) biopersistent nanomaterials with specific toxicity;

d) biopersistent fibre-like nanomaterials.

Interestingly, concerning the **first category**, the terms soluble/insoluble or biopersistent are commonly used in particle toxicology but no exact definition or measurement method for these terms is at hand. Therefore as a proxy the solubility of nanomaterials in water is used and substances with a solubility less than 100 mg/l are coined "practically insoluble" and nanomaterials with solubility in water greater than 100 mg/l belong to the category of soluble nanomaterials. Fully aware of the discussions on the possible enhanced proliferation or changed pathways of soluble nanomaterials to different targets in the body, the advice has been given to perform the risk assessment for nanomaterials in this category per default in treating them like bulk materials and neglecting possible nano-related properties.

For the **second category** (nano-GBP), reference was made to the study by Gebel[74] comparing the carcinogenicity of GBP micromaterials (micro-GBP) and nano-GBP in chronic rat inhalation studies. Gebel concluded that the difference in carcinogenic potency between GBP nanomaterials and GBP micromaterials is low and can be described by a factor of 2 to 2,5 referring to the dose metric mass concentration. The statistical methods for pooling data across studies, such as in the Gebel[74] study, have been discussed[66][75][76].

In July 2011, the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the German Research Foundation proposed a reduced value of 0,3 mg/m^3 for a density of 1 kg/m^3[77] for the respirable dust fraction (GBP) of the general dust limit

value. This value is intended to prevent high concentrations of these dusts from having a carcinogenic effect. Aware of this proposal and the on-going discussion, the recommendation is given in the announcement 527 to correct for the slightly higher potency of nano-GBP by applying a factor of 1/2 on the current occupational exposure limit for respirable dust in Germany, which is 3 mg/m^3 for materials with a density of 2 500 kg/m^3. For the time being this would result in a limit value of 1,5 mg/m^3. As this was regarded too high a value in terms of particle number concentration, it was stated that the REL for nano-GBP should not exceed 0,5 mg/m^3 for a density of 2 500 kg/m^3, measured as the respirable dust fraction. It is highlighted that all other options to utilize REL for the risk management are still available for the companies. They may use the recommendations given by NIOSH or other organisations/companies, use the benchmark levels proposed by DGUV-IFA or set their own in-house standards.

Concerning the **third category** (biopersistent nanomaterials with a specific toxicity), reference is made to the handling of the bulk (non-nano) forms of these materials. With regard to existing OELs for most of these nanomaterials, it is stated that companies of course have to comply with the existing OELs. In Germany these OELs are usually below 0,1 mg/m^3. In fact, in the discussion on deriving exposure-risk relationships and the corresponding concentrations for carcinogenic metals or metal compounds, like cobalt or nickel, mass concentrations in the range of 0,000 1 mg/m^3 to 0,01 mg/m^3 are proposed. Announcement 527 states that in complying with OELs in this range of concentrations a strict regime of control measures with a high efficacy has to be employed and in the case of handling the nanomaterial a further discrimination of control measures is not feasible.

For materials belonging to the **fourth category** (biopersistent fibre-like nanomaterials), the distinction is made between biopersistent, rigid nanofibres adhering to the World Health Organization (WHO) fibre paradigm, for which one has to assume an asbestos-like effect, and biopersistent, entangled or spaghetti-like nanofibres. For the latter asbestos-like effects can only be excluded in the risk assessment, if the manufacturer or supplier of the given nanomaterial can provide evidence that the nanomaterial does not exhibit asbestos-like effects. Overall companies are strongly discouraged to use biopersistent, rigid nanofibres and a very strict regime of control measures has to be followed, if these materials are handled.

In conclusion, one can summarize Announcement 527 on “Manufactured Nanomaterials” in the way that at least for the time being and for the handling of the first, passive generation of nanomaterials these materials are mostly treated at the workplace like ordinary hazardous substances. The only exception being the evaluation of control measures for nano-GBP, as in this case a factor of 1/2 is applied to the respirable dust limit values may be used. The Announcement will be adapted if new evidence on toxicological properties of manufactured nanomaterials emerges or if future generations of active nanomaterials find its way to the workplace and pose new hazards.

7.1.2.2 German Social Accident Insurance

In Germany, the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA)[78] recommended the following benchmark limits to be used for an 8 h work shift and to be used for monitoring the effectiveness of protective measures in the workplace[78].

— For metals, metal oxides and other biopersistent granular nanomaterials with a density of >6 000 kg/m^3, a particle number concentration of 20 000 p/cm^3 in the range of measurement between 1 nm and 100 nm should not be exceeded.

— For biopersistent granular nanomaterials with a density below 6 000 kg/m^3, a particle number concentration of 40 000 p/cm^3 in the measured range between 1 nm and 100 nm should not be exceeded.

— For CNT for which no such manufacturer’s declaration is available, a provisional fibre concentration of 0,01 f/cm^3 should not be exceeded, based upon the exposure risk ratio for asbestos. It is recommended that only carbon nanotubes that have been tested for adverse health effects similar to those of asbestos (according to the manufacturer’s declaration) be used.

— For nanoscale liquid particles (such as fats, hydrocarbons, siloxanes), the applicable maximum workplace limit (MAK) or workplace limit (AGW) values should be employed owing to the absence of effects of solid particles.

These recommended benchmark limits are geared to minimizing the exposure in accordance with the state of the art in measurements. Since these limits are not based on observed health effects, a health risk may still exist for workers, even where these recommended limits are followed. Therefore, benchmark limits should not be confused with health-based OELs[78].

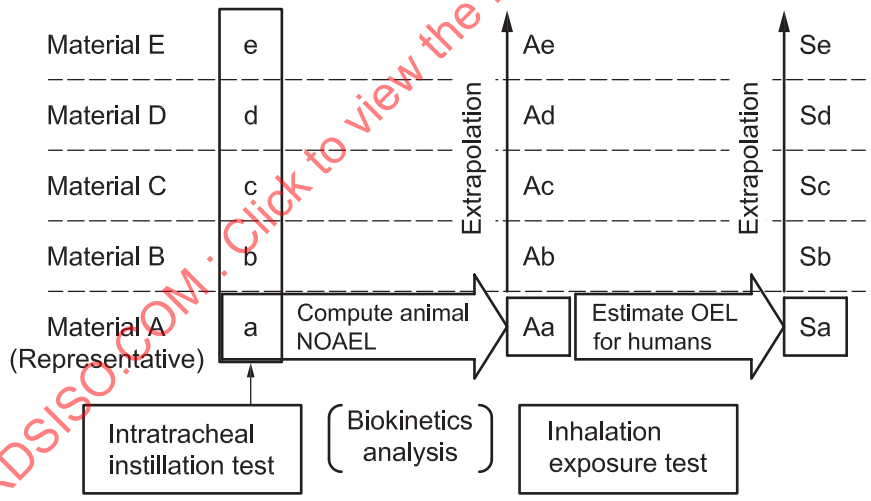
7.1.3 NIOSH

NIOSH has not formally proposed a categorical approach to developing OELs for nanomaterials, although efforts are underway to evaluate the available science and methodologies for developing categorical OELs or OEBs for nanomaterials (described in Reference [20]). In some respects, the NIOSH RELs for nanoscale titanium dioxide[50] and carbon nanotubes and nanofibres[58] are categorical since these RELs are intended to apply to various forms of these substances, which may include variability in their hazard potential.

7.1.4 Japan's (AIST's) approaches

7.1.4.1 Biaxial approach

Under a NEDO project (P06041) "Research and Development of Nanoparticle Characterization Methods", Nakanishi[55][79] adopted a method called the biaxial approach. Figure 2 shows a conceptual diagram of the biaxial approach.



NOTE See Reference [49].

Figure 2 — Biaxial approach

The idea was to fill up the whole diagram by conducting detailed examinations of the representative test samples along the horizontal axis, and obtained relative values of many nanomaterials through fairly simple tests on the vertical axis. On the horizontal axis, *in vivo* tests (intratracheal instillation and inhalation exposure tests) using rats, biokinetics and gene expression analyses were conducted, and the NOAELs regarding the inhalation exposure of rats were computed. Then, the knowledge accumulated thus far was used to extrapolate the extent of the effects on humans, i.e. OELs were derived. Meanwhile, along the vertical axis, Nakanishi, et al.[55][79] conducted as simple a test as possible to find out the values of the materials relative to one another, which was to determine harmful effect values and then the OEL of various materials. They had initially considered *in vitro* tests for the vertical axis tests, but they decided to use the intratracheal instillation method instead.

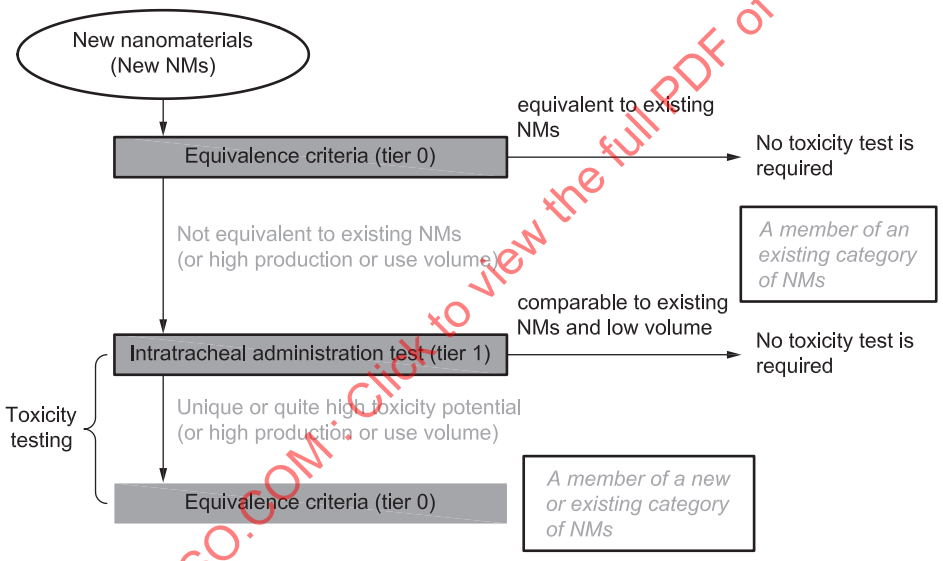
7.1.4.2 Equivalence criteria

The Ministry of Economy, Trade and Industry of Japan launched a five-year program for the "Development of Innovative methodology for Safety Assessment of Industrial Nanomaterials" in September 2011, which aims to develop fundamental hazard assessment methodology leading to a tiered risk assessment approach for industrial nanomaterials. The program has two R&D themes:

a) establishment of "equivalence criteria" of nanomaterials;

b) establishment of an intratracheal (IT) administration method as a low-cost and convenient method for hazard assessment to acquire basic hazard information, both of which are for regulatory purposes[80].

The Japanese National Institute of Advanced Industrial Science and Technology (AIST) is developing the "equivalence criteria" based on the data from a set of IT administration tests using nanomaterials with different physico-chemical properties such as size, surface area, shape, surface chemistry, composition, etc., when focusing on effects in the lungs. If the toxicity of nanomaterials is insensitive to a property, two nanomaterials can be regarded equivalent regardless of large difference in the property. On the other hand, if a property is found dominating toxicity, slight difference in the property would compromise equivalence between two nanomaterials. Figure 3 explains a possible use of "equivalence criteria" in an efficient hazard assessment framework of nanomaterials[80].



NOTE See http://metinanoen.aist-riss.jp/.

Figure 3 — Equivalence criteria used in an efficient hazard assessment framework of nanomaterials

7.1.4.3 Possible index of comparative potency of nanomaterials

The Japanese National Institute of Advanced Industrial Science and Technology (AIST) has selected the rate of increase in neutrophil in bronchoalveolar lavage fluid (BALF) as a biomarker indicating potency of pulmonary toxicity of nanomaterials. Nakanishi, et al.[49] further showed a future possibility that BET specific surface area, a physical property of nanomaterials, could be used as an index of comparative potency of nanomaterials.

7.1.5 OECD

OECD defines a categorical approach as follows. Chemicals whose physico-chemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of chemicals[27]. The assessment of chemicals by

using this category approach differs from the approach of assessing them on an individual basis, since the properties of the individual chemicals within a category are assessed on the basis of the evaluation of the category as a whole, rather than based on measured data for any one particular chemical alone. The increasing amount of toxicology data for NOAAs provides opportunities to develop criteria for hazard- and risk-categories for NOAAs[27][81][82][83].

The OECD Working Party on Manufactured Nanomaterials (WPMN) organized an expert meeting in September 2014 to further develop categorization approach for manufactured NOAAs and to provide recommendations on how manufactured NOAAs should be categorized for the purposes of testing, read across/Structure-Activity Relationship models, risk assessment and risk management[17]. It also analysed information collected by a questionnaire-based survey about OECD member countries' approaches to develop or use concepts of grouping, equivalence and read-across based on physico-chemical properties of NOAAs for their hazard assessment in regulatory regimes[84].

The OECD Working Party on Manufactured Nanomaterials expert meeting also discussed differences in hazard properties possibly arising from differences in shape (e.g. fibre, plate), physical properties (e.g. zeta potential, solubility) and bio-persistence and if this could be addressed in a categorization scheme.

7.2 Evaluation of categorical OEL

7.2.1 Similarities and differences

All approaches to derivation of categorical OEL presented in 7.1 are based on the anticipated primary mode of action and arrive at very similar categories and values of categorical OELs. They differ in details of category descriptions and scaling factors applied to OELs for corresponding bulk materials (see Table 4).

Table 4 — Comparison of categorical OELs

	BSI[44]	**BAuA**[46]	**IFA**[78]
Low toxicity immune effects			
Category description	insoluble or poorly soluble nanomaterials not in the fibrous or CMAR category	nanomaterials with density of 2 500 kg/m^3, measured as the respirable dust fraction	High Density: biopersistent granular nanomaterials with a density of >6 000 kg/m^3 Low Density: biopersistent granular nanomaterials with a density below 6 000 kg/m^3
Categorical OEL value	20 000 p/cm^3	1,5 mg/m^3 (0,5 mg/m^3 recommended)	0,1 mg/m^3 High Density: 20 000 p/ cm^3 Low Density: 40 000 p/cm^3
Scale factor for bulk OELs	0,067	0,5 (0,167 recommended)	0,333
Toxicity of dissolved ions/molecules			
Category description	soluble nanomaterial not in fibrous or CMAR category	nanomaterials with solubility in water greater than 100 mg/l	High Density: biopersistent granular nanomaterials with a density of >6 000 kg/m^3 Low Density: biopersistent granular nanomaterials with a density below 6 000 kg/m^3

Table 4 *(continued)*

	BSI[44]	BAuA[46]	IFA[78]
Categorical OEL value	based on bulk OEL	based on bulk OEL	0,1 mg/m^3 High Density 20 000 p/ cm^3 Low Density: 40 000 p/cm^3
Scale factor for bulk OELs	0,5	1	0,333
Frustrated phagocytosis from biopersistent rigid fibres			
Category description	insoluble nanomaterial with a high aspect ratio (ratio >3:1 and length >5 000 nm)	rigid nanofibres adhering to the World Health Organization (WHO) fibre paradigm	CNT untested for asbestos-like toxicity
Categorical OEL value	0,01 f/ cm^3	0,1 f/cm^3	0,01 f/cm^3
Scale factor for bulk OELs	1 (asbestos)	1 (asbestos)	1 (asbestos)
Specific toxicity/specific form			
Category description	nanomaterial which is already classified in its larger particle form as a Carcinogenic, Mutagenic, Asthmagenic, or Reproductive toxicant	nanomaterial which is already classified in its larger particle form for specific toxicity	liquid nanoparticles
Categorical OEL value	based on bulk OEL	<0,1 mg/m^3	based on bulk OEL
Scale factor for bulk OELs	0,1	1	1

Most variation in categorical OELs is observed for poorly soluble, low toxicity category (shown as "Low toxicity immune effects" category in Table 4). It is mostly due to the lack of consensus about best approaches for measuring exposures to these nanomaterials in the workplace at the time when these categorical OELs have been developed.

Organizations which derived these categorical OELs stated that they are not substantiated toxicologically. Therefore, even where they are observed, a health risk may still exist for workers and it is further recommended to maintain exposure levels below categorical OELs if feasible.

7.2.2 State of the science supporting categorical OELs

Presently, most approaches for categorical OELs are characterized by very broad categories of nanomaterials, which lump together materials with very different hazard properties and which are based more on the exposure measuring capabilities than on potential health outcomes. As such they come with a warning that they should not be regarded as safe OELs and that exposures should be minimized as much as possible. Rigid biopersistent nanofibres falling into the WHO definition for fibre paradigm is the only better defined consensus category of nanomaterials. Asbestos OEL based on fibre count is recommended for this category as a protective measure although challenges with measuring the number concentration of nanofibres in workplace air remain.

Exposure measurement challenges that exist for individual OELs can carry over to categorical OELs for the same types of materials (with similar physico-chemical properties). Additional measurement challenges may apply to ENMs. For example, individual nanoscale-diameter CNTs would not be visible by phase contrast microscopy (PCM), which has a resolution limit of approximately 0,25 µm diameter. Existing OELs for asbestos rely on PCM methods for airborne exposure measurement. Asbestos OELs (e.g. the U.S. OSHA PEL) apply to structures of length >5 µm, with length:width aspect ratio of 3:1, counted by PCM[24].

Another challenge with fibre-shaped nanomaterials (e.g. CNTs) is a measure of rigidity, which has been associated with differences in the inflammatory and carcinogenic properties of CNTs[85][86]. Long, rigid CNTs induced inflammation with asbestos-like pathogenicity, while entangled CNTs were less

potent (reviewed in Reference [85]). The rigidity of MWCNTs can be estimated by ISO/TS 11888[87]. The Technical Specification provides methods for the characterization of mesoscopic shape factors of MWCNTs, including sample preparation procedures. In particular, it provides a statistical method for characterizing MWCNTs produced by the CVD method. During MWCNT synthesis, axial structures are not perfectly linear but include permanent bend points. ISO/TS 11888 provides methods for determining a statistical quantity, representing a maximum straight length that is not deformed by permanent bending called the "static bending persistence length" (SBPL). The SBPL gives information regarding the relationship between the MWCNT mesoscopic shape and size.

As knowledge about hazard properties of nanomaterials further develops it can be expected that the approach for categorical OELs will be refined and will shift towards narrower categories of nanomaterials. Examples of such categories are NIOSH and OECD approaches described in 7.1. These approaches could be based on comparing potency of the NOAA to a benchmark (reference) particle in the same mode-of-action category. For example the "parallelogram" approach[30][31][88] could be used to extrapolate animal data for the NOAA to human hazards and to assign the NOAA to the appropriate categorical OEL[20]. A reliance on short-term animal experiments could move us towards rapid toxicological profiling for a large variety of NOAAs. Such experimental systems and data analysis methods need to be validated before they can replace traditional OELs. Categorical OELs or OEBs, based on best available information from other materials in that biological and physico-chemical category, can be useful to provide initial exposure limit estimates. The BSI guidance is an early example of four broad categories of nanomaterials, each associated with a "pragmatic guidance level"[44]. Such schemes could be refined as the nanotoxicology data increase to become sufficient for the development and validation of evidence-based models (e.g. QSAR) that are predictive of the hazard and risk of a nanomaterial. In the meantime, as the state of the science remains limited for the development of individual OELs for NOAAs, hazard and control banding schemes are being used to fill the gap. Some hazard band approaches include OEBs (range of exposures) associated with the hazard (nature and severity of adverse effect).

8 OEBs and control banding for nanomaterials

8.1 Overview of current hazard and control banding schemes

Hazard and control banding have been used for many years to make decisions on workplace exposure controls when OELs are not available and to support hazard communication labelling, for chemicals in general (HSE[9], GHS[23], OSHA[89]) and more recently for NOAAs (ISO/TS 12901-2, ANSES[90], CB nanotool[91], Stoffenmanager Nano[92], reviewed in Brouwer[93]). Control banding is a pragmatic tool that can be used to identify the types of engineering controls and performance capabilities to achieve the specified levels (e.g. order-of-magnitude bands) of exposure control. The typical control banding framework is a matrix consisting of hazard bands and exposure potential bands to indicate the appropriate control band for a chemical substance given its properties and production/use (Table 5). In this example of the ISO control banding scheme for NOAAs (Table 5), CBs 1-3 include general, local, or enclosed ventilation (CB 1, 2, or 3, respectively) or full containment options (CB 4 or 5).

Table 5 — Control band matrix with hazard and exposure potential bands (EBs)

		Exposure band			
		EB1	**EB2**	**EB3**	**EB4**
Hazard band	**A**	CB1	CB1	CB1	CB2
	B	CB1	CB1	CB2	CB3
	C	CB2	CB3	CB3	CB4
	D	CB3	CB4	CB4	CB5
	E	CB4	CB5	CB5	CB5
NOTE See ISO/TS 12901-2.					

Some control banding systems for NOAAs have a score-based hazard band allocation system that utilizes information on the physico-chemical properties of the nanomaterial (and its parent or bulk form) along with expert judgment on what is known about the hazard potential given those properties

(CB Nanotool[41][42] and Stoffenmanager Nano[92]). Other hazard banding schemes have associated order-of-magnitude occupational exposure concentration ranges; see Table 5 (HSE[9], ANSES[90] and ISO/TS 12901-2), although these concentration ranges were not necessarily derived specifically for NOAAs. OEBs are a general term for these concentration ranges. OEBs and OELs should not be confused with exposure potential bands (EBs). OEBs and OELs indicate the levels of exposure that are considered to be adequate to prevent adverse effects in workers and/or that are technically feasible to achieve. EBs are qualitative descriptors of potential exposure levels based on the factors that influence exposure, such as the propensity of the material to become airborne (dustiness), the type of process, and amount of material being handled[3].

NIOSH is currently evaluating the scientific evidence including nanotoxicology studies for use in developing categorical OELs or OEBs for NOAAs (5.1)[16]. In addition, NIOSH is developing and evaluating a general hazard banding framework which involves a systematic and tiered approach to hazard band/OEB allocation of chemical substances; this approach is also being evaluated for its applicability to nanomaterials[16].

One of the first approaches to hazard banding was proposed by Henry and Schaper[7] based on acute inhalation data in rats (airborne concentration of gases/vapours or dust/fumes/mists associated with 50 % lethality in 1 h). Naumann, et al.[8] also proposed order-of-magnitude bands, called performance-based exposure control limits (PB-ECLs), which link the engineering performance bands to the health effects data and uses the most protective health end point for banding a chemical. Their scheme expresses potency as the mass dose/day, and severity as a qualitative range of acute and/or chronic effects (none, slight, moderate, severe). Their classification scheme is similar to those by Henry and Schaper[7], EEC[94] and ANSI[95], which were developed to support hazard communication labelling. Each of these control banding schemes include a hazard banding scheme with up to four or five hazard groups. Brooke[96] shows the alignment of order-of-magnitude exposure bands with five hazard bands (A-E) and the associated R-phrases. The HSE COSHH Essentials[9] hazard banding approach is based on that by Brooke[96] and is extended to include the more recent H-statements. ISO/TS 12901-2 and ANSES[90] control banding schemes use a hazard band allocation based on the HSE[9] hazard/OEB groups and the GHS[23] hazard classes. All of these control banding schemes use the common matrix approach of aligning the hazard band/OEB with the exposure or emission potential band to identify the appropriate control band.

Key areas of uncertainty include the applicability of the order-of-magnitude OEBs to NOAAs and how the emission potential relates to actual worker exposures. Important research needs include evaluating the effectiveness of these general approaches to assessing the hazards and exposures in specific job tasks and workplaces using nanomaterials.

8.1.1 Comparison of hazard bands and OEBs as applied to inhaled NOAAs

A summary of published hazard banding schemes is provided for selected acute and chronic health end points in Table 6. This summary is provided to facilitate comparison of key qualitative and quantitative elements of each scheme, with a focus on inhalation exposures. (Original references should be consulted for information on the full range of adverse health end points and routes of exposures.) These hazard and OEB schemes have common elements as well as some differences. Each scheme includes qualitative descriptors of the level of severity of a hazard based (usually in rats). Some schemes provide both qualitative and quantitative indicators of severity. ISO hazard allocation scheme (ISO/TS 12901-2:2014, Table 1) has several elements in common with other hazard banding schemes, as shown in Table 6 for acute and chronic end points that are relevant to inhalation hazards.

Table 6 — Hazard and occupational exposure band (OEB) schemes for inhaled dusts, fumes, or mists: Acute and chronic effects (selected)

Reference	Hazard bands and OEBs				
ISO/TS 12901-2:2014[3], **Table 1** **ANSES 2010, Annex 2**[90]	**Category A** No significant risk to health	**Category B** Slight hazard — Slightly toxic	**Category C** Moderate hazard	**Category D** Serious hazard	**Category E** Severe hazard
OEL (8 h TWA) (mg/m^3)	1 to 10	0,1 to 1	0,01 to 0,1	<0,01	Seek specialist advice[a]
Acute toxicity: Rat LC50 inhalation 4 h (mg/m^3) (converted from mg/l). Aerosols/particles.	>5000	1 000 to 5 000	250 to 1 000	<250	—
Likelihood of chronic effects (e.g. systemic)	Unlikely	Unlikely	Possible STOT RE 2	Probable STOT RE 2	
Adverse effects by inhalation, 90 d, 6 h/d (mg/m^3) (converted from mg/l). Aerosols/particles[a]			<200	<20	
GHS[23]; **OSHA**[89] [b]	**Category 5**	**Category 4**	**Category 3** Exclamation mark — Warning	**Category 2** Health hazard — Warning	**Category 1** Health hazard — Danger
Acute toxicity: Rat LC50 inhalation 4 h (mg/m^3) (converted from mg/l). Dusts and mists.	[c] Warning: May be harmful if inhaled	5 000 Warning: Harmful if inhaled	1 000 Danger: Toxic if inhaled	500 Danger: Fatal if inhaled	50 Danger: Fatal if inhaled
STOT-SE: Rat inhalation 4 h single exposure (mg/m^3) (converted from mg/l). Dust, mist, fume.				1 000 < STOT-SE < 5 000	<1 000
STOT-RE Rat inhalation 6 h/d repeated exposure (mg/m^3) (converted from mg/l). Dust, mist, fume.				20 to 200 Warning: May cause damage to organs through prolonged or repeated exposure	<20 Danger: Causes damage to organs through prolonged or repeated exposure
HSE COSHH Essentials (Table 3)[9]	**Hazard Group A**	**Hazard Group B**	**Hazard Group C**	**Hazard Group D**	**Hazard Group E**
Concentration range (mg/m^3)[d]	1 to 10	0,1 to 1	0,01 to 0,1	<0,01	—
Brooke (Table 1)[96]	**Hazard Band A**	**Hazard Band B**	**Hazard Band C**	**Hazard Band D**	**Hazard Band E**
Target airborne concentration range (mg/m^3)	>1 to 10	>0,1 to 1	>0,01 to 0,1	<0,01	Seek specialist advice
Key R-phrase[e]			Harmful: R48/20	Toxic: R48/23	
Repeated exposure: Rat inhalation 6 h/d for at least 90 d (mg/m^3) (converted from mg/l)			25 to 250	<25	

Table 6 *(continued)*

Naumann, et al. (Table 1)[8][f]	**PB-ECL 1**	**PB-ECL 2**	**PB-ECL 3**	**PB-ECL 4**	**PB-ECL 5**
"Typical" OEL (8 h TWA) (mg/m^3)	>1	0,1 to 1	0,001 to 0,1	<0,001	
Acute effects potency (mg/m^3) (converted from mg/d, assuming humans and occupational air intake of 10 m^3/d)	>10	>1 to 10	>0,01 to 1	<0,01	<0,01
Severity of acute effects	Low	Low/Moderate	Moderate	Moderate/ High	High
Severity of chronic effects	None	None	Slight	Moderate	Severe
Henry and Schaper (Tables I and XI)[7][g]	**Hazard 0** Minimal	**Hazard 1** Slight	**Hazard 2** Moderate	**Hazard 3** Serious	**Hazard 4** Severe
Acute health hazard criteria: Rat LC50 inhalation 1 h (mg/m^3) (converted from mg/l). Dusts, fumes, mists.	>200 000	>20 000 to <200 000	>2 000 to <20 000	>200 to <2 000	>0 to <200

[a] Listed in ANSES[90], not ISO/TS 12901-2[3].

[b] GHS[23] information is from Tables 3.1.1 and 3.1.3 (acute toxicity); Figure 3.8.1, Table 3.8.1, and Table 3.8.3 (STOT-SE); Figure 3.9.1, Table 3.9.1, 3.9.2, and 3.9.3 (STOT-RE). OSHA[89] criteria are essentially the same, except that only Categories 1 through 4 are used; see Table A.1.1 (acute toxicity); Table A.8.1 (single dose); Tables A.9.1 and A.9.2 (90-day study)[89].

NOTE GHS[23] and OSHA[89] do not include OEBs. Comparison of the animal exposure concentrations across schemes suggests that Categories 2 and 1 of GHS[23] and OSHA[89] would align, respectively, with Categories C and D of ISO/TS 12901-2, HSE[9] and Brooke[96].

[c] GHS[23]includes a Category 5 for substances with relatively low acute toxicity; LD50 in range of 2 000 mg/kg to 5 000 mg/kg BW or equivalent for inhalation.

[d] See Table 3 of Reference [9] for specific R-phrases and H-statements that are used to assign hazard group; allocation based on Brooke[96]. Hazard group E with "—" indicates that no airborne concentration can be found to provide adequate control[9].

[e] The EU CLP Regulation [Regulation (EC) No 1272/2008] phases in the use of H phrases instead of R-phrases, in most cases. The deadline for transition from R to H was 1 June 2015.

[f] PB-ECL: performance-based exposure control limit.

[g] Safety and Health Index System (SHIS).

For example, the HSE[9] COSHH Essentials hazard allocation (banding) scheme provides the same order-of-magnitude exposure concentration ranges for groups A through D, as well as the absence of an exposure concentration for Group E. HSE[9] states that the groups with exposure concentration indicates that exposures could be identified as providing adequate control given the hazards identified in Groups A to D; Group E is intended for serious health hazards, where no appropriate airborne range could be identified[9]. COSHH Essentials utilizes "risk (R) phrases" and "hazard (H) statements" to assign groups. A list of R- and H-phrases used in COSHH Essentials and their associated hazard band assignments are provided in Appendix 3 of HSE[9]. Several of the toxicity databases provide the R-phrases or H-statements for chemical substances generally and for NOAAs or their parent materials, e.g. (CEC[97], Annex VI); and GESTIS[98]. In concept, the use of H-statements or R-phrases should be applicable to NOAAs. This is because the hazard phrases describe the adverse health effects that may occur to specific organs from exposure to chemical substances by various routes of exposure. However, uncertainty exists as to whether the data on which hazard phrases were derived for chemically similar materials are also applicable to NOAAs. Further evaluation is needed to determine if the use of general hazard banding schemes would result in the appropriate hazard bands and OEBs for NOAAs.

For acute toxicity, the GHS[23] hazard categories 4 through 1 are based on animal data that are numerically similar to HSE[9] and ISO/TS 12901-2 hazard categories A through D. That is, the ISO/HSE categories and GHS categories are in reverse order of each other. Category E and category 1 are the

highest hazard categories for the ISO/HSE and the GHS hazard banding systems, respectively. GHS category 5 (lowest toxicity) does not appear to have a comparable HSE[9] or ISO/TS 12901-2 category (i.e. the GHS categories in Table 5 would be shifted to the left by one category). The OSHA[89] scheme is essentially the same as the GHS[23] scheme, but OSHA[89] uses only hazard categories of 4 through 1. Other adverse health end points are categorized differently. For example, a chemical is categorized according to "specific target organ toxicity with repeated exposure (STOT-RE)" in hazard band A or B for unlikely, C for possible, and D for probable chronic adverse health effects[3][90] (Table 6).

Much of the quantitative data used in these general hazard banding schemes is based on acute exposure (typically LC50 for inhalation). However, little information is available on acute effects for nanomaterials, in part because of the decreased use of animal testing and a greater emphasis on earlier (more sensitive) adverse health end points. As such, a refinement of the general hazard banding schemes may be needed to capture the dose-response relationships observed in current toxicology studies of NOAAs, including for the earlier-stage adverse end points (e.g. pulmonary inflammation and early-stage fibrosis, which may not yet be associated with functional changes but could be with chronic exposure to the biopersistent NOAA). As discussed in 8.3, the exposure concentration criteria for STOT-RE band C or D (≤200 or ≤20 mg/m^3 in a 90 d animal study) may not be particularly relevant for NOAAs. It is also of interest that the exposure concentration criteria for hazard banding based on acute toxicity/lethality have decreased since the early hazard banding system of Henry and Schaper[7] compared to the more recent GHS[23] and related systems (Table 6).

8.1.2 ISO hazard banding scheme for NOAAs

The ISO hazard group allocation scheme (ISO/TS 12901-2:2014, Table 1) refers to the International Labour Organization Control Banding Toolkit (Table 2 of Reference [99]) and the GHS health hazard classification[23]. The ISO hazard banding uses a decision tree approach, as described in ISO/TS 12901-2:2014, 7.2.2 and illustrated in ISO/TS 12901-2:2014, Figure 2. The derived hazard band is used in control banding for NOAAs[3].

A summary of the hazard banding steps for NOAAs (ISO/TS 12901-2:2014, 7.2) is as follows.

— Question 1: Has the NOAA already been classified and labelled according to national or region legislation or GHS?

  — If yes, assign the NOAA to the corresponding hazard band.

  — If no, or if labelling is based on lack of information, go to next question.

— Question 2: Is the NOAA solubility in water higher than 0,1 g/l?

  — If yes, evaluate the NOAA as a classical chemical hazard using a general hazard banding scheme.

  — If no, go to next question.

— Question 3: Does the NOAA contain biopersistent fibres or fibre-like structures [defined as rigid fibre with length (L) >5 µm, diameter (d) <3 µm, and L/d ratio of >3]?

  — If yes, assign to hazard band E.

  — If no, go to next question.

— Question 4: Are there hazardous indications for the NOAA?

  — Question 4a: Do screening tests indicate carcinogenicity, mutagenicity, reproductive toxicity, or sensitivity by inhalation (CMRS) properties?

    — If yes, assign to hazard band E.

- If no, go to next question.

- Question 4b: Are comprehensive hazard data available for the NOAA?
  - If yes, assign to most protective hazard band (starting with E), according to toxicological data.
  - If no, go to next question.

- Question 5: Is there a hazard band for the bulk material or an analogous material?
  - If yes, and the bulk hazard band is A, then assign the NOAA to hazard band A; if yes, and the bulk hazard band is B, C, or D, then add one band and assign the NOAA to hazard band C, D, or E.
  - If no, assign to hazard band E.

As described, the ISO hazard banding process is heavily dependent on the general hazard banding schemes. Specific data on NOAA hazard (Question 4) are evaluated according to the hazard banding criteria. Data on the bulk material are also used with the addition of one band (i.e. exposure is reduced by an order of magnitude).

8.2 Case studies on banding NOAAs

It is instructive to evaluate a set of NOAAs for how they would be assessed for hazard according to ISO/TS 12901-2 and related schemes. This evaluation shows that the acute toxicity criteria of <50 mg/m^3 or <250 mg/m^3 (GHS[23] and ISO/TS 12901-2, respectively; Table 6) to band NOAAs may have limited utility for hazard allocation and control banding since most acute *in vivo* studies use much lower concentrations. For example, an acute inhalation toxicity study of silver nanoparticles[100] reported no adverse effects in rats following a 4 h inhalation exposure to silver nanoparticles at the highest exposure concentration of 750 µg/m^3. This highest exposure concentration of <1 mg/m^3 silver nanoparticles is substantially below the lowest exposure concentration values of 50 mg/m^3 to 250 mg/m^3 used for acute toxicity hazard allocation in ISO/TS 12901-2, GHS[23] and other hazard banding schemes. Thus, the Sung, et al.[100] study exposures are not informative with regard to evaluating silver nanoparticles according to ISO/TS 12901-2 and GHS[23] acute toxicity criteria; and those criteria may be too broad and nonspecific to adequately identify and distinguish acute toxicity hazards for NOAAs.

Table 7 lists NOAAs for which OELs have been developed along with the associated hazard band and OEB based on STOT-RE. The proposed OELs for CNTs range from 1 µg/m^3 to 50 µg/m^3. Thus, depending on which OEL is used, CNT could be placed in either hazard category C (moderate hazard) or hazard category D (serious hazard) according to ISO/TS 12901-2 and related schemes. In addition, according to ISO/TS 12901-2 hazard banding decision logic, if the CNT material contains rigid fibres (a free standing fibre in collected samples would appear in electron-microscopic images as a straight fibre with L >5 µm, d <3 µm, L/d ratio >3), this material would be considered as a material whose toxicity is driven by the fibre paradigm and allocated to the highest hazard band (E, severe hazard), unless toxicological data provide evidence that it is not the case.

Proposed OELs for fullerene also differ substantially, with an associated hazard band of either B or D depending on the method used to derive the OEL. The EU methods for estimating human indicative no-effect levels (INELs) for workers as used by Aschberger, et al. 2010[56] tend to result in lower OELs than those based on several other hazard and risk assessment methods (Table 7).

Table 7 — Hazard category associated with NOAA OEL or as derived based on animal studies

NOAA	OEL (µg/m³)	References	Associated OEB (mg/m³) (ISO/TS 12901-2)	Associated hazard category (ISO/TS 12901-2)	Derived hazard category (ISO/TS 12901-2)[a]
Titanium dioxide (ultrafine)	610	Gamo 2011[48]; Nakanishi 2011[49]	0,1 to 1	B	D
	300	NIOSH 2011[50]; JSOH 2013[51]	0,1 to 1	B	D[b]
	17	Aschberger, et al. 2011[52]	0,01 to 0,1	C	D
Fullerene (C_{60})	390	Shinohara 2011[53]; Nakanishi 2011[49]	0,1 to 1	B	D
	7,4	Aschberger, et al. 2011[52]	0,001 to 0,01	D	D
MWCNT (Baytubes®) CNT MWCNT CNT and CNF	50	Pauluhn 2010[54]	0,01 to 0,1	C	D
	30	Nakanishi 2011[55]	0,01 to 0,1	C	D
	1 to 2	Aschberger, et al. 2010[52]; Aschberger, et al. 2011[56]; Nanocyl 2009[57]	<0,01	D	D
	1	NIOSH 2013[58]	<0,01	D	D
Silver (nano particles)	0,33 to 0,67	Aschberger, et al. 2011[56]	<0,01	D	D

[a] Based on comparison of the NOAEL or LOAEL exposure concentrations (see text) used to derive the OELs to the repeated exposure concentration criteria (<25 mg/m³) in Brooke[96].

[b] Category 2 carcinogen.

The OELs in Table 7 were derived from animal (rat) studies of inhaled (or instilled) NOAAs, with exposure durations of a few days to two years. The no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) reported in these studies include the following:

a) Fullerene (C_{60}):

   — NOAEL: 3,1 mg/m³ (Shinohara, et al. 2011[53]; estimated from intratracheal instillation in rats);

   — NOAEL: 2,22 mg/m³ (Aschberger, et al. 2010[56], citing Baker, et al. [2008], inhalation in rats, 3 h/d for 10 days);

b) MWCNT:

   — NOAEL: 0,1 mg/m³ (Pauluhn 2010[54]; rat 13-wk inhalation, 6 h/d);

   — LOAEL: 0,1 mg/m³ (Ma-Hock, et al. 2009[101]; rat 13 wk inhalation, 6 h/d);

c) TiO_2:

   — LOAEL (cancer): 10 mg/m³ (only concentration) in Heinrich, et al. 1995[69]; rat 2-year inhalation, 18 h/d);

d) Silver nanoparticles:

   — LOAEL (reduced lung function): 0,049 mg/m³ (Aschberger, et al. 2011[52], citing Sung, et al. [2008]);

   — LOAEL (other effects): 0,133 mg/m³ (Aschberger, et al. 2011[52], citing Sung, et al. [2009]).

These animal effect levels (NOAEL or LOAEL) are all low mass concentrations compared to the lowest repeated exposure (STOT-RE) criteria (<20 mg/m^3 or <25 mg/m^3) for assigning a substance to Hazard Category D[9][90][96] or Category 1[3][89]. Those repeated exposure criteria are for dusts, mists, or fumes in general (not for NOAAs specifically, although some studies may have included nanoscale particles). The severity of the effects may also differ in the studies used to develop the STOT-RE criteria compared to the studies used to develop OELs for NOAAs. If these NOAA NOAELs or LOAELs from the rat studies are compared to STOT-RE criteria, the result would be to assign each of these NOAAs to a Hazard Category D and an OEB of <0,01 mg/m^3 (8 h TWA)[3][9][90][96].

In summary, this evaluation indicates that the current hazard banding schemes (including ISO, ANSES, GHS, OSHA, and COSHH) may be too broad and nonspecific to accurately group the hazards of NOAAs in terms of the acute and chronic adverse health end points data from nanotoxicology studies. Some of these early-stage adverse health effects have been used in developing OELs for NOAAs, yet all of these effect levels are substantially lower on a mass basis than the lowest effect levels in the current hazard banding schemes. The acute and chronic hazard banding criteria resulted in the allocation of a hazard band D (serious hazard) and the associated OEB (<0,01 mg/m^3) for all NOAAs evaluated. Thus, the application of hazard banding in this example resulted in equal or greater protection compared to the proposed OELs for these NOAAs.

8.3 Evaluation of the evidence for initial (default) OEBs for categories of NOAAs

8.3.1 Categorical analyses and read-across

Several OEL and OEB approaches discuss the use of read-across to fill data gaps and to derive OEL or OEB estimates for data-poor substances using toxicity data from a similar substance with sufficient data[27][102]. Both qualitative and quantitative read-across approaches are available[27].

A provisional OEL could be derived by direct read-across with a similar substance, although the inherent variability and uncertainty may not be well known. The derivation of an OEB based on analogy/read-across from data on a similar substance may be more applicable to the pragmatic purpose of selecting and evaluating occupational exposure controls. That is, given the order-of-magnitude exposure bands based on performance of engineering control options, a certain level of uncertainty in the hazard estimates for NOAAs need not preclude decision-making using a control banding scheme. In other words, despite the wide variety of physico-chemical properties of NOAAs, the exposure control options are more limited, e.g. four or five groups based on order-of-magnitude performance criteria[8]. Although data may be insufficient to develop a substance-specific OEL, information may be sufficient to derive an initial hazard band or OEB for use in control banding.

Broad hazard categories that have been suggested by several agencies or researchers include: soluble, poorly-soluble low toxicity, poorly-soluble high toxicity, and fibrous particles (BSI[44], Kuempel[20], BAuA[46], IFA[78]). This MOA-based framework is illustrated in Table 8. Example hazard/OEB allocations of three NOAAs in Table 8 (ultrafine TiO_2, CNT/CNF, and silver) are based on the US. NIOSH recommended exposure limits (RELs) for those materials[24][50][58]. The REL for soluble and insoluble silver is 0,01 mg/m^3 (which would fall into category C of ISO/TS 12901-2 hazard banding scheme); however, since that REL is not specific to NOAA, silver NOAA is placed into the next higher hazard category D (<0,01 mg/m^3) according to ISO/TS 12901-2 criteria. The severity of adverse health end points associated with repeated or chronic exposure to these three substances varies from relatively benign argyria (pigmentation of skin) in workers to pulmonary inflammation, fibrosis and lung cancer in rats or mice.

In the current example, the description of category D (serious hazard) for both silver nanoparticles and CNT/CNF in the same hazard/OEB category could be confusing given the different adverse health end points. In addition, the REL for ultrafine TiO_2 of 0,3 µg/m^3, which places it in category B (0,1 mg/m^3 to 1 mg/m^3) may be difficult to understand since it is based on lung cancer, a severe chronic adverse health effect. Yet, the NIOSH REL was set at an exposure concentration that would have a relatively low probability (95 % lower confidence limit of a 1/1 000 excess risk) of lung cancer if a worker is exposed at the REL for up to a 45-year working lifetime. (In contrast, the acute toxicity criteria in ISO, GHS and other hazard banding schemes are based on the LC50, or the exposure concentration associated with 50 % lethality in rats.) These examples illustrate that clear descriptions of the adverse effects and other

key data and information on which the hazard band/OEB allocation is made are essential to providing consistent and transparent information for risk management decision-making. The goal of the hazard band/OEB allocation is to identify an exposure concentration expected not to be associated with significant risk of any adverse health effects.

Additional research and data analysis needs include obtaining relevant dose-response data for a number of other NOAAs that fall into the main four MOA/PC property categories. Combined analyses of dose-response relationships as modified by variations in the PC properties can then be evaluated to determine the need for sub-categories based on end point and/or potency. The more data that are obtained from a standard set of assays and end points, the greater the robustness of the categorical OEL/OEB estimates. Statistical models and methods will be needed that can accommodate mixed dose-response relationships and account for variability and heterogeneity in data from multiple assays, end points, and experimental conditions (e.g. Wang, et al. 2014[103]).

Table 8 — Alignment of ISO/TS 12901-2 hazard banding framework and broad MOA categories[20][44][46][78], with examples of NOAAs based on NIOSH-recommended exposure limits to prevent adverse lung or systemic responses given chronic inhalation exposures[a]

	Hazard and Occupational Exposure Bands				
	Category A No significant risk to health	**Category B** Slight hazard — Slightly toxic	**Category C** Moderate hazard	**Category D** Serious hazard	**Category E** Severe hazard
OEL (8 h TWA) (mg/m^3)	1 to 10	0,1 to 1	0,01 to 0,1	<0,01	—
MOA and PC category	**Example NOAAs**				
Higher solubility	—	—	—	Silver (UF)	—
Poorly-soluble lower toxicity	—	UF TiO_2	—	—	—
Poorly-soluble higher toxicity	—	—	—	—	—
Fibrous	—	—	—	CNT/CNF	—

[a] Adverse end points include argyria in humans (silver), pulmonary fibrosis and inflammation in rats and mice (CNT/CNF) and lung cancer in rats (UF TiO_2)[24][50][58].

8.3.2 Utility of *in vitro* data in OEL/OEB development for NOAAs

Given the limited data available for many substances used in the workplace, including high production volume chemicals, pharmaceuticals, and NOAAs, the use of *in vitro* data for screening hazard assessments and prioritization of substances for tiered toxicology testing has been proposed (e.g. ToxCast, NexGen) [45][104].

The use of *in vitro* data to fill data gaps for new pharmaceutical substances has been proposed by Maier[105] using a parallelogram approach[31][32]. In this approach, a provisional OEL is estimated for an unstudied compound that has structure-activity similarity to a data-rich compound with available in vitro and *in vivo* data and an OEL value. In applying such methods to nanomaterials, the *in vitro* test system, toxicity end points, and test article concentrations should be carefully selected for relevance to the anticipated hazards and workplace exposures of the nanomaterial(s) being evaluated (Gordon, et al.[6]).

Several studies have shown good concordance of the relative hazard of metal oxide and other NOAAs in *in vitro* and *in vivo* assays of inflammation responses[106][107][108]. However, other studies show wide variability of *in vitro* and *in vivo* results across experimental assays and laboratories[109][110].

Standardized and validated *in vitro* assays can provide mechanistic data and information on which to develop QSAR models to describe the relationship between the dose of a substance and the biological response given the physico-chemical properties. QSAR models using *in vitro* data have been used to classify or cluster metal oxide nanomaterials into bioactivity groups[111][112][113]. The use of *in vitro*

dose-response data to estimate critical effect levels (e.g. BMD, vs. NOAEL or LOAEL) has been proposed, using methods similar to those used for *in vivo* data[114]. Such quantitative analyses could provide the basis for evaluating the evidence for possible hazard subcategories, where the relationship between member substances can be described by a set of predictors PC properties in addition to dose.

CNT/CNF is an example of a category of NOAAs within the fibrous MOA group for which sufficient data (including *in vitro* data) may be available to evaluate the relative hazard of various types of substances within this category of NOAAs. Recent studies have reported wide differences in the pulmonary inflammatory responses based on surface functionalization, including reduced inflammatory and fibrogenic responses to various types of CNT[115][116][117] or to TiO_2 nanospheres and nanobelts[118]. The influence of these differences relative to other sources of variability and uncertainty in the risk assessment process has not yet been evaluated.

While more research needs to be done, *in vitro* assays may be capable of predicting acute *in vivo* responses (i.e. within 24 h of exposure). For example, acute assays may be useful for highly reactive substances. In addition, several recent studies have shown correlation between the activation of the NLRP3 inflammasome and pro-fibrogenic end points *in vitro* or fibrosis *in vivo* associated with exposure to CNT[115][116][117][119][120]. An *in vitro* study in human lung small airway epithelial cells showed distinct patterns of CNT neoplastic-like transformation compared to asbestos[121]. Thus, some *in vitro* assays may be useful for initial screening of NOAAs to determine whether further testing is necessary.

In summary, several recent nanotoxicology studies provide specific examples of good concordance of acute *in vitro* and *in vivo* inflammatory responses to carbon and metal nanomaterials. In addition, some *in vitro* assays may be useful as screening assays for potential chronic effects of pulmonary fibrosis and neoplastic lesions from occupational inhalation exposure to NOAAs. Validation of these findings would provide support for using *in vitro* data from validated assays to fill gaps in the hazard data needed to derive OELs or OEBs.

8.3.3 Options for deriving an OEL or OEB for NOAAs

Based on the current state of the science, the options available to derive OELs or OEBs for nanomaterials include the following:

a) use OEL developed for specific NOAA or group of NOAAs, if available (e.g. Table 7);

b) use qualitative or quantitative read-across from the OEL of a similar substance to the NOAA (e.g. benchmark particles);[20][27]

c) derive an OEB for NOAA based on the OEL or OEB for the bulk material (i.e. add one hazard band; see ISO/TS 12901-2);

d) derive an initial OEB for NOAA based on screening data (e.g. *in vitro*); see 8.3.2.

Weight of evidence evaluation is generally regarded as the preferred approach to making hazard determinations[27][102][122]. Standard data quality criteria should be applied to such evaluations (e.g. as cited in OECD 2007[27]). Current databases available to evaluate the hazard of general chemical substances, including NOAAs, include the following: EPA Integrated Risk Information System (IRIS) [123]; the Commission of the European Communities, Annex XI[97] and the German GESTIS database[98]. The purpose of this document is to describe and evaluate the state-of-the-art in available data and methods for developing OELs or OEBs for NOAAs. Ultimately, the best available evidence should be used to evaluate the hazard and risk of occupational exposure to NOAAs and to support risk management decision-making, which includes the selection of effective exposure controls.

9 Feasibility considerations in the OEL and OEB setting process

Development and use of OELs and OEBs are intertwined with available risk management measures to maintain acceptable level of risk. Often, the determination of an OEL involves consideration of both the health effects data and the technological feasibility of measuring and controlling exposures at or below that concentration. Regulatory OELs also consider economic feasibility. As with other occupational

hazards, recommending an OEL for a specific NOAA may be contingent on having adequate health effect information, an appropriate sampling and analytical method, and the ability to control exposures at the OEL[5].

Annex A
(informative)

Standard processes for OEL setting

A.1 Overview

A.1.1 Purpose

The purpose of this annex is to provide an overview of the scientific methods, policies, and procedures of authoritative agencies worldwide that develop occupational exposure limits. These include procedures of both regulatory and non-regulatory governmental agencies as well as nongovernmental industrial hygiene associations utilized internationally. The countries represented are those that volunteered to provide a description. By describing the similarities and differences in these processes, it is intended that this chapter may facilitate the understanding and harmonization of the scientific evidence basis for developing OELs and OEBs for NOAAs.

A.1.2 OEL types and adjustment models

A.1.2.1 Time weighted average (TWA) exposure limit

A TWA exposure limit is the average airborne concentration of a particular substance permitted over a certain period of work usually expressed as a total number of hours per day. These are the most common types of exposure limits.

It is preferable to keep exposure levels continually below the TWA exposure limit. In practice, the actual concentration of an airborne contaminant arising from a particular process may fluctuate significantly with time. However, during periods of continuous daily exposure to an airborne contaminant, the TWA exposure limit allows short-term excursions above the exposure limit provided they are compensated for by extended periods of exposure below the limit during the working day. The TWA exposure does not allow exceedance of ceiling limits during the working day.

In cases when work shifts exceed 8 h, TWA limits can be adjusted using several models described in A.1.2.4, A.1.2.5 and A.1.2.6. For work shifts shorter than 8 h, TWA limits are not adjusted[124].

A.1.2.2 Short-term exposure limit (STEL)

A STEL is the time-weighted maximum average airborne concentration of a particular substance permitted over a short period of time (usually 15 min).

Some substances or mixtures can cause intolerable irritation or other acute effects upon brief exposure, although the primary toxic effects may occur with long term exposure through accumulation of the substance or mixture in the body or through gradual health impairment with repeated exposures.

The STEL provides limits only for the control of short-term exposure. STELs are important supplements to the TWA exposure limits which are more concerned with the total intake over long periods of time. Generally, STELs are established to minimize the risk of

— intolerable irritation,

— irreversible tissue change, and

— narcosis to an extent that could precipitate workplace incidents.

STELs are recommended where there is evidence that adverse health effects can be caused by high short-term exposure.

A STEL should not be exceeded at any time during a working day even if the TWA average is within the TWA exposure limit.

A.1.2.3 Peak/ceiling limits

Peak or ceiling exposure limits are a maximum or peak airborne concentration of a particular substance determined over the shortest analytically practicable period of time.

For some rapidly acting substances and mixtures the averaging of the airborne concentration over a workday period is not appropriate. These substances may induce acute effects after relatively brief exposure to high concentrations, so the exposure standard for these substances represents a maximum or peak concentration to which workers may be exposed. A peak exposure limit should not be exceeded at any time.

A.1.2.4 Brief and Scala model for adjusting TWA limits

The TWA limit is based on the number of hours worked per 24 h day and the period of time between exposures. This model is intended to ensure the daily dose of the toxicant under an altered work shift is below that for a conventional shift to take account of the reduced time for elimination, i.e. recovery time between exposures.

The Brief and Scala model is recommended for calculating adjustments to exposure limits. This model is preferred because it

— is simple to use,

— takes into account both increased hours of exposure and decreased exposure free time, and

— is more conservative than other models.

$$\text{Adjusted exposure limit (TWA)} = \frac{8 \times (24 - h) \times \text{exposure limit (8-hour TWA)}}{16 \times h} \quad \text{(A.1)}$$

where h = hours worked per day.

The Brief and Scala model is based on a 40 h work week. Formula (A.1) takes into account both the period of exposure and period of recovery.

A.1.2.5 Pharmacokinetic models for adjusting TWA limits

There are several different pharmacokinetic models available. These are suitable for application to exposure standards based on accumulated body burden. These models take into account the expected behaviour of the hazardous substance in the body based on knowledge of the properties of the substance. These models use information such as the biological half-life of a substance and exposure time to predict body burden. The use of pharmacokinetic models can be complicated by the lack of biological half-lives for many substances.

The most widely used pharmacokinetic model is the Hickey and Reist model which requires knowledge of the substance's biological half-life, the hours worked per day and hours worked per week. The Hickey and Reist model like other pharmacokinetic models assumes the body is one compartment, i.e. a homogeneous mass.

Pharmacokinetic models are less conservative than the Brief and Scala model, usually recommending smaller reductions of the exposure limit. While pharmacokinetic models are theoretically more exact than other models, their lack of conservatism may not allow adequately for the unknown adverse effects on the body from night work or extended shifts that may affect how well the body metabolises and eliminates the substance.

A.1.2.6 Quebec model for adjusting TWA limits

The Quebec Model developed by the Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail (IRSST) uses the most recent toxicological data to assign substances into categories. Depending on the category assigned, a recommendation is made that

— no adjustment is made to the exposure limit,

— a daily or weekly adjustment, or

— the most conservative of the daily or weekly adjustments where both apply.

The Quebec model is supported by a comprehensive technical guide and a selection tool to assist in determining the most appropriate adjustment category.

A.2 Australia

A.2.1 Regulatory exposure limits

A.2.1.1 Legislation, organization and processes

In Australia, an exposure standard means a *workplace exposure standard* listed in the *Workplace Exposure Standards for Airborne Contaminants*[125]. Australia's model Work Health and Safety (WHS) Regulations, requires that exposure standards representing the airborne concentration of a particular substance or mixture are not exceeded.

There are exposure standards for 644 substances and mixtures in Australia. There are, however, many other substances and mixtures hazardous to human health and used in workplaces that do not have a mandatory exposure standard established. Currently exposure standards are not updated regularly and may not always reflect the latest research or state of knowledge on the hazardous effects of chemicals. Exposure standards do not identify a dividing line between a healthy or unhealthy working environment. Natural biological variation and the range of individual susceptibilities mean some people may experience adverse health effects below the exposure standard. In addition in some cases, workplace exposure standards are set based on consideration of both health effects and also what is achievable in practice. Exposure standards establish a statutory maximum upper limit[125].

Exposure standards in Australia are not designed to be applied to situations outside of a workplace or to the exposure of people, like bystanders or nearby residents, not directly engaged in the work involving the hazardous chemical. However, the model Work Health and Safety (WHS) Act also requires a Person Conducting a Business or Undertaking (PCBU) to minimize risk to third parties. This is regardless of whether an exposure standard has been established or not. The WHS Regulations require that the primary focus should always be on eliminating or, if this is not possible, minimizing risk through use of exposure controls.

The exposure standards represent airborne concentrations of individual chemical substances which, according to current knowledge, should neither impair the health of nor cause undue discomfort to nearly all workers. Under Australia's federal system, the workplace exposure standards have legal status when they are specifically incorporated into Commonwealth, State or Territory legislation. In recommending appropriate exposure standards, Safe Work Australia and its predecessors have been guided by the standards and experience of a number of Australian and overseas organizations.

In the many cases where there is no mandatory exposure standard established in Australia, other established exposure standards or action levels can be used by PCBUs and occupational hygienists to assist minimizing exposure to chemicals.

A.2.1.2 Science and methods for OEL setting

Many of the adopted exposure standards have been obtained from the American Conference of Governmental Industrial Hygienists' list of threshold limit values. These values have been considered

by Safe Work Australia and its predecessors and those found to be acceptable were adopted. A small number of exposure standards were also taken from a list maintained by Great Britain's Health and Safety Executive. A small number of substances were also reviewed in detail by an Exposure Standards Working Group and appropriate values assigned.

The *Guidance on the Interpretation of Workplace Exposure Standards for Airborne Contaminants*[125] notes that the Brief and Scala Model, the Pharmacokinetic Model of Hickey and Reist and the Quebec Model all provide valid methods for adjusting exposure standards, the main difference is the degree of conservatism. It further notes that use of adjustment models other than the Brief and Scala model should only be done by an appropriately qualified health and safety professional as the use of other models requires a sound understanding of the toxicology and pharmacokinetics of the substance, as well as the rationale for setting the exposure standard.

A.2.1.3 Occupational health risk assessment policies

In Australia, TWA exposure limits are calculated over an 8 h working day and a 5 d working week. Australian regulations require that these limits are not exceeded. In addition, a process is not considered to be under reasonable control if short-term exposures exceed three times the 8 h TWA exposure limit for more than a total of 30 min per 8 h working day, or if a single short-term value exceeds 5 times the 8 h TWA exposure limit.

Australia also has STELs. Exposures at the STEL should not be longer than 15 min and not be repeated more than four times per day. There should be at least 60 min between successive exposures at the STEL.

In exposure standards, the airborne concentrations of gases, vapours and particulate contaminants are expressed as mass concentrations (mg/m^3). For gases and vapours the concentration is usually indicated in parts per million by volume. Where both gravimetric and volumetric values are quoted, the volumetric (ppm) value is exact as its value is not affected by changes in temperature or pressure and should be used as the common means of reference to the exposure standard[125].

As the gravimetric units of mg/m^3 are affected by temperature and pressure variations, all exposure standards are expressed relative to standard conditions of 25 °C and 1 atmosphere pressure (101,3 kPa).

Formula (A.2) is used to convert from ppm to mg/m^3:

$$\text{Concentration (mg/m}^3) = \frac{\text{molecular weight} \times \text{concentration (ppm)}}{24,4} \quad \text{(A.2)}$$

where 24,4 is the standard molar volume in litres at 25 °C and 101,3 kPa.

A.2.1.4 NOAA-specific OELs

Engineered, or manufactured, nanomaterials are particles that have at least one dimension between approximately 1 nm and 100 nm, and are manufactured to have specific properties or composition.

While there are hundreds of manufactured nanomaterials in existence, there are currently only two Australian exposure standards relating to specific nanomaterials. The Workplace Exposure Standard for carbon black is 3 mg/m^3 (8 h TWA, inhalable) and the Workplace Exposure Standard for amorphous silica is 2 mg/m^3 (8 h TWA, respirable).

In general terms it is recommended that exposure to nanomaterials should be eliminated or minimized so far as reasonably practicable through containment of materials, local exhaust ventilation (LEV) and work processes.

A.2.2 Non-regulatory exposure limits

There are currently no exposure limits set under this category in Australia.

A.3 Canada

A.3.1 Legislation, organization and processes

A.3.1.1 General

Canadian autonomous regions have different occupational health and safety (OH&S) legislation, which are applied according to the province, territory or federal jurisdiction.

There are 14 jurisdictions in Canada, one federal, 10 provincial and three territorial, each having its own occupational health and safety legislation. Federal legislation covers employees of the federal government and Crown agencies and corporations that operate across provincial or international borders (such as airports, banks, railways, telecommunications) regardless of the workplace's location within Canada.

OH&S legislation in Canada outlines the general rights and responsibilities of the employer, the supervisor and the worker.

Federally, the health and safety legislation includes the Canada Labour Code (CLC) Part II and Canada Occupational Health and Safety Regulations (COHS).

In each province or territory, there is an act (typically called the Occupational Health and Safety Act or similar) which applies to most workplaces in that region. The Act usually applies to all workplaces except private homes where work is done by the owner, occupant or servants. Generally, it does not apply to farming operations unless made to do so by a specific regulation. The specific jurisdiction should be consulted to find out who is or is not covered.

At the provincial and territorial level, the name of the government department responsible for occupational health and safety varies with each jurisdiction. Usually it is called a ministry or department of labour. In some jurisdictions, it is a workers' compensation board or commission that has the responsibility for occupational health and safety. Each provincial or territorial department is responsible for the administration and enforcement of its occupational health and safety act and regulations[126].

A.3.1.2 Common legislation

There is "right-to-know" legislation that applies to hazardous products. It comprises several pieces of legislation and is known as WHMIS (the Workplace Hazardous Materials Information System). WHMIS applies in all Canadian workplaces which are covered by occupational health and safety legislation and where hazardous products controlled by WHMIS are used.

All Canadian occupational health and safety legislation have a common clause known as the "General Duty Clause" which requires that an employer provides a safe and healthy workplace. As it is the jurisdiction's inspectors who enforce health and safety legislation, it is expected that each jurisdiction would enforce legislation when protecting workers from exposure to nanomaterials.

A.3.1.3 Occupational exposure limits (OELs)

A.3.1.3.1 Canada (Federally legislated workplaces)

The OELs that apply to employees covered by the Canada Labour Code are the ACGIH® TLVs® and BEIs® for 1994-1995, "as amended from time to time", which are referenced in section 10.19 (1) (a) of the Canada Occupational Health and Safety Regulations (SOR/86-304 as amended) made under the Canada Labour Code Part II (R.S.C. 1985, c. L-2). The OELs are not listed in the regulations so the current ACGIH TLV and BEI should be consulted for specific limits.

The 1986-1987 TLVs of the ACGIH have been adopted for the purposes of the following federal regulations:

— On Board Trains Occupational Safety and Health Regulations [s. 7.20(1)];

— Oil and Gas Occupational Safety and Health Regulations [s. 11.23(1)].

A.3.1.3.2 Alberta

In Alberta, OELs are described in Part 4 "Chemical Hazards, Biological Hazards and Harmful Substances" (Sections 16 to 20) of the Occupational Health and Safety Code[127]. Substances are listed in Schedule 1, Table 2. Substances and processes requiring a code of practice are outlined in Section 26 and listed in Table 1.

If no OEL is established for a harmful substance present at a work site, the code requires that an employer ensures that a worker's exposure to that substance is kept as low as reasonably achievable.

A.3.1.3.3 British Columbia

In British Columbia, Part 5 and Section 5.48 reference current ACGIH values except where otherwise determined the board in the Occupational Health and Safety Regulations (B.C. 296/97) made under the Workers' Compensation Act (R.S.B.C. 1979, c 437).

A.3.1.3.4 Manitoba

In Manitoba, the OELs are referenced in Section 36.5 of the Workplace Safety and Health Regulation (Man. Reg. 217/2006) which is made under the Workplace Safety and Health Act (R.S.M. 1987, c W210). When available, employers are expected to establish OELs that do not exceed ACGIH TLVs. Importantly, there is a requirement for employers, in some circumstances, to set their own occupational exposure limit to ensure workers are not exposed to health hazards.

A.3.1.3.5 New Brunswick

In New Brunswick, the term "threshold limit value" is defined in Section 2 of the New Brunswick General Regulations and it specifically references the 1997 ACGIH TLVs in the Regulations (N.B. Reg. 91-191) made under their Occupational Health and Safety Act (S.N.B. 1983, c. O-0.2). The ACGIH TLVs are indirectly referenced in Section 24 "Air Contaminants" of the Regulations. There are some exceptions such as the threshold limit value for lead sulphide in Section 23.1 and in a code of practice for working with material containing asbestos regulations made under their Act.

A.3.1.3.6 Newfoundland and Labrador

In Newfoundland and Labrador, the ACGIH TLVs established "annually or more often" (i.e. the most recent edition) are referenced in Section 42 of the Occupational Health and Safety Regulations, 2012 (N.L.R. 5/09) made under the Occupational Health and Safety Act (R.S.N.L. 1990, c. O-3). There are also a number of sections specific to silica, asbestos, lead, etc.

A.3.1.3.7 Northwest Territories

In the Northwest Territories, Section 1 of the General Safety Regulations (R.R.N.W.T. 1990, c. S-1) made under the Safety Act (R.S.N.W.T. 1988, c. S-1) defines "contaminant" and makes specific reference to OELs as set out in Tables 2 and 3 within Schedule A. There are also specific regulations for silica sandblasting and asbestos.

A.3.1.3.8 Nova Scotia

In Nova Scotia, the latest edition of the ACGIH TLVs is referenced, but again, not listed in Part 2 of the Workplace Health and Safety Regulations (N.S. Reg. 52/2013) made under the Occupational Health and

Safety Act. The ACGIH TLVs for 1976 and its subsequent amendments or revisions are referenced in Section 4 of the Occupational Health Regulations (N.S. Reg. 112/76), made under the same Act. There are Codes of Practice for asbestos and lead under the Act.

A.3.1.3.9 Nunavut Territory

Unless specified, Nunavut territory follows the corresponding legislation from the Northwest Territories.

A.3.1.3.10 Ontario

In Ontario, the OELs are listed in Section 4 of the Regulation respecting the Control of Exposure to Biological or Chemical Agents (Ont. Reg. 833) under the Occupational Health and Safety Act (R.S.O. 1990, c.O.1). The Ontario Table contains the Ontario OELs; the ACGIH TLVs are to be applied if an agent is not listed in the Ontario Table.

There are also exposure limits in some of the Designated Substances Regulation (O. Reg. 490/09). These regulations are made under the Occupational Health and Safety Act as well.

A.3.1.3.11 Prince Edward Island

In PEI, ACGIH TLVs and BEIs for "1985-86, with (annual update)", are referenced, not listed, in Section 11.3 of the Occupational Health and Safety Act General Regulations (E.C. 180/87) made under the Occupational Health and Safety Act (R.S.P.E.I. 1988, c. O-1.01).

A.3.1.3.12 Quebec

In Quebec, permissible exposure values for gases, dusts, fumes, vapours or mists in the work environment are referenced in Section 41 and are listed in Schedule I of the Quebec Regulation respecting occupational health and safety (O.C. 885-2001) made under the Act Respecting Occupational Health and Safety (R.S.Q. c. S-2.1).

A.3.1.3.13 Saskatchewan

In Saskatchewan, contamination limits that act as TLVs (8 hour average and 15 minute average contamination limits) are listed for a number of chemicals in Table 21 of the Saskatchewan Occupational Health and Safety Regulations, 1996. This table is referenced in Sections 307, 309 and 346(f) of the Regulations. The Regulations are made under the Occupational Health and Safety Act (S.S. 1993, c. O-1).

A.3.1.3.14 Yukon Territory

In the Yukon, Section 27 "Air Contaminants" refers to Tables 8 to 15 which lists permissible concentrations in the Occupational Health Regulations (Yukon O.I.C. 1986/164) made under the Occupational Health and Safety Act (R.S.Y. 2002, c. 159).

Canadian legislation referencing OELs is summarized in Table A.1.

Table A.1 — Summary of Canadian OEL Legislation

Jurisdiction	Legislation Referencing OELs	Reference ACGIH® TLVs®?	Values located in
Canada (Federal)	Canada Occupational Health and Safety Regulations (SOR/86–304 as amended) *Section 10.19 (1) (a)*	Yes	ACGIH TLV booklet
Alberta	Occupational Health and Safety Code (2009) *Sections 16–20* *If no OEL established, the Code requires that employer keeps worker exposure as low as reasonably achievable.*	No	Schedule 1, Table 2
British Columbia	Occupational Health and Safety Regulations (B.C. 296/97) *Part 5*	Yes	Section 5.48
Manitoba	Workplace Safety and Health Regulation (Man. Reg. 217/2006) *Section 36.5* *The regulations require that employer sets OELs – TLVs (if available) are maximum unless reasons to set lower (process, etc.)*	Yes	ACGIH TLV booklet
New Brunswick	New Brunswick General Regulations (N.B. Reg. 91–191) *Section 23.1–24.1*	Yes	1997 ACGIH TLV booklet
Newfoundland and Labrador	Occupational Health and Safety Regulations, 2012 (N.L.R. 5/09) *Section 42; additional sections for silica, asbestos, lead*	Yes	ACGIH TLV booklet
Northwest Territories	General Safety Regulations (R.R.N.W.T. 1990, c. S-1) *Section 1 (defines "contaminant")*	No	Schedule A, Table 2
Nova Scotia	Workplace Health and Safety Regulations (N.S. Reg. 52/2013) *Part 2*	Yes	ACGIH TLV booklet
Nunavut	General Safety Regulations (R.R.N.W.T. 1990, c. S-1) *Section 1 (defines "contaminant")*	No	Schedule A, Table 2
Ontario	Regulation respecting the Control of Exposure to Biological or Chemical Agents (Ont. Reg. 833) *Section 4* *Additional regulations for asbestos and designated substances*	Yes (partial)	Ontario Table (check 1st) 2011 ACGIH TLV booklet (check 2nd)
Prince Edward Island	Occupational Health and Safety Act Regulations (E.C. 180/87) *Section 11.3*	Yes	ACGIH TLV booklet

Table A.1 *(continued)*

Jurisdiction	Legislation Referencing OELs	Reference ACGIH® TLVs®?	Values located in
Quebec	Regulation respecting occupational health and safety (O.C. 885–2001) *Section 41*	No	Schedule I
Saskatchewan	Occupational Health and Safety Regulations, 1996 *Sections 307, 309, 346(f)*	No	Table 21
Yukon	Occupational Health Regulations (Yukon O.I.C. 1986/164) *Section 27*	No	Tables 8–15

A.3.2 NOAA-specific OELs

Currently, there are no specific OEL for engineered nanomaterial nor has any province indicated to date, that they are planning to develop any OEL in this area.

A.4 European Union

A.4.1 General

The European Union (EU) has legislation at community level, i.e. addressed to the 28 member states, which have to implement and enforce the legislation. EU legislation is accessible and searchable on the web[128].

Occupational exposure is addressed in EU legislation relevant for health, safety and environment and is covered by several legislative areas, such as worker protection, chemicals and legislation addressing specific product groups; within each area there are then a number of legal acts addressing different issues. Occupational safety is addressed in two main ways:

a) by legal acts that specifically cover the working environment as is the case, for example for Council Directive 89/391/EEC "Safety and health of workers at work"[129], or

b) by legislation addressing safety in general, including safety at work, for example the Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)[97] that addresses safety of chemicals.

Table A.2 gives an overview of the most relevant legislation; the information in the table is not exhaustive, and the user/reader should always consult the European Union database on EU legislation[128] to ensure that the most recently amended legislation is used. Furthermore, the European Agency on Safety and Health at work (EU-OSHA) has a website where a collection of relevant information is available[130].

Table A.2 — Main legislation addressing occupational exposure, either directly or through evaluation of worker exposure

Framework for safety and health of workers at work: Council Directive 89/391/EEC	Directive 89/655/EEC Minimum safety and health requirements for the use of work equipment by workers at work[131] Directive 89/656/EEC Minimum health and safety requirements for the use by workers of personal protective equipment at the workplace[132] Directive 98/24/EC Protection of the health and safety of workers from the risks related to chemical agents at work[133] Directive 1999/92/EC Improving the safety and health protection of workers potentially at risk from explosive atmospheres[134] Directive 2004/37/EC Protection of workers from the risks related to exposure to carcinogens or mutagens at work[135]
Framework for chemicals: Council Directive 67/548/EEC amended by Directive 2006/121/EC[136]	Directive 2006/121/EC of the European Parliament and of the Council of 18 December 2006 amending Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances in order to adapt it to Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) and establishing a European Chemicals Agency[136] REACH. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC[97] GHS. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006[137] Test methods. Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH)[138]
Specific use of chemicals	Regulationo (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC[139] Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products[140]

Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work[133] is important for setting OELs. It is aimed at controlling and reducing occupational exposure risks, which is achieved, among others, by establishing indicative and binding OEL values, as well as biological limit values for specific substances. The term "Occupational Exposure Limit value" is defined in the Directive, Article 2(d), as "… the limit of the time-weighted average of the concentration of a chemical agent in the air within the breathing zone of a worker in relation to a specified reference period." Also the term "Biological limit value" is defined as "… the limit of the concentration in the appropriate biological medium of the relevant agent, its metabolite, or an indicator effect." Thus, OELs concern the concentration of the chemical in the air inhaled by workers and the biological limit is an internal dose of a chemical or its metabolite for which the route of entry is not defined (so it may be oral, dermal and/or inhalation).

OEL values developed within Directive 98/24/EC are given as 8 h TWA for airborne concentrations and/or as a STEL of 15 m. Directive 98/24/EC has been amended by three directives that lists the specific substances for which limits values have been agreed;[141][142][143] limit values directly relevant for manufactured nanomaterials are currently available for amorphous silica[141] and silver[142].

The directives addressing health and safety at work introduce minimum requirements, e.g. by setting binding exposure limit ceilings, which are incorporated into national legislation. In addition, EU member states are entitled to include additional or more stringent provisions for the protection of workers, e.g. lower occupational exposure limits than the EU ceiling. Therefore, it is important to check the specific legislation in each member state addressing the use of dangerous substances in the workplace.

Candidate priority substances for setting an EU-wide OEL are selected, taking the following criteria into account: epidemiological evidence (including reported cases of ill-health at the place of work); availability of toxicological data and the severity of effects; the number of persons exposed; and the availability of data on exposure and of measurement methods.

The EU wide OELs are set by the Scientific Committee on Occupational Exposure Limit Values (SCOEL), which was set up by Commission Decision No. 95/320/EC[144] with the mandate to advise the European Commission on occupational exposure limits for chemicals in the workplace. It prepares scientific recommendations for the Commission, which are used to underpin regulatory proposals on Occupational Exposure Limit Values (OELVs) for chemicals in the workplace. The draft recommendations from SCOEL undergo a stakeholder consultation to allow interested parties to submit health-based scientific comments and further data. The SCOEL is composed of a maximum of 21 members, acting as independent scientific experts, selected from candidates proposed by the EU Member States and appointed by the Commission.

Under the REACH legislation a Derived No-Effect Level (DNEL) and, for certain groups of substances, a Derived Minimum Exposure Level (DMEL) are two key concepts. The DNEL is defined as the level of exposure to a substance above which humans should not be exposed. For certain substances, e.g. carcinogens, it is not possible to set a DNEL, and then a DMEL is set. The DMEL values represent exposure levels where the likelihood that the identified adverse effect occurs in a population is sufficiently low to be of no concern.

With respect to the derivation of DNEL(s), REACH (Annex I, 1.4.1) specifies that:

"(a) DNEL(s) shall be established for the substance, reflecting the likely route(s), duration and frequency of exposure. For some endpoints, especially mutagenicity and carcinogenicity, the available information may not enable a threshold, and therefore a DNEL, to be established. If justified by the exposure pattern(s), a single DNEL may be sufficient. However, taking into account the available information and, where available, the exposure scenario(s) in Section 9 of the chemical safety report it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans liable to exposure indirectly via the environment) and possibly for certain vulnerable subpopulations (e.g. children, pregnant women) and for different routes of exposure. A full justification shall be given specifying, *inter alia*, the choice of the information used, the route of exposure (oral, dermal, inhalation) and the duration and frequency of exposure to the substance for which the DNEL is valid. If more than one route of exposure is likely to occur, then a DNEL shall be established for each route of exposure and as appropriate, also combined exposure through different routes needs to be addressed…"

Manufacturers and importers of chemical substances are required to calculate DNELs for their Chemical Safety Assessment (CSA) for chemicals used in quantities of 10 tonnes or more per year and publish the DNEL both in the manufacturer's Chemical Safety Report (CSR) and, for hazard communication, in an extended Safety Data Sheet. The European Chemicals Agency has developed extensive guidance on developing DNELs and these should be consulted at ECHA's home page[145]. Especially relevant are the REACH guidance documents "Guidance on information requirements and chemical safety assessment. Chapter R.14: Occupational exposure estimation"[146] and "Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health"[71].

The REACH frequently asked questions has the following question "If there is a derived no effect level and an occupational exposure limit, which one should be used?", with the answer:

"How far you are obliged to adhere to the occupational exposure limit depends on your national occupational health and safety legislation. When the occupational exposure limit is a binding limit, you should always adhere to this limit. If the derived no effect level for the same route and duration of exposure is lower than the occupational exposure limit and if this results in more stringent conditions and risk management measures, you should adhere to the more stringent conditions and risk management measures as communicated in the exposure scenario with the workers safety data sheet. You should also comply with the lower derived no effect level to ensure safe use. In case of doubt, you may also contact the national authority or your supplier. In many cases the occupational exposure limit will only pertain to inhalation exposure. In that case the conditions and risk management measures for dermal exposure in the exposure scenario, that are derived from the derived no effect level for dermal exposure, should be adhered to in order to ensure safe use in case of dermal exposure."

A.4.2 EU agencies, committees and advisory bodies

In addition to the legislation relevant for manufactured nanomaterials and SCOEL, there are a number of EU committees and advisory bodies that may be consulted on nanomaterials and these are

— the standing Advisory Committee on Safety and Health at Work (ACSHW) that advises on worker protection legislation,

— the European Agency for Safety and Health at Work (EU-OSHA), and

— the Scientific Committee on Emerging and Newly Identified Health and environmental Risks (SCENIHR).

The standing Advisory Committee on Safety and Health at Work[147] has been set up to assist the Commission in the preparation and implementation of decisions taken in the field of safety and health at work and to facilitate cooperation between national administrations, trade unions and employers' organizations.

The European Agency for Safety and Health at Work supports the EU policy to achieve measurable improvements of the working conditions and a reduction of occupational accidents and diseases. In addition to the implementation of the legislation at workplace level, monitored by the member states, EU-OSHA promotes a variety of other instruments, such as social dialogue, good practices, awareness raising, corporate social responsibility, economic incentives and mainstreaming. These activities are, of course, also relevant for manufactured nanomaterials.

The Scientific Committee on Emerging and Newly Identified Health and environmental Risks is available for consultation on scientific questions and the European Commission has consulted it on several questions related to nanomaterials. The answers, in the form of opinions[148][149][150][151], are published at the webpage[152]. The questions posed by the Commission to SCENIHR concern definitions of relevant physical parameters for nanomaterials and the validity of application of current risk assessment methodologies. The SCENIHR opinions identify knowledge gaps with regard to risk assessment of nanomaterials, and especially the gaps in relation to exposure assessment are also relevant for occupational exposure. For workers the most relevant route of exposure is inhalation and for airborne exposure the size of inhaled particles is a determining factor in the internal dose where the very small particles are not exhaled. The exposure measurements is one of the areas where more work is needed, as data on airborne exposure are still scarce and do not always clearly differentiate ambient from manufactured particles. In addition to particle size and number as metrics, other metrics can be determined to express exposure. These include particle surface area, surface charge (zeta potential), surface area reactivity (radical formation, photo-catalysis, oxidation/reduction), etc. The choice of dose metrics depends on the end point of interest.

Overall, the information base for exposure assessment to manufactured nanomaterials in workplaces is currently built on a limited database that has to be improved in volume, comparability and reproducibility. This can be achieved by working on the feasibility of routine assessments, developing reliable measurement techniques, standardizing measurement techniques, developing measurement strategies and implementing the screening and monitoring of nanoscale particles in sensitive work areas.

A.5 Germany

A.5.1 Regulatory exposure limits (AGW)

A.5.1.1 Legislation, organization and processes

The binding national OEL in Germany is called Arbeitsplatzgrenzwert (AGW). AGW values are proposed to the Federal Minister of Labour and Social Affairs by the German Committee on Hazardous Substances (Ausschuss für Gefahrstoffe – AGS). Its members represent *inter alia* workforce, employers, enforcing authorities, the German social accident insurance institutions, and academic science. As a rule, the AGS evaluates OEL proposals elaborated by other organizations, predominantly by the German "MAK Commission" (see below), and examines whether or not they are compatible with the AGW definition.

Once adopted by the Ministry, the German AGWs are listed in the Technical Rule for Hazardous Substances No. 900[153]. The criteria documents of the AGWs, which were directly derived by the AGS, are published (in German) on the website of the Federal Institute for Occupational Safety and Health (BAuA)[154].

A.5.1.2 Science and methods for OEL setting

According to the German Hazardous Substances Ordinance (Gefahrstoffverordnung)[155], an AGW is a time-weighted average concentration in the workplace air, referring to a given period of time. The AGW states the concentration of a substance below which acute or chronic adverse health effects are not generally expected. AGWs are thus based exclusively on available occupational medical experience and toxicological findings.

In case of lacking reference, especially if the scientific database is limited, the AGS itself derives AGWs as health-based occupational exposure limits, usually starting from a no observed adverse effect level (NOAEL) for any critical health effects and applying certain extrapolation factors specified in the Announcement 901 on Hazardous Substances[156] (available in German only). These extrapolation factors are similar to those assessment factors proposed in the ECHA Guidance on information requirements and chemical safety assessment (chapter R.8)[71] for the derivation of derived no-effect levels (DNELs).

A guide for the quantification of cancer risk values is an integral component of the Announcement 910. If human data are available for risk quantification, the Announcement requires that these are primarily reviewed for their suitability and used, if appropriate. As a default, linear extrapolation to low-dose range from a calculated point of departure ($BMD_{0.1}$, T25) is recommended, although modelling of a sublinear dose-response curve is possible if supported by sound mode of action data. Substance-specific exposure-risk relationship documentations are published on the internet by the Federal Institute for Occupational Safety and Health (BAuA)[157].

A.5.1.3 Occupational health risk assessment policies

Considering the problem that no health-based workplace exposure limit can currently be derived for the majority of carcinogenic substances, the AGS has proposed an overall concept for setting risk-based limit values for carcinogens without known toxicological threshold as part of a social policy establishment. The following limits of occupational exposure-related lifetime cancer risks were adopted:

— "Acceptable risk", interim limit: 4:10 000;

— not later than as of 2018: 4:100 000;

below which a risk is accepted. Above these limits, a risk will be tolerated if the measures specified in a corresponding catalogue are conformed with. The second risk limit is the:

— "Tolerable Risk": 4:1 000.

The risks refer to a working lifetime of 40 years and continuous exposure every working day. Substance-specific concentration figures derived from well-founded exposure-risk models are compiled in the Announcement 910[157] and should be taken into account by the employers when performing their risk assessment. During a testing phase lasting over several years, the risk limits do not, however, draw legal consequences.

A.5.2 Non-regulatory exposure limits (MAK)

A.5.2.1 Legislation, organization and processes

"MAK" values, or maximum workplace concentrations, originate from the "DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area", better known as the "MAK Commission". This independent body has been mandated by the German Research Foundation (DFG) to determine the current state of research relating to the health risks posed by substances and materials used at the workplace, and to advise public authorities accordingly.

MAK Commission Members are appointed *ad personam* in their capacity as authoritative experts and not as representatives of the institutions or companies in which they work. In discussions and decision-making, only scientific arguments regarding health at the workplace are considered. Other aspects such as competitive socio-political, economic or technological reasons are excluded.

A.5.2.2 Science and methods for OEL setting

The MAK value is defined as the maximum concentration of a chemical substance (a gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of employees nor causes unreasonable annoyance (e.g. by nauseous odour), even when a person is repeatedly exposed during long periods, usually for eight hours daily but assuming on average a 40 hour working week. Principles of deriving MAK values are laid down in the brochure "List of MAK and BAT Values"[158], which is updated annually. Known effects of a substance in humans are given highest priority in the derivation of the MAK value, which is based on the NOAEL for the most sensitive effect with relevance to health. If a NOAEL cannot be derived from the available data, a MAK value is not established. In general, safety factors are not applied by the MAK Commission.

A.5.2.3 Occupational health risk assessment policies

For the establishment of a MAK value, the carcinogenicity, the sensitizing effects, the contribution to systemic toxicity after percutaneous absorption, the risks during pregnancy and the germ cell mutagenicity of a substance are evaluated and classified or designated accordingly. Under defined circumstances, a MAK value may even be established for carcinogens, namely if the particular substance (a) exerts a mode of action which is primarily non-genotoxic or (b) proven genotoxic effects are considered to only contribute very slightly to human cancer risk, provided the MAK value is observed.

MAK values are to be taken into account by the employers when performing their risk assessment if no official AGW exists for the substance of interest.

A.6 Italy

A.6.1 Regulatory exposure limits

A.6.1.1 Legislation, organization and processes

The VLEP (Occupational Exposure Level Value), unless otherwise specified, is the limit of the time-weighted average concentration of a chemical agent in the air within the breathing zone of a worker in relation to a given reference period as indicate in Article 222, paragraph 1, letter d, Italian Legislative Decree N. 81/2008 and subsequent amendments[159].

In Italy, the determination of VLEP is due to the guidelines publication of European Occupational Exposure Limit Values (OELVs). The European legislative process for the definition of VLEP is as follows:

a) the European Commission, in its Decision (95/320/EC), relies on the Scientific Committee on Occupational Exposure Limit Values (SCOEL), the task of proposing the OELVs after an analysis of scientific publications and best practices;

b) then there is an approval process that takes into consideration the socio-economic and technical feasibility involving also the Commission's Directorate General for Employment, Social Affairs which in turn refer to the appropriate Committee for Health and Safety in the Workplace;

c) completed the approval process, the OELVs, which meant purely indicative for the Member State, will be published in the Guidelines that, at this point, are transposed or modified by individual States, which may establish their own procedures according VLEP national approval. At this point the VLEP approved acquire within the State who approves a required value. The Decree requires that first employers comply with Italian VLEP approved by the Italian State.

In Italian law, the VLEP constitute one of the elements to be taken into consideration in the risk assessment. In fact, Art. 223 of Legislative Decree N. 81/2008 and subsequent amendments states that, "... in the risk assessment, the employer determines in advance the possible presence of hazardous chemicals in the workplace and assess the risks to the safety and health of workers arising from the presence of these agents, taking into consideration in particular:[... omitted...]e) occupational exposure limit values or biological limit values." The list of VLEP in force at national level is set out in Schedule XXXVIII of Legislative Decree N. 81/2008 and subsequent amendments.

A.6.1.2 Science and methods for OEL setting

In 2012, the Permanent Advisory Commission for Safety and Health at Work, which was reconstituted by the Ministerial Decree of 3 December 2008, drafted the document "Criteria and tools for risk chemical assessment and management in the workplace " pursuant to Legislative Decree N. 81/2008, to provide clear and complete information about updates of the requirements and procedures resulting from the impact of Regulation (EC) N° 1907/2006 of the European Parliament and of the Council of 18 December 2006 (REACH, Registration, Evaluation, Authorization of Chemicals)[97][160]. The Commission invites the adoption of the following frame of reference, about the sources from which it is possible to deduce the occupational exposure limit values to be complied with:

a) as a priority: the occupational exposure limit values set out in Annex XXXVIII of Legislative Decree N. 81/2008 and subsequent amendments;

b) the limit values set out in the EC directives not yet transposed into Italian law;

c) the threshold limit values (TLVs) published by the American Conference of Governmental Industrial Hygienists (ACGIH), where compliance of these is provided by the respective national collective labour agreements, as part of the national legislation in force call-back the Art. 225, paragraph 3, of Legislative Decree N. 81/2008 and subsequent amendments. In all other cases, in the course of a legislative reference, the Decree requires that the employer carries out the choice of the limits of scientifically appropriate reference .

A.6.1.3 Occupational health risk assessment policies

Legislative Decree No. 81/2008 and subsequent amendments require that the path of the risk assessment of hazardous chemical agents is, primarily, able to identify and classify the chemical agents that may constitute risk factors for the workers taking into account the intrinsic properties of substances and mixtures that may pose a danger to 'act normal handling or use'. The carcinogenic and mutagenic substances do not exhibit levels of exposure below which it may assume the absence of effects on health. Therefore it is always necessary to perform the exposure assessment for the purposes of the obligations provided for in Chapter II of Title IX of the Decree N. 81/2008 and subsequent amendments. For substances (or work that require the use) for which there is currently no harmonized classification within the EU, but which are otherwise known in the scientific field, or recognized by international bodies (such as IARC), the carcinogenic or mutagenic there is, however, obliged to adopt the protections

provided under Chapter I of Title IX of the Decree n. 81/2008 and subsequent amendments in the case of non-negligible risk. Given that the Occupational Exposure Limit Values and VLEP for carcinogens and mutagens, have not undergone change with the enactment of the REACH and CLP Regulations, it should be noted that the same are those currently set out in Appendix XLIII of Legislative Decree No. 81/2008 and subsequent amendments and relative to benzene, vinyl chloride monomer and wood dust. For other carcinogens and mutagens, reference may be made, in the identification of occupational exposure limit values, to those proposed by European standards or specifications by internationally recognized organizations (such as, for example, ACGIH, NIOSH and OSHA).

A.6.2 Non-regulatory exposure limits

A.6.2.1 Legislation, organization and processes

Exposure scenarios foreseen by the REACH Regulation, contain a description of both the risk management measures and operational conditions, which the manufacturer or importer has implemented or recommends to be implemented by downstream users. The Derived No-Effect Level/Derived Minimal Effect Level (DNEL/DMELs) are created to be used as a benchmark in mathematical models for prediction of exposures provided in the scheme of risk assessment of substances under REACH[97][160]. And only in this context these values see their applicability. In accordance with local regulations concerning health and safety at work and the regulation of chemicals, you should take into consideration both the values predicted by Legislative Decree no. N. 81/2008 and subsequent amendments or, if present, the values of DNEL/DMELs in relation to the exposure scenarios set out in the Safety Data Sheet (SDS). So in this case the employer may encounter the following situations:

a) the substance does not have a VLEP but only DNEL/DMELs: the employer considers the possible existence of OELVs defined at European level, which have not yet been transposed into national legislation or limit values, by bodies of undisputed importance (i.e. ACGIH). In any case, the REACH Regulation requires that the employer complies with the measures set out in the risk management/exposure scenarios relevant to its activities and, in doing so, it operates in accordance with the presumption of DNEL/DMELs used by the registrant subject to the Chemical Safety Assessment of the substance. The exposure levels may be measured which are not comparable with those DNEL/DMELs;

b) the substance has no reference value: the employer is required to apply the general protection measures and, as a precaution, also the specific measures found in more restrictive provisions of Art. 224 and, where necessary, Art. 225 of Legislative Decree No. 81/2008 and subsequent amendments.

A.7 Japan

A.7.1 Regulatory exposure limits

A.7.1.1 Legislation, organization and process

Since 1972, the Industrial Safety and Health Law, Articles 65-1 and 65-2, require periodic measurement and evaluation of the indoor working environment. The working environment is evaluated and categorized into three control levels by comparing the Administrative Control Level (ACL), which are set for more than 90 substances, and the calculated values based on the measured data of area and source. The notification “Working Environment Measurement Standard” from the Ministry of Health, Labour and Welfare (MHLW) describes requirements for carrying out the measurement and evaluation[161]. The standard specifies the methods of collecting air samples, the design of sampling points, and analytical methods, etc. The Working Environment Measurement Law stipulates the qualifications of the persons for adequate evaluation of measurement results, etc.

The following is the evaluation procedure.

a) Multi-point area monitoring and one source monitoring are performed in a Unit Work Area for each different process. For area measurement (A-measurement), sampling points are set at equal

distances and sampling duration is more than 10 min. Source measurement (B-measurement) is performed near the source for 10 min sampling.

b) An example of evaluation of a Control Class from the results of one-day monitoring is as follows (usually monitoring is performed for two consecutive days): The following calculations are performed to obtain evaluation values, E_{A1} and E_{A2}, as concentrations of A-Measurement in a Unit Work Area usually show log-normal distribution.

$\log E_{A1} = \log GM + 1.645 \log GSD$

GM: geometrical mean

GSD: geometrical standard deviation

E_{A1} is 95 % at concentration distribution.

$\log E_{A2} = \log GM + 1.151 \log^2 GSD$

E_{A2} is equivalent to arithmetic mean.

c) The working environment is assigned to one of three Control Classes according to Table A.3.

Table A.3 — Control classes

		Area (A-measurement)		
		$E_{A1} < E$	$E_{A2} \leq E \leq E_{A1}$	$E < E_{A2}$
Source (B-measure-ment)	$E_B < E$	Class 1	Class 2	Class 3
	$E \leq E_B \leq 1{,}5E$	Class 2	Class 2	Class 3
	$1{,}5E < E_B$	Class 3	Class 3	Class 3

The employer takes the actions, according to the assigned Control Class: In the case of Control Class 3, the facilities, equipment, working processes and working procedures should be immediately improved to enhance the class to Control Class 1 or 2. Workers should use effective respirators and undergo health examinations, etc. In the case of Control Class 2, facilities should be installed or improved ventilations, etc. The working processes or working procedures should be improved to enhance the class to Control Class 1. The working environment assigned to Control Class 1 is regarded as well controlled.

A.7.1.2 Science and methods for OEL setting

ACLs have been set for more than 90 substances and reviewed every year for the substances showing high toxicity and carcinogenicity. New ACL is suggested by the ACL review committee after reviewing process by taking into account the present JOEH OEL (See A.7.2), ACGIH TLV-TWA, the latest hazard assessment data from the peer-reviewed papers, and the test results conducted by Japan Bioassay Research Centre. When a certain level of ACL is considered, sampling and analytical method is also prepared for working environment evaluation to analyse 1/10 of ACL by 10-min sampling by conducting exposure measurement at the related facilities.

A.7.2 Non-regulatory exposure limits

The Japan Society for Occupational Health (JSOH) recommends OELs[51]. The OELs for chemical substances is defined as the concentration of a chemical substance in air which will be inhaled by a worker during a job without the use of protective respiratory equipment. OEL-Mean (OEL-M) is defined as the reference value to the mean exposure concentration at or below which adverse health effects caused by the substance do not appear in most workers working for 8 h/d, 40 h/w under a moderate work-load. OEL-Ceiling (OEL-C) is defined as the reference value to the maximal exposure concentration of the substance during a working day at or below which adverse health effects do not appear in most workers. Setting OELs follows the standard evidence-based procedure based on critical review of epidemiological and toxicological scientific literature.

A.7.3 NOAA-specific OELs

A.7.3.1 Carbon nanotubes

Under a NEDO project (P06041) "Research and Development of Nanoparticle Characterization Methods", Nakanishi[55] chose MWCNT(N) manufactured by N Co. from MWCNTs, and SWCNT(A) produced at a laboratory from SWCNTs as representatives, and conducted inhalation exposure tests, intratracheal (IT) instillation tests and biokinetic analysis on them. The IT instillation test alone was conducted on other MWCNTs, double-walled carbon nanotubes (DWCNTs) and SWCNTs. The NOAEL, which takes inflammation as an end point, was determined to be 0,37 mg/m^3 for MWCNT(N) and 0,13 mg/m^3 for SWCNT(A), respectively, based on sub-acute inhalation exposure tests. They converted these rat NOAEL values into the period-limited occupational exposure limit [OEL (PL)] for human and obtained 0,08 mg/m^3 for MWCNT(N) and 0,03 mg/m^3 for SWCNT(A), respectively. They employed the biaxial approach analysis, using the neutrophils increase in rats' lung lavage as inflammation indicators one month after IT instillation of CNTs one milligram per kg of body weight. In this analysis, they compared the inflammation activity of other CNTs with that of representative MWCNT and SWCNT. Their findings were twofold. First, the inflammation activity due to CNTs was strongly dependent on their BET specific surface area, that is to say, the bigger the BET specific surface area, the more inflammation activity was observed. Second, the relation between the two was determined by a common expression irrespective of CNT types. In other words, the distinction between multi-walled, double-walled and single-walled is not significant. Since the BET specific surface area is determined by the number of walls, the inflammation activity is controlled by the size of nanotube diameter or the number of nanotube walls. Based on such findings, they have proposed the single value of OEL 0,03 mg/m^3 irrespective of CNT classification, which should be applied according to the specific surface area of CNTs.

In this project, intratracheal instillation tests were conducted in addition to inhalation exposure tests, and attention was paid to whether there was any possibility of cancers, etc., developing in the case of long-term exposure by conducting observations at six months, one year, and two years after instillation. Nakanishi[55] considered that although cancers were unlikely to develop at the concentration less than the NOAEL estimated, more detailed studies were required regarding cancer, and that as nanomaterial toxicity tests were currently being conducted around the world, more reliable test results were likely to be obtained in time, where such being the case, it would be desirable to follow those findings, and that adopting such a flexible initiative is necessary for the toxicity assessment of new materials. They thought that they should instead come up with an approach based on the limitations of subchronic testing. Taking into account the possibility that the symptoms themselves would be different in subchronic exposure and long-term exposure, they standardized the periods based on lifespan, and applied this to the human exposure period similar to the subchronic test period for animals. Based on this thinking, the exposure period was set at approximately 15 years, after having also taken feasibility and other factors into account, with a period-limited OEL of exposure of a period of 1/2 to 1/3 of 30 to 45 years, based on the premise that the results will be reviewed within approximately 10 years using new test results obtained in the meantime. This is based on the concept of adaptive management, which will be a risk assessment model applicable to new materials that are in the process of development for which the rules used for ordinary chemicals may not be applicable.

A.7.3.2 Titanium dioxide

The Japanese National Institute of Advanced Industrial Science and Technology (AIST) conducted an occupational risk assessment of nanoscale TiO_2 under a NEDO project (P06041) "Research and Development of Nanoparticle Characterization Methods", and proposed a period-limited OEL[48] [49] from the viewpoint of adaptive management, that is, it is aimed at protecting workers against subchronic exposure (approximately 15 years) and should be subjected to revision in the next 10 years. They selected "pulmonary inflammation" as the assessment end point on the grounds that if the dose is such that "pulmonary inflammation" does not occur, there is no need to be concerned about the subsequent development of more severe effects (fibrosis or pulmonary tumour). The "pulmonary inflammation" was determined mainly based on histopathological test results, with also taking into account changes in inflammatory cell and cytokine in the bronchoalveolar lavage fluid (BALF). The NOAEL was determined from a three-month inhalation test using rats by Bermudez, et al.[67] to be 2 mg/m^3. Considering the difference in breathing rate, deposition rate, body weight, etc. between rat

and human, and determining uncertainty factors prudently, OEL (PL) was derived to be 0,6 mg/m^3 (respirable dust, 8 h TWA). According to the results of relative comparison of various nanoscale TiO_2 (bi-axial approach), the OEL (PL) value derived was considered conservative for managing the exposure to nanoscale TiO_2 in general.

A.7.3.3 Fullerene

In 2011, AIST published a report describing risk assessment of fullerenes[53]. Although information on biokinetics suggests that it is possible for pulmonary alveolar tissue to incorporate fullerene after inhalation exposure, which is the main and realistic path of exposure, it was thought that there is almost no translocation to the extrapulmonary organs. Based on the results of the intratracheal instillation tests, the half-life in the lung is 16 d to 24 d. In inhalation exposure (inhalation exposure tests, intratracheal instillation tests), only minor, transient, and partial inflammation was observed: no continuing inflammation was found. There was no evidence suggesting effects in other organs. However, in rats administered with 1,0 mg per lung there was a significant increase in neutrophilic count up to three months, though very slight. Some results of cell toxicity tests suggest that nanoscale particles have a higher toxicity than micron sized particles. No evidence of toxicity was found in oral and dermal exposure.

Since there have been no reports of fullerene translocating to extrapulmonary organs after inhalation exposure, adverse effects in the lung was chosen for selection of end points for risk assessment. Most of toxicological research of C_{60} measured indicators of lung inflammation such as the inflammation of lung tissue, BALF total cell count, neutrophilic cell count and cytokine amount. Therefore, the authors of the report used the presence or absence of inflammation in histopathological observation to obtain NOAEL. The BALF neutrophilic cell count and the amount of cytokine were used as supplementary information.

Some studies indicated that in the intratracheal instillation tests initial inflammatory response occurring within one day after instillation is a general response to large amount of foreign materials injected into the lung. Therefore, risk assessment analysis in the report did not take into account inflammatory response indicators one day after instillation.

The estimated human equivalent NOAEL for inhalation exposure to C_{60} was obtained using the results of inhalation exposure and intratracheal instillation tests in Morimoto, et al.[162] and Sayes, et al.[163], where subject rats were observed for three months or more. Tests in which toxic organic solvents were used to prepare C_{60} dispersions were excluded from the assessment.

Morimoto, et al.[162] reported no continuous inflammation and no changes in inflammation-related markers in BALF for up to three months after a 6 h/d, 5 d/w inhalation exposure for four weeks with C_{60} particles of 96 nm average size at 0,12 mg/m^3. This suggests an NOAEL of 0,12 mg/m^3.

In Morimoto, et al.'s intra-tracheal instillation test[162], no inflamed lung tissue and no increase in inflammatory cytokine were observed for six months after intra-tracheal instillation at 0,1 mg/l (0,33 mg/kg) and 0,2 mg/l (0,66 mg/kg). However, there was a slight but significant increase of neutrophilic cells up to three months after intra-tracheal instillation at 1,0 mg/l (3,3 mg/kg). Also, in Sayes, et al.[163], no inflammatory lung tissue and no increase in neutrophilic cells were observed up to three months with 0,7 mg/l (3,0 mg/kg) intra-tracheal instillation. Based on these results, it was determined that the NOAEL and LOAEL for intra-tracheal instillation tests of C_{60} nano particles were 0,7 mg/l and 1,0 mg/l, respectively. This NOAEL was converted into inhalation NOAEL assuming that the toxicity would be the same for both inhalation exposure and intra-tracheal instillation tests when the maximum lung retention was the same. The deposition fraction was assumed 0,14 and the respiratory volume of 0,27 m^3/d was used. Using these assumptions, NOAEL of C_{60} nanoparticles for 90 d inhalation exposure tests on rats was calculated to be 3,1 mg/m^3.

This rat NOAEL was converted into human NOAEL of 3,5 mg/m^3 in work environments after correcting for the exposure period and species differences.

Occupational exposure limit was obtained by dividing this NOAEL by the uncertainty factor. The uncertainty factor combines several factors accounting for differences in species response, exposure period, and individual sensitivities. Since inflammation in the lung was chosen as the end-point and it

is a localized effect dependent only on lung retention, which was already accounted for in extrapolation from rat to human in NOAEL calculations, species difference in toxicokinetics was chosen as 1. Since rats have been shown to have higher sensitivity to lung inflammation, the uncertainty factor to account for differences in toxicodynamics was chosen as 1. The uncertainty factor related to the extrapolation of NOAEL from rats to humans assuming equivalent lung retention and considering only one model of extrapolation based on body weight ratios, was set at 3. Since different models for extrapolating instillation exposure to inhalation exposure can lead to different estimates of NOAEL, the authors chose the uncertainty factor for the extrapolation of 3. The authors assumed that the workers are healthy and, therefore, there is no need to account for individual differences. Multiplication of these factors produces the overall uncertainty factor of 9.

By dividing the human NOAEL by the uncertainty factor occupational exposure limit (period-limited) [OEL (PL)] of 0,39 mg/m^3 was obtained. To account for differences in the lung deposition of particles of different sizes, the authors also suggested to adjust this OEL (PL) by the following multiplier: 0,0913/f (d = x, GSD = y), where f is the alveolar deposition fraction as a function of particle size and geometric standard deviation (GSD), when particle size distribution in the workplace air is available. The alveolar deposition fraction can be derived from the Multiple Path Particle Dosimetry (MPPD) model.

A.8 Netherlands

A.8.1 Regulatory exposure limits

A.8.1.1 Legislation, organization and processes

A.8.1.1.1 General

On 1 January 2007, a modified OEL system was introduced in the Netherlands.

A.8.1.1.2 Based on private OELs

The new OEL system is based on private OELs, i.e. OELs that are set by individual companies themselves. More than ever before, employers and employees are responsible for dealing safely with substances in the workplace. This means that now they set OELs together to prevent damage to the employees' health owing to exposure to particular substances.

A.8.1.1.3 Public OELs

In addition to these private OELs, the Ministry of Social Affairs and Employment sets public (i.e. statutory) OELs for the following substances:

— substances for which the EU requires limit values (in practice, these are Binding Limit Values and Indicative Limit Values);

— substances for which it is not expected that the EU will require a limit.

  This group comprises substances "without owners"' and substances with a large chance of causing damage to health (high-risk substances), including those for which the government deems it necessary to establish a public limit.

Public OELs are listed in Appendix XIII of the Working Conditions Regulations. Appendix XIIIA covers non-carcinogens, and Appendix XIIIB carcinogens. The first list of public OELs was published in the Government Gazette [*Staatscourant*] in 28 December 2006, no. 252 (Appendices XIIIA and XIIIB of the new, revised Working Conditions Regulations).

A.8.1.2 Science and methods for OEL setting

A.8.1.2.1 Health-based OELs

In principle, all OELs within the new system (i.e. both private and public OELs) are health-based OELs, with the exception of OELs for carcinogenic and mutagenic substances for which no safe health-based OEL can be set. These substances will continue to be subject to feasibility tests and the results of the tests will play an important role in establishing OEL levels.

A.8.1.2.2 Withdrawn statutory and administrative OELs

Provided they are health-based OELs, all statutory and administrative OELs set before 1 January 2007 that are not included in the list of public OELs can be used as the basis for determining private OELs.

Substances are divided into four categories:

a) "normal" health-damaging substances (i.e. non-carcinogenic substances) for which a safe threshold can be established;

b) carcinogenic and mutagenic substances with a safe threshold;

c) carcinogenic and mutagenic substances without a safe threshold;

d) inhalant allergens without a safe threshold.

NOTE Only for substances in categories c) and d) are the OELs based in part on the results of a feasibility test.

A.8.1.2.3 Substances with a safe threshold

A public (i.e. statutory) OEL is set, based on

— an ILV or BLV set by the European Commission, and

  These are usually based on the recommendations of the Scientific Committee on Occupational Exposure Limits (SCOEL). ILVs are incorporated in directives that require EU member states to establish a national OEL for those substances for which an ILV has been set. These national OELs may differ from the ILV.

— a report by the Dutch Health Council.

  The Ministry of Social Affairs and Employment creates a Working Programme for this, and issues a request for advice to the Working Conditions Committee of the Social and Economic Council of the Netherlands (SER). The Ministry's current position is that a statutory OEL can only be determined once the Health Council has made a recommendation.

A.8.1.2.4 Carcinogenic and mutagenic substances without a safe threshold

To date, this category concerns substances for which a national Working Programme has been established (see above). The Ministry of Social Affairs and Employment asks the Health Council to establish exposure levels for these substances on the basis of risk limits. These risk limits are based on what is considered as a "prohibitive risk level" (i.e. prohibiting an additional risk of cancer higher than 10-4 per substance per year) and as the "target risk level" of concentration (i.e. one extra fatality per year as a result of cancer per 1 million employees exposed to the substance)[164]. Below this target risk level, no additional protective measures need to be taken.

The Council's OEL Subcommittee evaluates the feasibility of implementing a statutory OEL at the target level and advises the Ministry on this. In addition to the employers' confederations and trade union federations, the Subcommittee involves industry organizations in these feasibility tests. These organizations are invited to register their interest in contributing to feasibility tests for certain

substances. Occupational Health and Safety Services are invited to indicate the substances about which they would like to be kept informed.

The results of the feasibility test may lead to a higher OEL being set. In principle, this higher OEL will be evaluated by the Subcommittee every four years to determine whether it can be lowered further, with the ultimate aim of reaching the target risk level.

A.8.1.2.5 Inhalant allergens

Exposure to inhalant allergens in the workplace can lead to work-related respiratory allergies. This generally begins with sensitization (to become sensitive to the relevant substance). Eventually, however, an allergy develops that is harmful to health, even when exposure is minimal.

It is often impossible to define a safe OEL for this group of substances. That is why it is chosen to apply the same approach as in the case of carcinogens for which no safe exposure limits can be set. Instead of an OEL, then, a target risk level will be identified, feasibility testing will be carried out, and a repeat test will be conducted every four years where necessary[165].

The target risk level states the extent to which exposure should be minimized in order to ensure that the extra risk of harm is negligible or will be reduced to a natural background risk. The feasibility test should not focus on technical feasibility alone, but also on operational and economic feasibility. The target risk level is a 1 per cent extra risk of sensitization owing to exposure to an inhalant allergen (beyond any inherent sensitization to a substance). The level of corresponding exposure may differ from one inhalant allergen to the next.

A.8.1.3 Occupational health risk assessment policies

A.8.1.3.1 Obligations/enforcement

As part of their Risk Inventory and Evaluation (RIE), companies should assess their compliance with the health-based OEL for all substances. If they do not comply, they should draw up a plan setting out how they will meet the OEL. This plan should include an overview of the measures to be taken and a time schedule.

In addition, the OEL Subcommittee of the Social and Economic Council is responsible for:

— advising on the implementation of OELs for carcinogenic and mutagenic substances without a safe threshold and inhalant allergens without a safe threshold, based on the results of a feasibility test. This includes advising every four years on whether the OEL can be lowered towards the target risk level;

— informing industry organizations (and Occupational Health and Safety Services) about developments affecting OELs in the public domain, including draft reports by the Health Council *(openbare conceptrapport, OCR)* and SCOEL, final reports by the Health Council and SCOEL, the Working Programme of the Ministry of Social Affairs and Employment and SCOEL, changes and/or developments abroad, and measurement methods;

— managing the OEL database, which gives interested parties access to information about current OELs, feasibility tests, the recommendations of the OEL Subcommittee, and more;

— supervising the development of guidelines for working responsibly with chemical substances in the workplace (development of a digital tool);

— drawing up and maintaining OELs for EU member states and other relevant countries, and making these OELs freely accessible to industry organizations and other interested parties via the OEL database.

A.8.1.3.2 Activities of the OEL subcommittee

First, the OEL Subcommittee informs industries and Occupational Health and Safety Services about developments concerning OELs, providing them with information about the draft and final reports of the Health Council and SCOEL. The focus here is on public OELs and changes to the comparative overview of OELs.

Second, the Subcommittee carries out feasibility tests for proposed public (i.e. statutory) OELs for carcinogenic and mutagenic substances and inhalant allergens that do not have a safe threshold. The current system is to invite parties to register their interest in contributing to feasibility tests for proposed OELs. The sectors indicate the substances in which they are interested or for which they would like to be kept up-to-date.

Third, the Subcommittee keeps the OEL database (and, of course, the comparative overview of OELs) up to date. Relevant news updates from the Netherlands and other countries is published in the newsroom[166].

A.8.1.4 NOAA-specific OELs

At the moment, NOAAs have no place yet in the new OEL system because of lack of knowledge to derive a health-based OEL.

A.8.2 Non-regulatory exposure limits

A.8.2.1 Legislation, organization and processes

Taken into account the different scope between private and public OELs, intentionally produced NOAA may be considered to be part of the private system for which a company OEL should be derived. For process-generated NOAAs (e.g. combustion-derived or engine-generated NOAAs), the current situation seems to be unclear: should they be considered in the public system or should they be part of the private system, meaning that for these groups' company limits should be derived?

A.8.2.2 Science and methods for OEL setting

Due to a lack of toxicity data for most NOAAs, the derivation of health-based OELs is not possible. A provisional solution has been found in the derivation of nano-reference values (NRVs) that can be used in practical situations to assess occupational exposure to NOAAs and thus serves as a risk management tool[167]. The following definition is used:

— NRV defines a maximum level for the concentration of NOAAs in the workplace atmosphere, corrected for the background concentration;

— It is not a scientifically derived health-based exposure limit and therefore should not be used as such;

— NRV is defined as an 8 h-TWA (Time Weighted Average) exposure level. For short-term exposure periods and peak exposures a separate NRV is defined.

An evaluation by the Dutch Expert platform and the National Institute for Public Health and the Environment in principle concluded to subscribe to the IFA approach as a provisional alternative for health-based recommended OELs and advises to use these benchmark levels as *provisional nano-reference values* (provisional P-NRVs)[165]. After discussions with IFA and the Dutch expert platform, slight adaptations were proposed in the description of categories 2 and 4 as presented in Table A.4 and the approach was applied to the most commonly applied nanomaterials.

Table A.4 — Provisional Nano-Reference Values (P-NRV) based on the benchmark levels as proposed by IFA and adapted according to discussion with IFA and the Dutch Expert platform

Description	Density	P-NRV (8 h TWA)	NOAAs
CNTs for which effects similar to those of asbestos cannot be excluded according to the manufacturer's declaration		0,01 f/cm^3	SWCNT or MWCNT for which asbestos-like effects are not excluded
Biopersistent granular nanomaterial in the range of 1 nm and 100 nm	>6 000 kg/m^3	20 000 p/cm^3	Ag, Au, CeO_2, CoO, Fe, Fe_xO_y, La, Pb, Sb_2O_5, SnO_2
Biopersistent granular nanomaterial in the range of 1 nm and 100 nm	<6 000 kg/m^3	40 000 p/cm^3	Al_2O_3, SiO_2, TiN, TiO_2, ZnO, nanoclay Carbon Black, C_{60}, dendrimers, polystyrene CNT for which asbestos-like effects are excluded
Non-biopersistent nanomaterial in the range of 1 nm and 100 nm		Applicable OEL	Fats, hydrocarbons, siloxanes, NaCl

A.8.2.3 Occupational health risk assessment policies

NRVs are considered to be a warning level. If this level is exceeded control measures should be taken immediately to reduce exposure. Because NRVs are not health-based, exposure-reducing measurements should also be considered for exposures below the NRVs, according to the As-Low-As-Reasonably-Achievable (ALARA) principle. As such, the concept of NRVs is an approach to bring the precautionary principle into operation[164][168][169]. It introduces practical exposure levels according to the principle *no data-no exposure.*

A.8.2.4 NOAA-specific OELs

Momentarily, no NOAA-specific OELS have been derived in the Netherlands.

A.9 South Korea

A.9.1 Legislation, organization and processes

The initial Korean OELs were included in the Korean Occupational Safety and Health Act approved on July 1, 1982, and took the form of a "notification" from the Korean Ministry of Employment and Labour (MOEL). According to the hierarchy of the Korean legal system, a notification is the lowest legal action by a Korean Ministry, where the stronger actions include an enforcement regulation, enforcement ordinance, and finally an Act. However, the reason the Korean OELs are issued as a notification is to allow easy revision in response to dynamic labour environment changes. The initial Korean OELs were a straight copy of the TLVs from the ACGIH, and were not subsequently revised until 1998. Many argued against using the ACGIH TLVs without revision and without considering the Korean work environment. Until 2003, the Korean workforce worked 6 d/w, approximately 45 h/w, and sometimes more than 10 h/d. Therefore, the labour unions and industrial hygiene professionals claimed that the ACGIH TLVs, which are based on 8 h, 5 d, and 40 h/w, were inappropriate for the Korean workplace with longer working hours. Furthermore, they claimed that the different work environment and chemical ADME (absorption, distribution, metabolism, and excretion) from the USA required different TLVs. However, technology for systemic hazard assessment and risk assessment to establish TLVs was lacking at that time. The first OEL determined in Korea was initiated in 1996 and involved the use of 2-bromopropane, which significantly and adversely affects the reproductive health of electronic industry workers. At the

time, this chemical had no TLV anywhere in the world. Following a petition from victims, the Korean MOEL eventually issued a notification establishing a TLV for 2-bromopropane in 1998[170].

There are two tracks of OELs under the Occupational Safety and Health Act in South Korea. One is regulatory Permissible Exposure limits (PELs) for designated harmful agents which could cause serious health problems to workers such as a carcinogen. The PELs are set up for 13 chemicals such as lead, benzene, trichloroethylene, and formaldehyde, etc. and is operated like the PELs of OSHA, meaning that an employer is required to keep the level of workplace exposure to such agents below the PELs, otherwise, an employer may be imposed a fine when an inspector of Area Office of Ministry of Employment and Labour inspects and monitors the work environment of the company. Plus, an employer is required to monitor and evaluate the work environment of the workplaces exposed to the agents. PELs system was included in the Occupational Safety and Health Act on 27 July 2007. The other is OELs for harmful agents. The OELs are set up for noise and 717 chemicals[171]. The most recent Korean OEL notification issued on 14 August 2013[171] includes carcinogen notations for 184 substances, in contrast 54 substances previously. However, these carcinogen notations are not legal regulations and only provide hazard information. The latest revisions also changed the OELs for ceramic fibres from mg/m^3 to n/cm^3. An employer is required to periodically monitor and evaluate the work environment of the workplaces exposed to noise and the 197 agents among them. These OELs become the decision standard whether the work environment monitored are needed to be taken proper measures by the employer under the Occupational Safety and Health Act.

There are no explicitly written procedures for establishing new OELs or revising any existing OELs in the Korean Occupational Safety and Health Act or internal guidance/procedures from the Korean MOEL. Instead, the Korean MOEL launches a research project responding specifically to a labour union, occupational health professionals, or from a requested relevant academic organization. Occasionally, there is a revision of TLVs by the ACGIH, which triggers the revision of existing Korean OELs. The scope of each research project includes investigating the quantity of the subject substance domestically, hazards, exposures, risk assessments, risk managements, and cost/benefit analysis. After reviewing the research project results and stakeholder hearings, the Korean MOEL convenes with the Hazardous Factor Management Committee that includes the labour union, employer representatives, experts from academic organizations, and government organizations. The final decision will be in the form of a notification and is then printed in an official gazette.

A.9.2 Science and methods for OEL setting

The concept of Korean OELs is very similar to that used by the ACGIH, which involves formulating a conclusion on the level of exposure that the typical worker can experience without adverse health effects. Korean OELs also represent the conditions under which nearly all workers can be repeatedly exposed without adverse health effects. Unlike recommended standards, such as ACGIH TLVs or NIOSH RELs, Korean OELs are legal notifications, similar to US. OSHA PELs. Korean OELs also include several levels, such as the TWA (time weighed average), STEL (short-term exposure limit), and C (ceiling). The Korean OEL units are ppm and mg/m^3 for gas and vapour, mg/m^3 for dusts, n/cm^3 for asbestos and ceramic fibres, dB for noise, and WBGT for temperature. There are also notations for skin and carcinogens, including GHS carcinogen classifications 1A, 1B, and 2. Plus, special consideration is applied to OELs when assessing the health hazards associated with exposure to a mixture of two or more chemicals[171].

A.9.3 Occupational health risk assessment policies

According to the Occupational Safety and Health Act, which was recently amended and enforced into effect on 13 March 2014, an employer is required to find and characterize risks in the workplaces and take proper measures necessary based on the result of the risk assessment. If human health effects caused by nanomaterials are revealed clearly and give concerns, an employer should perform risk assessment on nanomaterials as well as their chemicals. Due to lack of information on human health effects by nanomaterials, occupational health risk assessment policies seem to be discussed sooner or later in light of the results of research performed domestically or internationally.

A.9.4 NOAA-specific OELs

In regards to nanomaterials, there are no specific regulations, PELs or OELs. However, if necessary, the PELs and OELs can be applied as a standard in the management of work environment until the PELs or OELs are developed.

A.10 United Kingdom

The UK implements Indicative Occupational Exposure Limit Values (IOELVs) set under the EU Chemical Agents Directive (98/24/EC) as Workplace Exposure Limits (WELs) (see A.4.1 and A.4.2).

WELs are established under the legal framework of the Control of Substances Hazardous to Health Regulations (COSHH) and are published via EH40/2005 Workplace exposure limits[172].

A.11 United States of America

A.11.1 Regulatory exposure limits (OSHA, MSHA, EPA)

A.11.1.1 Legislation, organization and processes

The U.S. Federal regulatory agencies that develop and/or implement OSH guidance and regulations include the Occupational Safety and Health Administration (OSHA), the Mine Safety and Health Administration (MSHA), and the Environmental Protection Agency (EPA). The manufacturing and use of engineered nanomaterials in occupational settings for general industry falls under OSHA. Although there are no specific OSHA regulations on manufactured nanomaterials at this time, occupational exposures to nanomaterials would be covered in existing regulations and requirements, including the OSH Act General Duty Clause [29 USC 654, Section 5(a)1]; the Hazard Communications Standard (29 CFR 1910.1200); the Personal Protective Equipment Standard (29 CFR 1910.132); the Respiratory Protection Standard (29 CFR 1910.134); the Hazardous Chemical in Laboratories (29 CFR 1910.1450) [173][174], as well as several specific chemical substance regulations[175]. The OSHA and MSHA regulatory OELs are called permissible exposure limits (PELs). EPA regulates NOAAs under the authority of the Toxic Substances Control Act (TSCA) of 1976[175], which includes evaluating the risks of chemical substances to the environment and to humans, including workers.

A.11.1.2 Science and methods for OEL setting

In general, in developing regulatory standards, OSHA considers whether the standard eliminates or substantially reduces significant risk of harm, as well as the technological and the economic feasibility of the PEL. In a 1980 Supreme Court benzene decision, the court decided that it is the agency's responsibility to determine what is considered to be a significant risk[176]. They also suggested that a 1/1 000 lifetime excess risk of serious occupational disease (in this case, dying from cancer associated with exposure to benzene in gasoline) would be considered a significant risk that would warrant preventive action. As a general rule, OSHA uses risk at levels from 1/1 000 to 1/1 000 000 to determine the general boundaries for review in making significant risk determinations.

A.11.1.3 Occupational health risk assessment policies

In the U.S., regulatory OELs set by OSHA take into account technological and economic feasibility on an industry-by-industry basis, which requires that OSHA research all applications of the hazard being regulated, as well as the expected cost for mitigating exposure to that hazard, in every industry[177]. The assessment of technological feasibility includes identification of the controls required by the proposed OEL and determination if each of them is technologically feasible for employers to implement. The assessment of economic feasibility includes evaluation of the ability of the affected industries to maintain long-term profitability and competitiveness.

A.11.1.4 NOAA-specific OELs

Currently, most regulatory activities for nanomaterials in the U.S. are being performed according to criteria defined in TSCA, although none has resulted in OELs. Under TSCA, chemical substances are defined based on their molecular identity rather than on physical properties such as particle size[178]. Nanomaterials that have the same molecular identity as other substances on the TSCA inventory would be regulated the same way (on a mass or volume basis). Examples include titanium dioxide, silicon dioxide, iron, and gold[175]. Nanomaterials that are not on the TSCA inventory are considered new chemicals. New chemical nanomaterials include carbon nanotubes and fullerenes because they are different allotropes of carbon than currently on the TSCA inventory. Section 5 of TSCA requires that new chemicals undergo EPA review before they can be manufactured in the U.S. As part of this review process, EPA requires the submission of a Premanufacture Notice (PMN) including information on the anticipated production volume and use and any data on exposure or adverse health effects. Under TSCA, EPA has issued Significant New Use Rules (SNURs) for several types of CNTs, nano-metal oxides, and other nanomaterials, which specify certain requirements pertaining to the manufacture and use of these materials, including reporting requirements, and the use of respirators and other personal protective measures for workers when exposures are likely to occur.

At this time, no regulatory OELs have been adopted for NOAAs. In the absence of NOAA-specific OELs, the existing PELs for particulate substances also apply to NOAAs that have the same chemical composition. These PELs may include, for example, titanium dioxide (15 mg/m^3, total dust); Particles Not Otherwise Regulated (PNOR) (5 mg/m^3, respirable dust); graphite (5 mg/m^3, respirable); and carbon black (3,5 mg/m^3). In the absence of NOAA-specific PELs, these PELs for "bulk" materials may be cited on material Safety Data Sheets (SDSs).

Additionally, for the fibre-structured nanomaterials, no PELs have been developed. The asbestos PEL is 0,1 f/cc for structures with a >3:1 aspect ratio, >5 µm in length, and visible by Phase-Contrast Microscopy (i.e. >250 nm in width), and only applies to the six specific types of asbestos fibres classified by IARC and NIOSH. The applicability of the existing PELs to nanoscale particles and fibres has not been evaluated in most cases.

A.11.2 Non-regulatory exposure limits (NIOSH)

A.11.2.1 Legislative origin, organization and processes

Established in the OSH Act of 1970, NIOSH provides scientific research, evaluation, and guidance in occupational safety and health (OSH). Guidance includes recommended exposure limits (RELs), sampling and analytical methods, medical monitoring, training, labelling and record keeping. NIOSH recommendations are transmitted to the applicable U.S. regulatory agency (generally OSHA, or MSHA) for consideration in the development of OSH rules and regulations.

A.11.2.2 Science and methods for OEL setting

NIOSH incorporates data from multiple disciplines in its OSH recommendations, including findings from epidemiology, toxicology, risk assessment, and exposure measurement studies. When data are sufficient, NIOSH uses quantitative risk assessment methods[29][179]. A comprehensive risk assessment includes the following components: an initial problem formulation step, a four-step risk assessment process including hazard evaluation, exposure assessment, dose-response analysis, and risk characterization; as well as risk communication at each stage of the process, and utilization of the information in the comprehensive risk assessment for risk management decision-making.

Epidemiology and/or toxicology studies are evaluated in hazard and risk analyses that are performed to develop OSH recommendations. If sufficient exposure (and/or dose) and response data are available, quantitative risk analyses are performed to determine the likelihood of adverse health effects in a worker population. Epidemiology data, when available and of sufficient quality, are given priority for risk estimation. Toxicology data from experimental animal studies are also evaluated when these studies provide adequate dose-response data in a relevant animal model and for health endpoints of relevance to humans. Inhalation exposures and respiratory effects is a focus of many NIOSH RELs, generally measured as personal breathing zone samples. Quantitative risk assessments have evaluated

endpoints including pulmonary fibrosis and cancer. Benchmark dose (BMD) modelling to estimate a point of departure (for low-dose and interspecies extrapolations) is preferred over a NOAEL or LOAEL (lowest observed adverse effect level). BMD estimation is a standardized, statistically-based method to estimate the dose associated with a specified level of an adverse effect[22]. The BMDL (95 % lower confidence limit, LCL, estimate of the BMD) is a typical point of departure (for example, $BMDL_{0.1}$ is the dose associated with a 10 % added risk of an adverse effect).

A.11.2.3 Occupational health risk assessment policies

For carcinogenic substances, linear, low-dose extrapolation is the default assumption used by NIOSH in risk estimation unless adequate evidence is available to support a non-genotoxic mechanism and nonlinear dose-response relationship[50]. Limited guidance is available on acceptable risk levels for carcinogens. The U.S. Supreme Court[176] gave an opinion in the "benzene decision" that a risk of 1 case of leukaemia among 1 000 workers due to occupational exposure to benzene would be considered a significant risk and that regulatory efforts to reduce those risks would be warranted. For this reason, NIOSH adopted a policy in 1995 to perform quantitative risk assessment (QRA) and develop RELs for carcinogenic substances when sufficient data are available (vs. a default policy of "lowest feasible concentration"). In this QRA, NIOSH includes estimates of the exposures associated for a 1/1 000 risk of cancer over a 45-year working lifetime. The NIOSH carcinogen policy is currently undergoing review and update to incorporate more recent advancements in science and to facilitate the process of evaluating the scientific evidence with regard to carcinogenic hazard classification[180].

For non-carcinogens, the mode-of-action evidence is also considered in low-dose extrapolation and may include linear or nonlinear modelling assumptions. When data are limited, an alternative to model-based low-dose extrapolation is the use of uncertainty factors applied to the estimated point of departure (BMDL, NOEAL, or LOAEL). Acceptable/unacceptable levels of risk have not been well-established for non-carcinogenic occupational hazards.

NIOSH considers both the health effects data and the technological feasibility of measuring and controlling exposures in developing RELs for both carcinogens and non-carcinogens. Thus, RELs may be associated with residual risks of adverse health effects given exposures up to a full working lifetime. NIOSH recommends additional occupational risk management measures to reduce those risks, including evaluation of engineering control options[58], training and fit-testing of respirators[181] and medical surveillance considerations[182].

For example, technological feasibility played a key role in recommending the NIOSH REL for CNTs and CNFs. The NIOSH REL for CNTs and CNFs of 1 µg/m^3 was set at the analytical limit of quantification for the NIOSH sampling and analytical method for airborne elemental carbon[58]. NIOSH further recommended that exposures to CNTs and CNFs be kept below the REL since the risk assessment (based on subchronic or short-term studies in rodents) suggested a residual risk of early stage adverse lung effects at the REL of 1 µg/m^3 over a 45-year working lifetime.

A.11.2.4 NOAA-specific OELs

A.11.2.4.1 Titanium dioxide

In 2011, NIOSH issued a Current Intelligence Bulletin on Occupational Exposure to Titanium Dioxide which summarized hazard, exposure and risk assessment available up to the date of publication and proposed recommended exposure limits for two size fractions; nanoscale and fine particles[50].

In 1988, NIOSH recommended that TiO_2 be classified as a potential occupational carcinogen and that exposures be controlled as low as feasible[183]. This recommendation was based on the observation of lung tumours (non-malignant) in a chronic inhalation study in rats at 250 mg/m^3 of fine TiO_2[70] [184]. Later, a 2-year inhalation study showed a statistically significant increase in lung cancer in rats exposed to ultrafine TiO_2 at an average concentration of 10 mg/m^3[69]. Two epidemiologic studies have not found a relationship between exposure to total or respirable TiO_2 and lung cancer[185][186], although an elevation in lung cancer mortality was observed among male TiO_2 workers in the latter study when compared to the general population (standardized mortality ratio [SMR] 1,23; 95 % confidence interval [CI] = 1,10 to 1,38). However, there was no indication of an exposure-response relationship in that