

Nano reference values in the Netherlands

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B. Hendrikx, P. van Broekhuizen

Summary

Nano reference values were developed in the Netherlands as a risk management tool for manufactured nanomaterials (MNM), to be used as a provisional substitute when nano-specific OELs or DNELs are not available. This article describes the reasons for their development and the context in which the development took place. It also includes questions such as how to apply the precautionary principle to the practical use of MNMs in the workplace and identify barriers that may hamper full acceptance of nano reference values (NRVs).

1 Introduction

Manufactured nanomaterials (MNM) are used in Dutch companies and institutions despite continuing uncertainty as to their potential health risks and how to manage them. It is normal practice to assess exposure to chemicals in relation to their occupational exposure limit (OEL) which in principle also applies to exposure to MNMs. At present, existing scientific knowledge is insufficient to derive an occupational exposure limit for nanoparticles¹. The use of provisional NRVs has therefore been introduced as an alternative. NRVs are based on the precautionary principle and should be used by employers and employees as a risk management tool when working with MNMs. Moreover, applying the precautionary principle implies that the duration and intensity of exposure must be minimized when people are faced with uncertain risks.

It should be noted that the MNMs referred to in this article are ordinary first-generation MNMs, e.g. metals, metal oxides and carbon nanotubes. Second, third and even fourth-generation nanomaterials have been disregarded².

The article discusses the development of NRVs and outlines the context in which they can be used.

¹ It should also be noted that scientific knowledge is increasing rapidly but that a number of fundamental problems and dilemmas are looming which require a solution, such as the issue of particle toxicology.

² Examples of these generations are: nanoparticles that contain a dedicated drug-delivery system (second generation); third-generation nanotechnologies include new robot-like systems or three-dimensional networks; fourth-generation nanotechnologies could result in molecule-by-molecule design and self-assembly capabilities.

2 Background to the creation of nano reference values (NRVs)

2.1 SER advisory report: Nanoparticles in the Workplace: Health and Safety Precautions

What prompted the development of NRVs was the advisory report “Nanoparticles in the Workplace: Health and Safety Precautions” by the Working Conditions Committee of the Social and Economic Council of the Netherlands (hereafter: SER) from 2009 [1]. This advisory report described NRVs as a potentially useful tool for managing health risks.

The advisory report was a response to the request for a formal opinion as submitted by the Dutch Minister of Social Affairs and Employment which essentially concerned the question of how to deal with uncertainties relating to the risks posed by persistent synthetic nanoparticles in an occupational environment.

The focus for the SER was the health and safety of employees who work with nanoparticles on the shop floor, as well as the employer’s duty of care in providing a safe and healthy workplace, as enshrined in the Dutch Working Conditions Act. The basic principle was that substances attended by unknown or uncertain risks – which includes nanoparticles – should be treated as hazardous (or extremely hazardous) substances. This means that the policy and implementation measures in such cases should focus on preventing or minimizing exposure of employees to those substances. For the SER, the Dutch Working Conditions Act and the associated regulations form the basis for taking protective measures. EU chemicals legislation in the form of REACH, the OSH Framework Directive [2] and the Chemical Agents Directive (CAD) [3] are of great importance in this regard.

The SER stresses that the focus when working with MNMs is on dispersive, insoluble and persistent nanoparticles and therefore that working with dry, powdery MNMs requires a more thorough attention than working with MNMs which are embedded in solid or liquid matrices. After all, it is known that airborne nanoparticles behave like a gas and can penetrate deep into a person’s lungs. Any protective measures should therefore focus on this aspect and classic occupational health strategy should be the guiding principle.

In view of the unknown and uncertain risks associated with working with nanoparticles, the SER considers it advisable to apply the precautionary principle. This principle must be implemented in health and safety policy in a clear and easily understood manner. This means, *inter alia*, that it is or should be part of the mandatory RI&Es (Risk Inventories and Evaluations) and the resulting action plans. In other words, the employer’s efforts should focus on preventing exposure to nanoparticles and – where exposure is unavoidable – on keeping the duration and intensity of the exposure as low as possible, i.e. on minimizing exposure.

The precautionary principle

The precautionary principle was first explicitly defined at the worldwide policy forum in 1992 in the Declaration of the UN Conference on Environment and Development in Rio de Janeiro (Principle 15). The principle was subsequently reformulated a number of times by different committees and authors, but all the different versions share a number of key concepts for its application:

- Scientific uncertainty: in relation to the dangers and risks that substances pose to humans and the environment, but also uncertainties as to the likelihood and/or extent of possible damage.
- Concern for harm: this is about concern for the likelihood of serious or irreversible harmful consequences for the environment and for human, animal and plant health.
- Weighing up of advantages and disadvantages: the dangers and risks of an activity must where possible be expressly weighed against the societal pros and cons of that activity.
- Transparent decision-making process and involvement of stakeholders: transparency of the decision-making process, with a clear division of responsibilities between government, business and the public, and the involvement of all stakeholders at the earliest possible stage in the process.
- Active stance: a continuously active stance and attitude is required.

With regard to scientific uncertainty, the SER concluded that there are still insufficient data to obtain a complete picture of the potential health risks of exposure to MNMs, there is sufficient evidence to suggest that its effects could cause harm to health. This justifies adopting a precautionary approach, prioritizing concern for health and the environment over economic considerations and putting into practice the principle of “no data, no exposure”.

The application of the precautionary principle is a temporary measure. The SER therefore advised the Minister to request the Health Council of the Netherlands to give priority to establishing health-based occupational exposure limits for the most frequently used nanoparticles. And, the SER added, if this is not feasible, a practical reference value should be established.

The practical impossibility of reliably establishing exposure levels (OELs or DNELs) at the time was the reason that the SER provisionally accepted a different approach to the exposure limit concept: nano reference values (NRVs).

NRVs are a guide for employers to help them fulfil their duty of care: the statutory obligation to provide information on the nature, intensity and duration of the exposure and provide a means of taking measures within their business.

The NRV concept accepts a paradigm shift in risk assessment in which a “hazard-based approach” focusing on toxicity is replaced by a “concern-based approach”. In fact, it is an

approach based on expected and possible toxic effects and the concern that this generates. This means changing the way we think: risk is not regarded as the product of toxicity and exposure (risk = hazard x exposure) but the product of (the degree of) concern and exposure (risk = concern x exposure). This also emphasizes the importance of accepting the principle of “no data, no exposure”. As a precaution, a choice is now made on the basis of concern.

Furthermore, the SER considered enforcement and information to be of major importance, as were the broadening, generation and dissemination of knowledge. The SER also advised the Minister to ask the Health Council of the Netherlands to issue specific recommendations on the options for establishing an early warning system, to investigate the possibilities of imposing a notification requirement in the chain, to have standard information included in SDSs (Safety Data Sheets), to introduce an exposure register and help to encourage the development of a set of national guidelines and the dissemination of knowledge and information.

2.2 Government response to the SER’s advisory report

In the government response to the SER advisory report, the Minister of Social Affairs and Employment endorsed the application of the precautionary principle [4]. The Minister commented that with the current state of knowledge (mid-2009) it was not yet possible to establish health-based occupational exposure limits for nanoparticles.

As far as NRVs were concerned, the Minister did decide to recommend them, but not to enshrine them in law. The reason for this was that it would take away the responsibility for safety in the workplace from where it belonged, i.e. with any employer who decides to use nanoparticles on technical or commercial grounds. Moreover, enshrining NRVs in law could cause confusion because they would then be the first statutory occupational exposure limits not to be health-based³.

2.3 Actions arising from the SER advisory report

Coinciding with the government response was the publication of the strategy letter from the Minister of Housing, Spatial Planning and the Environment (now known as the Ministry of Infrastructure and the Environment) "Dealing with the risks associated with nanoparticles" which provided the Dutch Parliament with detailed information on the course taken to deal responsibly with the (uncertain) risks posed by nanoparticles [5]⁴.

The Dutch Parliament carried a motion on the subject which urged the government to establish nano reference values and investigate the possibilities of setting up an exposure register and an early warning system for working with nanoparticles [6]. The Minister

³ We do not subscribe to this argument because, we believe, statutory exposure limits for genotoxic, carcinogenic substances without safety thresholds based on the calculation of risk data are not, strictly speaking, health-based either.

⁴ The Health Council's advisory report *Working with nanoparticles: exposure register and health monitoring*, was published in 2012, Pub. No. 2012/13.

wasted no time in addressing these issues [7] and arranged for a group of experts on working conditions to be established under the direction of RIVM/KIR-*nano* to assess the usefulness of the concept of nano reference values (KIR-*nano* = Knowledge and Information Centre for Risks of Nanotechnology operated by the National Institute for Public Health and the Environment (RIVM)).

2.4 RIVM report on provisional nano reference values

The RIVM reached the following conclusions [8]:

- The concept of nano reference values was, in principle, considered useful.
- The NRVs were to be used as a provisional pragmatic benchmark pending the establishment of specific health-based occupational exposure levels for nanomaterials. In practice, employers must always try to keep exposure to nano materials as low as possible (the ALARA principle, ALARA = as low as reasonably achievable), even if this means that the exposure is much lower than the provisional nano reference value.
- The method used by the British Standards Institution (BSI) to establish nano reference values⁵ is not directly applicable.
- The generic approach adopted by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA) [9] involving benchmarks for groups of nanomaterials expressed as a number of particles per cm³ is directly applicable in the Netherlands.

It should be stressed that the unit chosen in which to express the NRV, i.e. the nanoparticle concentration (the number of nanoparticles per cm³), is preferred over the mass concentration. The mass-based approach is normal for molecular chemicals but, according to experts, less suitable for nanomaterials. This is because nanoparticles can differ substantially from each other in shape and size and an approach involving the number of particles similarly reflects the observed effects of exposure to MNMs and is also a good approach for the particle surface concentration approach actually desired. The preferred unit for fibrous nanomaterials is the number of fibres per cm³.

2.5 The social partners' pilot reference values

The benchmark level concept as developed by IFA was adopted by the Dutch social partners – the main employers' organization VNO-NCW (VNO Verbond van Nederlandse Ondernemingen and NCW Nederlands Christelijk Werkgeversverbond) and the trade unions FNV (Federatie Nederlandse Vakbeweging) and CNV (Christelijk Nationaal Vakverbond) – as a precautionary, generic hazard-banding concept which assumes that

⁵ It implicitly includes the method used by the National Institute for Occupational Safety and Health (NIOSH), which forms an integral part of the BSI method.

the particles' surface triggers the potential effects and can be characterized by the size and the density of the nanomaterials. The benchmark levels were referred to as NRVs and used in the pilot NRV (carried out in practice by a consortium consisting of: IVAM University of Amsterdam, University of Twente and Industox Consult), with the aim of exploring the practical usefulness of NRVs. The level of the NRVs was calculated as the particles' number concentration required to attain a mass concentration of 0,1 mg/m³ for particles in the size range up to 100 nm.

For granular nanoparticles with a sphere-like shape, and normalized at a diameter of 100 nm, these calculations lead to two risk bands for insoluble granular nanoparticles: a risk band of 40,000 particles/cm³ for nanomaterials with a density < 6,000kg/m³ and a risk band of 20,000 particles/cm³ for nanomaterials with a density > 6,000kg/m³. Consequently, for granular nanoparticles with a smaller diameter the mass-based benchmark level is stricter: for nanoparticles with a 50 nm diameter, a factor 8, and with a 20 nm diameter, a factor 125. For rigid, biopersistent nanofibers for which asbestos-like effects cannot be ruled out (including carbon as well as metal(oxide) nanotubes), a provisional fibre concentration of 10,000 fibres/m³ applies, based upon the German exposure risk ratio for asbestos [10]. Regarding the Dutch limit value for asbestos, which will be further reduced in the near future, this benchmark might even have to be set at a lower level [11]⁶. For soluble nanomaterials a risk-band similar to the OEL for the coarse (or molecular) form applies. In addition to the calculated values for an 8-hours time weighed average exposure, an approach for short term peak exposures of 15-minutes time weighed average was introduced. **Table 1** shows the four hazard bands for MNMs.

In 2010 to 2011, twelve companies assessed the feasibility of the NRVs in the "nano workplace", identified the barriers and further implemented the tool for NRVs [12; 13].

The pilot NRVs [14] recommend splitting the NRVs into four classes of nanomaterials and regarding them as provisional values, defined as 8-hour time-weighted average concentrations (8-hour TWA), which will be replaced as soon as HBR-OELs or DNELs (HBR-OELs = health-based recommended occupational exposure limits; DNELs = derived no effect levels, drawn up as part of REACH) become available for the specific nanoparticles or for a group of similar nanoparticles. NRVs are also defined for short-term peak exposures, for a 15-minute TWA. One important conclusion is that the NRVs are useful as a tool for managing risks in companies that work with MNMs. The pilot NRV also contains a number of recommendations on the scope of NRVs, nanoparticles in the workplace and legislation.

The conclusions and recommendations were discussed and assessed at the International Workshop on Nano Reference Values [15], held on 29 September 2011 [16].

The actual recommendations made by the social partners with regard to the NRV were then set out in an SER advisory report [17].

⁶ The new limit value will be valid from 1 January 2014.

Table 1: NRVs for four hazard bands for MNMs; SWCNT = SWCNT = single-wall carbon nanotubes, MWCNT = multi-walled carbon nanotubes.

Class	Description	Density in kg/m ³	NRV (8-hour TWA)	Examples
1	Rigid, biopersistent nanofibres for which asbestos-like effects cannot be ruled out	-	0.1 fibres/cm ³ (= 10,000 fibres/m ³)	SWCNT, MWCNT or metal oxide fibres for which the manufacturer cannot rule out asbestos-like effects.
2	Biopersistent granular nanomaterials in the range of 1 and 100 nm	> 6,000	20,000 particles/cm ³	Ag, Au, CeO ₂ , CoO, Fe, Fe _x O _y , La, Pb, Sb ₂ O ₅ , SnO ₂ ,
3	Biopersistent granular and fibrous nanomaterials in the range of 1 and 100 nm	< 6,000	40,000 particles/cm ³	Al ₂ O ₃ , SiO ₂ , TiN, TiO ₂ , ZnO, nanoclay, carbon black, C ₆₀ , dendrimers, polystyrene Nanofibres for which asbestos-like effects have been explicitly ruled out
4	Non-biopersistent granular nanomaterials in the range of 1 and 100 nm	-	Normal exposure limit	Examples: fats, table salt (= NaCl)
NB:	For short peak exposures: $NRV_{15\text{-min TWA}} = 2 \times NRV_{8\text{-hour-TWA}}$			

3 Provisional nano reference values

3.1 The recommendation

On 23 March 2012, the SER (i.e. the SER's Working Conditions Committee) adopted its recommendation on provisional nano reference values for synthetic nanomaterials (MNMs). It made this recommendation on its own initiative.

3.2 The reference value

The NRV is a pragmatic limit which serves as a warning that measures (or preventive measures) have to be taken. Companies that exceed the NRV must act immediately and take appropriate measures to prevent exposure or reduce it to the level of the reference values. Businesses and companies that comply with the NRVs do not need to take any additional measures. They are however required to keep exposure (to nanoparticles) as low as possible. Health-based exposure limits already exist for many small (ultra-fine) particulate concentrations, e.g. in the case of welding (for welding fumes). The current exposure level should be applied for these substances.

For the definition of the NRV with regard to the dimensions of nanoparticles, it has been decided to adhere to the definition used by the European Commission, where 100 nm is the upper limit for the diameter of nanomaterial [18]⁷. This definition does not provide any conclusion as to the potential risks of nanoparticles. It should be stressed that larger agglomerates exceeding 100 nm in size can cause a correspondingly harmful impact on health and therefore that nanoparticles with a diameter larger than 100 nm cannot simply be disregarded in the risk assessment.

3.3 Considerations on the use of NRVs

One consideration in the agreements made on the use of NRVs is that there is always a background concentration of nanoparticles of natural and anthropogenic origin in the open air. In addition, nanoparticles can also be created in the workplace, i.e. process-generated nanoparticles (PGNPs) from electrical equipment, combustion and heating (combustion-derived nanoparticles, CDNPs) and other high-energy processes (e.g. laser). They can also be released when some "conventional" components of products are used which contain a fraction of particles with nano dimensions of "larger particle components". In terms of toxicity, PGNPs are similar to MNMs (there are also still many ambiguities for PGNPs in this regard) and it is probable that PGNPs also agglomerate or aggregate with the MNMs. Using simple measuring equipment, it is difficult to distinguish the nanoparticles in the background and the PGNPs from the MNMs and they are usually measured as a single total concentration. However, it is possible to distinguish them to some extent with a meticulous measurement protocol, but extensive and costly laboratory analyses are necessary to make a clear distinction.

The concentration gradient of MNMs in the workplace air is usually characterized by short bursts of high peak concentrations. Added to this is the fact that concentrations of MNMs which are released are usually occasional occurrences whereas PGNPs are often permanent and can therefore increase exposure levels.

The schematic structure of nanoparticles in the workplace air is shown in **Figure 1**.

The concentration of MNMs in the breathing zone in the workplace may be lower or higher than the NRV, in which case a different action applies. This is explained in an action plan in **Table 2**.

The actions outlined in Table 2 are graphically represented in the diagram below. The following measurement strategy can be used to determine whether the concentration of nanoparticles in the workplace exceeds the NRV (see **Figure 2**).

⁷ "Nanomaterial" means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm to 100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.

Figure 1: Schematic (possible) structure of nanoparticles in the workplace air.

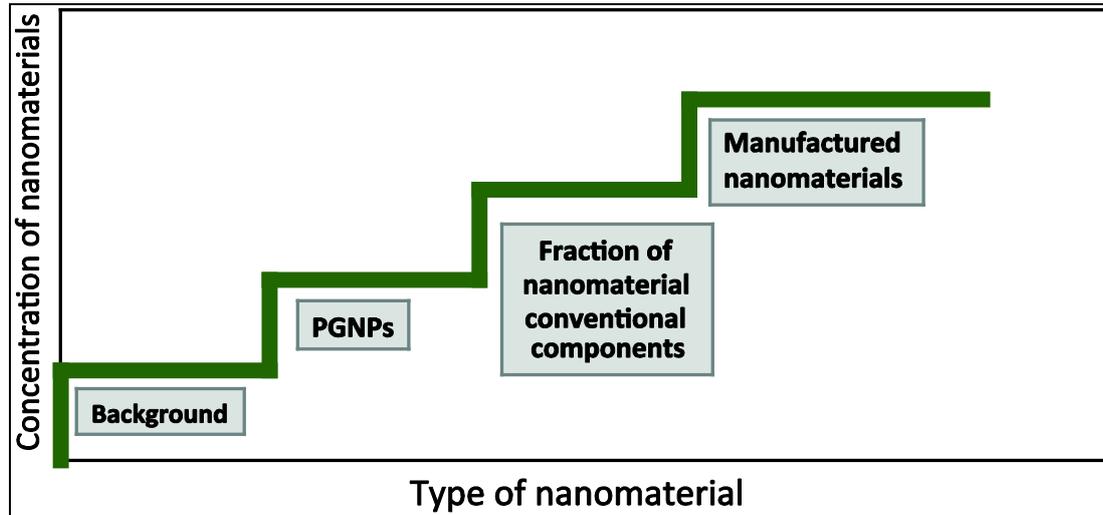
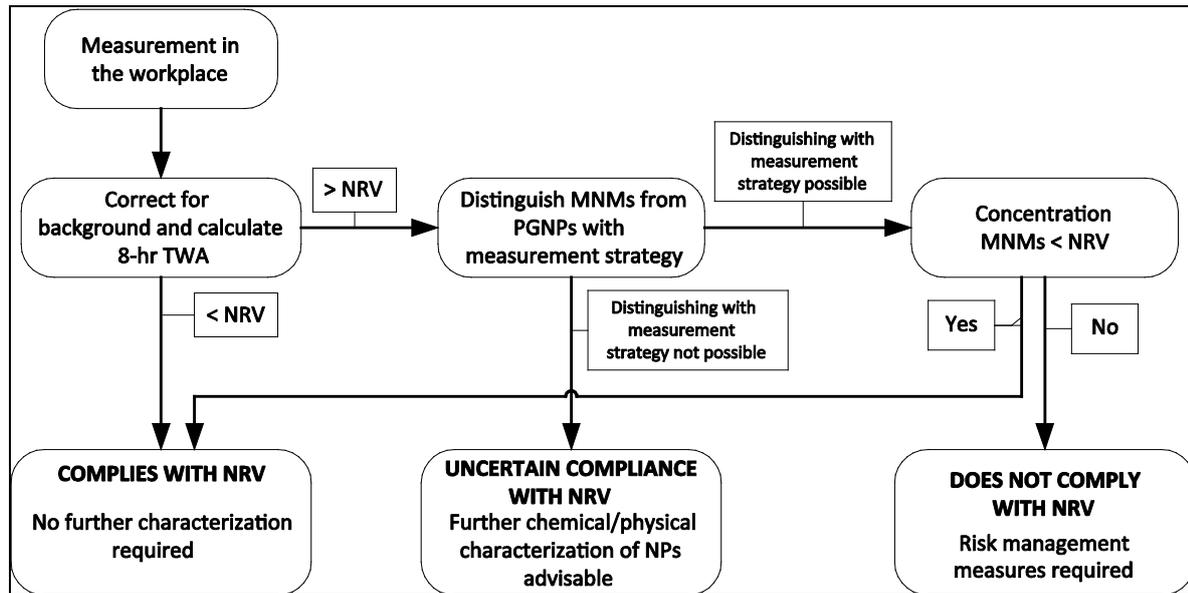


Table 2: Actions following application of the NRV.

	Action
<p>Concentration < NRV</p> <p>No further chemical/physical characterization required</p>	<ol style="list-style-type: none"> 1. Measurements indicate that the 8-hr time weighted average (TWA) concentration of MNMs in the breathing zone (nanoparticles/cm³), corrected for the background concentration, is lower than the NRV for the MNM. 2. There may be nanoparticles in the breathing zone generated by process-based MNMs, by the processing equipment used or by the use of heating or combustion processes. In addition, conventional products may sometimes also contain a fraction of nanoparticles that are dispersed into the breathing zone when used. 3. There is no need to further characterize (chemical/physical analysis) the nanoparticles in the breathing zone. 4. The recommendation is that reasonable measures must be taken (the aim being to reduce the duration and intensity of exposure to nanoparticles as much as possible). 5. Repeated exposure measurements are recommended whenever the process is altered.

	Action
<p>Concentration > NRV</p> <p>Risk management measures required</p>	<ol style="list-style-type: none"> 1. Measurements indicate that the 8-hr TWA concentration of MNMs in the breathing zone (nanoparticles/cm³), corrected for the background concentration, is higher than the NRV for the MNM. 2. There may be nanoparticles in the breathing zone generated by the processing equipment used, or by the use of heating or combustion processes. In addition, conventional products may sometimes also contain a fraction of nanoparticles that are dispersed into the breathing zone when used. 3. All possible technical measures must be taken in order to reduce exposure to below the NRV or..... 4. The nanoparticles in the breathing zone must be distinguished into MNMs and process-generated nanoparticles (PGNPs). It may be possible to make this distinction by using a special measurement strategy. If this is not possible, then the two categories must be distinguished by means of an elaborate physical/chemical analysis. 5. If the elaborate analysis shows that the concentration of MNMs in the breathing zone is lower than the NRV, the recommendation is that reasonable measures must be taken (the aim being to reduce the length and intensity of exposure to small particles as much as possible). 6. If detailed analysis shows that the concentration of MNMs in the breathing zone is higher than the NRV, the recommendation is that all possible technical measures must be taken to reduce exposure to below the NRV.
<p>PGNP > NRV</p> <p>Further chemical/physical characterization of NP advisable</p>	<p>It is possible that the elaborate physical/chemical analysis shows that the production process is generating PGNPs in a concentration higher than the NRVs. This means that many other nanoparticles are being generated in the workplace, even if engineered nanomaterials are not being used. In many cases, an OEL has not (as yet) been set for such particles, and Table 1 for NRVs does not apply to them. The recommendation, however, is to take reasonable measures to reduce the concentration of particles in the workplace (after all, it is better for health to reduce the length and intensity of exposure to small particles as much as possible).</p> <p>An exception concerns particles for which a health-based occupational exposure limit has already been set (for example welding fumes). The applicable OEL should be enforced for those particles and agreed operational procedures for these activities should be followed.</p>

Figure 2: Measurement strategy used to determine the concentration of nanoparticles.



- The workplace concentration can be measured in accordance with the strategy as described in Dutch standard NEN 689 which states that the criterion for effective management is satisfied if the standard is not exceeded 95% of the time (95 percentile of the frequency distribution is < NRV). In one measurement, 10% of the standard is used to comply with this because of the wide variability of exposure.
- A measurement strategy that distinguishes between MNMs and PGNPs is, for example, to carry out a measurement on live equipment without using nanomaterials, followed by completion of the process using nanomaterials. The difference between the two concentration measurements may indicate the emission of MNMs (the situation has to be carefully interpreted in this case as well).

The Precaution Characterization Ratio (PCR) can be used as a way of communicating measurement data.

$$PCR = \frac{\text{concentration of nanoparticles}}{NRV}$$

The PCR concept is consistent with health and safety policy. If the PCR is greater than 1, further characterization of the nanoparticles and an initiative to take risk mitigation measures are required.

3.4 Recommendations for the social partners and the government

The SER recommends that the social partners draw the NRVs to the attention of employers and employees in industry and to encourage them to use these values. It also recom-

mends that industry-specific good practices should be developed to show them safe and acceptable ways of working with MNMs.

Ideally, the NRVs and the good practices should be laid down in a health and safety catalogue. The NRVs are also included in the action plan in the guide "Safe working with nanomaterials" (a joint publication by the employers' association VNO-NCW and employee organizations FNV and CNV).

The SER recommends that the Dutch government should use the NRVs in inspections (by the Labour Inspectorate). It recommends that industry should use NRVs. The SER is also asking the government to commission research to ascertain whether it is possible, following the appropriate procedure, to establish an occupational exposure limit for the PGNPs (EGNPs and CDNPs).

3.5 Response of the Minister of Social Affairs and Employment to the advisory report

The Minister for Social Affairs and Employment published his position with regard to this recommendation on 11 December 2012: The Minister accepted all of the proposals and recommendations.

He endorsed the recommendation that the social partners should draw the NRVs to the attention of employers and employees and encourage them to apply these values. The NRVs should also be included in the action plan in the guide "Safe working with nanomaterials". He agreed that, ideally, the NRVs and the (industry-specific) good practices (which show safe and acceptable ways of working with MNMs) should be laid down in a health and safety catalogue.

The Minister agreed that the NRVs should be used in inspections of industrial premises by the Labour Inspectorate.

In order to increase the use of NRVs, he posted the recommendation on the Dutch government's health and safety portal on the Internet.

He kept his promise to inform the European Commission of the advisory report on NRVs and to advocate the use of NRVs for MNMs in Europe by writing a letter to Commissioner *László Andor* on 6 June 2013 [19].

4 Conclusions

The NRVs can be expected to receive wide support from industry and government. The careful consideration given by the social partners has played a major part in the achievement of this acceptance. In addition, political pressure to adopt a provisional approach also had an effect.

The principle of "no data, no exposure", the generally accepted interpretation of the precautionary approach, has been put into practice by adopting a concern-based approach to

the use of NRVs when working with MNMs. The importance of this should not be underestimated: it provides a practical and easy to understand point of reference (as at 2013) for a situation in which there is still a great deal of uncertainty among employers and employees with regard to the potential risks of MNMs and how to deal with them. As such, the NRVs are a practical aid for employers that enables them to fulfil their statutory obligation to provide a safe and healthy workplace. They enable employers to weigh up the acceptability of the current nature, intensity and duration of the exposure and also provide them with guidance on the measures to take in order to manage the risk. This guidance is usually successful with conventional management measures, which is an additional practical advantage.

In principle, NRVs are a temporary measure: when health-based occupational exposure levels for MNMs become available, they will be the preferred option. However, this is expected to take some time.

In conclusion: the NRVs are not only regarded as a practical, provisional tool in the Netherlands. The Finnish Institute for Occupational Health recommends the use of NRVs [20]. With the announcement on manufactured nanomaterials [21], it appears that Germany also accepts the NRVs as a provisional approach to dealing with MNMs.

Translated from Dutch by: Balance Amsterdam/Maastricht

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Brigitte Hendrikx,
Sociaal-Economische Raad, Den Haag, Nederlande.
Pieter van Broekhuizen,
Research office IVAM of the University Amsterdam.