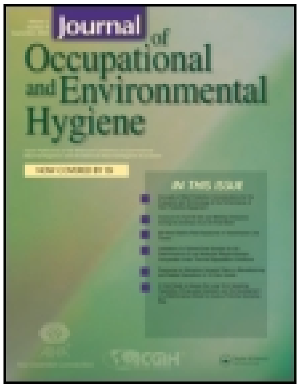

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Exposure Limit Values for Nanomaterials—Capacity and Willingness of Users to Apply a Precautionary Approach

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In the European Union, the legal obligation for employers to provide a safe workplace for processing manufactured nanomaterials is a challenge when there is a lack of hazard information. The attitude of key stakeholders in industry, trade unions, branch and employers' organizations, and government policy advisors toward nano reference values (NRVs) has been investigated in a pilot study that was initiated by a coalition of Dutch employers' organizations and Dutch trade unions. NRVs are developed as provisional substitutes for health-based occupational exposure limits or derived no-effect levels and are based on a precautionary approach. NRVs have been introduced as a voluntary risk management instrument for airborne nanomaterials at the workplace. A measurement strategy to deal with simultaneously emitting process-generated nanoparticles was developed, allowing employers to use the NRVs for risk assessment. The motivational posture of most companies involved in the pilot study appears to be pro-active regarding worker protection and acquiescent to NRVs. An important driver to use NRVs seems to be a temporary certainty employers experience with regard to their legal obligation to take preventive action. Many interviewees welcome the voluntary character of NRVs, though trade unions and a few companies advocate a more binding status.

Keywords nanomaterials, nano reference values, precautionary approach, occupational exposure limits, soft regulation

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The Chemical Agents Directive [1] lays down the minimum requirements for protecting workers from the adverse effects of chemical agents that are present at the workplace, or as a result of any work activity involving chemical agents. In principle, these minimum requirements regard nanomaterials as well. Dutch employers are required to assess the risks and control them.[2] In the case of nanomaterials for which toxicology information is lacking,[3] producers and users of nanomaterials are required to proactively obtain state of the art knowledge about managing exposure and health risk. Considerable gaps exist regarding hazard data and occupational exposure limits (OELs) for nanomaterials. To date, attempts have been made to derive health-based limit values only for several frequently used manufactured nanomaterials (MNMs): for carbon nanotubes (MWCNT),[4–7] for fullerenes (C60),[8] for TiO_2,[9,10] and for nano-Ag.[5]

However, a derivation of an OEL requires large amounts of toxicity data. It is complicated and expensive. Note that the term MNM is synonymous with the term engineered nanoparticle (ENP) as used by other hygienists. The composition of MNMs may be complex, being for example a multi-component material (e.g., with a surface coating of another composition or a material with specific active sites at the surface) and having a large particle size distribution with a possibly different hazard for different sizes.[11–13] The workplace air may also contain incidental nanoparticles that are generated by electrical equipment or combustion processes. In risk assessment these process-generated nanoparticles (PGNPs) and agglomerates thereof with MNMs have to be taken into account as well. In view of a lack of data a precautionary approach has been advocated.[14,15]

As a provisional alternative to OELs, the German Institute for Occupational Safety and Health (IFA) has developed benchmark levels for evaluating exposure to MNMs.[16] The benchmarks draw on the finding that the surface of the nanoparticles is an important determinant of hazard,[17–19] and use size, form, biopersistence, and density as parameters to distinguish four groups. For low-density (<6000 kg/m^3) and high-density (>6000 kg/m^3) granular nanomaterials, with a supposed sphere-like shape (diameter <100 nm), number-based benchmarks were established corresponding to a mass concentration of 0.1 mg/m^3. For carbon nanotubes (CNTs), which possibly exhibit asbestos-like effects the asbestos OEL is used as a benchmark level. The fourth group is composed of non-biopersistent nanomaterials. These benchmarks were further developed as nano reference values (NRVs) by social partners in the Netherlands.[20–23] The four classes of NRVs (8-hr time-weighted average; 8-hr TWA), as adopted by the Dutch Social Economic Council in 2012,[24] are shown in Table I.

NRVs are intended to be precautionary warning levels: when they are exceeded, exposure control measures should

TABLE I. NRVs for Four Classes of Manufactured Nanomaterials

Class	Description	Density	NRV (8-Hour TWA)	Examples
1	Rigid, biopersistent nanofibers for which effects similar to those of asbestos are not excluded	—	0.01 fibers/cm^3	SWCNT or MWCNT or metal oxide fibers for which asbestos-like effects are not excluded
2	Biopersistent granular nanomaterial in the range of 1 and 100 nm	>6000 kg/m^3	20,000 particles/cm^3	Ag, Au, CeO_2, CoO, Fe, Fe_xO_y, La, Pb, Sb_2O_5, SnO_2,
3	Biopersistent granular and fiber form nanomaterials in the range of 1 and 100 nm	<6000 kg/m^3	40,000 particles/cm^3	Al_2O_3, SiO_2, TiN, TiO_2, ZnO, nanoclay Carbon Black, C_{60}, dendrimers, polystyrene Nanofibers with excluded asbestos-like effects
4	Non-biopersistent granular nanomaterial in the range of 1 and 100 nm	—	Applicable OEL	For example, fats, NaCl

be taken. As such, they support compliance with the legal duty to control the health risks of MNMs. Use of NRVs requires measurement of the particle concentration and diameter and requires limited information about the identity of the processed (and measured) MNMs. For identification, information is required about the shape of the MNMs (fiber or sphere-like shape), its biopersistency, and information on the density of the nanomaterial.

Concurrently, NRVs are not legally binding. By regarding NRVs as part of the current state of science the Dutch Minister of Social Affairs and Employment has recommended the use of NRVs as provisional limit values that should be accompanied by additional measures to minimize exposure.[25,26] The Minister's recommendation can be regarded as a "soft" regulation.[27,28] Although not legally binding, this regulatory measure involves certain commitments to either employ the NRVs or search for alternatives.

In 2010 the Dutch social partners initiated a pilot study to investigate whether NRVs are accepted in practice and how their usefulness is perceived. One of the goals was to explore whether producers and users of nanomaterials are capable and willing to use NRVs. Such information can inform further regulatory action.

METHODS

The potential of compliance with the NRVs in the Netherlands was studied in a pilot program involving the nanomaterials-using industry. Workplace concentrations of nanoparticles (NPs) (and simultaneously their diameter) were measured and compared with NRVs. The results are published elsewhere.[21] The measurements were followed by in-depth interviews with representatives of the involved companies (who were previously informed about the results of the measurements) and with representatives of trade unions, branch organizations, and government authorities to get insight into perceived feasibility and advisability of the use of NRVs, as well as into activities and ideas to stimulate compliance. The topics of the interviews covered the issues of the requirements of rule compliance according to the analytical framework that has been developed in regulatory governance studies to get insight into effectiveness issues of soft-regulation that is established to comply with legal obligations.[29–35] Governance studies suggest that the successful use of soft regulation in the case of the NRVs depends first on the preconditions of appropriate and easily available measurement strategies at low cost, as well as on adequate information supply about nanomaterials used in products, and their possible release during intended use.

Second, the potential users of NRVs must know the rules, have an accurate understanding of them, and have the financial resources to employ NRVs. Third, the value of NRVs in practice depends on the willingness of companies to employ them. Willingness builds on ideas on the usefulness of the NRVs, the interests of the companies in using the NRVs, and the compliance culture of the company and the social responsibility within the industrial sector. It builds also on the available sanctions, pressures/binding force and incentives, and pro-active and knowledgeable oversight and enforcement.

Candidate companies were selected based on the MNMs they used. The MNMs had to be biopersistent and insoluble, and present on the Organization for Economic Cooperation and Development (OECD) list of manufactured nanomaterials.[36] The companies included manufacturers and users of products containing MNMs, and small to large companies. Low priority was given to the involvement of raw nanomaterial producers because these are not a key industry in the Netherlands. Involvement of R&D institutes also had a low priority because these institutes were subject to an earlier study, indicating a general use of small amounts of MNMs and a potentially low exposure.[37] Sixty candidate companies were identified, of which 26 were approached and 12 agreed to participate (Table II). Some companies refused cooperation without giving a reason or based on their own assessment of low MNMs' exposure

TABLE II. Selected Companies for Measurement of Airborne NPs

Type of Industry	No. of Interviewees
R&D, Innovation support	1
Paint, coating manufacturer	4
Glass industry	1
Electronic industry	1
Transport industry	1
Construction industry	1
Metal/machine industry	2
Service industry	1
Total	12

risk (23%). Two companies not using MNMs were included to provide some information on nanoparticulate emissions generated by conventional activities.

In-depth interviews were carried out with representatives from the companies involved (Table II), with representatives of R&D institutions involved in health and safety management, with key persons from branch organizations, and with government authorities. The interviewees generally were experts involved in health and safety management. In a few cases they were part of the companies' management board. For the branch organizations and trade unions, health and safety policy advisors were interviewed. Interviewed government authorities were involved in regulating chemical substances (and nanotechnologies). In total, 25 interviews were carried out. Table III gives an overview of the interviewees.

All participating companies and interviewees were informed about the concept of NRVs through an informative flyer, an introductory presentation by the study team, their involvement in measurements, the consequential reporting of the results, and a discussion on the consequences with the research team.

RESULTS

Interviewees emphasize that NRVs are useful only if there is appropriate measuring equipment available. Workplace monitoring of nanoparticles' concentrations and diameters was provided to the participating companies. For most interviewed companies, the actual measurements in the pilot were their first structured activity to assess airborne nanoparticles at the workplace. Some interviewees believed that using a particles/m^3 metric for airborne MNMs was not as informative for risk assessment as a mg/m^3 metric.

TABLE III. Characterization Interviews

Background Interviewee	No. of Interviewees
R&D organization	3
Company large	5
Company SME	7
Branch organization	2
Employers' organization	1
Trade union	3
Governmental authority	3
Labor Inspectorate	1
Total	25

Two interviewees stated it was difficult to distinguish airborne MNMs from nanoparticles in ambient air and nanoparticles generated by processes like combustion (or PGNPs). They concluded that NRVs are useful for workplaces that process pure MNMs. Two interviewees from a trade union and a branch organization suggested that extending the scope of the NRVs to cover both MNMs and PGNPs is an excellent idea. Their argument is that with the existing uncertainties on the toxicity of both MNMs and PGNPs, the use of a generic NRV covering both sources is appropriate, and, as one of the interviewees said: "Adopting NRVs to control both MNMs and PGNPs is in line with a precautionary approach."

Hazard identification is one of the key issues for downstream users of products containing MNMs. In general, the end user is not informed about a possible release of MNMs during intended use of the product. The interviewed Labour Inspectorate stated that 70% of the upstream manufacturers do not inform the users of their products about the MNMs contained in those products because there is no requirement to do so.[38] Interviewees from the car repair industry stated that downstream users, confronted with this lack of information, are forced to use a precautionary approach for all activities where airborne MNMs might be generated.

All of the company interviewees appeared to be well informed about existing chemicals legislation and workplace health and safety regulations.[1,39] They were acquainted with the concept of OELs. The company interviewees agreed that legal duty means minimizing exposure to MNMs. They know as well that NRVs are considered to be measures of best practice. Some interviewees concluded that this implies that NRVs are binding, while others are not sure about the binding character.

One interviewee emphasized the warning function of NRVs: "Their value lies in signaling the importance to handle nanoproducts with care." Another company representative adds that NRVs helps risk management, provided exposure measurements can be carried out reliably. Most interviewees see a direct link between the legal obligation to provide a safe workplace and the use of NRVs. One interviewee summarizes: "NRVs are a good instrument to fulfill the *duty of care* responsibility, provided there is an efficient way to apply them in practice." A representative of a trade union stated: "It is clear that the company has to substantiate their activities to control exposures. They have to prove that they take the new risks into account. The NRVs are perceived to be an excellent tool for this."

According to another interviewee, "NRVs are the latest state of the art of risk management and therefore it is the responsibility of the employer to act accordingly." Some interviewees held that additional measures have to be taken to reduce exposure to nanomaterials at the workplace when exposure measurement shows NRVs are exceeded. An interviewee from a branch organization noted that a role of the NRVs is to raise awareness. He thinks the usefulness of NRVs lies in anticipating legislation and mandates to supply information, and as a stimulus to become active in relation to the REACH legislation and the safety data sheets (SDS).

All interviewees preferred to use OELs based on specific toxicological information for specific MNMs, but they were aware that it will take time before such OELs become available. They recognized that the use of NRVs is a provisional solution and that it is useful to "forestall/reduce fear of employees, industry and consumers." The NRVs reassure the company that measures are adequate in view of the current state of science. One of the interviewees remarked that the OELs are limited just as the NRVs are limited because they also involve information gaps and uncertainty.

The impression of the research group during workplace visits[(21)] was that source-oriented exposure control measures in place were often designed to control the emission of conventional substances. None of the companies involved had installed extra equipment to control NP emissions. One interviewee stated that his company does not need additional control measures for working with MNMs because their control measures for conventional hazardous substances (such as abrasion dust, welding fumes, isocyanates, and organic solvents) are thought to be sufficient. On the other hand, one of the companies applied a precautionary exposure control protocol for working with nanomaterials, including separate storage of them, the use of additional personal protective equipment for the operations, the registration of personnel involved in working with MNMs and, indirectly, the personnel involved in transport of MNMs and waste management.

Interviewees emphasized that NRVs motivate a company to consider uncertainty in the degree of health risk posed by MNMs and to stimulate a continuous effort to reduce exposure. Yet, undesirable overprotection is also a concern. An end user states that overprotection may lead to unnecessary fears among the employees rather than reassurance. A plant manager remarked that overprotection (irrespective of the use of NRVs) may lead to eliminating the production process using MNMs.

The motivational posture of most of the interviewees (particularly producers) toward using the NRVs can be characterized as pro-active and acquiescent. Most of them see the usefulness of the NRVs in providing temporary certainty, supporting the employer's legal obligation to care and to take precautionary action, as well as anticipating coming legislation and process innovation. The usefulness is questioned by some end users with critical remarks on over- or underprotection of the NRVs.

With regard to *social responsibility* of the industry, interviewees from the chemical and paint industry mention the European Commission's Code of Conduct (EC-CoC) for responsible nanosciences and nanotechnologies research,[(40)] and the ResponsibleCare program of the chemical industry.[(41)] Chemical sector companies argue that a culture of responsibility has emerged, based on the ResponsibleCare program, which has been specified in company-specific CoCs that have been implemented and are controlled and enforced. They stress that the ResponsibleCare program covers all aspects of corporate responsibility and that there is no need for an additional CoC for nanomaterials and to implement the EC-CoC.

Paint industry interviewees mention their "normal" safety, health, and environmental measures, referring to the policy to keep the components in the product and to prevent release into the environment. This also holds for nanomaterials and is stimulated by the employers' association and the trade unions. These organizations proactively provide online information and organize meetings with companies that use and produce nanomaterials. Furthermore, interviewees feel that the recommendations of the Dutch Social Economic Council,[(14)] the control-banding tool Stoffenmanager,[(42)] and the Guidance working safely with nanomaterials and nanoproducts[(43)] support the development of social responsibility.

With regard to sanctioning, rewarding, and other issues of enforcement that can stimulate or hinder the use of NRVs, we draw on an activity that has been run by the The Dutch Labour Inspectorate in 2011.[((38)] This inspection of companies using manufactured nanomaterials concluded that 86% of the inspected companies paid little or no attention to MNMs in their risk assessments. These companies were warned and committed to live up to their obligation. The Labour Inspectorate also referred to the Social Economic Council's advice, to apply the precautionary principle when working with MNMs.[(14)] It advised companies to restrict exposure as much as possible and to use the Guidance for working safely with nanoparticles,[(43)] or a control banding tool[(42,44)] for risk assessment and to guide risk management.

Occasionally, the inspectors referred to the NRVs as an optional instrument for risk management of MNMs. However, they doubted whether the Inspectorate has the legal right to enforce the use of NRVs (or other risk management measures) in the context of uncertain risks. They observed strong disagreement among Dutch lawyers on the question of whether the Dutch Labour Law requires application of the precautionary principle. Due to these problems in the interpretation of the legal framework, inspectors seemed to avoid referring explicitly to the precautionary principle, tending to use the employers' legal duty of care as an incentive for enforcement of employers.

DISCUSSION

The precondition regarding appropriate information supply is identified as an issue of major concern. Many professional end users seem to be poorly informed about the MNMs in the products they use and their possible release during intended use. At a majority of the inspected companies in the Netherlands, MNMs are not taken into account where mandatory risk assessments are made. The issue of hazard identification, the definition for nanoproducts, and the question of what to communicate in the production chain should be addressed to allow for good governance. Within this framework of poor information supply, confidentiality about MNMs used in the products and insufficient knowledge about NPs' release and possible adverse effects, the NRVs may also be a useful tool for the employer to inform the workers about potential exposure to NPs (MNMs + PGNPs) and to explain in what way the risk management measures take this source into account.

Whether NRVs can be easily applied in regulatory practice emerges particularly in view of their provisional and pragmatic character and the consequential necessity to consider additional control measures even if exposure remains below the NRVs. Important in this respect is also that the level of the NRVs were shown to be significantly lower than mass-based proposals for OELs for MNMs.[21] The simultaneous generic assessment of MNMs with PGNPs (simply as particle number concentration), as advocated in the pragmatic measurement strategy from the SER[45] (Figure 1), accepts as a consequence even lower levels for MNMs. But notwithstanding the precautionary approach, a guarantee of an absence of health risks below the NRVs cannot be given. As such, NRVs may be regarded as providing temporary certainty. A precautionary approach implies an incentive to stimulate research, to find out under what conditions and to what extent exposure to specific MNMs is acceptable. Such research may take time in view of the pace of toxicological research on nanomaterials and the fundamental emerging questions in the development of the "new" discipline of *nanotoxicology*.[46]

An unambiguous acceptance of the NRV concept by relevant authorities may solve remaining uncertainties. In this respect, (1) the international recognition—as reflected by the discussion in the international workshop on NRVs at The Hague, in 2011,[23]—and (2) the recognition of the NRV concept as an "overarching principle" for risk management at the 7th Joint EU/US Conference on Occupational Safety and Health in Brussels in 2012[47] is a step in that direction. This "overarching principle" states: "In case exposure limit values

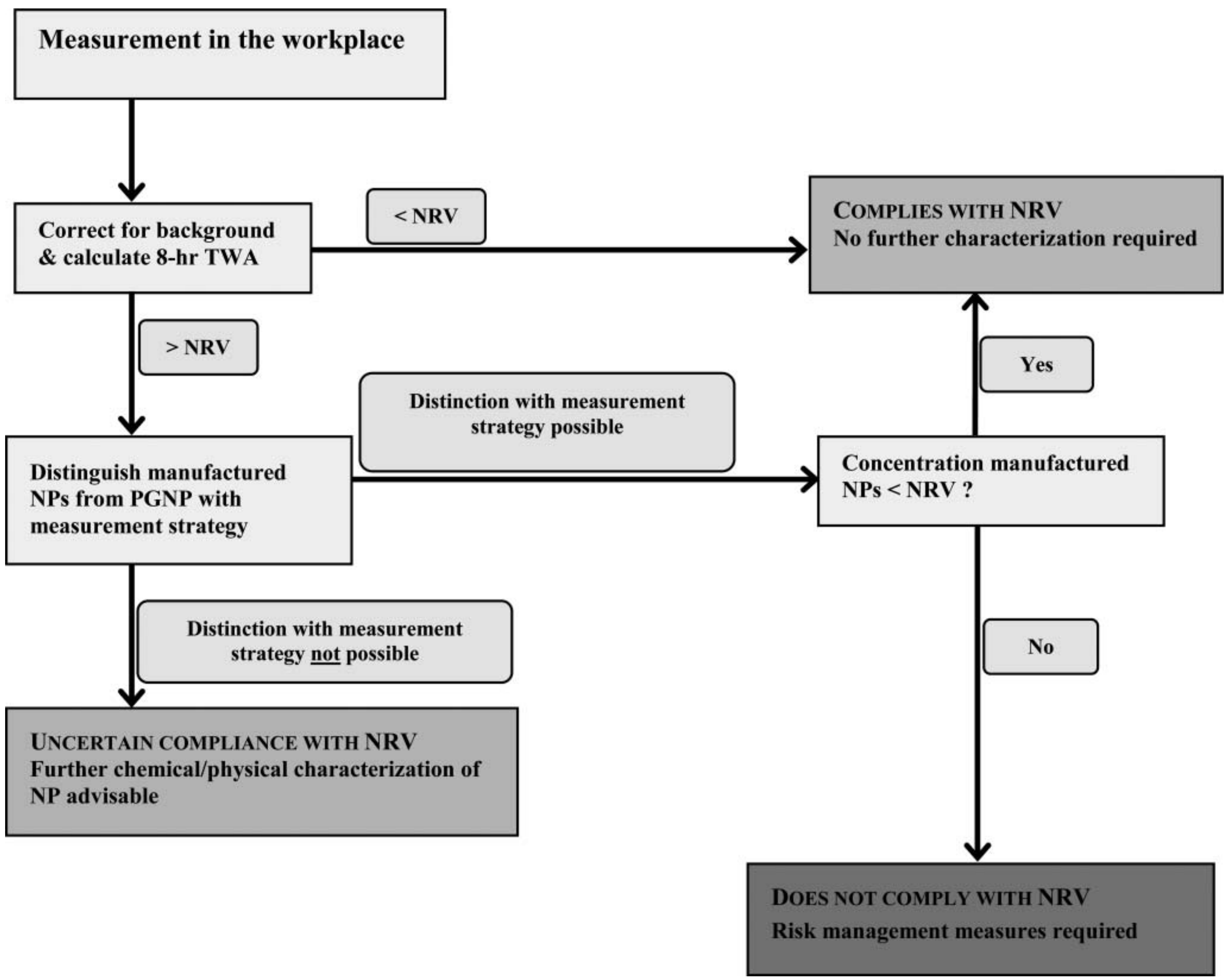

FIGURE 1. Strategy for workplace assessment of nanoparticles and use of NRVs.

are not available for specific nanomaterials a precautionary approach should be applied—generic nano reference values should be considered as a tool for setting provisional limits."

Regarding the willingness to use NRVs, participants of the pilot program accept that for risk assessment and management of nanomaterials, sometimes non-preferential provisional choices have to be made. The particle number concentration is at variance with the usually mass-based OELs[17,18,48,49] and requires a change of mind-set. A change of mind-set is also needed for acceptance of the precautionary approach used for NRVs, though it may be noted that precautionary NRVs, as advised by employers' organizations and trade unions, are perceived as important.

However, it might as well be that the *provisional* and *voluntary* character of the NRVs is perceived as less of a threat, which would be in line with the findings of Engeman et al.[50] who find that an industry may identify the lack of regulation as a problem, due to their mistrust regarding responsible behavior of other industry. The voluntary character of NRVs is welcomed by government policymakers because this characteristic ensures that it does not interfere with principles used in existing OHS regulations that are based on health or risk considerations. A reason for the easy acceptance of NRVs might also be the finding that 8-hr TWA exposures to airborne MNMs, as measured in the accompanying pilot project, generally remain below the NRVs if conventional risk management measures are used.[20] For companies, these are reassuring findings. The pre-existing knowledge of the interviewees about the feasibility of applying NRVs without further organizational or risk management consequences might lead to a bias favoring acceptance of the concept.

The experience of the Labour Inspectorate shows that active enforcement is an important driver to use supplied risk management tools such as the NRV and the control banding tools. Contrasting findings regarding a pro-active attitude of well-informed industry are published by Engeman et al.[50] These authors conclude that risk perceptions and safety practices are narrow and inconsistent and that because health and safety guidance is not reaching industry, a mandatory approach may be needed. Regarding the interest of companies to forestall more regulation, regulators could clarify that they are forced to come up with top-down measures if NRVs or well-underpinned alternative measures to safeguard occupational health and safety are not used in the work with nanomaterials.

CONCLUSION

This small pilot study found that most companies working with nanomaterials accept NRVs as a tool to minimize possible adverse health effects among employees. Companies tend to be pro-active and acquiescent toward using the NRVs for risk assessment and management. An important driver to employ NRVs seems to be a temporary certainty employers experience with regard to their legal obligation to take preventive action. A contribution to the positive attitude of companies toward NRVs may be the reassuring finding that conventional exposure control measures are generally adequate to control airborne MNMs. Although many of the interviewees welcome the voluntary character of NRVs, trade unions and a few companies advocate stronger regulation. Regulators are recommended to take account of technology-related preconditions to compliance, such as appropriate and easy available measurement strategies at low cost; appropriate information supply about nanomaterials used in products; and their possible release during intended use. The NRV pilot study shows how important these preconditions are for compliance.

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REFERENCES

1. Council Directive 98/24/EC of 7 April 1998 (as supplemented by Directives 2000/39/EC and 2006/15/EC) on the Protection of the Health and Safety of Workers from the Risks Related to Chemical Agents at Work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC). (1998).
2. "Dutch Labour Conditions Act, Articles 3 and 5." Available at http://www.arboportaal.nl/onderwerpen/arbowet–en–regelgeving/arbowet/arbowetgeving.html (April 25, 2012). [In Dutch]
3. **Vogelezang-Stoute, E.M.**, **J.R. Popma**, **M.V.C. Aalders, and T. Gaarthuis:** "Regulering van onzekere Risicos van Nanomaterialen—Mogelijkheden en Knelpunten in de Regelgeving op het Gebied van Milieu" [Regulation of Uncertain Risks of Nanomaterials—Possibilities and Problems in the Regulatory Area of the Environment, Consumer Protection and Working Conditions]. Available at http://www.rijksoverheid.nl/documenten-en-publicaties/rapporten/2010/11/30/regulering-van-onzekere-risico-s-van-nanomaterialen.html (accessed April 25, 2012). [In Dutch]
4. **Pauluhn, J.:** Multi-walled carbon nanotubes (Baytubes): Approach for derivation of occupational exposure limit. *Regul. Toxicol. Pharmacol. 57(1)*:78–89 (2010).
5. **Edinburgh Napier University:** "Engineered Nanoparticles: Review of Health and Environmental Safety." Available at http://www.temas.ch/Impart/ImpartProj.nsf/7903C02E1083D0C3C12576CC003DD7DE/$FILE/ENRHES+Review.pdf?OpenElement&enetarea=03 (accessed July 5, 2011).
6. **F. Luigi:** "Responsible Care and Nanomaterials Case Study Nanocyl." Available at http://www.cefic.org/Documents/ResponsibleCare/04_Nanocyl.pdf (accessed April 25, 2012)
7. **National Institute for Occupational Safety and Health (NIOSH):** "Occupational Exposure to Carbon Nanotubes and Nanofibers."

Available at http://www.cdc.gov/niosh/docket/review/docket161a/pdfs/carbonNanotubeCIB_PublicReviewOfDraft.pdf (accessed April 25, 2012).
8. **Shinohara, N., G. Masashi, and J. Naganishi:** "Risk Assessment of Manufactured Nanomaterials (Interim Report). Fullerene (C60)." Available at http://www.aist-riss.jp/main/modules/product/nano_rad_old.html?ml_lang=en (accessed April 25, 2012).
9. **Hanai, S., N. Kobayashi, M. Ema, I. Ogura, M. Gamo, and J. Naganishi:** "Risk Assessment of Manufactured Nanomaterials (Interim Report). Titanium Dioxide." Available at http://www.aist-riss.jp/main/modules/product/nano_rad_old.html?ml_lang=en (accessed April 25, 2012).
10. **National Institute for Occupational Safety and Health (NIOSH):** "Occupational Exposure to Titanium Dioxide." Available at http://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf (accessed April 25, 2012).
11. **Aillon, K.L., Y. Xie, N. El-Gendy, C.J. Berkland, and M.L. Forrest:** Effects of nanomaterial physicochemical properties on in vivo toxicity. *Adv. Drug Deliv. Rev*. *61*:457 (2009).
12. **Park, M.V.D.Z., A.M. Neigh, J.P. Vermeulen, et al.:** The effect of particle size on the cytotoxicity, inflammation, developmental toxicity and genotoxicity of silver nanoparticles. *Biomaterials 32*:9810 (2011).
13. **Li, Y., L. Sun, M. Jin, et al.:** Size-dependent cytotoxicity of amorphous silica nanoparticles in human hepatoma HepG2 cells. *Toxicol. in Vitro 25*:1343 (2011).
14. **Social and Economic Council of The Netherlands (SER):** "Nanoparticles in the Workplace: Health and Safety Precautions." Available at http://www.ser.nl/en/publications/publications/2009/2009_01.aspx (accessed April 25, 2012).
15. **German Advisory Council on the Environment (SRU):** "Precautionary Strategies for Managing Nanomaterials." Available at http://www.umweltrat.de/SharedDocs/Downloads/EN/02_Special_Reports/2011_09_Precautionary_Strategies_for_managing_Nanomaterials_KFE.pdf?__blob=publicationFile (accessed April 25, 2012).
16. **Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA):** "Criteria for Assessment of the Effectiveness of Protective Measures." Available at http://www.dguv.de/ifa/en/fac/nanopartikel/beurteilungsmassstaebe/index.jsp (accessed April 25, 2012).
17. **Abbott, L.C., and A.D. Maynard:** Exposure assessment approaches for engineered nanomaterials. *Risk Analysis 30*:11 (2010).
18. **Aschberger, K., and F.M. Christensen:** Approaches for establishing human health no effect levels for engineered nanomaterials. *J. Physics, Conference Series 304*(*1*):1–8 (2011).
19. **Ramachandran, G., M. Ostraat, D.E. Evans, et al.:** A strategy for assessing workplace exposures to nanomaterials. *J. Occup. Environ. Hyg. 8*:673–685 (2011).
20. **Broekhuizen, P. van, F. van Broekhuizen, R. Cornelissen, F. Jongeneelen, and B. Dorbeck-Jung:** *Pilot Nanoreferentiewaarden. Nanodeeltjes en de nanoreferentiewaarde in Nederlandse bedrijven—Eindverslag [Pilot Nano Reference Values. Nanoparticles and Nano Reference Value in Dutch Companies]*. 2011. [In Dutch]
21. **Broekhuizen, P. van, F. van Broekhuizen, R. Cornelissen, and L. Reijnders:** Workplace exposure to nanoparticles and the application of provisional nano reference values in times of uncertain risks. *J. Nanopart. Res. 14*:770 (2012).
22. **Dekkers, S., and C. de Heer:** Tijdelijke nano-referentiewaarden [Provisional Nano Reference Values]. Available at http://docs.minszw.nl/pdf/190/2010/190_2010_3_14399.pdf (accessed April 25, 2012). [In Dutch]
23. **Broekhuizen, P. van, W. Van Veelen, W.H. Streekstra, P. Schulte, and L. Reijnders:** Exposure limits for nano-particles: Report of an international workshop on nano reference values. *Ann. Occup. Hyg*. *56*(*5*):515–524 (2012).
24. **Social and Economic Council of The Netherlands (SER):** "Provisional Nano Reference Values for Engineered Nanomaterials." Available at http://www.ser.nl/∼/media/Files/Internet/Talen/Engels/2012/2012_01/2012_01.ashx (accessed August 10, 2012).
25. **Donner, J.P.H.:** Tijdelijke nano-referentiewaarden. Letter to the Voorzitter van de Tweede Kamer der Staten-Generaal s Gravenhage [Provisional Nano Reference Values. Letter to the Chairman of the Dutch Parliament]. August 10, 2010. Ref: G&VW/GW/2010/14925. [In Dutch]
26. **Atsma, J.:** Invulling strategie "omgang met risico's van nanodeeltjes. Letter to the Voorzitter van de Tweede Kamer der Staten-Generaal s Gravenhage [Operationalizing Strategy "Dealing with Nanoparticles' Risks." Letter to the Chairman of the Dutch Parliament]. RB/2010030882. January 20, 2011. [In Dutch]
27. **Dorbeck-Jung, B.:** Soft regulation and responsible nanotechnological development in the European Union: Regulating occupational health and safety in the Netherlands. *Eur. J. Law Technol. 2*(*3*):1–14 (2011).
28. **Senden, L.:** *Soft Law in European Community Law*. Oxford, UK: Hart Publishing, 2004.
29. **Griffiths, J.:** Legal knowledge and the social working of law: The case of euthanasia. In *Semiotics and Legislation*, H. van Schooten (ed.). Liverpool, UK: Deborah Charles Publications, 1999. pp. 81–108.
30. **Havinga, T.:** Private regulation of food safety by supermarkets. *Law Policy 28*:515–533 (2006).
31. **Karlsson-Vinkhuyzen, S.I., and A. Vihma:** Comparing the legitimacy and effectiveness of global hard and soft law: An analytical framework. *Regul. Governance 3*:400–420 (2009).
32. **Kagan, R.A., and J.T. Scholz:** The criminology of the cooperation and regulatory enforcement strategies. In *Enforcing Regulation*, K. Hawkins and J.M. Thomas (eds.). Boston, Mass.: Kluwer/Nijhoff Publishing, 1984.
33. **Braithwaite, J.:** Games and engagement: Postures within the regulatory community. *Law Policy 17*:225–255 (1995).
34. **Gunningham, N., R. Kagan, and D. Thornton:** *"Social License and Environmental Protection: Why Businesses Go beyond Compliance.*" Berkeley, Calif.: University of California, Berkeley, Center for the Study of Law and Society, 2002.
35. **Baldwin, R., and J. Black:** Really responsive regulation. *Modern Law Rev. 71*:59–64 (2008).
36. **Organization for Economic Cooperation and Development (OECD):** "List of Manufactured Nanomaterials and List of Endpoints for Phase One of the Sponsorship Programme for the Testing of Nanomaterials: Revision." Available at http://www.oecd.org/officialdocuments/displaydocumentpdf?cote = env/jm/mono(2010)46&doclanguage = en (accessed April 25, 2012).
37. **Borm, P., R. Houba, and F. Linker:** Omgaan met nanodeeltjes op de werkvloer [Dealing with nanoparticles in the workplace]. Available at http://www.ser.nl/en/publications/publications/2009/2009_01.aspx (accessed April 25, 2012).
38. **Arbeidsinspectie [Dutch Labour Inspectorate]:** Aandacht voor details: veilig werken met synthetische nanodeeltjes [Caring for the detail: Working safely with nanomaterials]. Available at http://www.rijksoverheid.nl/documenten-en-publicaties/circulaires/2011/09/08/factsheet-veilig-werken-met-synthetische-nanodeeltjes.html (accessed April 25, 2012). [In Dutch]
39. "Regulation No 1907/2006 of the European Parliament and the Council of 18 December 2006, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemical 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, 93/155/EEC and 2000/21/EC." Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri = CELEX:32006R1907:en:NOT (accessed April 25, 2012).
40. **Commission of the European Communities (EC):** "A Code of Conduct for Responsible Nanosciences and Nanotechnologies Research," and "Responsible Nanosciences and Nanotechnologies Research." Available at http://ec.europa.eu/research/science-society/document_library/pdf_06/nanocode-apr09_en.pdf (accessed April 25, 2012).

41. **International Council of Chemical Associations (ICCA):** "Responsible Care." Available at http://www.responsiblecare.org (accessed April 25, 2012).
42. **Duuren-Stuurman, B. van, S.R. Vink, K.J.M. Verbist, et al.:** Stoffenmanager nano version 1.0: A web-based tool for risk prioritization of airborne manufactured nano objects. *Ann. Occup. Hyg. 56*(*5*):525–541 (2012).
43. **Cornelissen, R., F. Jongeneelen, P. van Broekhuizen, and F. van Broekhuizen:** "Guidance Working Safely with Nanomaterials and Nanoproducts." Available at http://www.industox.nl/Guidance%20on%20safe%20handling%20nanomats&products.pdf (accessed April 25, 2012).
44. **Zalk, D.M., S.Y. Paik, and P. Swüste:** Evaluating the control banding nanotool: A qualitative risk assessment method for controlling nanoparticle exposures. *J. Nanopart. Res. 11*:1685–1704 (2009).
45. **Social and Economic Council of the Netherlands (SER):** Voorlopige nanoreferentiewaarden voor synthetische nanomaterialen [Provisional nano reference values for engineered nanomaterials]. Available at http://www.ser.nl/nl/publicaties/adviezen/2010-2019/2012/b30802.aspx (accessed April 25, 2012).
46. **Shvedova, A.A., V.E. Kagan, and B. Fadeel:** Close encounters of the small kind: Adverse effects of man-made materials interfacing with the nano-cosmos of biological systems. *Ann. Rev. Pharmacol. Toxicol. 50*:63–88 (2010).
47. **W. van Veelen, P. Schulte, and J. Carter:** "Workshop Nanotechnology in the Workplace." Paper presented at the 7th Joint EU/US Conference on Occupational Safety and Health, Brussels, July 11–13, 2012.
48. **Bermudez, E., J.B. Mangum, B.A. Wong, et al.:** Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. *Toxicol. Sci. 77*:347–357 (2004).
49. **Oberdorster, G., E. Oberdorster, and J. Oberdorster:** Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. *Environ. Health Perspect. 113*(*7*):823–839 (2004).
50. **Engeman, C.D., L. Baumgartner, B.M. Carr, et al.:** Governance implications of nanomaterials companies' inconsistent risk perceptions and safety practices. *J. Nanopart. Res. 14*:749–761 (2012).