Defining Occupational and Consumer Exposure Limits for Nanomaterials – First Experiences from REACH Registrations

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Abstract. By 1 December 2010 substances manufactured or imported in the EU ≥ 1000 t (as well as certain other substances) had to be registered under the REACH Regulation 1907/2006. The Joint Research Centre (JRC) in close cooperation with the European Chemicals Agency (ECHA) carried out an analysis and assessment of what type of information on nanomaterials was provided in the received registrations. The aim of the assessment was to develop options for an adaptation of the REACH regulation to ensure proper information generation and reporting and an appropriate risk/safety assessment of nanomaterials (Nano Support project). It should be noted that this analysis and assessment was not a compliance check of the dossiers. From 26000 submitted registration dossiers covering 4700 substances finally 25 dossiers (19 substances) were identified to cover nanomaterials or nanoforms of a substance. It is possible that other dossiers could not be identified to address nanoforms given the information contained in those dossiers. The identified 25 dossiers were subject to a detailed analysis and assessment of information provided for all endpoints including substance identity, physico-chemical properties, human health, environmental fate & behaviour, ecotoxicity, PBT⁶ assessment, Classification and Labelling as well as the attached Chemical Safety Report documenting the Chemical Risk/Safety Assessment. In order to evaluate how the safety of workers and consumers was ensured, it was appropriate to check how the "Derived No (Minimum) Effect Levels" (DN(M)ELs) were established for substances, covering nanomaterials or nanoforms. DNELs were established mainly for long term inhalation exposure of workers. Half of the assessed dossiers included an oral long term DNEL for the general population. DNELs were usually not specific for nanosized forms and, in the few cases where they were calculated for nanosized materials, they were not derived from hazard data for the nanoform. Different methods for deriving the DNELs were applied and few dossiers

⁴ The opinions expressed in this publication are those of the authors and not necessarily those of the European Commission
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derived DNELs by applying the default assessment factors in the REACH guidance. Several DNELs were based on available Occupational Exposure Limits (OELs) for inhalable and respirable dust or the nuisance dust levels, which have not been established for nanosized materials. In general lower (i.e. less strict) assessment factors were applied with different types of justification. All DNELs were expressed in the mass metrics. It is important to note that submission, identification and selection of the dossiers addressed in this study was done before the adoption of the EC recommendation (2011/696/EU) on a definition of nanomaterial and before the publication of the revised ECHA guidance documents that include recommendations for nanomaterials.

1. Introduction/Background

Nanomaterials are covered by the "substance definition" of Regulation 1907/2006 on Registration, Evaluation, Authorisation and Restriction of chemicals (REACH) [1] as REACH addresses chemicals in whatever size, shape or physical state. By 1 December 2010 substances produced and imported ≥ 1000 t in the EU had to be registered under REACH which potentially also included nanomaterials. In addition a number of very toxic and a number of "new" (under REACH "non phase-in") substances were registered. As part of an Administrative Arrangement with Directorate General Environment of the European Commission (DG ENV), the Joint Research Centre (JRC) in close cooperation with the European Chemicals Agency (ECHA) made an analysis and assessment of what type of information on nanomaterials was available in received registration dossiers (the Nano Support Project7). For dossiers that included information on nanomaterials or nanoforms, it was assessed whether the information submitted was adequate for a risk assessment of the nanomaterials/nanoforms and based on that developed options for specific nanomaterial provisions building on the current REACH framework [2]. An assessment of the consequences of these options for industry, consumers, human health and the environment is currently ongoing.

45 registration dossiers possibly addressing nanoforms/nanomaterials were identified (see figure 1) based on a combination of:
- automated searches of the IUCLID8 database (IT tool used for submitting Registration under REACH) with the 26000 submitted registration dossiers covering 4700 substances
- focused searches on substances selected for assessment in the OECD WPNM (Working Party on Manufactured Nanomaterials), and
- other substances considered to include nanoform from a technical perspective.

Following an examination of the information on substance identity, state, granulometry and other relevant endpoints, 20 dossiers were excluded from further assessment as based on the information provided it could not be concluded whether they were actually covering nanomaterials or nanoforms. The remaining 25 dossiers, covering 19 different substances were identified as likely to cover nanoforms/nanomaterials. These dossiers included three registrations that had explicitly selected "nanomaterial" as the form of the substance in an optional IUCLID field. The further assessment identified three categories of registration dossiers, where

I) the registrants recognised that nanoforms or particle size < 100 nm were inside the scope of the dossier (8 dossiers /5 substances);

II) substances considered to exist only as nanomaterial without a bulk form (12/9), and

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7 Administrative Arrangement between JRC and DG ENV No. 07.0307/2010/581080/AA/D3:Scientific technical support on assessment of nanomaterials in REACH registration dossiers and adequacy of available information. The support from all colleagues contributing to this project is acknowledged: ECHA: Bernadette Quinn, Abdelquadar Sumrein, Julia Fabrega Climent; JRC: Stefania Gottardo, Nanna Hartmann, Christian Micheletti, Hubert Rauscher, Juan Riego Sintes, Birgit Sokull-Külltgen, Stefania Vegro.

8 International Uniform Chemical Information Database
III) the assessors identified nanomaterials on the basis of the presence of a 'nanotail' in the provided particle size distributions (5/5) (see figure 1).

It is recognised that since December 2010 some additional nanomaterials have been registered as non phase-in substances, but these were not within the scope of the Nano Support project.

![Diagram of dossier identification, categorisation, analysis and assessment](image)

**Figure 1: Overview of dossier identification, categorisation, analysis and assessment**

### 2. Assessment of information on nanomaterials/nanoforms in REACH registration dossiers

The identified REACH registration dossiers concluded to be likely to address nanomaterials or nanoforms were subject to a detailed analysis and assessment of all endpoints including substance identity, physico-chemical properties, human health, environmental fate & behaviour, ecotoxicity, PBT assessment, classification and labelling, as well as the attached Chemical Safety Report documenting the Chemical Risk/Safety Assessment. The results and conclusions of this analysis and assessment are briefly summarised below with focus on issues of relevance for this paper, namely to present and discuss how "derived no effect levels" (DNELs) for workers and consumers had been addressed in the dossiers investigated.

It should be stressed that the assessment was not a compliance check of individual registration dossiers but focused on how the REACH regulation could be adapted/clarified to ensure a proper information generation and risk/safety assessment of nanomaterials. Substance names cannot be revealed as this information was considered confidential in relation to dissemination from this project.

#### 2.1. Substance Identity and physico-chemical properties

The examination of substance identity and key physico-chemical properties (granulometry, surface area and other physico-chemical properties) revealed that the identification of substances was mainly based on the chemical composition and the information provided in the substance identity sections of
the dossiers alone did generally not enable the assessors to identify the form(s) of the substance or to
categorise it as a nanomaterial or nanoform of a substance. When the particle size was reported, it
was generally not specified, whether it referred to primary particles, aggregates, agglomerates or other
and usually detailed information on the method and the sample preparation was not provided. For
granulometry usually only one data set per substance was submitted even for joint registration
dossiers, irrespective of the fact that these data depend on the manufacturing process of individual
registrants. The methods for particle size measurements were often incapable of measuring particles
with a size below 100 nm. Measurements of the surface area were provided in a few cases. Surface
treatment/modification was described in general terms in a few dossiers, but was generally not
provided. Generally one set of physicochemical data or waiving arguments were provided without
specifically addressing whether the data would also apply to the nanoform.

In conclusion: the information provided in the dossiers was in general not sufficient to identify a
nanomaterial or nanoform and would not also not be sufficient in relation to the EC definition
recommendation 2011/696/EU [3]. Based on that, the proposed options for an amendment of REACH
suggests that nanomaterials/nanoforms should be explicitly described in the scope of the registration
dossier, including more detailed characterisation of the nanomaterial/nanoforms.

2.2. General observations for human health and environment
The general observations for human health and environmental endpoints were that the test material
was usually not well characterised and sometimes only trade names were reported. There was no or
little distinction between different forms (bulk, micro/nanoform) in the test material description and
particle sizes were very rarely reported. For inhalation studies usually only the mass median
aerodynamic diameter (MMAD) was reported. When read across was applied to other related
substances, this was based on the chemical composition (e.g. Metal-ion) or physico-chemical
properties (e.g. (in)solubility), however a size dependency or particle specific effects were not
addressed. As some of these substances exist in various forms with different particle sizes and
aggregation/agglomeration status, it was difficult to assess the appropriateness of the provided test
data in relation to the form(s) registered without a better and more detailed characterisation of the test
material. This applies also to substances of category II, which are considered to exist only as
nanomaterial without a bulkform.

Based on that, the developed options require that nanoforms within the scope of a registration
dossier should be explicitly addressed in the endpoint sections and a detailed description of the test
material and sample preparation should be provided.

2.3. Specific observations for Human Health

2.3.1. Biokineti cs. Knowledge of the biokinetics of nanomaterials provides an important basis for the
estimation of systemic exposure and systemic toxicity. In addition, it could provide a basis for the
decision on the validity of extrapolating available data from the bulk material to the nanomaterial or
between different nanoforms of the same nanomaterial, and the justification for read across to other
related substances and grouping. It should be noted that REACH (Annex VIII, point 8.8) does not
require a specific toxicokinetic study but an assessment of the toxicokinetic behaviour of the substance
to the extent that can be derived from the relevant available information. Information on absorption,
distribution, metabolism and excretion via different application routes was provided in most
registration dossiers. The conclusions were often made either based on data from toxicity studies
(often not with nanoform) or read across to chemically related substances, without giving special
attention to the particular nature of the nanof orm. Dermal penetration was tested specifically for 2
substances, where dermal exposure to the nanoform is significant, suggesting that these nanoparticles
were not absorbed. Altogether, studies with different forms of substances were presented, however the
fact that size and other characterisers may alter the toxicokinetics of a substance/particle was not specifically addressed.

2.3.2. Acute and repeated dose toxicity/reproductive toxicity. Most studies were performed using the oral or inhalation route with either bulk forms or no specific test materials information was provided that would allow identifying nanoforms. If read across was applied it was based on the leading ion, not taking into consideration the particle nature of the material. Dermal toxicity tests were usually waived, mostly referring to the insolubility of the substance. In repeated dose inhalation studies, some effects of different particle sizes have been observed, with the smaller particle size being more potent in inducing toxic effects. Information on particle size specific potency was not further elaborated in the dossiers, rather observed effects in the lung were not used for deriving nano- or size-specific conclusions. All materials tested showed low acute toxicity via all exposure routes and all but 2 substances were not classified for repeated dose toxicity.

Little information was provided for reproductive and developmental effects and studies were waived for the arguments that no systemic toxicity is anticipated or that long term studies or developmental screening studies did not indicate a reproductive toxicity hazard. In addition, for some substances, the natural abundance and high tolerance of the elements of the substance, and the absence of effects with the leading ion or structural analogues, were used as justification. One dossier provided a study (OECD 422; Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) with a nanoform.

2.3.3. Irritation and Sensitisation. Results specific for nanomaterials/nanoforms were reported from one in vitro skin and one eye irritation test, respectively. Some dossiers reported unspecific effects, either to the eye or respiratory tract, which could be the consequence of deposition of particles, but was not considered as inherent property of the substance and to warrant classification. Few sensitisation studies were provided and most dossiers concluded on non-sensitising effects based on physico-chemical properties or on the absence of effects in humans over long exposure periods (however without exact knowledge on the particle size exposed to). All substances were concluded to be non-irritating to skin, eye and respiratory tract and one substance was classified for skin sensitisation. In general, the nanoform of the substance was not explicitly addressed.

2.3.4. Genotoxicity and Carcinogenicity. All dossiers addressed the endpoint genotoxicity either by presenting data with the registered substance, by reading across from related substances or by concluding based on a weight of evidence approach. Some substances were explicitly tested in the nanoform for mutagenicity in vitro and this mostly with bacterial mutagenicity tests. The suitability of this test for (nano)particles was not specifically discussed, although it is known that insoluble particle may not penetrate the bacterial cell wall and this test has not a good predictivity for mutagenic effects in mammalian cells/organisms. Few nanoforms were tested in vivo and results with the bulkform were usually taken to draw conclusions. Three dossiers provided data for carcinogenicity including inhalation and oral feeding studies, which were (except on study) however not specific for nanomaterials. Carcinogenic effects observed in rats for one nanoform were attributed to rat lung overload and therefore considered not relevant for humans. Several dossiers concluded 'non-carcinogenic' by applying a weight of evidence approach based on data from repeated dose toxicity studies, read across, mutagenicity and/or epidemiological data. One substance was classified as carcinogenic (II B) in one of the three submitted dossiers. Another substance was classified as mutagenic and carcinogenic, but this was based on a category approach based on the leading ion rather that effects attributable to particle nature.
3. Human health exposure limits – DN(M)ELs

3.1. Derived No(Minimal)-Effect Levels - DN(M)ELs
For substances produced or imported ≥ 10 tons, derivation of no-effect levels is part of a Chemical Safety Assessment (CSA) if required. Thus, the registrant based on the available and generated hazard information has to define the relevant threshold levels for exposure below which risks for human health (and for the environment) are considered to be controlled [4, 5]. The Derived No-Effect Level (DNEL) is the level of exposure to the substance above which humans should not be exposed.

The DNEL may vary depending on the exposure pattern to the substance which is usually defined by a combination of the population likely to be exposed to the chemical, i.e. workers, consumers or humans exposed through the environment; the frequency and duration of the exposure, e.g. single/acute exposure or continuous exposure for eight hours, and the route of exposure: dermal, inhalation or oral.

The DNELs are normally calculated by dividing the dose descriptor for no/lowest health effects from a toxicity study (e.g. no(lowest) observed adverse effect level = N(L)OAEL) by an assessment factor (AF). Since those dose descriptors are usually obtained from experimental animal data, assessment factors are required to allow for extrapolation to real human exposure situations.

From all health effects, the lowest DNEL for each exposure pattern is documented in the Chemical Safety Report (CSR) and in the safety data sheet, where required. In case no safe threshold level can be obtained, like for example, for genotoxic substances, a semi-quantitative value, known as the DMEL or Derived Minimal Effect level may be developed if data allow. The DMEL values represent exposure levels where the likelihood that the identified adverse effect occurs in a population is sufficiently low to be of tolerable concern.

3.2. DNELs in registration dossiers covering nanomaterials
The 25 dossiers likely to cover nanomaterials/nanoforms were analysed, whether and how nanomaterial/nanoform specific DNELs were derived and on which data they were based.

One dossier (Category II, nano only) derived DNELs for all exposure routes and for workers, consumers and the general public. For all other dossiers, DNELs were established mainly for long term inhalation exposure of workers, either for systemic or local effects in the lung. In 11 dossiers, in addition to the DNEL for workers, a long term oral DNEL for the general population was provided. Two dossiers did not present any DNELs for consumers.

Justifications for not providing DNELs for various routes (mostly the acute DNELs) included
- Absence of acute toxic and/or local effects,
- No systemic availability and effects anticipated,
- Absence of or negligible exposure either due to route of exposure (oral, dermal), use (consumer) or particle nature (hardly respirable as aggregated/agglomerated),
- Absence of classification for hazardous effects or
- The long term DNEL was considered sufficient to protect also for short term effects.

Different methods were used for deriving the DNEL in the 19 dossiers:
1. Use of animal data and application of AFs for inter-/intraspecies differences, or duration using REACH default values for AFs
2. Applying AFs different from REACH default values, as they were considered too conservative, e.g. in comparison to existing limit values (OEL, MAK\textsuperscript{9} values) for similar compounds
3. Use of general dust limit or OEL for inhalable (10 mg/m\textsuperscript{3} or 4 mg/m\textsuperscript{3}) and respirable dust (3 mg/m\textsuperscript{3})

\textsuperscript{9} Maximale Arbeitsplatzkonzentration (Maximum workplace concentration)
4. Use of NIOSH Recommended Exposure Levels (REL) (divided by 2 for the general public)
5. Use of human data: large multi-centre studies, NOAEL = 3/5 of concentration with prevalences of symptoms (chronic bronchitis) without any further AF (DNEL = NOAEL in humans) or internal values from human data without further consideration of additional AFs
6. Route to route extrapolation from oral data to inhalation exposure e.g. using a specific method or by a specific absorption rate for the different exposure routes (= evaluation based on ion and not on particle nature)
7. DNEL derived from structural analogue
8. Recommendations for oral intake of the specific ion

All DNELs were expressed in the mass metric. In the analysed and assessed dossiers covering several forms, the DNELs were not derived or generally not indicated to be specific for nanosized forms, nor were they derived from hazard data for the nanoform. Even the dossiers that had used the IUCLID picklist for the nanoform did not derive a nanospecific DNEL from the available hazard data. For a substance that is used in high tonnages for both, bulk and nanoform, the DNEL was derived from hazard data with the bulk form, and considered by the registrant to be also valid for the nanoform. An available chronic inhalation study with the nanoform of this substance, which was included in the dossier was not taken into consideration in relation to the DNEL derivation.

For inhalation DNELs, the assessment factors for interspecies variability were usually lower than the default values in the REACH guidance or no interspecies factors were applied, as the rat was considered more sensitive than humans. In general no assessment factors for extrapolation of duration (e.g. from subchronic to chronic) was applied, for example in one case with the justification that the NOAEC for effects seen in the lung would not depend on time, due to constantly operating clearance mechanisms (while recognising that the severity of effects may increase with increased exposure duration).

Some dossiers discussed why NOAECs from animal studies would not be appropriate as a starting point for a DNEL – as the exposure patterns and particle characteristics do not mimic the conditions in the occupational environment, where particles form aggregates/agglomerates that are hardly respirable, – as prolonged exposure does not give the animals the normal recovery period for lung clearance and – as rats (more than other rodents or humans) are specifically sensitive to develop lung tumours from lung overload to poorly soluble particles due to ineffective clearance.

Two dossiers derived the DNEL from human data which in principle should be considered the most relevant source of information on human toxicity. Several issues addressing the reliability should however be considered when using human data, e.g. valid method for observing effects, confounding factors, statistical power, sufficient length of follow up, causal association etc. [6]. One major weakness of the use of human data is the difficulty of exposure characterisation. Quantification of exposure especially over longer periods as well as characterisation of particle sizes to which people were exposed are a challenge, especially when production processes may have changed. The absence of effects with bulk materials should therefore not be used for deriving DNELs for the nanoform and the use of human data should in general be critically discussed.

### 3.3. Discussion on different methods to derive exposure limits

There are in general different approaches to determine maximum level of exposure to nanomaterials and some of them have been discussed and published in the recent years [7-12]. The applicability of the REACH methodology for deriving DNELs for nanomaterials was assessed in the REACH Implementation project on Nanomaterials (RIPoN [13]) which aimed at providing the basis for the updated guidance on the information requirements and safety assessment of nanomaterials under
REACH. The report concluded that for most part, the current guidance provided sufficient flexibility to address areas of uncertainty, data gaps and if justified, deviations from the default approach/AFs. Based on risk assessment approaches, case study results and the wider particle toxicology literature, an alternative approach for extrapolating from experimental animals to humans for inhalation exposure was suggested for consideration and development in relation to its suitability for possible future incorporation into guidance. Some of the conclusions of the RIP-On projects were implemented into the updated REACH guidance [4]. There it is recognised that in deviation from the default assessment factor during the derivation of a DN(M)EL for (nano)particles, a calculation of the actual lung dose could be performed. However as there are considerable differences in ventilation rates, deposition patterns, and clearance rates between humans and animals, all of these factors should be taken into account. It is recognised that a higher factor maybe appropriate if there is the potential for accumulation of particles. This may be especially prudent for such exposure routes as the lung and certain particle morphologies associated with reduce clearance, e.g. long straight, biopersistent fibres which are likely to be retained if deposited in the non-ciliated airways leading accumulation of particles following repeated exposure.

Other approaches for deriving human exposure limits from animal studies are usually based on differences between humans and animals in particle deposition, ventilation rate and lung retention biokinetics in the lung [9-11]. The US National Institute for Occupational Safety and Health (NIOSH) [9] found that for carbon nanotubes a working lifetime exposure 0.2 – 2 µg/ m³ (8-h time-weighted average, for deposited and retained lung doses respectively) would be sufficient to protect from early-stage pulmonary effects. For the Recommended Exposure level (REL) however they had to consider the upper limit of quantification (LOQ) of the currently recommended analytical method for measuring airborne CNT (7 µg/m³), which might not assure an appropriate protection of the worker.

Current exposure limits are predominantly mass based approaches. It is however recognised that for nanomaterials mass might not be the best predictor of certain lung diseases. Based on current knowledge toxicological evidence is primarily relating inflammation to particle surface area [13] and therefore also surface area and/or particle number should be taken into account. NIOSH recognised that the particle surface area of nano-TiO₂ seems to be the dominating factor in toxicity and therefore lower exposure limits for the nanosized (ultrafine) TiO₂ [8] were recommended. The suggested REL for ultrafine/nano TiO₂ is thus lower than for the micro form, however still based on the mass metric due to acknowledged differences with measuring other metrics.

A general problem of hazard based exposure limits is the currently large deficiencies in hazard data. This was also a conclusion of our previous assessment of nanomaterials risks and appraisals to derive safe exposure levels (DNELs) for specific nanomaterials such as carbon nanotubes, fullerenes, silver and titanium dioxide [11, 14-17]. In the absence of sufficient hazard data and a commonly agreed methodology to derive hazard based exposure limits, precautionary nano reference values could be used as a comprehensive and useful risk management tool [18]. It is therefore strongly recommend that research efforts focus on the development of exposure assessment strategies and tools to improve the effectiveness of methods for controlling occupational and consumer exposure to nanomaterials.

4. Summary and conclusions
From the huge amount of dossier submitted for the first registration deadline, 25 dossiers covering 19 substances could be identified to likely address nanomaterials or nanoforms. An analysis and assessment of these dossiers showed that the information provided in the substance identity sections did generally not provide sufficient information to enable identification and characterisation of nanomaterials or nanoforms of the registered substances. Few toxicity studies provided in the dossiers were performed with nanoforms of a material. Very often the provided test material descriptions for toxicity studies did not allow identifying what form had been tested. DNELs were derived predominantly for long term inhalation exposure and rarely for other exposure routes or short term
exposure. DNELs were not specific for nanoforms, even in dossiers which were flagged as nanomaterials and in dossiers clearly addressing different forms, including nanoforms. Different methods were used for establishing DNELs. Besides following the REACH guidance, different calculations were used or already established exposure limits for respirable and inhalable dust were used.

Therefore it is concluded that from the analysed and assessed registration dossiers, very little information and experience on nanospecific exposure limits can be retrieved. In that context it should be noted that most of the high tonnage substances exist in different forms/sizes and that the submission, identification and selection of dossiers was done prior to the adoption of the EC recommendation (2011/696/EU )[3] on the definition of nanomaterial. It was therefore up to the registrant to decide how to address different form(s) within the dossier. In addition, the dossiers had to be prepared prior to the publication of ECHA guidance documents including recommendations for nanomaterials.

Registration deadlines for substances of lower tonnages are pending. It can be assumed that due to the definition recommendation, the available guidance and the increased awareness and experience, the thoroughness of the dossiers with respect to information specific for nanomaterials will be improved. Nano Support and results from similar projects might also trigger an amendment of the legal requirements to more explicitly require information on nanomaterials.

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