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Risk-based classification system of nanomaterials

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Abstract Various stakeholders are increasingly interested in the potential toxicity and other risks associated with nanomaterials throughout the different stages of a product's life cycle (e.g., development, production, use, disposal). Risk assessment methods and tools developed and applied to chemical and biological materials may not be readily adaptable for nanomaterials because of the current uncertainty in identifying the relevant physico-chemical and biological properties that adequately describe the materials. Such uncertainty is further driven by the substantial variations in the properties of the original material due to variable manufacturing processes employed in nanomaterial production. To guide scientists and engineers in nanomaterial research and application as well as to promote the safe handling and use of these materials, we propose a decision support system for classifying nanomaterials into different risk categories. The classification system is based on a set of performance metrics that measure both the toxicity and physico-chemical characteristics of the original materials, as well as the expected environmental impacts through the product life cycle. Stochastic multicriteria acceptability analysis (SMAA-TRI), a formal decision analysis method, was used as the foundation for this task. This method allowed us to cluster various nanomaterials in different ecological

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risk categories based on our current knowledge of nanomaterial physico-chemical characteristics, variation in produced material, and best professional judgments. SMAA-TRI uses Monte Carlo simulations to explore all feasible values for weights, criteria measurements, and other model parameters to assess the robustness of nanomaterial grouping for risk management purposes.

Keywords Nanotechnology · Risk assessment · Toxicology · Decision analysis · Governance

Introduction

Nanotechnology is a rapidly growing field of research that is already having a great impact on consumer products. The field of nanotechnology can be defined as the production and use of materials at the nanoscale, normally characterized as smaller than 100 nm in one dimension (Oberdörster et al. 2007). Nanomaterials are formed through both natural (e.g., combustion by-products) and synthetic processes. For the purposes of this article, we focus our discussion solely on engineered nanomaterials, which are currently used in more than 600 different consumer products (Woodrow Wilson Institute, Online database, 2008). In spite of their potential commercial benefits, some nanomaterials have been identified as toxic in in vivo and in vitro tests. Clearly, our knowledge of the potential toxicity of these materials is far from comprehensive (Oberdörster et al. 2005; Thomas and Sayre 2005). The potential environmental fate and toxicity (as well as potential for exposure and risk) of nanomaterials may be strongly impacted by the material's physico-chemical characteristics. For example, potentially toxic nanoparticles (NPs) that tightly bind to soil surfaces may exhibit limited movement through the environment. In this case, such materials may be deemed relatively safe for certain specific uses. Such information is important as a lack of understanding of nanomaterial toxicity and risk may delay full-scale industrial application of nanotechnologies.

Nanomaterial research and regulations could be guided by a systematic characterization of factors leading to toxicity and risks in the absence of definitive data (Linkov and Satterstrom 2008). In this article, we propose a risk-based classification system for nanomaterials that takes into account several nanomaterial parameters commonly associated with ecotoxicity and environmental risk. These parameters vary from nanomaterial physico-chemical characteristics to expected environmental concentrations to fate and transport mechanisms. We focus primarily on ecological risks, although the same methodology could be applied to human health risk assessment. This work does not attempt to draw exact conclusions about the environmental risks associated with different nanomaterials, but rather to provide reasonable recommendations about which nanomaterials may need more precise measurements and testing to be safely deployed in consumer products.

MCDA approaches to classification

Clustering nanomaterials into ordered risk categories can be treated as a sorting problem in the context of multi-criteria decision analysis (MCDA). MCDA refers to a group of methods used to impart structure to the decision-making process. Generally, the MCDA process consists of four steps: (1) structuring the problem by identifying stakeholders and criteria (nanomaterial properties in this case) relevant to the decision at hand, (2) eliciting the parameters of the model (weights, thresholds, etc.) and assigning measurements for each alternative (e.g., nanomaterial risk group), (3) executing the model through computer software, and (4) interpreting results of the model and possibly re-iterating the process from step 1 or step 2 by re-evaluating the model. The goal of this MCDA process is not to select a single best alternative, but to rank or group alternatives through a structured process. A detailed analysis of the theoretical foundations for different MCDA methods and their comparative strengths and weaknesses is presented in Belton and Stewart (2002). A review of MCDA applications to environmental management can be found in Linkov et al. (2006); risk-based decision framework for selecting nanomaterial for specific use is discussed in Linkov et al. (2007).

The SMAA-TRI sorting method (Tervonen et al. 2009) is well suited for the proposed classification system given the uncertainty of available information regarding the physico-chemical characteristics of nanomaterials (see Figueira et al. 2005a, for a review of other MCDA sorting methods). Many of the

characteristics attributed to nanomaterials are limited to a solely qualitative assessment. We used SMAA-TRI, an outranking model based on ELECTRE TRI (see e.g., Figueira et al. 2005b) for the assignment procedure. If an alternative outranked another, then the alternative was considered at least as good as or better than another alternative. We preferred SMAA-TRI, since it extends the capabilities of ELECTRE TRI by allowing the use of imprecise parameter values. ELECTRE TRI assigns the alternatives (different nanomaterials in this study) to ordered categories (risk classes). Three types of thresholds are used to construct the outranking relationships by defining preferences with respect to a single criterion. The indifference threshold defines the difference in a criterion that is deemed insignificant. The preference threshold is the smallest difference that would change the expert preference. Between these two lay a zone of "hesitation" or indifference. The veto threshold is the smallest difference that completely nullifies (raises a "veto" against) the outranking relation. The assignment procedure involves comparing the properties associated with a specific nanomaterial (g_1, g_2, …, g_m) against a profile that includes ranges of criteria metric values corresponding to several risk classes. Comparisons are performed with respect to each criterion, taking into account the specified thresholds. The final classification decision is based on the profile criteria weights and specified cutoff level (lambda). For example, Class 4 represents the highest risk while Class 1 is the lowest risk (Fig. 1).

The assigned criteria weights represent the subjective importance of the criteria. For this reason, ELECTRE TRI was particularly attractive for these

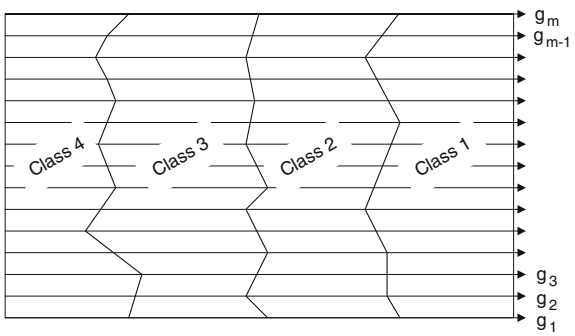

Fig. 1 Example measurements of profiles for each criterion g_j (adapted from Merad et al. 2004). Profiles are marked with *horizontal lines*

classifications because the weights represent "votes" for each criterion which are not affected by criteria scales. The lambda cutting level represents the minimum weighted sum of criteria that have to be in concordance with the outranking relation for it to hold: the lambda cutting level is used to transform the "fuzzy" outranking relation into an exact one (whether an alternative outranks a profile or not). For example, a lambda cutting level of 0.6 means that 60% of the weighted criteria have to be "at least as good" for the outranking relation to hold.

Alternatives were compared by accounting for the three thresholds. An alternative and profile with scores of 0.4 and 0.6 (for the same criterion), respectively, and an indifference threshold of at least 0.2 demonstrates that this criterion fully supports the conclusion that the alternative outranks the profile. Sometimes the support is not binary but is further affected by linear interpolation in the hesitation zone of both veto and preference thresholds (see e.g., Tervonen 2007). In this case the support can have real values between 0 (no support) and 1 (full support).

All the parameters of ELECTRE TRI can be imprecise and represented by arbitrary joint distributions in SMAA-TRI. This feature allows us to make conclusions about risks related to different nanomaterials even though the information about their characteristics is limited. Monte Carlo simulations were used in SMAA-TRI to compute acceptability indices for alternative categorizations (i.e., for assigning nanomaterials in different risk classes). SMAA-TRI allows automatic sensitivity analysis.

SMAA-TRI output comes as a set of category acceptability indices which describes the share of feasible parameter values that assign alternatives to each category. The category acceptability indices are measures indicating the stability of the parameters, i.e., if the parameters are too uncertain to make informed decisions. A high index (>95%) signals a reasonably safe assignment of the alternative into the corresponding category. With lower indices, the risk attitude of the decision maker defines the final assignment. For example, if an alternative has an 80% acceptability for the lowest risk category and a 20% acceptability for the second lowest risk category, a risk-averse decision maker could assign the alternative to the higher risk category.

SMAA-TRI conducts the numerical simulation by comparing the effects of changing parameter values

and criteria evaluations on the modeling outcomes. Parameter imprecision can be quantified by Monte Carlo simulations using different probability distributions (uniform, normal, log-normal, etc.). Gaussian or uniform distributions are typically used (for more information about SMAA methods, see Tervonen and Figueira 2008).

If some model parameters need to have their sensitivity assessed, they can be considered imprecise and defined as probability distributions.

Criteria

Recent articles, as well as the frameworks reviewed in this study, generally propose several different characteristics in the risk assessment of nanomaterials. These characteristics are generally based on *extrinsic* particle characteristics (size, agglomeration, surface reactivity, number of critical function groups, dissociation abilities) (Biswas and Wu 2005; Borm and Müller-Schulte 2006; Borm et al. 2006; Gwinn and Vallyathan 2006; Kreyling et al. 2006; Medina et al. 2007; Nel et al. 2006; Oberdörster et al. 2005; Thomas and Sayre 2005). These various parameters are critical because they define the fate and relevant intact exposure pathways as well as internal dose required to assess risk (Tsuji et al. 2006). Summary descriptions of five basic extrinsic nanomaterial properties (agglomeration and aggregation, reactivity, critical functional groups, particle size, and contaminant dissociation) are presented below:

- Agglomeration, weakly bound particles, and aggregation, strongly bound or fused particles (ISO 2008), are important risk criteria because they provide a description of the physical state of NPs in the aquatic system (Kennedy et al. 2008; Wang et al. 2008). In aqueous solutions, NP agglomeration generally occurs by two mechanisms: colloid settling and flocculation. Flocculation occurs when Brownian-driven collisions bind unassociated particles together through Van der Walls forces by dehydrating the interacting surfaces. Consequently, the particle separates out of the solution containing the mass of the previously unassociated particles. Settling, on the other hand, occurs due to the pull of gravity, as described by Stokes law relationships. Particles may settle but remain non-flocculated, settling at interparticle distances with the lowest free energies. In the absence of surfactive agents, particle flocculation is fairly predictable using particle charge. Charged functional groups give way to the development of a surface electrostatic potential which extends out a few nanometers at the solid–liquid interface, forming a diffuse double layer or DDL (Bowden et al. 1977; Uehara and Gillman 1981). Classical DLVO theory predicts that repulsive forces between particles (arising from overlapping DDLs) increase with increasing ion concentrations (or increasing ionic strength, I) because of rising osmotic pressures at the solid–solution interface force the DDL to swell (Evangelou 1998, and references therein). Yet, classical Debeye–Huckel theory predicts a competing case where increasing ion concentration decreases DDL thickness, throwing a system into flocculation. Thus, at a fundamental level, the process of agglomeration represents the balance of these two competing charge interactions.
- Reactivity/charge: A NP may become charged either by design (such as through functionalization) or by spontaneous degradative reactions. NPs may be functionalized with various types of groups, such as COOH, NH_2, and SH_2 through standard organic synthesis methods. Such functionalizations may be useful for manufacturing processes. For example, single-walled carbon nanotubes (SWNTs) are typically carboxylated at their ends as part of the isolation/purification processes (Anita Lewin, RTI International, personal communication). The type of charge occurring on functionalized NPs is called variable charge, which means that the magnitude of the surface electrostatic potential varies with solution pH (Uehara and Gillman 1981). Variably charged groups characteristically exhibit a surface pK_a. Thus, variably charged surface groups may be speciated (e.g., protonated versus deprotonated) by the classical Henderson–Hasselbauch equation. Furthermore, the magnitude of the surface electrical potential may be suppressed by increasing I, as described previously. Thus, the reactivity of variably charged functional groups varies with the difference in solution pH from the surface pK_a and the magnitude of I.

- Critical functional groups: Related to the reactivity/charge, critical functional groups make up an important criterion given the fact that nanomaterial functionality and bioavailability is directly related to chemical species. Basing risk criteria on elemental speciation is superior to elemental composition alone because it identifies the unique set of reactions available to each species. For example, suspended zero-valent Fe NPs have been shown to catalyze reductive degradations of aqueous organic contaminants (Joo et al. 2004). The same degradative ability has been shown for structural Fe^{2+} (higher oxidation state than zero-valent Fe but different speciation in terms of its complexation environment) domains at clay-edge and -interlayer nanosites in soil (Hofstetter et al. 1999, 2003). The Cd^{2+} cation in quantum dots exhibits no toxicity to organisms as long as it remains complexed with Se (Derfus et al. 2004). Speciation also determines solubility or potential dissociation of nanomaterials.
- Contaminant dissociation: This criterion describes risk associated with residual impurities contained within the NP. For example, Fe oxide NPs may contain S impurities depending on whether $FeCl_3$ or $Fe_2(SO_4)_3$ was used in manufacturing. Carbon nanotubes may contain Ni, Y, or Rb metal cation impurities (Bortoleto et al. 2007; Chen et al. 2004), which may either be entrained within or adsorbed onto the surface of the tubes. However, little is actually known about the extent to which metallic and organic contaminants remain with the manufactured product. Thus, the assignment of this risk criterion could change with better information.
- Size: Particle size is a criterion related to the agglomeration and reactivity criteria. Obviously, smaller particles agglomerate at slower rates. However, agglomeration is also related to the particle size distribution or polydispersivity. For example, greater monodispersivity of particles sizes appears to promote more stable dispersions (Chappell et al. 2008). Also, NP reactivity is also impacted by the magnitude of NP surface relative to the bulk of the solid. While the surface is the reactive portion of solids, the bulk component may suppress the surface reactivity through internal reorganizations, etc. NPs are essentially surfaces with limited bulk. Surfaces with low accompanying bulk have been shown to possess enhanced reactivities, such as high-affinity adsorption of metals or unique structures of assembly during agglomeration (Auffan et al. 2008; Erbs et al. 2008). Particle size is particularly important in terms of distinguishing the unique size-dependent chemistry of NPs from classical colloid chemistry.

Factors that may influence the potential hazards of engineered nanomaterials include bioavailability, bioaccumulation and translocation potential, and potential for toxicity. These factors have been described in empirical studies and are dependent on the characteristics of the particles as described above. It is difficult to predict the behavior of nanomaterials; however, future computational approaches are expected to provide additional tools to estimate these properties from physical and chemical parameters.

- Bioavailability: Bioavailability describes the likelihood of a material to be absorbed across cell membranes from the various exposure routes (e.g., dermal, inhalation, oral exposures) into system circulation in an organism (Medinsky and Valentine 2001). This process is controlled by the characteristics described above. For example, particle charge may influence agglomeration and hence limit the ability of the particle to cross gastrointestinal membranes after oral ingestion. However, several pathways enable NPs to cross cell membranes, including pinocytosis, endocytosis, and diffusion (as summarized by Unfried et al. 2007). The mechanism by which particles are absorbed is highly dependent on particle composition, surface modification, size, shape, and agglomeration.
- Bioaccumulation potential: Bioaccumulation is the net accumulation of particles absorbed from all sources (soil, water, air, and food) and exposure routes listed above into an organism. Accumulation must consider the temporal aspects of exposure and include kinetic factors such as exposure concentration, duration of exposure, clearance, biotransformation, and degradation. Most studies to date have focused on the potential for uptake and translocation in specific tissues (Ryman-Rasmussen et al. 2006; Gopee et al. 2007; Kashiwada 2006) and have not addressed the toxicokinetics of NPs.

- Toxic potential: The toxicity of engineered nanomaterials and particles in mammalian and other animal systems has been assessed primarily through cytotoxicity screening assays, although some in vivo studies have been completed. It is proposed that toxicological effects of nanomaterials occur through oxidative stress, inflammation from physical irritation, dissolution of free metal from metal NPs, and impurities in nanomaterials (e.g., catalysts) (Oberdörster et al. 2007). The characteristics of NPs that influence toxicity include size, surface area, morphology, and dissolution. To date, screening studies using in vitro approaches have observed toxicity from metal NPs at lower concentrations (Braydich-Stolle et al. 2007) than toxicity from carbon-based NPs (Murr et al. 2005; Grabinski et al. 2007).

Proposed classification framework

The purpose of the proposed classification system is to preliminarily group nanomaterials in risk classes for screening level risk assessments. Such groupings should aid in prioritizing materials for further study. In this article, we considered five risk categories: extreme, high, medium, low, and very low risk. In order to assign particular nanomaterials to these categories, we need to define criteria scales, thresholds, and measurements (Table 1).

The quantitative criterion, particle size, was evaluated as the mean size of the material in units of nanometers as obtained from literature review and expert estimates. Bioavailability, bioaccumulation, and toxic potential were measured through subjective probabilities that the nanomaterial has significant potential in the criterion. These, as well as the rest of the criteria (agglomeration, reactivity/charge, critical function groups), were measured based on expert judgments. The qualitative criteria were measured in terms of ordinal classes: 1 was the most favorable (least risk) value class, while 5 the least favorable (highest risk) (Table 1).

For the qualitative criteria, we encoded the classes with integers. The indifference thresholds were set to 0 and the preference thresholds to 1. This choice of thresholds represented an ordinal scale: a smaller number was preferred to a larger one, but the intervals did not carry any information (e.g., 1 is as much preferred to 2 as 1 is to 3). If there were multiple possible classes for an alternative, the measurement was modeled with a discrete uniform distribution, meaning that the density function for the distribution was such that the integers corresponding to these classes were equiprobable. Veto thresholds were not used in this phase of the framework but will be added later when more information about the criteria becomes available. Size is a criterion that should have some veto associated with it so that very small materials cannot be assigned to the safer (lower risk) categories.

Even though nanomaterial size is believed to be a factor influencing toxicity, there is little specific information available characterizing toxic effects relative to the 1–100 nm size range (Powers et al. 2007). More research is needed to define the thresholds in a more exact manner. If a "smaller"-sized NP represents higher risk, it follows that a larger size is "more preferable" because of its inherently lower risk. Due to these knowledge gaps, imprecise thresholds were used for nanomaterial size with indifference threshold of $10 \pm 5\%$ and preference threshold of $25 \pm 5\%$.

Bioavailability, bioaccumulation, and toxic potential were all measured using a cardinal but subjective scale as described above. Because of the subjectivity of this scale, we applied imprecise thresholds. Indifference thresholds were set to vary uniformly from 0 to 10, and preference thresholds from 10 to 20.

The SMAA-TRI model separated the risk categories using profiles formed from measurements of the same criteria as the alternatives. In our framework, the profile measurements were all exact (Table 2).

Our model applied imprecise preference information in the form of weight bounds. For more information on how these were implemented, see Tervonen and Lahdelma (2007). We judged the toxic potential to be the most important criterion, and thus it was assigned weight bounds of 0.3–0.5. Bioavailability and bioaccumulation potentials were deemed the least important criteria, and as a result, we were undecided on their relative importance. Both of these criteria were given weight bounds ranging from 0.02 to 0.08. The rest of the criteria were assigned weight bounds of 0.05–0.15.

Table 1 Criteria measurements

	Agglomeration	Reactivity/charge	Critical function groups	Contaminant dissociation	Bioavailability potential (±10)	Bioaccumulation potential (±10)	Toxic potential (±10)	Size (±10%)
C60	4	2, 3	3	2	25	50	10	100
MWCNT	4	2, 3	4	3	25	50	25	50
CdSe	4	4, 5	1	4	50	75	75	20
Ag NP	3	4, 5	1	4	50	75	75	50
Al NP	5	1, 2	1	1	25	75	10	50

The first four criteria are measured as ordinal classes. Measurements of reactivity/charge have associated uncertainty in that the materials can belong to either of the indicated classes. The following three criteria have linear imprecision of 10 in both directions from the indicated mean value. Size has uncertainty of 10% of the shown mean value

Table 2 Profile measurements

Profile	Agglomeration	Reactivity/charge	Critical function groups	Contaminant dissociation	Bioavailability potential	Bioaccumulation potential	Toxic potential	Size
Extreme–high	4	4	4	4	100	100	100	5
High–medium	3	3	3	3	80	80	80	50
Medium–low	2	2	2	2	70	70	70	100
Low–very low	1	1	1	1	60	60	60	200

Each row corresponds to a profile differentiating the categories presented in the first column

We used imprecise values for the lambda cutting level within the range of 0.65–0.85. Lambda defines the minimum sum of weights for the criteria that must be in concordance with the outranking relation to hold. The classification was performed according to the pessimistic assignment rule, which in risk assessment applications represents a more conservative approach.

Example

We demonstrated application of the framework by classifying five nanomaterials: nC$_{60}$ (a fullerene), multi-walled carbon nanotube (MWCNT), CdSe (quantum dot), silver nanoparticles (Ag NPs), and aluminum nanoparticles (Al NPs). Typical size ranges for these materials were estimated based on in situ measurements from the available literature. Other properties were assessed using authors' expert judgments, taking into account the characteristics for each criterion described in "Criteria" section. Metrics for the five materials used in our case study (Table 2) as well other model parameters were input into the SMAA-TRI software. Even though criteria metrics used in the article were assessed using expert judgment, and its objectivity can be questioned, the outranking algorithms used in SMAA-TRI together with the choice of absolute thresholds implemented in this study allows us to obtain robust results (Tervonen 2007).

Category acceptability indices obtained from the simulation are presented in Fig. 2. These indices show that the data was too imprecise to make definite decisions about the risks related to the different nanomaterials. However, there was sufficient data to make preliminary classifications. For example, CdSe exhibited a very high index in the high risk class. On the other hand, Al NP may be considered relatively safe; its category acceptability indices for low and very low risk were 34 and 34, respectively. Summing these indices gave the material an estimated 68%

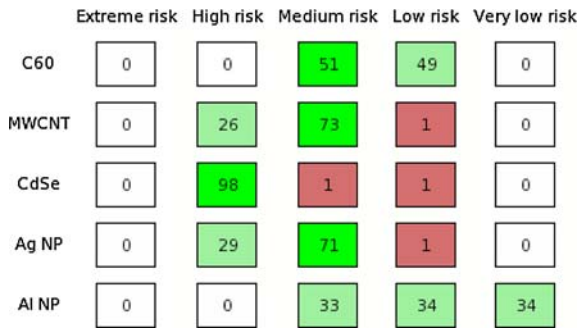

Fig. 2 Category acceptability indices of the example. A high index means that the material is assigned to the corresponding category with a high confidence, as measured by a larger percentage share of possible parameter values corresponding to this category

probability of being classified as "low to very low risk." C60 showed a reasonable acceptability index (49%) for the low risk category. In terms of making risk-aware decisions for C60 and Al NPs, we feel that further studies into expanding the potential applications of Al NP and C60 (as opposed to CdSe) are justified.

It is important to point out that in spite of the high uncertainty of the above results, this work represents a reasonable starting point for a more thorough follow-up analysis. Indeed, more data is required to improve our estimates. Risk estimates based on acceptability indices below a certain threshold (e.g., 80%) should be viewed with caution. For example, should C60 be deemed viable for further research and application, additional measurements will be required to further refine the risk estimates. In spite of its limitations, the quantified risk values obtained from our simulations are helpful in characterizing the risk and uncertainty for limited and variable data.

Concluding remarks

Nanotechnology is a rapidly growing research field with an increasing impact on our everyday lives. Although nanomaterials are used in common consumer products, the lack of information about human health and environmental risks may hamper the full-scale implementation of this technology. In this article, we presented a systematic multi-criteria approach that enables nanomaterials to be assigned into ordered risk classes. Materials assigned to the highest risk class potentially represent areas of important future toxicological studies, while materials exhibiting low risk may be recommended as targets of research aimed at commercial use. The proposed framework takes into account measurements and expert estimates for multiple criteria that are known to impact the toxicity of the material.

The use of an SMAA-TRI approach allows for the explicit incorporation of uncertainty parameters in the model. An appealing characteristic of the outranking model applied in SMAA-TRI is that it allows the veto effect to be modeled, meaning that a nanomaterial's poor performance in one criterion cannot be compensated for by good performance in other criteria (as is the case for compensatory MCDA models, e.g., utility theory). This convention prevents decisions about the risk of a particular nanomaterial being unduly based on one particular criterion (such as size versus surface reactivity relationships), as the material may have other physico-chemical characteristics related to size that exhibit a greater impact on its toxicity.

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