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Implementing the DF4 in a robust model, allowing for enhanced comparison, prioritisation and grouping of Nanomaterials

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ABSTRACT

It is here shown how partial order can be used to provide a robust and consistent implementation of the DF4 approach which provides unbiased information enabling comparison and open up the possibility for grouping. The approach is based on few assumptions, works well with the data, can include different types of input parameters, and can provide fundamental information about the ranks of tested materials. It is shown that the materials in many cases are below one threshold within a tier, but above another threshold within the same tier. It is also observed that the ranks of the materials can differ between tiers, although this is less relevant for DF4 since parameters evaluation may be hierarchical.

1. Introduction

An approach to group nanomaterials (NMs) using both intrinsic and extrinsic parameters has been outlined in Arts et al. (2015a), the DF4nanoGrouping approach. In summary, the DF4 has been evaluated on 22 NMs (Arts et al., 2015b) using 10 NMs related parameters (here termed attributes), which includes a mixture of intrinsic and extrinsic material related parameters (see Table 1). The principle is to describe grouping of NMs through three tiers, based on the attributes. The DF4nanoGrouping covers all relevant aspects of a nanomaterial's life cycle and biological pathways, and aims to group nanomaterials by their specific mode-of-action that results in an apical toxic effect (Arts et al., 2015a). Thus, each of the attributes partly contribute to the relative knowledge and all attributes describe all aspects.

The DF4 approach works well for comparing few materials using all parameters binary see examples in Arts et al. (2015b). When more than a few materials are being evaluated it will be difficult or impossible to get a clear overview of the possible similarities between the evaluated materials; and how the various thresholds relate across the materials. Hence, there is a need for a formalized, clear and robust approach, where similarities can be observed. The present scarcity of data suggests that such an approach should not require a data rich foundation, but be able to incorporate novel data while being consistent with already taken decisions.

The parameters in DF4 include data of different formats i.e. (i) continuous (e.g. dissolution), semi-categorical (dispersibility) and categorical (e.g. shape or cell effects), (ii) containing different degrees of uncertainty related to each parameters, (iii) with an unknown covariance between the parameters, and finally (iv) the data comes from different sources. This implies that robust models should be used when dealing with such data.

2. Methods

We here outline a robust partial order implementation of the DF4 approach that is used in various parts of the European regulation. Partial order ranking will be applied for the NMs, using the three tiers, and in the final step we will illustrate the possible dimension reduction of the whole dataset.

The partial order is described by Brüggeman and Patil (2011), and various tools exists here the analysis were performed with a customized program based on Excel VBA. The principle is ordering of attributes for which monotonic ranks can be assumed for each. For example, given that we have three nanomaterials each with two parameters (attributes) described, e.g. size and solubility (see Table 2, which is a subset of Table 1). Then these can be ranked compared to each other, the individual ranks show that for Solubility: CeO2 > BaSO4 > CuO and for Size: BaSO4 > CeO2 > CuO. Hence, it is clear that for both parameters CuO is the lowest rank, whereas the two other materials cannot be ranked in one order when including both parameters. Graphically, this can be shown as a Hasse-diagram (Table 2):

The rank direction for Hazard ranking (high rank level equal high hazard) needs to be assumed based on theoretical reasoning or based on empirical toxicological data.

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Table 1
Data from Arts et al., (2015b) (see Table 3 and 7 in original paper). The original Tables in Arts et al. (2015b) contains more text information within each cell of the Table, here one single information entry (data point) has been derived for each cell. It should be mentioned that it is not always clear (from the original table) what the single value is and in some cases the information is just stated as < X etc., without further explanation. Biopersistence is converted letters, with original values in the brackets, this has no impact on the ranks. Nevertheless, the table is converted and used as a proof of concept for the method. When further refinement of the table is available this can be updated. They key here is that the items in each column (attributes) has an order i.e. for each attribute the will be a certain rank of the materials (one material ranking higher, lower or the same as another material, see example in the figure of Table 2). "Wat. Solub." = Water solubility, "Comp." = Composition, "Surface Reactiv." = Surface reactivity, "Dispers." = Dispersability, "Bio. Persist." = biological persistence.

NM	Tier 1				Tier 2				Tier 3	
	Wat. Solub. (mg/L)	Size (nm)	Comp. (%)	Purity (%)	Surface	Surface Reactiv*	Dispers. (AAN)	Effects (1–4)	NOEC	Bio Persist.
Threshold	100	5000	99.9	99.9	100	0.19	3	4	10	C (40)
BaSO4	6	32	100	93.8	7	0.0503	9	1	50 (> 50)	B (< 40)
CeO2_211	10	15	100	95	10	0.0073	1	2	0.5 (< 0.5)	D (> 40)
CeO2_212	20	40	100	99.5	10	0.0324	23	2	0.5 (< 0.5)	D (> 40)
CuO	0.4	10	100	100	120	2.205	1	2	0.6	ND**
Fe2O3	1	15	100	100	1	0.0372	2	1	30 (> 30)	B (< 40)
TiO2	0.1	21	100	99	1.5	0.0244	10	2	2 (< 2)	D (> 40)
ZnO_110	0	70	100	99	100	0.0978	1	2	8 (< 8)	A (RC)
ZnO_111	0	82	100	99	640	0.0389	1	2	50 (0.5)	A (RC)

* μUFRAS/m^2*h; ** ND Not determined, RC = rapid clearance (here assumed to be lower than t_{50} < 40days).

Table 2
Example of simple ranking of a few of the materials, i.e. using BaSO4, CeO2_211 and CuO (see Table 1). The rank principle can be done for all materials. On the right side are three derived Hasse-diagrams: Left diagram is a ranking of water solubility (Wat. Sol.) alone, middle is size alone, and the right when water solubility and size are ranked together.

NM	Water Solubility (mg/L)	Size (nm)	Wat. Sol.	Size	Wat. Sol. and Size
BaSO4	6	32			
CeO2_211	10	15			
CuO	0,4	10			

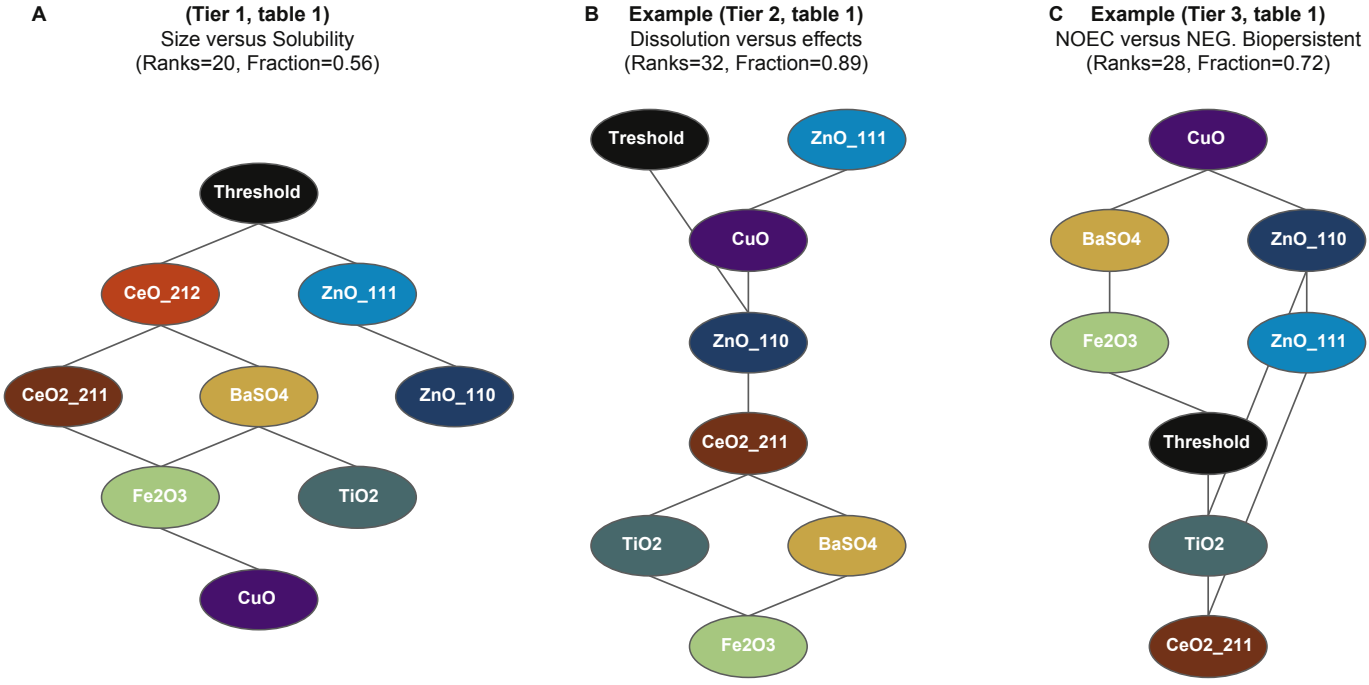

Fig. 1. Tier based Rank Trees, Hasse diagrams, for the NMs listed in Table 1. The "Ranks" is the number of ranks obtained and "fraction" is the relative ratio out of the total possible ranks.

3. Results

3.1. Step 1

A first step for the data analysis is to look at the data structure. The DF4 data, see Table 1, for each NM are obviously of multivariate nature hence an initial approach could be to study the possibility of dimension reduction techniques e.g. Partial Order Scaling (POSAC, Shye, 1985, see examples Fig. 5). This will enlighten on possible familiarity of attributes in the way they result in a rank of the objects in the present dataset.