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Qualitative and quantitative differences between common control banding tools for nanomaterials in workplaces

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A number of control banding (CB) tools have been developed specifically for managing the risk of exposure to engineered nanomaterials. However, data on the methodological differences between common CB tools for nanomaterials in workplaces are rare. A comparative study with different CB tools, such as Nanosafer, Stoffenmanager-Nano, Nanotool, Precautionary Matrix, ECguidance, IVAM Guidance, ISO, and ANSES, was performed to investigate their qualitative and quantitative differences in real exposure scenarios. These tools were developed for different purposes, with different application domains, methodological principles, and criteria. Multi-criteria analysis showed that there was a diverse distribution of these eight CB tools across different evaluation indicators. The total evaluation scores for Nanotool, Stoffenmanager-Nano, and Nanosafer were higher than the other tools. Quantitative comparisons demonstrated that ANSES, ECguidance, and IVAM Guidance tools were better in terms of information availability. Nanotool, Stoffenmanager-Nano, and ECguidance were better in terms of the sensitivity of outputs to changes in exposure parameters. The Nanotool, ANSES, and ECguidance tools were better in terms of accuracy of hazard outcomes evaluated with toxicological data. The Stoffenmanager-Nano, Nanotool, and Nanosafer tools' exposure scores for seven scenarios had a good correlation with measurement data. The Nanotool and Stoffenmanager-Nano tools had much higher comprehensive advantages based on quantitative and qualitative assessment. More comparative studies evaluating different tools are required, using more types of nanomaterials in real exposure scenarios.

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1. Introduction

Nanoparticles are increasingly being produced and handled in workplaces.[1] Therefore, a large population of workers experience potentially high health risks, and exposure to nanoparticles is an emerging concern in the field of occupational health. Currently, the pace of health risk assessment does not match the pace of development of new nanomaterials, owing to a scarcity of toxicology and exposure data, and the uncertainty surrounding the hazardous risks they pose.[2]

A number of control banding (CB) tools have been developed as pragmatic tools for managing the risks from exposure to a wide variety of potentially hazardous substances in the absence of firm toxicological and/or detailed exposure information.[3] These tools offer simplified guidance based on the combination of a substance's hazard and its potential exposure to minimize occupational risks. In principle, CB tools generally use limited physicochemical and task/scenario information to place the substance of interest into a hazard and exposure band and to classify the substance into risk categories with recommended control measures.[4,5]

Control banding tools lay a foundation for the risk assessment of novel substances in workplaces, such as nanomaterials. Many CB tools, such as Nanosafer, Stoffenmanager-Nano, Nanotool, Precautionary Matrix, ECguidance, IVAM Guidance, ISO, and ANSES, have been developed specifically to manage the potential risk from occupational exposure to nanomaterials.[6] Typically, these CB strategies, which are constituted of hazard and exposure bands,[7] were used to derive the risk band or associated engineering control band for a given occupational scenario for nanomaterials. The CB tools have been promoted by governments or international organizations. For example, the Stoffenmanager-Nano has been recommended for evaluating the safety of purposely produced insoluble particles. Nanotool has been used to assess the health risks of metal nanoparticles such as copper, nickel, and silver, as well as carbon nanotubes.[3]

The different CB tools for nanomaterials have some similarities and differences in their methodologies. Thus far, little guidance has been reported for choosing the most suitable CB tool for a given application because different tools might give

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very different results. It is therefore strongly desirable to strengthen the theoretical framework for assessing and minimizing the potential risks from occupational exposure to nanomaterials, which is dependent, to some extent, on an understanding of the similarities and differences in the methodologies between the different CB tools for nanomaterials. At present, there are few comparative studies on the quantitative and qualitative differences between the different banding methodologies for nanomaterials. Sánchez *et al.*[4] and Brouwer[6] compared CB tools in terms of scope, parameters, and classification. The authors found that different approaches to estimate hazard and exposure bands can result in different outcomes and preventive recommendations, and the outputs should be interpreted carefully. Dunn *et al.*[7] provided a detailed overview of the eight CB tools and the review was further updated by Liguori *et al.*[8] However, the hypotheses from these studies lacked the support of real exposure scenarios. Therefore, it is necessary to carry out comparative studies between different CB tools under real nanomaterial exposure scenarios to understand their methodological differences, as well as to improve the theoretical framework for occupational health risk assessment of nanomaterials in workplaces.

The aim of this study was to assess the above mentioned eight common CB tools and to investigate their qualitative and quantitative differences in real exposure scenarios involving nano-Fe_2O_3, nano-Al_2O_3, and nano-$CaCO_3$. The following five CB tool aspects were investigated: (1) nano-relevance; (2) amount and availability of information required; (3) sensitivity of outputs to changes in hazard and exposure parameters; (4) accuracy of outcomes of hazards evaluated with toxicological data; and (5) accuracy of exposure classification evaluated with measurement data.

2. Materials and methods

2.1 Description of nanomaterial exposure scenarios

Three typical factories producing nano-Fe_2O_3, nano-Al_2O_3, and nano-$CaCO_3$ were selected for field investigation. They are small-scale enterprises or enterprises in the trial production stage, and are located in eastern and central China. A total of seven exposure scenarios involving nanomaterials, *e.g.* packaging, screening and feeding for nano-Fe_2O_3, packaging and separation for nano-Al_2O_3, and packaging and drying for nano-$CaCO_3$, were screened for performing the comparative study across different CB tools.

The nano-Fe_2O_3 was produced by chemical synthesis and is used as a dye for automobile surface paints. During the production of nano-Fe_2O_3, there were three processes that can generate potential exposure to airborne nano-Fe_2O_3: (1) powder screening: a portion of the α-$Fe_2O_3 \cdot nH_2O$ product was manually spread onto a flat plate; (2) material feeding: the α-Fe_2O_3 material was manually fed into a semi-open container for washing; and (3) α-Fe_2O_3 or α-$Fe_2O_3 \cdot nH_2O$ packaging. A local exhaust ventilation (LEV) system was installed in the packaging area; only general ventilation was installed for the powder screening area; and the feeding process did not have any ventilation measures.

The nano-Al_2O_3 was produced using a gas-phase method in a pilot factory and is used as a catalyst and as a surface protector. Two processes that can generate nanomaterial aerosols were selected for the exposure scenarios, *e.g.* the separation of HCL gas and nano-Al_2O_3 particles *via* air-blowing in a separator, and automatic packaging. The packaging process was performed in a relatively closed environment. The separation process was performed in a workplace with general ventilation.

The nano-$CaCO_3$, used for cable coating, was produced by chemical synthesis in a nano-$CaCO_3$ manufacturing factory. The processes of drying of wet product and packaging were selected as the exposure scenarios. There were no control measures for the two processes.

2.2 Air monitoring for exposure to nanomaterials

The total particle number concentration (TNC), as a sensitive exposure indicator, was determined for airborne nanoparticles using a P-Trak ultrafine particle counter (Model 8525, TSI, USA). The counter is a portable condensation particle counter (CPC) calibrated by the manufacturer, and was set to zero prior to sampling. It counts particles enlarged in a saturated vapor environment using optical sensing.

The size distribution by number for airborne nanoparticles was determined using a scanning mobility particle sizer (SMPS, Model 3034, TSI, USA). The SMPS contains a differential mobility analyzer (DMA) and a CPC that can determine the particle size distribution based on electrical-mobility diameters. The instrument was calibrated using the manufacturer's instructions.

The sampling/testing protocol was as follows:[9,10] (1) background measurements: outdoor background particles from the atmosphere were characterized; and (2) activity-based measurements: the instruments' inlets were positioned close to the breathing zone of workers potentially exposed to nanomaterials at the sampling locations. The sampling period covered a complete duration of the activity. The TNCs were corrected using background concentrations to get the concentration ratios (CR) (sampling location *vs.* background), which reflect the degree of nanoparticles released from the particle generation source.

The risk ratio (RR),[11] which is defined as the ratio between the risk level of a particular nanomaterial (obtained through the given CB tool) and the maximum risk level for that tool, was used for comparing assessment results obtained from different tools. For example, in Nanosafer the risk level of nano-Al_2O_3 at the separation sampling location is 4, while the maximum risk level for the tool is 5. Hence the RR of nano-Al_2O_3 using Nanosafer is 0.8 (4/5). RRs represent the relative risk levels and are therefore comparable across different tools. Similarly, the exposure band ratio is defined as the ratio between the exposure band and the maximum exposure level for the tool and the hazard band ratio is defined as the ratio between the hazard band and the maximum hazard level for the tool. Both of them were used for comparing the sensitivity of exposure classifications and the reliability of hazard classifications.

2.3 Methodology for CB tool modelling

The control banding methodology for each tool is briefly described as follows. (1) The NanoSafer (http://nanosafer.org/Default)[12] was developed by Denmark's National Research Center for the Working Environment (NRCWE).[13] Its hazard assessment is based on binary grouping principles, which combines the scores assigned to each individual hazard. Nanosafer allocates four hazard bands, with ranking values from 0.2 to 1. The exposure band allocation is based on the principles of the source-to-receptor model described in Schneider *et al.*[14]

(2) The Stoffenmanager-Nano (http://nano.stoffenmanager.nl/)[15] was developed by a consortium led by the Organization for Applied Scientific Research based in the Netherlands.[16,17] It follows a stepwise binary decision tree, which provides five hazard bands. The exposure band gets a score with four value ranges (<0.002; 0.002–0.2; 0.2–20; >20). The hazard and exposure banding system are combined in a two-dimensional decision matrix, ranked from I to III.

(3) The Nanotool (http://www.controlbanding.net/)[18] was developed by Paik and Zalk *et al.* at the Lawrence Livermore National Laboratory, USA.[19,20] It assigns the hazard and exposure bands using a points scoring system ranging from 0 to 10 for a single factor, and then combining them to get the risk band, which is equally divided into four bands.[21,22]

(4)The Precautionary Matrix (https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und-gesundheit/chemikalien/nanotechnologie/sicherer-umgang-mit-nanomaterialien/vorsorgeraster-nanomaterialien-webanwendung.html) was developed by the Swiss Federal Office of Public Health and the Federal Office for the Environment in 2008,[23] and was revised in 2010.[24,25] Unlike other tools, it combines hazard and exposure potential in a single score which is subdivided into two bands to determine the precautionary need. For the purposes of calculating the precautionary need, the input parameters are scored from 1 to 9 (*e.g.* low = 1, medium = 5, high = 9).[26]

(5) The ECguidance developed by the European Commission is meant to assist employers, health and safety practitioners, and workers in fulfilling their regulatory obligations.[27] It follows a stepwise binary decision tree, which allocates 4 bands for the hazard and the exposure rankings, and 4 control level bands.

(6) The IVAM Guidance was developed to provide a guidance for working safely with engineered nano-materials and end-products (http://www.industox.nl/Guidanceonsafehandlingnanomats&products.pdf).[28] It follows a stepwise binary decision tree, which allocates 3 bands for the hazard ranking and the exposure ranking, and 3 control level bands. The control level bands are classified into three control levels A, B, C with A the lowest to C the highest, with corresponding advice for control measures for each control level.

(7) The ISO control banding (http://www.iso.org/iso/catalogue_detail.htm?csnumber=53375)[29] is specifically designed for inhalation control, focusing on nano-objects such as nanoparticles, nanopowders, nanofibers, nanotubes, nanowires, as well as aggregates and agglomerates. The guidance is based on a stepwise binary decision tree driven by information. It applies 5 hazard bands, 4 exposure bands, and 5 control bands.

(8) The ANSES tool was developed by the French Agency for Food, Environmental and Occupational Health & Safety (https://www.anses.fr/en/content/anses-proposes-innovative-approach-prevention-occupational-risks-nanomaterials) for conducting risk assessment of work with manufactured nanomaterials in industrial settings.[30,31] It applies 5 hazard bands, 4 exposure bands (emission potential), and 5 control bands for risk. The control levels are derived by combinations of the hazard and exposure bands in a two-dimensional decision matrix, ranking from lower CL1 to higher CL5 associated with general recommendations.

2.4 The comparative study across different CB tools

The comparative study across different CB tools consisted of two parts: a qualitative and a quantitative comparison. Analysis of the key information and multi-criteria analysis were performed for comparing the qualitative differences. Quantitative comparisons between the different CB tools were performed in terms of nano-relevance, availability of information required by tools, sensitivity of tool output to changes in hazard and exposure, and reliability of tool hazard bands and exposure bands.[4] The associations between the different tools were tested using correlation analysis. Finally, the consistency of qualitative and quantitative comparisons was evaluated.

(1) Qualitative comparisons. The eight CB tools were evaluated qualitatively by analyzing key information and by multi-criteria qualitative analysis. Key information regarding scope, substance of interest, assessment method, aim of evaluation, and the number of risk bands were qualitatively analyzed based on a review of the literature and discussions with experts. The literature databases queried were Web of Science, Pub-Med, Medline, Scopus, and related official government regulatory websites. Search terms used were "nanomaterial", "risk assessment", "control banding", "methodology", and "tool".

A multi-criteria qualitative analysis was subsequently established based on this analysis of key information[11,32] and included the following steps: determination of evaluation indicators, assignment of indicator values and weights, expert consultation, interview with key informants, and comprehensive analysis. The evaluation indicators were determined based on the literature review and expert consultation, in which 20 experts in the field of health management or occupational health were asked for advice on evaluating the indicators in two rounds. The nine selected indicators are shown in Table 1. Rather than using different quantification scores, most of the consulted experts (85%) considered it appropriate to divide each indicator into low, medium, and high levels, which were assigned 1, 2, and 3 points, respectively. The practicability, accuracy, sensitivity, reliability of exposure ranking, and operability indicators were only divided into 2 levels (high and low) because the medium level was difficult to define. To assign indicator weights, 85% of experts agreed that the weight of the six indicators should be equivalent, meaning that each indicator was equally important. The rationality of the framework

Table 1 Scoring system used for the multi-criteria analysis

	Scores (levels)		
Criteria (Indicators)	1 (Low)	2 (Medium)	3 (High)
Evaluated substance (the tool that evaluates more types of substances is more useful.)	Powders	Powders, liquids	Powders, liquids, and solid materials
Validation (the tool is validated by documents containing independent data and may be more accurate.)	No	The tool is validated by a few documents	The tool is validated by adequate documents with independent data
Accuracy of nano-relevance (the tool with high consistence between the nano-relevance assessment and the particle size.)	The results of nano-relevance is not accuracy	—	The results of nano-relevance is accuracy
Reliability of hazard ranking the tool based on experimental or epidemiological data is more reliable.)	The results of hazard ranking is not based on experimental or epidemiological data	The results of hazard ranking is partly based on experimental or epidemiological data	The results of hazard ranking is based on experimental or epidemiological data
Reliability of exposure ranking (the tool with better correlation between the exposure assessment or the exposure concentration is reliable.)	No correlation between the exposure assessment and the exposure concentration	—	The exposure assessment has a correlation with the exposure concentration
Sensitivity (the tool with high variability to input parameters is sensitive)	No sensitivity	—	The tool is sensitive to the variation of input parameters
Guidance (the tool provides explanatory guidance that helps implementation.)	No guidance available	Guidance manuals are available, but lack examples of applications	Guidance manuals are available and give many examples of applications
Practicability (the tool that provides a control strategy to reduce health risks is more practical)	No control strategy is available	—	Control strategy is available with classification
Operability (the tool is convenient to use.)	Complicated to use	—	Easy to use

for qualitative comparisons was further discussed by 10 additional core expert practitioners.

A radar diagram was drawn to directly reflect the level distribution of the eight tools for each evaluation indicator. Table 1 shows the scoring system used for the multi-criteria analysis. The total scores of each tool in the nine evaluation indicators (*e.g.* evaluated substance, validation, accuracy of nano-relevance, reliability of hazard ranking, reliability of exposure ranking, sensitivity, guidance, practicability, and operability) were calculated to determine whether there was a comprehensive advantage for each tool.

(2) Quantitative comparisons

(a) Nano-relevance assessment. Among the eight CB tools, the Stoffenmanager-Nano, Nanosafer, Nanotool, and Precautionary matrix required nano-related information (such as the size, diameter, shape) to assess whether or not the material was nano-relevant. In addition, the ECguidance, IVAM Guidance, ISO, and ANSES tools also provided nano-relevant results based on user subjective judgments. In this study, the accuracy of nano-relevance results obtained from the CB tools was evaluated using the airborne nanoparticles' size distributions determined by SMPS.

(b) Availability of information required. The tools required different information to estimate hazard and exposure scores. The ratios of the number of available information and acquired information for hazard and exposure was used to evaluate the availability of information for each tool. Hazard information was obtained from the Safety Data Sheets (SDS) and open literature for each nanomaterial. Information on exposure was provided by the three nanomaterial manufacturing enterprises or obtained from the field investigation.

(c) Sensitivity of tool output to changes in hazard and exposure. The tools' sensitivity to changes in hazard characteristics and exposure determinants were evaluated by using nano-Fe_2O_3, nano-Al_2O_3, and nano-$CaCO_3$ with different characteristics. Table 2 shows the hazard input data for the nano-Fe_2O_3, nano-Al_2O_3, and nano-$CaCO_3$ required by the different tools. The hazards were generally determined from the physicochemical characteristics and toxicity of materials by the eight tools.

Physicochemical characteristics were presented as diameter, dustiness, and solubility in Nanosafer; as dustiness, moisture content and concentration in Stoffenmanager-Nano; as shape, diameter, and solubility in Nanotool; as solubility and dustiness in the ECguidance, the IVAM Guidance and ANSES. The toxicity data used in Nanosafer, ECguidance, ISO, and ANSES are similar, and were based on the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). For Nanotool, the toxicity data covered reproductive hazard, mutagenicity,

Table 2 Hazard input data of the evaluated materials required by different CB tools

		Materials		
CB Tools	Information requested	Fe_2O_3	Al_2O_3	$CaCO_3$
Nanosafer	Is the material named with any of the following words: Nano, dot, cluster, ultrafine, *et al.*?	Yes	Yes	Yes
	Is the material chemically surface-modified (coated / functionalized)?	No	No	No
	Is the shape of the primary particles known?	No	No	No
	Shortest dimension (nm)	10.4	10	—
	Shortest dimension (nm)	24.33	26.58	—
	Longest dimension (nm)	67.3	32.78	—
	What is the surface area of the powder material? $M^2\ g^{-1}$	Assumed 150	Assumed 150	Assumed 150
	Is there any information on the size of the primary particles?	—	—	No
	Is the specific surface area known?	—	—	No
	What is the relative density (specific gravity) of the material? (g cm^{-3})	5.24	3.97	2.8
	What is the solubility of the material in water?	Insoluble (<1 g L^{-1})	Insoluble (<1 g L^{-1})	Soluble (>1 g L^{-1})
	What is the respirable dustiness index (choose dustiness level if you do not have test results)	937.5 mg kg^{-1}	937.5 mg kg^{-1}	937.5 mg kg^{-1}
	Exposure limit for respirable dust (mg m^{-3})[a]	5	4	5
	Carcinogenic effect	No	May cause cancer	No
	Acute toxicity	Yes	Yes	No
	Severity of acute effects	STOT SE2	STOT SE2	STOT SE3
	Sensitization	No	Skin Sens.1	No
	Mutagenicity/genotoxicity	No	Muta.2	No
	Irritant/corrosiveness	Eye irrit.2; eye dam. 1 skin irrit. 2	Eye irrit.2; skin irrit. 2	Eye irrit.2; eye dam. 1 skin irrit. 2
	Carcinogenicity	No	Carc. 2	No
	Developmental/reproductive toxicity	No	Repr.2	No
	Likelihood of chronic effect	STOT RE 2	STOT RE 2	STOT RE 1
Stoffenmanager nano	Product appearance	Powder	Powder	Powder
	Dustiness	Very high	Very high	High
	Moisture content	Dry product (<5% moisture content)	Dry product (<5% moisture content)	Dry product (<5% moisture content)
	Do you know the exact concentration of the nano component in the product?	No	No	No
	Concentration	Pure product (100%)	Pure product (100%)	Pure product (100%)
	Does the product contain fibers/fiber like particles?	No	No	No
	Inhalation hazard	Unknown	Unknown	Unknown
	Does it concern one of the following OECD components?	Fe	Al_2O_3	Other MNOs
	Is the parent material classified with one or more of the following R-phrases: R40, R42, R43, R45, R46, R49, R68?	—	—	No
	Is the primary particle diameter larger than 50 nm?	No	No	No
Nanotool-*Parent material*	Lowest occupational exposure limit (mg m^{-3})[a]	5	4	5
	Carcinogen	No	Yes	No
	Reproductive hazard	Unknown	Yes	No
	Mutagen	No	Yes	No
	Dermal hazard	No	No	No
	Asthmagen	No	No	No
Nanotool-*Nanoscale material*	Surface reactivity	Unknown	Unknown	Unknown
	Particle shape	Compact or spherical	Compact or spherical	Compact or spherical
	Particle diameter	11–40 nm	11–40 nm	11–40 nm
	Solubility	Insoluble	Insoluble	Soluble
	Carcinogen	Unknown	Unknown	Unknown
	Reproductive hazard	Unknown	Unknown	Unknown
	Mutagen	Unknown	Unknown	Unknown
	Dermal hazard	Unknown	Unknown	Unknown
	Asthmagen	Unknown	Unknown	Unknown
Precautionary matrix-*Nanorelevant*	Size of primary particle	1–500 nm	1–500 nm	1–500 nm
	Do the primary particles form agglomerates >500 nm?	Yes	Yes	Yes
		Yes	Yes	Yes

Table 2 (*Contd.*)

		Materials		
CB Tools	Information requested	Fe_2O_3	Al_2O_3	$CaCO_3$
	In the body does deagglomeration of agglomerates (or aggregates) to primary particles or agglomerates <500 nm occur?			
	Under the respective environmental conditions does deagglomeration of agglomerates (or aggregates) to primary particles or agglomerates <500 nm occur?	Yes	Yes	Yes
Precautionary matrix-*Potential effect*	Redox activity of the nanomaterial	Medium	Medium	Low
	Catalytic activity of the nanomaterial	Medium	Low	Low
	Oxygen radical formation potential of the nanomaterial	Unknown	Unknown	Unknown
	Induction potential for inflammatory reactions of the nanomaterial	Unknown	Unknown	Unknown
	Stability (half-life) of the primary particles present in the nanomaterial in the body	Unknown	Unknown	Unknown
	Stability (half-life) of the primary particles present in the nanomaterial under environmental conditions	Unknown	Unknown	Unknown
ECguidance	Chemical formula/Chemical structure	Fe	Al	Ca
	Appearance	Powder	Powder	Powder
	Physical hazard classification of the bulk form	Unknown	Unknown	Unknown
	Health hazard classification of the bulk form	Acute Tox. 4	Acute Tox. 4, Carc. 2, Muta.2	No
	Environmental classification of the bulk form	Aquatic Acute 2	Aquatic Acute 2	Unknown
	Geometry/Shape, rigidity	Nanoparticle	Nanoparticle	Nanoparticle
	Surface composition	No modified	No modified	No modified
	Water solubility	Insoluble (<100 mg l^{-1})	Insoluble (<100 mg l^{-1})	Soluble (>100 mg l^{-1})
	Dustiness	High	High	High
ISO	OEL dust	A	A	A
	Acute toxicity	B	B	A
	LD_{50} oral route	A	A	A
	LD_{50} dermal route	Unknown	Unknown	Unknown
	LD_{50} inhalation 4H	Unknown	Unknown	Unknown
	Severity of acute effects	B	B	B
	Sensitization	No	C	No
	Mutagenicity/Genotoxicity	No	E, Muta. 2	No
	Irritant/Corrosiveness	C	A	C
	Carcinogenicity	A	C	A
	Developmental/Reproductive toxicity	Unknown	D	Unknown
	Likelihood of chronic effect	C	C	C
	IH/Occupational health experience	Unknown	Unknown	Unknown
IVAM guidance	CAS number	1309-37-1	1344-28-1	1317-65-3
	Size distribution of the primary particles in the material or product (in nm)	<40 nm	<40 nm	<40 nm
	Does the material or product involve fibrous particles	No	No	No
	Has the nanomaterial (or its mother material) been classified as CMR substance?	No	Yes	No
	Water solubility	No	No	Yes
	Density (in kg/dm3)	5.24 g cm^{-3}	3.97 g cm^{-3}	2.8 g cm^{-3}
	Physical state of the nanomaterial	Solid	Solid	Solid
ANSES *Preliminary question*	Does the product contain nanomaterials?	Yes	Yes	Yes
	Is the nanosubstance already classified by a relevant authority?	No	No	No
	Is it a bio persistent fiber?	No	No	No
	Is there a preliminary HB for the bulk material or most toxic analogous?	Yes	Yes	Yes
ANSES *Bulk material*	Substance dissolution time >1 h	Yes	Yes	No
	Evidence of higher reactivity than bulk/ analogous material?	—	—	No
ANSES *Parent material*	Acute toxicity	Yes	Yes	No
	Severity of acute effects	STOT SE2	STOT SE2	STOT SE3
	Sensitization	No	Skin Sens.1	No
	Mutagenicity/Genotoxicity	No	Muta. 2	No
	Irritant/Corrosiveness	Eye irrit.2; eye dam. 1 skin irrit. 2	Eye irrit.2; skin irrit. 2	Eye irrit.2; eye dam. 1 skin irrit. 2
	Carcinogenicity	No	Carc. 2	No

Table 2 (*Contd.*)

CB Tools	Information requested	Materials Fe_2O_3	Al_2O_3	$CaCO_3$
	Developmental/Reproductive toxicity	Unknown	Repr.2	Unknown
	Likelihood of chronic effect	STOT RE 2	STOT RE 2	STOT RE 1

[a] The occupational exposure limits (respirable 8 h TWA recommended by the NIOSH) of Fe_2O_3, Al_2O_3, and $CaCO_3$ are 5, 4, and 5, respectively; "—" represents "unable to fill due to lack of information".

dermal hazard and asthma-inducing potential of the parent material and the nanoscale material. In the IVAM Guidance, only carcinogenicity, mutagenicity and reproductive toxicity were considered. There was no toxicity parameter in Stoffenmanager-Nano. The output hazard sensitivity of the CB tools was investigated by varying the following: dustiness, solubility, carcinogenicity, and mutagenicity.

Table 3 shows a summary of the exposure input data for all the tools and scenarios. Exposure was determined by the substance emission potential, the activity emission potential, and exposure control. The substance emission potential is determined by physical form and dustiness. All the three substances are powders and had high dustiness. The activity emission was implemented as a description of energy in Nanosafer, as a task characterization in Stoffenmanager-Nano, and as the amount of material used in Nanotool. For ECguidance, ISO and IVAM Guidance, the activity emission referred to the amount of materials used and the process description. In ANSES, the activity emission was indicated by the process description. The Nanosafer had three energy level categories (high, moderate and low) for activity emission. In Stoffenmanager-Nano, the classification "handling of products with a relatively high speed/force, which leads to dispersion of dust" is equivalent to high energy and "handling of products with medium speed/force" as moderate energy. For Nanotool there was no energy or activity parameter but there was an "amount handled" parameter, with an amount >100 mg as the highest level. For ISO, "amount of powders >1 kg" is equivalent to high energy, "amount of powders >0.1 g" is equivalent to moderate energy and "amount of powders <0.1 g" is equivalent to low energy. For the ECguidance, IVAM Guidance, and ANSES, the amount handled was not an exposure band parameter. In the ECguidance, "handling of dry powders" was classified as high energy and "dry blending of material into a matrix" was classified as medium high energy. In the IVAM Guidance, "filling/packaging of end product, handling of free nanoparticles" was classified as high energy, "weighing or adding nanomaterials" was classified as medium energy, and "working with a fully contained production process" was classified as low energy.

ANSES took only substance emission potential (physical form and dustiness) into account for estimating the exposure band. Nanosafer and Stoffenmanager-Nano took exposure controls into account for estimating the exposure band. The difference was that number of air exchanges was only required by Nanosafer. Stoffenmanager-Nano had different categories for general ventilation and control at the source (containment, local exhaust). The sensitivity of the tools to exposure was investigated by varying the following: (i) the activity emission: high, moderate and low; and (ii) the exposure control: no ventilation (0.5 air exchanges h-1), general mechanical ventilation (2.5 air exchanges h-1) and containment (10 air exchanges h-1).

We compared the output of Nanotool with the exposure band for short-term in the near field (Nanosafer) and the exposure during the task (Stoffenmanager-Nano). For the purpose of comparison, results were presented with a score ranking from 0–100. The score for Nanosafer, which was lower than 1, was multiplied by ten. As for the Stoffenmanager-Nano, the score for intrinsic emission multiplier was the product of dustiness, moisture content, and weight fraction, and was also multiplied by ten.

(d) Comparison of hazard estimates with known toxicity data. The hazard classification of the three materials given by the CB tools were quantitative compared to their inherent toxicity classified by GHS. The toxicity data of the parent and nanoscale materials were obtained from various institutions, including the National Institute for Occupational Safety and Health (NIOSH), US National Library of Medicine, and the European Chemicals Agency.

The Al_2O_3 is classified as a class 2 carcinogen that can induce DNA damage, whereas the Fe_2O_3 and $CaCO_3$ have not been reported.[40,41] The median lethal dose through oral in rat (LD_{50}) for Al_2O_3 was 2000 mg kg^{-1}, while the values (through oral or dermal in rat) for Fe_2O_3 and $CaCO_3$ were 5000–10 000 and 20 000 mg kg^{-1}, respectively.[42] Furthermore, the Fe_2O_3 might have a chronic aquatic toxicity, as many studies showed that the short-term toxicity of Fe_2O_3 to aquatic algae EC50 was 100 mg L^{-1}. While no studies indicated there was a short-term toxicity for Al_2O_3 or $CaCO_3$ to aquatic algae.[42] Based on the above comparisons of toxicity data, the order of inherent toxicity was: $Al_2O_3 > Fe_2O_3 > CaCO_3$.

(e) Comparison of exposure estimates with measurement data. The exposure scores or exposure band ratios obtained from Nanotool, Nanosafer, Stoffenmanager-Nano, ECguidance, IVAM Guidance, ANSES, and ISO for the three nanomaterials were compared with their measured exposure concentrations in workplaces.

Table 3 Exposure scenario data input for the three evaluated materials

		Materials		
CB tools	Information requested	Fe_2O_3 Packaging, screening and feeding	Al_2O_3 Packaging and separation	$CaCO_3$ Packaging and drying
All tools	Substance emission potential/ physical form	Powder	Powder	Powder
	Activity emission potential/ amount handled	20 kg	Packaging-20 kg; Separation-0.05 kg	Packaging-50 kg; Drying-20 kg
	Task duration	Packaging-60 min; Screening-50 min; Feeding-20 min	Packaging-40 min; Separation-15 min	Packaging-90 min; drying-20 min
	Task frequency	Daily	Daily	Daily
	Volume of the working room	9600 m^3	2380 m^3	Assumed 10 000 m^3
Nanosafer	Energy level	Moderate	Packaging-moderate Separation-very low	Packaging-high Drying-moderate
	Activity level in the work room	Packaging-high Screening-moderate Feeding-low quiet	Packaging-high Separation-low quiet	Packaging-high Drying-low quiet
	Air exchanges	Packaging-10 n h^{-1}; Screening-2.5 n h^{-1}; feeding-0.5 n h^{-1}	0.5 n/h	0.5 n h^{-1}
Stoffenmanager nano	Task characterization	Handling of products with medium speed which leads to some dispersion of dust	Packaging-handling of products with medium speed which leads to some dispersion of dust; Separation-handing of product in small amounts or in situations where only low quantities of products are likely to be released	Packaging-handing of products with a relative high speed/force, which leads to dispersion of dust; drying-handling of products with medium speed which leads to some dispersion of dust
	Is the task being carried out in the breathing zone of an employee (distance head-product <1 meter)	Yes	Yes	Yes
	Is there more than one employee carrying out the same task simultaneously	Yes	Yes	Yes
	Is the working room being cleaned daily?	Yes	Yes	Yes
	Are inspections and maintenance of machines/ancillary equipment being done at least monthly to ensure good condition and proper functioning and performance?	No	No	No
	Volume of the working room	>1000 m^3	>1000 m^3	>1000 m^3
	Ventilation of the working room	Mechanical and or natural ventilation	Mechanical and or natural ventilation	Mechanical and or natural ventilation
	Local control measures	Packaging-containment of source with local exhaust ventilation; screening-use of a product that limits the emission; Feeding-no control measures at the source	Packaging-containment of source Separation-no control measures at the source	No control measures at the source
	Is the employee situated in a cabin	No	No	No
	Is personal protective equipment applied?	No	No	No
Nanotool	Activity classification	Handling nanoparticles in powder form	Handling nanoparticles in powder form	Handling nanoparticles in powder form
	Current engineering control	Packaging-Fume hood or local exhaust ventilation Screening and feeding – General ventilation	Packaging-containment Separation-general ventilation	General ventilation
	Number of employees with similar exposure	1–5	1–5	1–5

Table 3 (*Contd.*)

		Materials		
CB tools	Information requested	Fe_2O_3 Packaging, screening and feeding	Al_2O_3 Packaging and separation	$CaCO_3$ Packaging and drying
	Frequency of operation (annual)	Daily	Daily	Daily
Precautionary matrix	Carrier material	Solid matrix, stable under relevant process conditions or conditions of use, nanomaterial mobile	Solid matrix, stable under relevant process conditions or conditions of use, nanomaterial mobile	Solid matrix, stable under relevant process conditions or conditions of use, nanomaterial mobile
	Amount of nanomaterials reaching the environment from wastewater, exhaust gases, solid waste per year	5–500 kg	5–500 kg	5–500 kg
	Amount of nanomaterials with which a worker comes into contact in the "worst case"	>120 mg	>120 mg	>120 mg
	Frequency with which a worker handles the nanomaterial	Daily	Daily	Daily
ECguidance	Activity	Packaging–packaging of end product; feeding-filling; screening-transferring	Packaging–packaging of end product; separation-sampling for quality control	Packaging–packaging of end product; drying-transferring
	Amount	20 kg	Packaging-20 kg; Separation-0.05 kg	Packaging-50 kg; Drying-20 kg
	Dust emission	Yes	Packaging-yes; separation – No	Yes
	Number of workers	Packaging-2; Feeding-2; Screening-2	Packaging-1; separation-1	Packaging-2; drying-1
	The potential routes of human exposure	Inhalation	Inhalation	Inhalation
ISO	The form of substance (powder, solid, suspension in a liquid)	Powder	Powder	Powder
	Amount	>1 kg	Packaging – >1 kg; separation – >0.1g	>1 kg
	Potential of dust generation dustiness/process dependent	High	Packaging-high; separation – low	Packaging-high; drying-low
IVAM guidance	Activity	Packaging–packaging of end product; feeding-filling; screening-transferring	Packaging–packaging of end product; separation – sampling for quality control	Packaging–packaging of end product; drying-transferring
	Used amount	20 kg	Packaging-20 kg; Separation-0.05 kg	Packaging-50 kg; Drying-20 kg
	Emission of dust/mist/haze possible	Yes	Packaging-yes; separation – No	Yes
	Amount of workers exposed	Packaging-2; Feeding-2; Screening-2	Packaging-1; separation-1	Packaging-2; Drying-1
ANSES	Physical form	Powder	Powder	Powder
	Natural tendency of the material	High or moderate dustiness	Packaging-high or moderate dustiness	High or moderate dustiness
	Process operation	Manual operation	Manual operation	Manual operation

(f) Comprehensive evaluation of quantitative results. According to the results of quantitative comparisons, each of the quantitative evaluation indicators were divided into low, medium, and high levels, which were allocated 1, 2, and 3 points, respectively. For the Precautionary Matrix, the sensitivity/accuracy of hazard and exposure was assigned 0, because it combines hazard and exposure potential in a single score.

3. Statistical analysis

One-way analysis of variance (ANOVA) was used to analyze the RRs across different CB tools (using the LSD comparison method when variances were equal, or the Dunnett T3 comparison method when variances were heterogeneous). The Spearman correlation analysis (abnormal distribution) was utilized to analyze the correlation of RRs.

4. Results

4.1 Qualitative comparisons

(a) Qualitative differences in key information between different tools. Table 4 summarizes key information for the different CB tools. The methodological principles of the various CB tools were different in their hazard and exposure assessment approaches. For example, the Nanosafer tool uses a combination of score-based approach and binary grouping principles for hazards, and a score-based approach for exposure; Stoffenmanager-Nano uses the decision tree for hazards and the score-based approach for exposure; Nanotool and the Precautionary matrix use the score-based approach for both hazards and exposure; while the other tools apply the decision tree. In addition, there are differences in application scope, substances of interest, aim of evaluation, and number of risk bands between different tools.

(b) Qualitative differences obtained from the multi-criteria analysis. Fig. 1 shows the radar diagram directly illustrating the level distribution of the eight tools for each evaluation indicator. Nanosafer, Nanotool, and Stoffenmanager-Nano can achieve more accurate outcomes since they are better validated. These three tools also provide medium guidance in their implementation and were relatively easy to use in terms of operability. The total scores for Nanotool, Stoffenmanager-Nano, Nanosafer, and ECguidance were 19, 17, 15 and 15 respectively, which were relatively higher than those (14, 14, 12, and 13) for the Precautionary matrix, ISO, IVAM Guidance, and ANSES.

4.2 Quantitative comparisons between different CB tools

(a) Similarity of nano-relevance among different CB tools. Among the evaluated CB tools, four tools (Stoffenmanager-Nano, Nanosafer, Nanotool, and Precautionary matrix) need detailed information to assess whether the materials belong to nanomaterials. The accuracy of the four tools' results were compared with the mode sizes determined from SMPS. The mode sizes of the three materials in different exposure scenarios are as follows: the mode size of Al_2O_3 was 26.11 ± 3.51 nm and 26.58 ± 5.13 nm at the separation and packaging locations, respectively; the mode size of Fe_2O_3 was 24.33 ± 2.13 nm, 25.42 ± 3.12 nm, and 12.2 ± 1.91 nm at the screening, feeding, and packaging locations, respectively; and the mode size of $CaCO_3$ at the packaging location was 55.45 ± 5.12 nm.

Therefore, the mode sizes of the three materials in all exposure scenarios were less than 100 nm, indicating that the particles in air were airborne nanoparticles. The nano-relevant measurement results supported the evaluation results of the four CB tools that answered "Yes" for three substances in all exposure scenarios. In addition, the measurement results were

Table 4 Qualitative differences in key information between different CB tools for nanomaterials in workplaces

Tool	Time of establishment	Scope	Substance evaluated	Assessment method	Aim of evaluation	Number of risk bands
Nanosafer[12,14]	2010	Small and medium-sized enterprises	Powders	A combination of score-based approach and binary grouping principles for hazard, score-based approach for exposure	Precautionary risk assessment	5
Stoffenmanager-nano[33]	2012	Employers, employees	Powders, liquids	Decision tree for hazard and score-based approach for exposure	Prioritization for health risks and implementation of control measures	3
Nanotool[12,13]	2008	Nanotechnology researchers	Powders, liquids, and solid materials	Score-based approach for hazard and exposure	Risk assessment and management	4
Precautionary matrix[14,15]	2011	Employees, consumers, and the environment	Powders, liquids, and solid materials	Score-based approach	Source identification and risk reduction	2
ECguidance[27]	2010	All types of enterprises	Powders	Decision tree	Selection of exposure control	4
ISO[29]	2014	Enterprises, research institutes or businesses engaged in the manufacturing and processing of nanomaterials	Powders, liquids, and solid materials	Decision tree	Controlling the risks associated with occupational exposure to nano-objects	5
IVAM guidance[34]	2011	Workers	Powders, liquids, and solid materials	Decision tree	Design of appropriate control measures for nanomaterials in workplaces	3
ANSES[19,20]	2010	Employers and employees	Powders, liquids, solid nanomaterials, and nano-products	Decision tree	Selection of exposure control	5

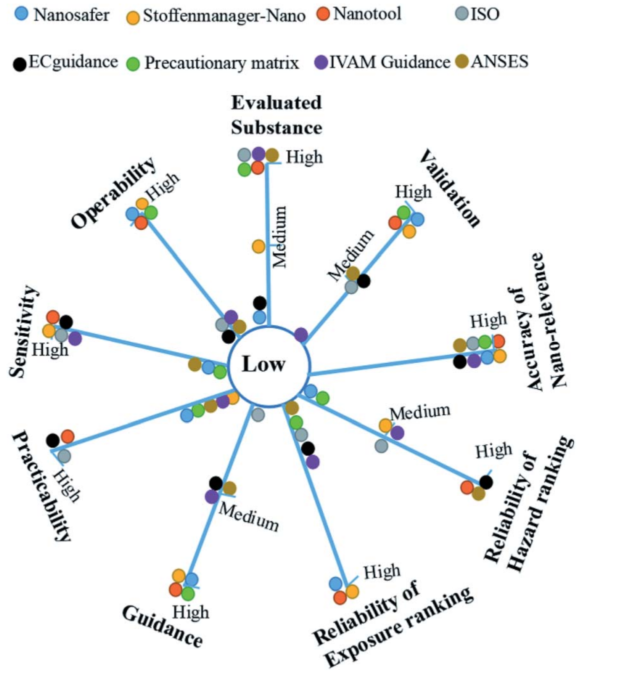

Fig. 1 A radar diagram of the qualitative differences between different CB tools. There was a diverse distribution of the CB tools across the different evaluation indicators. The total scores for Nanotool, Stoffenmanager-Nano, Nanosafer, and ECguidance were 19, 17, 15 and 15 respectively, which were higher than other tools.

also in agreement with other four tools including ECguidance, ISO, IVAM Guidance, and ANSES, which only require nano-relevant information based on users' subjective judgment.

(b) Quantitative differences in availability of information across different CB tools. Table 5 shows the percentage of information available for the three materials across different tools. The amount of information required by the CB tools for estimating the hazard and exposure varied. The order of amount information requested by the eight tools is: Nanosafer > Stoffenmanager-Nano > Nanotool > ISO = ANSES > Precautionary Matrix = ECguidance > IVAM Guidance. Nanosafer, Precautionary Matrix, ECguidance, ISO, ANSES, and Nanotool, require more information to characterize the hazard than the exposure. Only the Stoffenmanager-Nano requires more information to estimate the exposure than the hazard.

Furthermore, the ratio of available hazard information requested by the Precautionary Matrix, ISO, and Nanotool was lower than 70%, while in the Nanosafer, ECguidance, Stoffenmanager-Nano, and ANSES tools, the ratio of available information required for estimating the hazard was greater than 80%. The exposure parameters requested by the tools were easier to get than the hazard information. Table 5 shows that the ratios of available exposure information were higher than the hazard information. In general, the order of the average ratio of information available was: IVAM Guidance = ANSES > ECguidance > Stoffenmanager-Nano > ISO > Nanosafer > Precautionary Matrix > Nanotool.

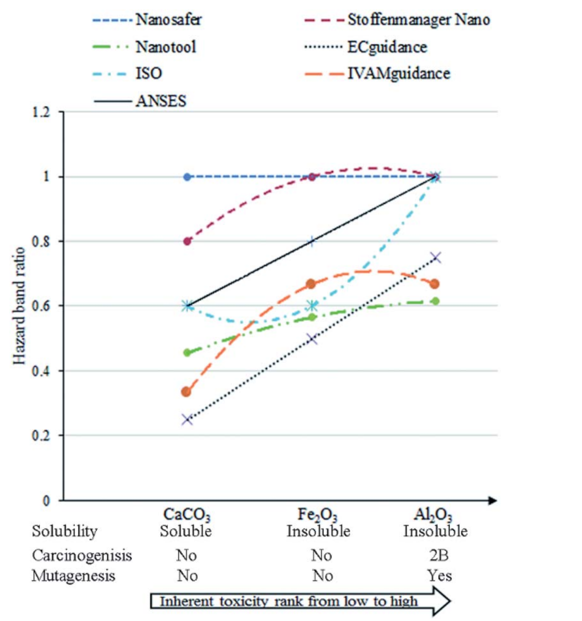

Fig. 2 Sensitivity of tool hazard band ratio output to changes in hazard input. The Nanotool, ECguidance, and ANSES tools' hazard band ratio outputs for the three materials increased with increasing inherent toxicity as the input parameter.

Table 5 The percentage of information available for the three materials across different CB tools

	Al_2O_3 (n, (%))		Fe_2O_3 (n, (%))		$CaCO_3$ (n, (%))		
CB tools	Hazard	Exposure	Hazard	Exposure	Hazard	Exposure	Average (%)
Nanosafer	15 (86.67)	12 (91.67)	15 (80.00)	12 (91.67)	15 (73.33)	12 (91.67)	85.84
Stoffenmanager nano	10 (80.00)	14 (100.00)	10 (80.00)	14 (100.00)	10 (80.00)	14 (100.00)	90.00
Nanotool	15 (53.33)	5 (100.00)	15 (53.33)	5 (100.00)	15 (66.67)	5 (100.00)	78.89
Precautionary matrix	10 (60.00)	5 (100.00)	10 (60.00)	5 (100.00)	10 (60.00)	5 (100.00)	80.00
ECguidance	9 (88.89)	6 (100.00)	9 (88.89)	6 (100.00)	9 (77.78)	6 (100.00)	92.59
ISO	13 (76.92)	4 (100.00)	13 (69.23)	4 (100.00)	13 (69.23)	4 (100.00)	85.90
IVAM guidance	7 (100.00)	7 (100.00)	7 (100.00)	7 (100.00)	7 (100.00)	7 (100.00)	100.00
ANSES	14 (100.00)	3 (100.00)	14 (100.00)	3 (100.00)	14 (100.00)	3 (100.00)	100.00
Average (%)	80.12	98.96	79.16	98.96	78.30	98.96	—

(c) Quantitative differences in sensitivity of the output to changes in hazard and exposure inputs. Fig. 2 shows the quantitative differences in the sensitivity of the output to changes in the hazard input for the CB tools except for the Precautionary matrix. The three input parameters of water solubility, carcinogenicity, and mutagenicity/genotoxicity for the three substances were changed, leading to a change in the inherent toxicity of the three materials from low to high (*i.e.* $CaCO_3$ < Fe_2O_3 < Al_2O_3). The changes in the hazard band ratio output achieved from Nanotool, ECguidance, and ANSES were consistent with the changes in the inputted inherent toxicity. The least sensitive tool was Nanosafer since its hazard band ratio output remained the same.

Fig. 2 shows the sensitivity of the tools' exposure band ratio to changes in exposure input. When the input exposure control measures were increased in the three Fe_2O_3 scenarios, the output exposure band ratio achieved from Nanotool also increased. The output exposure band ratio of the Stoffenmanager-Nano, IVAM Guidance, and ECguidance tools were relatively sensitive to changes in the exposure input and the exposure control measure. The exposure band ratios from Nanosafer, ISO, and ANSES remained the same even if the input parameters were changed.

In the nano-Al_2O_3 scenarios, both the activity emission and the level of exposure control measures were increased, leading to increases in the exposure band ratios from all tools except for ANSES.

In the nano-$CaCO_3$ scenarios, the activity emission was increased and the changes in exposure band ratio outputs from Nanotool, ISO, ECguidance, and IVAM Guidance were consistent with the change of input.

(d) Quantitative differences in accuracy of hazard classification across different tools. Fig. 2 shows that six CB tools (Nanotool, Stoffenmanager-Nano, ECguidance, ISO, IVAM Guidance, ANSES) were able to classify $CaCO_3$ and Al_2O_3 with the lowest and the highest hazard ratios, respectively, which agreed with the two material's inherent toxicity. The hazard band ratio of ISO for Fe_2O_3 was the same for $CaCO_3$, and the hazard band ratios of Stoffenmanager-Nano and the IVAM Guidance for Fe_2O_3 were the same for Al_2O_3. Nanosafer was unable to differentiate between the three materials and classified all of them into the highest hazard band.

As mentioned above, the order of inherent toxicities for three substances was: Al_2O_3 > Fe_2O_3 > $CaCO_3$, which was the same result achieved by Nanotool, ECguidance and ANSES, suggesting that the three CB tools were able to obtain relatively accurate results in hazard classification.

(e) Quantitative differences in accuracy of exposure classification across different tools. Table 6 shows the quantitative differences in the accuracy of exposure classification across different tools. The Stoffenmanager-Nano, Nanotool, and Nanosafer tools' exposure scores for seven scenarios correlated well with the particle number concentration ratios ($R = 0.967$, 0.825, and 0.697 respectively; $P < 0.05$). In addition, the Al_2O_3 separation scenario got the lowest exposure score/exposure band ratio with these tools which was in accordance with the CR value. All of the scenarios achieved the same exposure band ratio in ANSES.

(f) Comprehensive evaluation of quantitative results. Table 7 shows the scores of the eight tools for each evaluation indicator. The total scores for Nanotool, ECguidance, and Stoffenmanager-Nano were 13, 11, and 10 respectively, which were relatively higher than those (8, 9, 9, 7 and 2) of Nanosafer, ISO, IVAM Guidance, ANSES, and Precautionary matrix.

(g) Correlation between different CB tools. Nanosafer shows a high correlation with the IVAM Guidance ($R = 0.806$, $p < 0.05$), while the Precautionary matrix has a relativity good correlation with ANSES ($R = 1.000$, $p < 0.01$). Similarly, the correlation of ECguidance with ISO is good ($R = 0.764$, $p < 0.05$) in risk classification. The order of the average of risk ratios in all tools is as follows: Stoffenmanager-Nano > Nanosafer > ANSES > Precautionary matrix > IVAM Guidance > ISO > Nanotool > ECguidance.

5. Discussion

Qualitative analysis of key information for the different CB tools showed that the scope, the substance evaluated, the methodological principles, and the aim of the various CB tools were quite different, suggesting that different tools could produce different estimates for the same substance or scenario. This result also reminds users of the necessity for the careful selection of evaluation CB tools. The results obtained from our key information analysis were consistent with the research of Brouwer[6] and Ligouri *et al.*[8] However, the two studies did not make a systematic qualitative comparison between these CB tools. In this study, a multi-criteria analysis was used to evaluate the qualitative differences between the different CB tools. The results showed that there is a wide distribution of the CB tools across the nine evaluation indicators, indicating that our methodology can provide a good qualitative assessment of different CB tools. In addition, the total qualitative scores for Nanotool, Nanosafer, and Stoffenmanager-Nano were higher than the other five tools evaluated in this study. Therefore, these three tools may be more appropriate for the qualitative risk assessment of nanomaterials in workplaces due to their comparative advantages in the evaluation indicators, especially in the validation, reliability of exposure ranking, and operability. Both qualitative and quantitative comparison results showed that the judgment for nano-relevance in the eight CB tools was accurate for the three substances regardless of whether particle size or nanomaterial information was used for verification. This indicates that the eight CB tools can accurately determine the nano-relevance of the evaluated substances as a prerequisite, before proceeding smoothly to the next step of evaluation.

Different CB tools estimate the hazards and exposure associated with nanomaterials using different parameters. In this study, quantitative differences in availability of information across different CB tools showed that Nanosafer, the Precautionary Matrix, ECguidance, ISO, ANSES, and Nanotool needed more hazard information for substances than exposure information, and the hazard information required by the CB tools were often not available. For example, the information on

Table 6 The number concentration of particles and outcomes of CB tools

CB tools	Scenarios	CR	Exposure score	Exposure band ratio	Risk band ratio	Preventive measures
Nanosafer	$CaCO_3$ packaging	7.46	24.28	1	1	The work should be conducted under strict dust release control, such as in a fume-hood, separate enclosure *etc.* air-supplied respirators or highly efficient filter masks (PP3 or higher quality) maybe used as a supplement and must be readily available in case of accidents. Expert advice is recommended.
	$CaCO_3$ drying	4.66	22.96	1	1	
	Fe_2O_3 feeding	4.43	0.8359	1	1	
	Fe_2O_3 screening	3.43	0.4907	1	1	
	Al_2O_3 packaging	2.26	13.12	1	1	
	Fe_2O_3 packaging	1.93	0.1636	1	1	
	Al_2O_3 separation	1.79	0.0058	0.2	0.8	High toxicity suspected and/or high exposure potential. The work should be performed during use of highly efficient local exhaust ventilation, fume-hood, glove-box *etc.* Use of respiratory protection equipment (PP3 or higher quality) may be relevant depending on the work situation. Make sure to have the personal respiratory protection equipment (PP3 or higher quality) available in case of accidents.
	Average of risk band ratio	—	—	—	0.97	—
Nanotool	$CaCO_3$ packaging	7.46	80	0.75	0.75	Containment
	$CaCO_3$ drying	4.66	75	0.5	0.5	Fume hood or local exhaust ventilation
	Fe_2O_3 feeding	4.43	80	0.75	1	Seek specialist advice
	Fe_2O_3 screening	3.43	75	0.5	0.75	Containment
	Al_2O_3 packaging	2.26	75	0.5	0.75	
	Fe_2O_3 packaging	1.93	70	0.5	0.75	
	Al_2O_3 separation	1.79	70	0.5	0.75	Fume hood or local exhaust ventilation
	Average of risk band ratio	—	—	—	0.75	—
Stoffenmanager-Nano	$CaCO_3$ packaging	7.46	75.025	1	1	Enclosure of the source in combination with local exhaust ventilation
	$CaCO_3$ drying	4.66	25.025	1	1	—
	Fe_2O_3 feeding	4.43	25.025	1	1	
	Fe_2O_3 screening	3.43	7.525	0.67	1	
	Al_2O_3 packaging	2.26	7.525	1	1	
	Fe_2O_3 packaging	1.93	0.775	1	1	
	Al_2O_3 separation	1.79	0.0775	0.33	1	
	Average of risk band ratio	—	—	—	1	
ECguidance	$CaCO_3$ packaging	7.46	—	1	0.5	Specific prevention measures should be implemented. Engineering control measures such as local exhaust ventilation might suffice in minimizing the exposure and associated risk.
	$CaCO_3$ drying	4.66	—	0.75	0.5	
	Fe_2O_3 feeding	4.43	—	0.75	0.5	
	Fe_2O_3 screening	3.43	—	1	0.75	Closed systems or containment must be used and their efficiency ensured by checking regularly their performance
	Al_2O_3 packaging	2.26	—	1	1	It is essential that measures specifically designed for the processes in question are adopted.
	Fe_2O_3 packaging	1.93	—	1	0.75	Closed systems or containment must be used and their efficiency ensured by checking regularly their performance
	Al_2O_3 separation	1.79	—	0.75	0.75	

Table 6 (*Contd.*)

CB tools	Scenarios	CR	Exposure score	Exposure band ratio	Risk band ratio	Preventive measures
	Average of risk band ratio	—	—	—	0.68	—
ISO	$CaCO_3$ packaging	7.46	—	1	0.6	Enclosed ventilation: Ventilated booth, fume hood, closed reactor with regular opening
	$CaCO_3$ drying	4.66	—	0.75	0.8	Full containment: Glove box/bags, continuously closed systems
	Fe_2O_3 feeding	4.43	—	1	0.8	
	Fe_2O_3 screening	3.43	—	1	0.8	
	Al_2O_3 packaging	2.26	—	1	1	Full containment and review by a specialist
	Fe_2O_3 packaging	1.93	—	1	0.8	Full containment: Glove box/bags, continuously closed systems
	Al_2O_3 separation	1.79	—	0.5	0.8	
	Average of risk band ratio	—	—	—	0.8	—
IVAM Guidance	$CaCO_3$ packaging	7.46	—	1	1	The occupational hygienic strategy will be strictly applied and all protective measures that are both technically and organizationally feasible will be implemented.
	$CaCO_3$ drying	4.66	—	0.67	0.67	According to the occupational hygienic strategy, the technical and organizational control measures are evaluated on their economic feasibility. Control measures will be based on this evaluation.
	Fe_2O_3 feeding	4.43	—	0.67	0.67	
	Fe_2O_3 screening	3.43	—	1	1	The occupational hygienic strategy will be strictly applied and all protective measures that are both technically and organizationally feasible will be implemented.
	Al_2O_3 packaging	2.26	—	1	1	
	Fe_2O_3 packaging	1.93	—	1	1	
	Al_2O_3 separation	1.79	—	0.33	0.33	Apply sufficient (room) ventilation, if needed local exhaust ventilation and/or containment of the emission source and use appropriate personal protective equipment.
	Average of risk band ratio	—	—	—	0.81	—
ANSES	$CaCO_3$ packaging	7.46	—	1	0.8	Full containment: Continuously closed system
	$CaCO_3$ drying	4.66	—	1	0.8	
	Fe_2O_3 feeding	4.43	—	1	1	Full containment and review by a specialist required
	Fe_2O_3 screening	3.43	—	1	1	
	Al_2O_3 packaging	2.26	—	1	1	
	Fe_2O_3 packaging	1.93	—	1	1	
	Al_2O_3 separation	1.79	—	1	1	
	Average of risk band ratio	—	—	—	0.94	—
Precautionary matrix	$CaCO_3$ packaging	7.46	—	—	0.5	The nanospecific action can be rated as low if without further clarification.
	$CaCO_3$ drying	4.66	—	—	0.5	
	Fe_2O_3 feeding	4.43	—	—	1	Nanospecific action is needed. Existing measures should be reviewed, further clarification undertaken and, if necessary, measures to reduce the risk associated with manufacturing, use and disposal implemented in the interests of precaution.
	Fe_2O_3 screening	3.43	—	—	1	
	Al_2O_3 packaging	2.26	—	—	1	
	Fe_2O_3 packaging	1.93	—	—	1	

Table 6 (*Contd.*)

CB tools	Scenarios	CR	Exposure score	Exposure band ratio	Risk band ratio	Preventive measures
	Al_2O_3 separation	1.79	—	—	1	
	Average of risk band ratio	—	—	—	0.86	—

mutagenicity, carcinogenicity, dermal hazard, reproductive toxicology, deagglomeration, and redox activity for the three substances required by ISO, ANSES, and Nanotool were difficult to obtain, especially for non-professional occupational health managers. This limitation should remind users that the lack of information easily leads to the different tools producing different estimates for the same substance.[35–37] In contrast, the exposure parameters requested by the CB tools were generally classified as basic information that can be expected to be recorded, such as the amounts used, dustiness, room volume, and frequency and activity duration. These were readily available from occupational health surveys. These results regarding the availability of information were consistent with previous studies.[4,8]

In this study, the quantitative comparisons in the sensitivity of the output to changes in hazard input showed that the hazard band ratios given by Nanotool, ECguidance and ANSES changed with the input parameters, indicating that these three tools are more sensitive to the changes in input. The hazard band ratios given by Stoffenmanager-Nano, IVAM Guidance, and ISO changed with the input parameters in two out of three substances. The hazard band ratios given by Nanosafer remained the same, indicating that it was the least sensitive CB tool. These results are consistent with the study of Sanchez Jiménez *et al.*,[4] which demonstrated that the Nanotool was more sensitive to the changes of input in nine substances, Stoffenmanager-Nano was a relatively sensitive tool, and Nanosafer was the least sensitive tool.

In terms of the sensitivity of output to changes in exposure input, the results showed that Nanotool was sensitive to activity emission and exposure control measures, which is similar to the results of the study by Sanchez Jiménez *et al.*[4] Sanchez Jiménez *et al.* also reported that Nanosafer and Stoffenmanager-Nano were sensitive to activity emission, but these two tools did not show sensitivity to activity emission in this study. As noted by Dunn *et al.*, the CB tools differ considerably in the grading standard for the amount of nanomaterial handled.[7] The inconsistency between the two studies may be related to the total amount of nanomaterial handled which is a key factor affecting the exposure banding in Nanosafer. The amount of each nanomaterial was more than 1 kg (equivalent to high energy in Nanosafer) in this study, while the amount of nanomaterials handled was 1 mg, 100 mg and 1 kg for each nanomaterial respectively (equivalent to low, medium, and high energy respectively) in Sanchez Jiménez *et al.* However, in Stoffenmanager-Nano, the amount of nanomaterial handled is not an input parameter but a description of the energy put into the process. The Stoffenmanager-Nano classified "handling of products with a relative high speed/force, which leads to dispersion of dust" as high exposure and "handling of products with medium speed/force" as moderate energy. This partitioning may result in the same output for different amounts handled.

The quantitative accuracy comparisons and the qualitative assessments in hazard classification showed that the hazard band ratio given by Nanotool, ECguidance, and ANSES were consistent with the order of inherent toxicity. While Stoffenmanager-Nano, ISO, and IVAM Guidance were consistent with the inherent toxicity to some extent. Interestingly, the article of Sanchez Jiménez *et al.* provided that the Nanotool classification followed approximately the experimental hazard assessment, and Stoffenmanager-Nano ranked the nanomaterials in the same order as the experimental results,[38] which are partially consistent with our results. It is possible that the differences in evaluated nanomaterials and their information availability led to the inconsistency in the results of the two

Table 7 The score of each CB tools in all quantitative evaluation indicators

CB tools Evaluation indicators	Nanosafer	Stoffenmanager-Nano	Nanotool	Precautionary matrix	ECguidance	ISO	IVAM Guidance	ANSES
Nano-relevance	2	2	2	2	2	2	2	2
Sensitivity of hazard	1	2	3	0	3	2	2	1
Sensitivity of exposure	2	2	3	0	2	2	2	0
Reliability of hazard ranking	1	2	3	0	3	2	2	3
Reliability of exposure ranking	2	2	2	0	1	1	1	1
Total score	8	10	13	2	11	9	9	7

studies. For example, in Stoffenmanager-Nano, the potential hazard level is assessed based on how it relates to the properties (*i.e.* size, shape and solubility) and the toxicological data available, together with the properties of the parent material.[16,39] When the substance is described as having unknown inhalation effects but being one of the OECD-listed (Organization for Economic Cooperation and Development) nanomaterials such as Al_2O_3 and Fe_2O_3, the hazard score will be very high. In contrast, $CaCO_3$ was not an OECD-listed nanomaterial and was described as "harmful if swallowed or inhaled, and may cause respiratory irritation", so it was given a relatively low score. In this study, the evaluated substances were given the same band in Nanosafer which is similar with the results of Sanchez Jiménez *et al.* This may be related to the classification rules of Nanosafer and the evaluated nanomaterials. Nanosafer estimated the hazard based on occupational exposure limits (OEL) and toxicity data used in GHS or R-phase, but only when the OEL is lower than 1 mg m^{-1},[3] the hazard score will increase 0.06. Otherwise there will be no change in the hazard output. Therefore, when the OELs of evaluated nanomaterials are all lower than 1 mg m^{-3} or all higher than 1 mg m^{-1},[3] the substances will be classified in the same band in Nanosafer.

The qualitative assessments of accuracy in exposure classification were supported by the quantitative comparisons. Fig. 1 showed that the reliability of exposure rankings for Stoffenmanager-Nano, Nanotool, and Nanosafer was high. The quantitative comparison showed that the classification of Stoffenmanager-Nano, Nanotool, and Nanosafer correlated with the particle number concentration ratios. In this study, the quantitative results also showed that in ANSES there was no change in exposure band ratio, suggesting that the reliability of exposure ranking was low, which is consistent with the qualitative result.

The qualitative and quantitative comparison results showed some degrees of consistency. The qualitative comparison result showed that the total scores for Nanotool, Stoffenmanager-Nano and Nanosafer were higher than other tools, while the quantitative result showed that Nanotool, ECguidance, and Stoffenmanager-Nano got higher scores than other tools. Therefore, it can be concluded that Nanotool and Stoffenmanager-Nano might have comprehensive advantages over the other tools.

Further, correlation analysis showed that there were no correlations between multiple models, indicating that each tool was relatively independent, except for the correlations between two specific combinations: between the Precautionary matrix and ANSES, and between Nanosafer and IVAM Guidance.

The risk bands and preventive measures for different scenarios were also analyzed. Interestingly, Table 6 showed that the average risk ratio given by Stoffenmanager-Nano was the most stringent. This may be because Stoffenmanager-Nano was developed as a practical approach for employers and employees for risk prioritization, and its risk bands were classified in three priority bands corresponding to low/medium/high priorities of action.

More information is needed to validate these CB tools in order to determine whether the use of CB tools can adequately reduce worker's nanomaterial exposure to safe levels. It would be useful to replicate the study using more substances from various factories to further compare the tools and to see if they perform similarly across multiple samples and scenarios.

6. Conclusions

In summary, the following conclusions can be drawn: (i) Nanotool, Nanosafer, and Stoffenmanager-Nano tools have a higher comprehensive advantage over other tools based on qualitative assessment; (ii) the input exposure information was more readily available than the hazard information; (iii) the hazard band ratios given by Nanotool, ECguidance, and ANSES were sensitive to changes in hazard input and were consistent with the order of inherent toxicity; (iv) Nanotool was the most sensitive, and ISO, ECguidance, and IVAM Guidance had good sensitivity in exposure band ratio output to changes in exposure input; (v) the exposure classification given by Stoffenmanager-Nano, Nanotool, and Nanosafer had good correlation with the particle number concentration ratios; (vi) each tool has its own characteristics and scope of application; (vii) Nanotool and Stoffenmanager-Nano have a comprehensive advantage over other tools based on both qualitative and quantitative assessments.

This study provides a recommendation for joint application of risk assessment methods for nanomaterials in workplaces, which will help developing countries establish and refine their own methodologies. The eight tools may be useful as a first step in risk assessment, but it is also important to consider the objective and the information needed when selecting a tool. Ideally, more than one tool should be selected for comparing findings and to better inform decision making.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 K. Savolainen, H. Alenius, H. Norppa, L. Pylkkanen, T. Tuomi and G. Kasper, *Toxicology*, 2010, **269**, 92–104.
2 A. D. Maynard, *Nat. Nanotechnol.*, 2014, **9**, 159–160.
3 D. M. Zalk and D. I. Nelson, *J. Occup. Environ. Hyg.*, 2008, **5**, 330–346.

4 A. Sanchez Jimenez, J. Varet, C. Poland, G. J. Fern, S. M. Hankin and M. van Tongeren, *J. Occup. Environ. Hyg.*, 2016, **13**, 936–949.
5 H. D. Xu, L. Zhao, S. C. Tang, J. Zhang, F. L. Kong and G. Jia, *Chin. J. Ind. Hyg. Occup. Dis.*, 2016, **34**, 905–910.
6 D. H. Brouwer, *Ann. Occup. Hyg.*, 2012, **56**, 506–514.
7 K. H. Dunn, A. C. Eastlake, M. Story and E. D. Kuempel, *Ann. Work Exposures Health*, 2018, **62**, 362–388.
8 B. Liguori, S. F. Hansen, A. Baun and K. A. Jensen, *NanoImpact*, 2016, **2**, 1–17.
9 M. Xing, Y. Zhang, H. Zou, C. Quan, B. Chang, S. Tang and M. Zhang, *Inhalation Toxicol.*, 2015, **27**, 138–148.
10 M. Xing, H. Zou, X. Gao, B. Chang, S. Tang and M. Zhang, *Environ. Sci.: Processes Impacts*, 2015, **17**, 656–666.
11 F. Tian, M. Zhang, L. Zhou, H. Zou, A. Wang and M. Hao, *J. Occup. Health*, 2018, **60**, 337–347.
12 N. R. C. f. t. W. Environment, NanoSafer v 1.1, http://nanosafer.org/Default, 1.1 beta.
13 J. Höck, T. Epprecht and E. Furrer, *et al.*, *Federal Office of Public Health and Federal Office for the Environment*, 2011, Berne, Version 2.1.
14 T. Schneider, D. H. Brouwer, I. K. Koponen, K. A. Jensen, W. Fransman, B. Van Duuren-Stuurman, M. Van Tongeren and E. Tielemans, *J. Exposure Sci. Environ. Epidemiol.*, 2011, **21**, 450–463.
15 O. f. S. R. (TNO), Stoffenmanager Nano, https://nano.stoffenmanager.nl/.
16 B. Van Duuren-Stuurman, S. R. Vink, K. J. Verbist, H. G. Heussen, D. H. Brouwer, D. E. Kroese, M. F. Van Niftrik, E. Tielemans and W. Fransman, *Ann. Occup. Hyg.*, 2012, **56**, 525–541.
17 K. Verbist, *Stoffenmanager Nano: How (Well) Does It Work?*, Edinburgh, UK, 2012.
18 D. M. Zalk, R. Kamerzell, S. Paik, J. Kapp, D. Harrington and P. Swuste, *J. Nanopart. Res.*, 2010, **11**, 1685–1704.
19 S. Y. Paik, D. M. Zalk and P. Swuste, *Ann. Occup. Hyg.*, 2008, **52**, 419–428.
20 Y. Astier, O. Uzun and F. Stellacci, *Small*, 2009, **5**, 1273–1278.
21 A. Eastlake, R. Zumwalde and C. Geraci, *J. Nanopart. Res.*, 2016, **18**, 1–24.
22 S. Foss, H. Og, A. Baun, D. Environment and K. Alstrup-Jensen, 2011.
23 J. Höck, H. Hofmann, H. Krug, C. Lorenz, L. Limbach, B. Nowack, M. Riediker, K. Schirmer, C. Som, W. Stark, C. Studer, N. von Götz, S. Wengert and P. Wick, *Precautionary Matrix for Synthetic Nanomaterials*, Federal Office for Public Health and Federal Office for the Environment, Berne, 2008.
24 J. Höck, T. Epprecht, H. Hofmann, K. Höhner, H. Krug, C. Lorenz, L. Limbach, P. Gehr, B. Nowack, M. Riediker, K. Schirmer, B. Schmid, C. Som, W. Stark, C. Studer, A. Ulrich, N. von Götz, S. Wengert and P. Wick, *Precautionary Matrix for Synthetic Nanomaterials*, Federal Office for Public Health and Federal Office for the Environment, Berne, 2010.
25 J. W. Stark, C. Studer and A. Ulrich, 2010.
26 E. T. Höck J., E. Furrer, M. Gautschi, H. Hofmann, K. Höhener, K. Knauer, H. Krug, *et al.*, *Federal Office of Public Health and Federal Office for the Environment*, 2013, BAG/BAFU, Version 3.0.
27 R. P. A. Ltd, *Guidance on the protection of the health and safety of workers from the potential risks related to nanomaterials at work*, 2014.
28 F. Jongeneelen, R. Cornelissen, P. van Broekhuizen and F. van Broekhuizen, *Guidance working safely with nanomaterials and products, the guide for employers and employees*, IVAM UvA bv, 2011.
29 R. D. Via, T. Winters, J. W. Bennie, B. Bryant, J. M. Cousineau, J. Deakin, S. Dénommée, J. Forget, J. Dumont and H. M. Gillis, ISO/TS 12901-2:2014, 31, 2014.
30 M. Riediker, C. Ostiguy, J. Triolet, P. Troisfontaine, D. Vernez, G. Bourdel, N. Thieriet and A. Cadène, *J. Nanomater.*, 2012, **2012**, 8.
31 C. Ostiguy, M. Riediker, J. Triolet, P. Troisfontaines, and D. Vernez, *French Agency for food, environmental and occupational health and safety* (ANSES), 2010.
32 C. Lesmes-Fabian, *Int. J. Environ. Res. Public Health*, 2015, **12**, 4670–4696.
33 D. B. Van, S. R. Vink, K. J. Verbist, H. G. Heussen, D. H. Brouwer, D. E. Kroese, *et al.*, *Ann. Occup. Hyg.*, 2012, **56**, 525.
34 R. Cornelissen, F. Jongeneelen, P. van Broekhuizen, and F. van Broekhuizen, *Guidance working safely with nanomaterials and products, the guide for employers and employees*, Amsterdam, The Netherlands, 2011.
35 M. Kupczewskadobecka, S. Czerczak and S. Brzeźnicki, *Environ. Toxicol. Pharmacol.*, 2012, **34**, 512–518.
36 E. Hofstetter, J. W. Spencer, K. Hiteshew, M. Coutu and M. Nealley, *Ann. Occup. Hyg.*, 2013, **57**, 210–220.
37 N. Savic, D. Racordon, D. Buchs, B. Gasic and D. Vernez, *Ann. Occup. Hyg.*, 2016, **60**, 991–1008.
38 F. L. Andrea Spinazzè1, D. Campagnolo, S. Rovelli1, M. Locatelli, A. Cattaneo and D. M. Cavallo, *Ann. Work Exposures Health*, 2017, **61**, 284–298.
39 B. Xing, N. Senesi and D. Chad, *Engineered Nanoparticles and the Environment: Biophysicochemical Processes and Toxicity*, John Wiley & Sons, 2016, vol. 4, pp. 28–29.
40 International Labour Organization, *International Chemical Safety Cards database*, https://www.ilo.org/dyn/icsc/showcard.home.
41 P. Koedrith, R. Boonprasert, J. Y. Kwon, Im-S. Kim and Y. R. Seo, *Mol. Cell. Toxicol.*, 2014, **2**, 107–126.
42 European Chemicals agency, https://echa.europa.eu/.