



National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*

## **Description of a NanoCosmetics Tool for Risk Assessment**

RIVM Briefrapport 2015-0157  
W.H. de Jong et al.





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and the Environment  
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## Colophon

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## Publiekssamenvatting

### **Beschrijving van een NanoCosmetica model voor de risicobeoordeling**

Nanomaterialen (deeltjes kleiner dan 0,1 micrometer) worden steeds meer gebruikt in consumentenartikelen zoals cosmetica. Ze worden bijvoorbeeld gebruikt in zonnebrandcrèmes om een hoge beschermingsfactor tegen UV-stralen te realiseren. Zowel voor handhavers (NVWA) als fabrikanten is het belangrijk om vast te stellen of het gebruik van nanomaterialen in cosmetica risico's met zich meebrengt. Uit een inventarisatie van het RIVM blijkt dat het mogelijk is een computermodel te ontwikkelen waarmee mogelijke risico's kunnen worden geschat. De uitkomst van deze risicobeoordeling geeft aan wanneer maatregelen nodig zijn om een mogelijk risico te verminderen.

In dit rapport is beschreven hoe dit 'NanoCosmetica-model' eruit moet zien en aan welke eisen het moet voldoen. Hierbij komen alle aspecten van een risicobeoordeling aan bod. De beschrijving bevat de karakterisering van de nanomaterialen, het vaststellen van de blootstelling van consumenten aan de nanomaterialen, de mogelijke schadelijkheid van de nanomaterialen, en de uiteindelijke risicobeoordeling.

Als gegevens die nodig zijn voor de risicoschatting niet aanwezig zijn, worden ze in het computermodel vervangen door standaardwaarden om toch een uitkomst te krijgen. Om een veilig gebruik van het product te waarborgen zullen deze standaardwaarden in het algemeen een conservatief karakter hebben.

Kernwoorden: nanomaterialen, cosmetica, cosmeticatool, risicobeoordeling.



## Synopsis

### **Description of a NanoCosmetics Tool for Risk Assessment**

Nanomaterials consisting of particles smaller than 0.1µm are increasingly used in consumer products including cosmetics. Both regulators and manufacturers need to evaluate and manage consumer health risks that may be posed by the use of nanomaterials in cosmetics. This risk assessment is important as the outcome of the risk assessment indicates whether measures need to be taken to mitigate and/or reduce the observed risks.

This report describes the content of an electronic tool (computer program) that can be used for a risk assessment. The NanoCosmetics tool needs to cover all aspects of the risk assessment. So, the tool needs to contain the following components: the physicochemical characterization of the nanomaterials, the estimation of the consumer exposure, the possible hazards (toxicity) induced by the nanomaterials, and finally the risk assessment itself. In cases where only limited information is available, the tool will use default values as input data for the risk assessment. These default values will generally result in a conservative outcome. The overall outcome will be an estimation of potential risk indicating whether specific measures for risk mitigation and/or reduction need to be implemented.

The conclusion of the report is that it is feasible to develop an electronic tool (program) that allows an estimation of the risk of the use of nanomaterials as cosmetic ingredients.

Keywords: Nanomaterials, cosmetics, cosmetics tool, risk assessment.





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## Summary

**Aim:** Nanotechnology and nanomaterials (NM) are increasingly used in consumer products including cosmetics. This results in a need to evaluate and manage consumer health risks of NM-enabled cosmetic products during the use phase of the product. The Netherlands Food and Consumer Product Safety Authority (NVWA) commissioned the development of a NanoCosmetics tool for the risk assessment of nanomaterials (NMs) used as cosmetic ingredients. The NanoCosmetics tool described can be used by both regulators and manufacturers for a fast evaluation of the potential risk of a NM to be used as cosmetic ingredient. This report contains the description of a NanoCosmetics tool to be developed for the risk assessment of nanomaterials (NMs) used as cosmetic ingredients. The tool may help enforcement and regulation to evaluate and assess potential risks of a NM-enabled cosmetic product available on the market and may guide manufacturers of NM-enabled cosmetic products in the design and risk assessment of their products.

**NM characterization:** For a proper evaluation of the potential risk(s) of NMs, it is of high importance to have an accurate characterization of the NMs. A high quality characterization is necessary for a proper identification of a NM. Unfortunately, identification of a hazard based on physicochemical properties of NMs is not yet possible. However, the physicochemical characterization may be used for extrapolation of information by using read-across and grouping of NMs in general, and more specifically for NMs used as cosmetic ingredients. The NanoCosmetics tool should provide information on the quality of the data for read-across and grouping, expressed as similarity and/or uncertainty scores.

**Exposure:** For any risk assessment, exposure estimation is crucial. For exposure assessment, information present in the ConsExpo model could be used for cosmetic products i.e. the 'Cosmetics Fact Sheet'. Various routes of exposure (dermal, oral and inhalation exposure) need to be considered depending on the intended use of the product. In general, for NMs the exposure to (or release of) free NMs is considered to have the highest risk in terms of toxicological hazard. So, data on the actual release of the NM from a cosmetic product including its specific physicochemical characteristics should aid in the exposure estimation. When no data on potential exposure or release of the NM is available default data may be applied. Generally, this leads to a conservative outcome in the risk assessment.

**Hazard identification:** The hazard assessment component for the NanoCosmetics tool contains common endpoints for cosmetic ingredients such as irritation, sensitisation, mutagenicity, acute toxicity, repeated dose toxicity, carcinogenicity, and reproductive toxicity and considers all existing human health hazard data. A qualification score regarding the hazard data needs to be included in the tool to indicate the reliability of the data. When limit values for certain endpoints or hazards are available these can directly be included in the tool and used in the risk assessment. Both the ban on animal experiments and the multitude of potential NMs as cosmetic ingredient drives the need for read-across and grouping, especially for hazard identification. As this is accompanied with uncertainty on the applicability and reliability of the data for the NM

under investigation, evaluation of the uncertainty needs to be included in the NanoCosmetics tool.

Risk assessment: The input in the exposure and hazard endpoints will be used for the final risk assessment of the NM as cosmetic ingredient. The risk assessment strategy will be performed for each relevant exposure scenario. For the most sensitive relevant hazard endpoint in each exposure scenario, a Margin of Safety is calculated, being the ratio between the estimated exposure and the dose causing no harm in an animal model. The outcome of the risk assessment should be an indication of the potential risk in the use of the NM as cosmetic ingredient (low, intermediate, high).

Conclusion: The development of a risk assessment tool for cosmetic ingredients and products is feasible, although several challenges remain especially with regard to the foreseen lack of data. However, parameters for which data are lacking can be replaced with default factors. It is expected that data on read-across and grouping will become available in the future, to fill in potential gaps in the risk assessment of nanomaterials.

## 1 Introduction

The Netherlands Food and Consumer Product Safety Authority (NVWA) has both an enforcement role and a signaling and risk assessment task. The Office for Risk Assessment and Research (BuRO) identifies (new) risks and generates knowledge which is then used for further monitoring and advising policymakers. BuRO pays attention to all consumer products, including products with nanomaterials.

GUIDEnano is a European FP7 project in which a web-based tool will be developed to identify the risks of nanomaterials throughout the lifecycle. This will aid in better overview of the risks of some nanomaterials used in consumer products following a systematic approach. Furthermore, GUIDEnano ensures that there is better visibility on knowledge that is lacking. Cosmetics (and food) are outside the scope of GUIDEnano. The NVWA expects to come across many nanomaterials in cosmetics in the years to come. On the basis of the Cosmetics Regulation, for cosmetics there exists the obligation to indicate nanomaterials on the label. Recently a European monitoring project (PROSAFE) was launched to investigate, together with a number of Member States, by means of monitoring which nanomaterials are used in cosmetics. It is desirable to carry out the risk assessment of nanomaterials in cosmetics through a systematic approach. Based on these developments and wishes, the NVWA has asked the RIVM to establish the possibility, in line with GUIDEnano, to develop a tool that can estimate the risks of nanomaterials in cosmetics. The tool should be able to assist in determining whether there is a risk of consumers from the use of a particular nanomaterial in a product. In cases of doubt, there should still be a notion of the possible risks or where specific information for an assessment is lacking.

The voluntary inventory as published in The Project on Emerging Nanotechnologies of the Woodrow Wilson International Center for Scholars, Washington DC, USA (<http://www.nanotechproject.org/>) registers the presence and availability of nanomaterials in various consumer products since 2005. This registration shows over the last 10 years a continuous increase in consumer products with a nanoclaim of which cosmetics comprise a large group. It can be expected that this trend for an increase will continue in the near future. Table 1 shows the developments between 2005 and 2015. In 2013, 788 products were registered in the category "Health and Fitness" of which 292 and 154 were in the "Cosmetics" and "Personal Care" subcategories, respectively. It is noted that for quite a number (n=742) of products the claim of NMs or the availability of the products could not be verified.

Table 1. Consumer products with NMs, according to The Nanotechnology Consumer Products Inventory (<http://www.nanotechproject.org/>).

Year	Number of products with nanomaterial claim	Comments
2005	54	
2010	1317	
2013	1628	
2015	1824	+742 of which availability / nano-claim cannot be verified

The main objective of the NanoCosmetics tool is to develop innovative methodologies to evaluate and manage consumer health risks of NM-enabled cosmetic products during the use phase of the product. These developments will be incorporated into an interactive web-based NanoCosmetics tool. The tool will be primarily made for use as a risk assessment instrument for an evaluation of the potential risk of NMs as present in NM-enabled cosmetic products. Only the consumer use phase and its related risk will be taken into account. We propose that other categories of consumer products and life cycle stages, worker and environmental risks will not be included by the NanoCosmetics Tool. These additional categories of products are included in the GUIDEnano tool that is under development (<http://www.guidenano.eu/>). The GUIDEnano Tool covers consumer products in general, including all life cycle stages (e.g. risks for worker exposure during manufacturing until environmental risks due to exposure at the end of product life).

The goal of the NanoCosmetics tool will be to:

1. Help the enforcer/ regulator to evaluate and assess potential risks of a NM-enabled cosmetic product available on the market
2. Guide the NM-enabled cosmetic product developer (mainly cosmetic industry) into the design and application of the most appropriate risk assessment & mitigation strategy for a specific product.

The tool is relevant for both regulators and manufacturers of cosmetic products. The aim of using the tool will be slightly different for these two user groups. Regulators (i.e. enforcement agencies) will be aiming at the result of risk assessment of a specific product of interest. They will have a need for an estimation of the potential risks and are highly interested in the amount of uncertainty around this result: which source has the largest uncertainty, and what should the message be to the manufacturer of the product? When the product appears to present a high risk (i.e. be unsafe), it should be possible to immediately withdraw such a product from the market. However, a warning to the manufacturer to take measures might be sufficient for the time being. For product manufacturers that would like to bring a new product comprising new ingredients to the market, the use of the tool may be different. First, comparison of the specifications of the new ingredient with known nanomaterials already in use is very relevant in order to screen in a fast way the potential risk of using the new ingredient in a cosmetic product. Second, in case of a potential risk of the new cosmetic product, the options for mitigation of uncertainty and/or risk are highly

relevant, as this can lead to a better chance for the product under development to be put on the market.

In addition to the above-mentioned goals, the evaluation of a NM-enabled product using this NanoCosmetics tool will also be useful for risk communication to regulators, manufacturers, insurance companies, and society.

The proposed tool is described below based on the four main elements: determination of physicochemical properties, exposure assessment, hazard assessment and risk assessment. The physicochemical properties may be indicative for possibilities for exposure (e.g. liquid, aerosol preparations) and potential hazards (e.g. local and/or systemic toxicity). The combination of exposure and hazard characterization will be the input for the final risk assessment that translated into a probability of a low, medium or high risk. The risk category indicates whether measures need to be taken for mitigation and/or reduction of the risk.





## 2 Physicochemical properties of nanomaterials

The physicochemical properties of a NM affect in theory both the potential hazard and exposure of a NM. However, as a NM is rarely used as a “naked” NM environmental factors e.g. the product in which the NM is used, are important for the ultimate exposure and hazard. Thus, the physicochemical properties of the suspending matrix (e.g. cream or powder), the exposure route (e.g. spray or application on the skin) also affect the exposure level and the potential hazard of a NM (Figure 1). This is important to realize because it causes differences in expected hazard and exposure between different uses or formulations of the same NM.

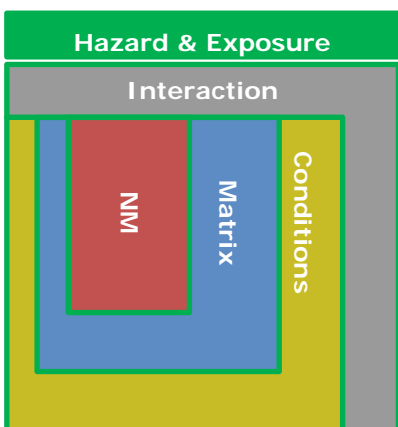


Figure 1. Categories of physicochemical properties affecting NM exposure and hazard.

We distinguish four situations for which it may be useful to evaluate the physicochemical properties of a NM:

- (a) the pristine as manufactured NM formulation before addition to a cosmetic formulation,
- (b) the NM formulation used during toxicity testing,
- (c) the NM formulation as present in the cosmetic product and
- (d) the NM formulation as the consumer is exposed to (released from the cosmetic formulation).

Formulations a, c and d are related to each other by the transport and transformation that takes place with the same NMs, from the source until use as a cosmetic product resulting in human exposure. For this reason for the risk assessment toxicity data is preferable for the NM formulation similar to the material that is released from the product (formulation d). However, most of the time data are only available for the NM formulation (b) present or used during toxicity testing. Also measurements of parameters needed for exposure assessment may be determined on the NM formulation a,b and c, and thus may be different from the NM formulation (d) that the consumer is really exposed to. This issue can be solved by quantifying the difference between these two formulations using read-across rules or including a safety factor. Read-across rules (see below) can be applied when data on a specific NM form (i.e. instance a - d) is insufficient or lacking.

A high quality of the determination of the various physicochemical parameters is not only important for the characterization and identification of the NM itself, but also for the possibility to use these parameters for comparison of the NM evaluated with other similar NMs. This offers the possibility for read-across and grouping of NMs. An example of such an approach is presented in the Opinions of the Scientific Committee on Consumer Safety (SCCS) on the use of TiO<sub>2</sub> and ZnO nanomaterials as UV-filter in sunscreens (SCCS 2012c, 2014a). NMs of different manufacturers were considered to have an acceptable risk as long as the physicochemical parameters were within specific limits. The physicochemical parameters can also be used to establish a similarity score that indicates whether read-across is possible.

The proposed physicochemical properties to be reported as advised by the SCCS (SCCS 2012a), are considered the most important parameters for identification and characterisation of a NM intended to be used in cosmetic products (Table 2).

*Table 2. The physicochemical properties advised to report by the SCCS (SCCS 2012).*

NM	chemical identity chemical composition size morphology surface characteristics surface area catalytic activity dustiness density and pour density redox potential
Matrix	pH
Conditions	concentration
Interaction	solubility viscosity stability

## 3 Exposure Assessment

### 3.1 Introduction

The NanoCosmetics tool will include when possible and feasible references to other tools used for exposure estimation of cosmetic ingredients. As a starting point for the assessment of consumer exposure to NMs from cosmetic products the 'Cosmetics Fact Sheet' of ConsExpo will be used (Bremmer et al. 2006). Furthermore, all routes of exposure (dermal, oral and inhalation exposure) will be considered in view of the intended use of the product. In general, for NMs exposure to (or release of) free NMs is considered to have the highest risk in terms of toxicological hazard that may occur. So, data on the actual release of the nanomaterial from a cosmetic product including its specific physicochemical characteristics should aid in the exposure estimation, although of course also exposure to NMs within a cosmetic formulation is likely. Table 3 provides an overview of cosmetic products for which the use of NMs is expected. They are listed per route of exposure, which all need to be considered in the NanoCosmetics Tool.

*Table 3: Cosmetics product categories (bold products are known to be containing NMs).*

<b>Route of exposure</b>	<b>Type of product</b>	<b>Product categories</b>
Dermal	Hair care	<b>Shampoo</b> Conditioner Hair dye <b>Hair styling: mouse, gel</b> Hair bleaching products Permanent wave - Perm lotion - Fixing lotion
	Bathing, showering	<b>Washing hands: soap, gel</b> <b>Showering: soap, gel</b> Bath foam, oil, salt
	Skin care	<b>Cream: face, hand, body lotion</b> <b>Peeling-gel</b> <b>Face pack</b> <b>Body pack</b> <b>Skin whitening products</b>
	Sun care	<b>Sunscreen lotion</b>
	Make-up and nail care	<b>Facial make-up</b> <b>Facial cleanser</b> Eye-shadow, <b>mascara</b> , eyeliner, eye make-up remover, lipstick, lip salve Nail polish, nail polish remover

	Deodorant	Stick/roller
	Men's cosmetics	Shaving cream
	Foot care	<b>Antiperspirant</b> <b>Antifungicides</b>
	Baby care	Baby salve, oil, powder
	Miscellaneous	Depilatories Essential oils Face paint: adults, children
Inhalation	Deodorant	Spray
	Fragrances	Eau de toilette
	Men's cosmetics	Aftershave
	Hair care	<b>Hair spray, aerosol can</b>
Oral	Oral hygiene	<b>Toothpaste: adults, children</b> <b>Mouth wash</b>

### 3.2 Information sources

The Cosmetics Fact sheet contains a number of models and default values that can be used, with or without the help of the ConsExpo software, to calculate human exposure levels to ingredients in these products. Many of these models and values are also used by the SCCS and can be directly applied to NM ingredients. However, although NMs are widely used as UV-filters a standard scenario for application of sunscreen products is not available in the Cosmetics fact sheet. The SCCS recently advised not to use NMs in sunscreen applications that would lead to any significant inhalation exposure, such as sprayable products (e.g. sunscreen) or powders (SCCS 2014b).

Recently, a new module has become available for exposure assessment of NMs in spray products. ConsExpo nano adapts the ConsExpo spray model to enable the estimation of the alveolar load of NMs after application of a consumer spray product containing a NM. To this end, ConsExpo nano combines the ConsExpo spray model with the International Commission on Radiological Protection (ICRP) deposition and alveolar clearance model (ICRP 1994). ConsExpo nano provides different metrics to express the exposure (dose) as calculated alveolar load (e.g. mass, number of nanoparticles, surface area of the nanomaterial, number and surface area of the inhaled aerosol particles). This is important as it is generally acknowledged that risk characterization based on inhaled mass (as is the current practice) of NMs is most likely not appropriate. However, consensus on a dose metric describing the dose response relationship in terms of toxicity is currently lacking. ConsExpo nano is focused on the inhalation route of exposure, since dermal and oral exposure to NM is covered by ConsExpo.

### 3.3 Information for exposure assessment

For exposure assessment of cosmetic NMs the following factors are considered to be important:

- Class of cosmetic product(s) in which the ingredient may be used; this determines the route of exposure (dermal, oral, inhalation or a combination thereof).
- Method of application: rubbed-on, applied and rinsed-off, sprayed, etc.; this determines the route of exposure as well as the amount of product that is applied.
- Concentration of the ingredient in the finished cosmetic product; this is important for the estimation of exposure. A higher concentration of the NM can lead to a higher external exposure.
- Quantity of the product used at each application; combined with the concentration this determines the potential exposure.
- Frequency of use; a product that will be used more frequently than another one, most likely results in higher exposure.
- Total area of skin contact; when a product is applied on a small area of the skin, e.g. face cream versus body lotion, this is mostly correlated with the amount used.
- Duration of exposure; this depends on the method of application and the class of cosmetic product. Penetration of NMs through the skin is generally considered to be absent or very low. Studies that have investigated skin penetration often report that NMs remain in the non-viable epidermal layers and hair follicles of the skin. Nevertheless, little information is currently available on the long-term fate of these NMs, whether they eventually are removed or are able to penetrate deeper into the skin. For this reason, cosmetic products that are likely used for a long time can be placed in a category with a higher default value for systemic exposure compared to products used for shorter periods of time, unless the composition of the nanomaterial indicates that it is not bio-persistent.
- Consumer target groups (e.g. children; people with sensitive, damaged or compromised skin) may need separate exposure assessment. Children can be higher exposed to NMs due to their behaviour. Swallowing of toothpaste, as well as hand-mouth contact of their skin lead to higher exposure compared to adults. Very few studies have investigated the fate of NMs on damaged skin. So far, these studies also show limited penetration of nanoparticles. The barrier of the skin to NMs may be compromised when (burn) wounds are present on the skin, when the skin is irritated (e.g., through contact with soap) or as a result of an intrinsic barrier defect (e.g., atopic dermatitis).
- Quantity likely to enter the body (fraction absorbed); this depends which NM is involved and the condition of the barrier (skin, lung, gastrointestinal tract). Whether or not a NM in a cosmetic product can become systemically available depends on whether it is able to cross the barriers as present in the lung, skin and/or gastrointestinal tract. This in turn depends on the material's physicochemical properties, but the most important properties may be different for each exposure route. It is generally considered that translocation of NMs over the oral and lung barriers, is easier compared to skin. Therefore, for oral and inhalation exposure, default values for potential systemic exposure will be derived, with higher values for products that are used for longer periods of time.

- Use area (indoors/outdoors) and ventilation; this is important for exposure through inhalation. Mostly, the smaller the room size where the exposure occurs, the higher the air concentration in that room. The air concentration also depends on the ventilation in the room.

### 3.4 Exposure dose

For practical reasons, exposure levels of NMs are generally expressed in dose metrics based on mass, similar to conventional materials. However, the use of mass in a dose metric for NMs may not be the most appropriate. Therefore, where relevant, the NanoCosmetics tool will allow conversion into different metrics describing the dose, e.g. weight/volume concentration, particle number concentration, and surface area, etc.

To determine systemic exposure after exposure to conventional substances via the skin, OECD recommends *in vitro* skin penetration studies (OECD 2004a, OECD 2004b, SCCS 2012b). However, these methods have not been validated for NMs. In addition, there is no validated method to measure effects and penetration of NMs on compromised skin (SCCS 2012a). For conventional cosmetic ingredients, in cases where no (adequate) information is available on dermal absorption, the SCCS assumes 100% absorption (SCCS 2012b). Where absorption of particles cannot be excluded either by experimental data, or justified based on solubility/degradation of the nanomaterial, the SCCS may apply a default approach and assumes that 100% of the absorbed material was in particle form (SCCS 2012a). From dermal absorption data, given in  $\mu\text{g}/\text{cm}^2$  or % of applied substance, the systemic exposure dose can be calculated with formulas given in the guidance document (SCCS 2012a). SCCS does not provide guidance on how to estimate systemic absorption after oral or inhalation exposure to NMs. However, when adequate data are unavailable, a default 100% absorption/uptake value may be used.

The SCCS assumptions and formulas in the guidance document will largely be included in the NanoCosmetics tool. However, the defaults for absorption may be modified depending on information becoming available in the near future. There are a number of ongoing efforts to elucidate the factors determining absorption over various biological barriers (e.g. within GUIDEnano and other EU projects). The NanoCosmetics tool for use of NMs as cosmetic ingredient will make use of this information as soon as it becomes available.

When information on exposure parameters for NMs in the cosmetic products to be assessed is unavailable, as will often be the case, the NanoCosmetics tool will revert to the use of default values for local and systemic exposure. Different default values will be derived for different categories of products.

Since local effects in the lung such as inflammation have been reported frequently for NMs, the local dose in the alveoli is expected to be a relevant metric to use in risk assessment of inhaled nanomaterials (Braakhuis et al. 2014). Therefore, for products leading to NM

inhalation, exposure levels should not only be given in air concentrations, but also in alveolar doses. This can be predicted by using mathematical models calculating particle deposition at various locations in the respiratory system: e.g. the Multiple Pathway Particle Dosimetry (MPPD) model based on information on air concentration and particle properties (aggregate size distribution and density) and the ICRP model (Cassee et al., 2002, ICRP 1994). The latter model is used in the already available ConsExpo spray model. Alternatively, if desired, a comparable model assessing alveolar dose of nanomaterials can be integrated into the NanoCosmetics tool. The outcome of these exposure models in terms of local dose/exposure in the lung is dependent on several physicochemical parameters of the particles including size, particle agglomeration/aggregation and aerosol size.

### **3.5 Routes of exposure**

Exposure to cosmetics can take place via the oral (e.g. toothpaste), dermal (e.g. sunscreen) or inhalation route (e.g. spray deodorant). The route of exposure should not only be assessed in exposure assessment; it also influences the type of hazard data that is needed to perform risk assessment. Preferably, the hazard data matches the exposure route, but e.g. in case only oral data is available to assess the dermal risk, route-to-route extrapolation should be performed. This, however, involves very high uncertainty. The characteristics of different biological barriers have a great impact on the absorption of NMs and their toxicity.





## 4 Hazard Assessment

### 4.1 General approach to hazard assessment

The NanoCosmetics tool will to a large extent follow the SCCS Guidance on the Safety Assessment of Nanomaterials in Cosmetics (SCCS 2012a), which states that risk assessment of cosmetic NMs may be driven by exposure considerations, with a focus on detailed characterization of the NMs and NM-related considerations during toxicological evaluation. The exposure driven risk assessment is advocated because *in vivo* testing of cosmetic ingredients is no longer permitted and the validated *in vitro* methods available only cover some toxicological endpoints.

The SCCS guidance further states that hazard data provided should relate to the same NM which is intended for use in the final product, but even more important should relate to the NM released from the product as this is the material to which a consumer is exposed. The material that is released from the product may differ from the material as it is added to the product, due to interaction with other ingredients and ageing processes (Mitrano et al. 2015). This emphasizes the need for a physicochemical characterisation at various phases of the production and/or uses of the NM (see above).

The hazard assessment component for the NanoCosmetics tool will guide the user to make the most use of available knowledge and data on the safety of the NM under consideration. In order to make optimal use of all existing data also data that have not been generated according to standard guidelines (e.g. ISO standards, OECD technical guidelines) and/or non-GLP studies can be considered and included in the NanoCosmetics tool. Such data, however, do need careful consideration and evaluation of the quality of those studies. In this evaluation, criteria for both the relevance of the data for the hazard endpoint and the quality of the reported data are considered. A qualification score regarding the hazard data needs to be included in the tool to indicate the reliability of the data. Ultimately, this will affect the uncertainty of the final risk assessment of the NM to be evaluated. In addition, the tool's hazard assessment component aims to extrapolate hazard information from one NM-form to another, using a read-across approach based on material properties that are considered crucial in determining their effects. The availability of *in vivo* toxicity data for NM-ingredients in cosmetics is very scarce, due to the ban of *in vivo* testing on cosmetic ingredients in general. However, the same or similar nanomaterials may be used in products other than cosmetics, and using the read-across approach, their hazard data may still be used for the safety evaluation in the NanoCosmetics tool.

As indicated above the exposure route is important for the hazard evaluation. However, data will not always be available for the exposure route of the intended product. In those cases route-to-route extrapolation might be useful for use of the available hazard data. For application on skin areas exposed to sunlight it needs to be considered that NMs can be activated or metabolised under the influence of

sunlight. So, this aspect needs to be included in the hazard evaluation in the NanoCosmetics tool.

#### 4.2 Hazard assessment

In the NanoCosmetics tool, hazard assessment will be performed by following a specific set of questions. Figure 2 shows the different questions to be followed and their interdependency.

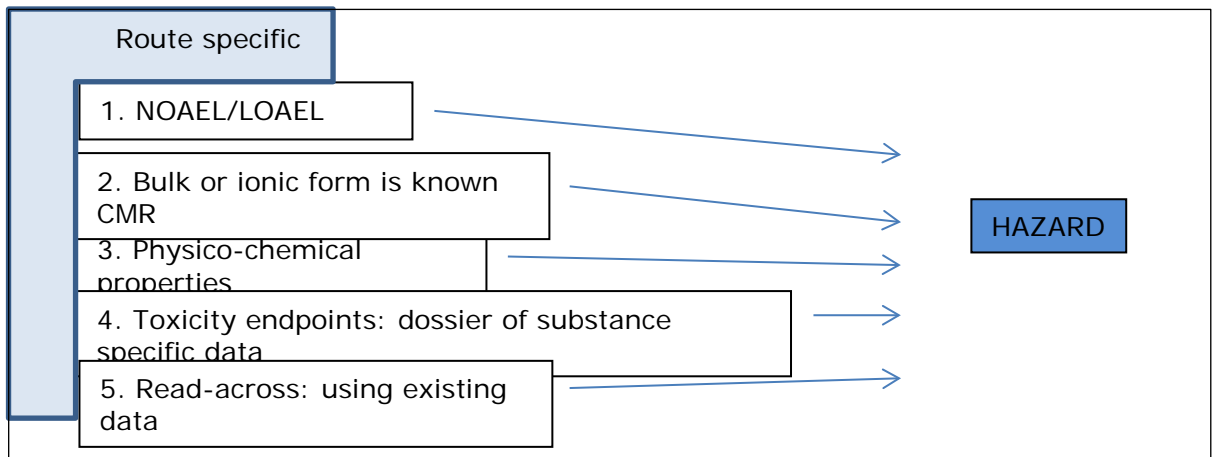


Figure 2. Hazard assessment.

1. The hazard can be assessed by determining whether there are already NOAEL or LOAEL values known for certain NMs that are used as a cosmetic ingredient. These data can give an input in the risk assessment and a maximal "safe" exposure value can be derived.

2. If the bulk material which is of similar elemental composition as the NM, or the NM dissolves into an ionic form that is a known CMR (Carcinogenic, Mutagenic, Reprotoxic) substance, this should automatically lead in the outcome of the risk assessment of the tool to unacceptable risk requiring "an action". However, mutagenicity itself is not a property to ban the use of an ingredient as demonstrated by the use of TiO<sub>2</sub> NM in sunscreens (SCCS 2014a), e.g. when there is no systemic exposure to be expected.

3. In an ideal situation, toxicity studies would not be needed and the hazard can be predicted entirely from the physicochemical characteristics of the NM, the formulation in the product and the duration of the exposure. The hazard potential has some relationship with the physicochemical characteristics of the NM, but in reality this relationship is not yet known (in a quantitative measure). The current state-of-the-art is that only for spherical metal(oxides) nanomaterials some Quantitative Nanostructure-Activity Relationships (QNARs) have been determined. This relationship is based on the redox-potential and can lead to a qualitative measure. It might be possible to apply here the reactivity table that has been developed in the EU GUIDEnano project for a qualitative estimation for metal (oxides) activity. For other types of NMs such a relationship is not known.

4. The NanoCosmetics tool will determine which endpoints need to be considered in the hazard assessment, based on the exposure scenario associated with the cosmetic product under consideration. When substance-specific hazard data are available these need to be put into

the NanoCosmetics tool. For in vivo hazard data this might be available in the context of a different regulatory Framework, as cosmetics-specific data cannot be generated anymore in view of the ban on animal testing for cosmetic ingredients. When data on the NM itself as manufactured are unavailable, the NanoCosmetics tool will use read-across as incorporated in the tool (see below). The read-across module may be used also for including data from other (closely related) NMs. When unrelated NMs are introduced for the risk assessment of a certain NM, a similarity score will be determined indicating whether the data can be accepted as read-across information in the risk assessment or not.

Available studies to date indicate that most nanoparticles are not able to penetrate intact skin far enough to be systemically absorbed. Therefore, for the dermal exposure route, toxicity endpoints for local effects are probably more relevant than toxicity endpoints for systemic effects. Especially the endpoints *irritation* and *sensitization* will be of relevance. For the inhalation and oral route, systemic effects may be more relevant.

In general, the hazard endpoints to be considered are:

1. Corrosion/Irritation: corrosion is not expected for NM to be applied in cosmetic products and is therefore less relevant. Irritation testing of chemical can be done by an in vitro irritation assay using reconstructed human epidermis (RhE) as described in OECD 439.
2. Sensitization: traditionally, sensitisation testing involved experimental animals: the Guinea Pig Maximization Test, the Buehler test, and the Local Lymph Node Assay were used as in vivo tests for sensitisation. Since the ban on animal studies for new cosmetic ingredients several alternative in vitro assays have been developed, e.g. the Direct Peptide Reactivity Assay (DPRA, OECD 442C), and the KeratinoSENS™ assay (OECD 442D) are now being used as in vitro tests for sensitisation testing of cosmetic ingredients. Other in vitro tests available are e.g. the human cell line activation test (h-CLAT), and gene expression in the VITOSENS® model. At least three tests should be used in an integrated testing system. A chemical is designated a sensitizer if two out of three models show a positive response. For identification of a chemical/cosmetic ingredient as a sensitizer also human in vivo data may be available from patch testing or use experiences.
3. Mutagenicity: Several OECD technical guidelines describe in vitro testing for the evaluation of mutagenicity (OECD 471, 473, 474, 475, 476, 477, 479, 480, 487). For NMs in general, an assay in a mammalian cell line is preferred over a bacterial system as there are doubts whether nanoparticles can enter bacteria.
4. Acute toxicity: Since animals studies on new cosmetic ingredients are banned, this part of the tool is only expected to be filled in case the exact same ingredient has been tested before the ban was in place or when the ingredient has also been tested for a different regulatory framework. However, in vitro cytotoxicity studies can be performed to give an indication of the relative toxicity of NMs. This will be included in the tool.

5. Repeated dose toxicity: Similar considerations as for the acute toxicity studies.
6. Carcinogenicity: Similar considerations as for the acute toxicity studies.
7. Reproductive toxicity: Similar considerations as for the acute toxicity studies. In addition, several in vitro assays are available that may indicate possible NM developmental toxicity e.g. the mouse or human embryonic stem cell test.

Explosive and flammable hazard is not added to this tool, as it is considered to be irrelevant for the consumer.

5. Read-across: Read-across rules developed in GUIDEnano can aid to determine whether data provided relate sufficiently to the NM to which the consumer is exposed. The read-across approach will be based on a set of criteria of similarity between the NM under consideration and the NM for which safety data is available. The uncertainty in using these alternative data will be made explicit by the use of uncertainty factors. For UV filters as cosmetic ingredients like nano-TiO<sub>2</sub> and nano-ZnO, criteria have been determined that can be considered "read-across" within one type of NM (SCCS 2012c, 2014a).

#### **4.3 Challenges in hazard identification of nanomaterials**

For the development of the NanoCosmetics tool major challenges exist. On the one hand there is the general ban on animal experiments for cosmetic ingredients. In addition, also the science regarding the hazard identification for NM i.e. nanotoxicology still offers challenges. The sample preparation of NMs to be used in an assay i.e. dispersion technique may be different from one NM to another. The characterization of the NM in the various stages of production and/or use of the cosmetic product may differ.

A positive development is the increase in efforts to read-across and grouping of NMs. This will likely make the use of electronic tools like the GUIDEnano tool and the NanoCosmetics tool more efficient as a number of data can be included in these tools that may ease the risk characterization without providing new data.

In addition to the possibility of read-across and grouping, the NanoCosmetics tool will contain certain default values when data on hazard cannot be provided. In general, these default values will be rather conservative.

## 5 Risk Assessment

### 5.1 General approach

All information obtained on the physicochemical characterisation, the exposure and the hazard identification will be used as input for the final risk assessment. In addition, data already present such as a limit value for a specific exposure route (e.g. inhalation) may also be useful input. Based on a limit value a maximal exposure can be derived that can be considered to present safe use of the NM as cosmetic ingredient.

The risk assessment strategy will be performed for each relevant exposure scenario and in each exposure scenario a Margin of Safety (MoS) is calculated for the most sensitive relevant hazard endpoints (i.e. having the lowest no-effect levels). The MoS is the ratio between the estimated exposure and the dose causing no harm in an animal model. The risk assessment itself will give an indication of the potential risk in the use of the NM as cosmetic ingredient (low, intermediate, high).

### 5.2 Human health hazard endpoints for risk assessment

As the focus lies on the consumer, the following human health hazard endpoints as presented in Table 4 are considered relevant for risk assessment. In addition, Table 5 shows the relevance of the endpoints for each exposure route.

Table 4: Human health hazard endpoints for risk assessment.

	<b>Endpoint description</b>	<b>Endpoints to be evaluated for human toxicity</b>
1	Irritation/corrosion	Qualitative
2	Sensitisation	Qualitative
3	Mutagenicity	Qualitative
4	Acute toxicity	Quantitative
5	Repeated dose toxicity	Quantitative
6	Carcinogenicity	Qualitative/ Quantitative
7	Reproductive toxicity	Quantitative

Table 5. Relevance of human health hazard endpoints for each exposure route.

<b>Route</b>	<b>Duration</b>	<b>Human Endpoints to be evaluated</b>
<b>Inhalation</b>	single	1,3,4
	repeated	1,2,3,5,6,7
<b>Dermal</b>	single	1,3,4
	repeated	1,2,3,5,6,7
<b>Oral</b>	single	1,3,4
	repeated	1,2,3,5,6,7

The outcome of the endpoint is different for the various endpoints:

- Qualitative endpoint: the outcome is yes/no
- Quantitative endpoint: the outcome is a continuous value. This value can be a NOAEL/LOAEL/BMD from a toxicity study or can be a worst-case default value for instance in case of lack of information.

The most sensitive hazard endpoints i.e. the endpoint in which the lowest dose causes an adverse effect will be used as input for the risk assessment and the calculation of a MoS. The MoS is the relationship between the exposure dose and the no-effect level (i.e. No Observed Adverse Effect Level, NOAEL). Generally a MoS of 100 is considered to indicate a negligible risk, representing an uncertainty (or safety) factor of 10 for extrapolation from an animal study to humans (interspecies factor) and a factor of 10 for intraspecies variability within humans. When the NOAEL cannot be obtained a Lowest Observed Adverse effect Level (LOAEL) may be used in the calculations for the risk assessment while adding an additional uncertainty factor.

### 5.3 Risk assessment

The output of the risk assessment is the (calculation of the) MoS. Based on the MoS, three risk categories will be described in the NanoCosmetics tool:

- Low probability of risk
- Medium probability of risk
- High probability of risk

Based on the MoS and its variance (standard deviation) it is decided whether the risk has a high, medium or low probability. When a MoS can be derived in the NanoCosmetics tool and if the MoS >100, the risk is negligible and the NM can be used as cosmetic ingredient in the proposed application. However, in case the MoS is < 100, there may be a risk for adverse effects.

When the MoS cannot be derived or is based on many default data included in the evaluation, the probability of the MoS being < 100 will be determined. For the decision of the risk to have a high, medium or low probability, the *probability* of the MoS (instead of only the *level* of the MoS) is leading. For this, the probability of a value of < 100 is determined based on the variance of the data.

The following provisional criteria, in line with GUIDEnano, have been established for the three categories of risk:

- Low probability of risk: <5% probability of a MoS <100
- Medium probability of risk: 5-75% probability of a MoS <100
- High probability of risk: >75% probability of a MoS <100

Figure 3 represents an overall view of the risk assessment in the NanoCosmetics tool, combining physicochemical characteristics, hazard assessment and risk assessment. In addition, it includes a sensitivity analysis to indicate how the uncertainty in the risk assessment output can be attributed to different sources of uncertainty in the input parameters.

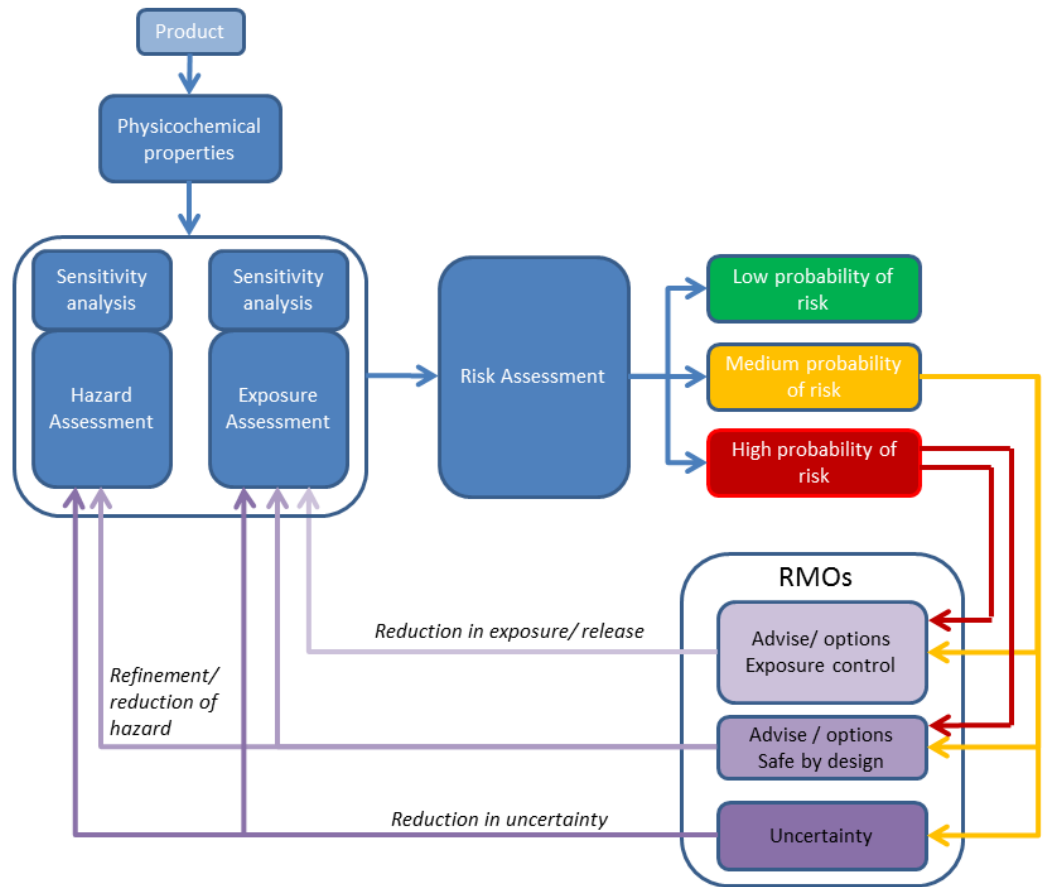


Figure 3: Base scheme for risk assessment in the NanoCosmetics tool.





## 6 NanoCosmetics Tool Report

The NanoCosmetics tool will produce an output report in which the results of the risk assessment are described. The overall risk output is a MoS for the most sensitive hazard endpoint (i.e. highest risk probability), whether or not in combination with a colour (green/ orange/ red). This will be done for each exposure scenario introduced in the tool. This risk output includes the most relevant assumptions made in the risk assessment process. Furthermore, an output on the sensitivity analysis is given which is performed for the parameters of both exposure and hazard. Based on this sensitivity analysis, more insight in the source of uncertainty in the exposure or hazard assessment is provided and can be used to reduce the uncertainty. When there is high uncertainty the NanoCosmetics tool will allow the calculation of MoS for additional hazard endpoints. The endpoint with the lowest uncertainty may then be chosen for the final evaluation.

After establishing the relative risk the NanoCosmetics tool may provide information for a risk modification/mitigation strategy depending on the user (either enforcer/regulator or manufacturer of cosmetic products). Different options for follow-up actions may be included. For all users, options for mitigations of uncertainty may be given. For industry, also options for mitigation of risk may be given; safe by design and/or exposure control.



## 7 Discussion/challenges

The development of this specific NanoCosmetics tool for risk assessment is based on the development of a general tool for risk assessment of NMs within the GUIDEnano project funded by the European Commission. The GUIDEnano project does not include in its risk assessment tool cosmetic ingredients and cosmetic products. This has led to the question to specifically develop a tool for cosmetic ingredients/products.

Both tools will use a read-across approach for those nanomaterials for which insufficient data is available. In case there is doubt about the similarity between the NM under study and the other NMs to be used for read-across, the degree of uncertainty in the read-across will be estimated. The degree of uncertainty in the read-across will be considered in the estimation of the relative quality (certainty) of the final risk assessment. The outcome of the risk assessment of the NanoCosmetics tool is as reliable as the data that are used as input for the tool. The advantage of using the tool is that an indication is obtained on the uncertainty (quality) of the outcome. This will give the user more insight in the possibilities (and need) to mitigate the risk.

Direct identification of a hazard based on physicochemical properties of NMs is not yet possible. The first quantitative relationships between physicochemical properties of NMs and hazard outcomes are being developed (QNARs), but these are currently only available for specific groups of NMs, such as metal oxides (Chen et al. 2015). Taking the properties mentioned in Table 2 into account, catalytic activity, redox potential, chemical composition, size, surface area, surface characteristics and solubility are important physicochemical characteristics related to the potential hazard of a NM. Because of the select group of NMs often used for making some of the recently reported QNARs their application in risk assessment is limited (Gajewicz et al. 2014, Pathakoti et al. 2014). In theory such a relationship can be used to estimate the toxicity of a NM, but such models need to be independently validated and made applicable to a broader range of conditions and NMs (Winkler et al. 2013). This means that based on only the physicochemical properties of a NM, predictions of the toxicity of that material cannot be made at this moment.

Different approaches are being developed to group certain NM types together based on their similarity (Kuhnel and Nickel 2014). This is also the reasoning behind read-across approaches (Patlewicz et al. 2013) that can be used to estimate the hazard of a NM based on available hazard data for a different, but similar NM. In the best case an estimate of the toxicity can be made based on read-across from already existing toxicity data on a similar NM with the same chemical composition. An example of such an approach is presented in the SCCS Opinions on the use of TiO<sub>2</sub> and ZnO NMs as UV-filter in sunscreens (SCCS 2012c, 2014a). TiO<sub>2</sub> and ZnO zinc oxide nanoparticles (within a described set of characteristics, SCCS 2012c, 2014a) may now be used at a concentration of up to 25% as a UV filter in sunscreens. This can be considered safe for humans after application on a healthy, intact or

sunburnt skin. These data can be included in the NanoCosmetics tool as baseline for TiO<sub>2</sub> and ZnO NMs. For producers and regulators such information already included in the tool will be useful in their risk assessment of new products using these NMs. If known limit values or exposure levels of an existing NM are exceeded this should result in an outcome of the risk assessment flagging the intended use as a risk. Depending on the concentration this may indicate a low, intermediate or high risk for which measures need to be taken.

Within the GuideNano project read-across rules are being developed. The NanoCosmetics tool can largely depend on these rules. The way the GUIDEnano project works is to define a minimum set of physicochemical properties that are compared to each other. For each property a similarity score is estimated. For the whole set of properties the lowest similarity score will indicate the relevance of the data considered. For this to work for the NanoCosmetics tool a base dataset which can be used for read-across is required. In addition, these read-across rules need to be established and if possible validated. The cut-off for a minimum similarity score to discard the data considered needs to be established. In addition, an indication of the increase in uncertainty of output depending on the similarity score can be introduced.

Although limit values may be an option as input for the NanoCosmetics tool, limit values only exist for those cosmetic ingredients that have already been evaluated by the SCCS. When available, these data will be included in the NanoCosmetics tool, the most well-known being TiO<sub>2</sub> and ZnO NMs (SCCS 2012c, 2014a).

A challenge will be the lack of good animal data as input for the NanoCosmetics tool as no new animal toxicity data will become available for cosmetic ingredients unless these ingredients are also used in other applications for which animal testing is not banned.

A promising development is the area of read-across and grouping of NMs for risk assessment, as many research groups are currently developing activities to come to a strategy to use read-across and grouping for NMs.

## 8 Conclusions

Although there remain several challenges, especially with regard to the foreseen lack of data, the development of a risk assessment tool (program) for cosmetic ingredients and products is feasible, especially when the development of the NanoCosmetics tool follows closely the development of the GUIDEnano tool in the GUIDEnano project. It is expected that data on read-across and grouping will become available in the future to fill in potential gaps in the risk assessment of nanomaterials.

During a workshop organized by RIVM on June the 4th 2015 some examples were presented on what the web-based NanoCosmetics tool might look like, based on the modules as presently available in the GUIDEnano project and ConsExpo. These examples are presented in Annex 1.



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10 Annex 1. Examples of possible screens for the NanoCosmetics tool



## Sign in


### Log in.

---

<b>Group</b>	<input type="text" value="RIVM"/>
<b>User name</b>	<input type="text" value="Susan"/>
<b>Password</b>	<input type="password" value="••••••••••"/>
<input type="checkbox"/>	Remember me?
<input type="button" value="Log in"/>	

## Case overview

[Create a new case »](#)



	<b>date/time</b>	<b>owner</b>	<b>name</b>
🗑	Jun 01 2015 16:39	Ralph	TiO2 enabled sunscreen
🗑	May 21 2015 15:55	Ralph	Nano silver enabled T-shirts
🗑	May 16 2015 13:30	Ralph	WP5 Case
🗑	Apr 24 2015 16:38	Ralph	WP Worldmodel WWTP
🗑	Mar 26 2015 12:26	Ralph	Test nanomaterial categorization DTU
🗑	Mar 21 2015 17:21	Ralph	ConsExpo scenarios
🗑	Mar 20 2015 11:44	Ralph	Paint
🗑	Mar 16 2015 09:45	Ralph	Cosmetica product
🗑	Mar 16 2015 09:45	Ralph	Test case coating boat

# Case

- Case
  - General
  - Analysis
  - Exposure
  - Hazard
  - Risk
  - Assessment

## nano cosmetics case

In version 1.0 of the GUIDEnano tool you can define the risk assessment scenario for your nano enabled product.

The focus of the first version is to enable the user to identify the possible human and environmental hazard hotspots where human and/or species are exposed to nanomaterials released during production, assembly, usage, maintenance and end of life of the nano enabled product.

Via the menu at the left you can define:

- the product and the relevant nanomaterial appearances;
- the activities related to the product before, during and after it's life;
- the environmental compartments and zones where nanomaterials may be released into;
- the processes distributing, transporting and transforming the nanomaterials;
- the exposed human and species;
- the nanomaterial flow between activities, the pathway(s), the linkage between zone and exposure routes;
- a reference amount for your product under consideration.

Finally, an overview of human and species hazard endpoints is presented showing the relevance for each individual hazard endpoint in relationship to the type of exposure.

Name of the case:

Goal of this case:

## Product info

- [General](#)
- [Product info](#)
- [Product use](#)

### Product | Nanomaterials

Describe your nano enabled product scenario.

Name of the nano (enabled) product:

General description:

Nano enabled sunscreen with Titanium Dioxide (TiO<sub>2</sub>, COLIPA No. S75, CAS No. 13463-67-7) is described as a solid, 34 white, odourless powder.

# Nanomaterials

- ▾ Product | Nanomaterials
  - Nanomaterials
    - NM: Synthesized TiO2
    - NM: Titanium Dioxide enabled sunscreen
    - NM: Tested/read across material
    - NM: Released TiO2 nano particles

## Nanomaterials

Below you can add '+' the different nanomaterial(s) which are relevant before, during and after the life of the nano enabled product. Think of synthesized nanomaterials, manufactured materials with nano features, released, exposed, transported or transformed nanomaterials once released into the environment. But also the nanomaterials used for toxicity tests and read across. To classify and characterize the nanomaterials select them in the menu at the left.

Within this tool a nanomaterial is defined according to the **[ISO/TS 80004 -1:2010, definition 2.4]**

A nanomaterial is a material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale.

This includes both **NANO-OBJECTS** and **NANOSTRUCTURED MATERIALS!**

	name of nanomaterial	description
☒	Synthesized TiO2	Raw material as manufactured
☒	Titanium Dioxide enabled sunscreen	Material after cosmetic formulation
☒	Tested/read across material	Material during toxicity testing
☒	Released TiO2 nano particles	Material coming from product
+		

# Nanomaterial (1)

▾ Nanomaterials

- NM: Synthesized TiO<sub>2</sub>
- NM: Titanium Dioxide enabled sunscreen
- NM: Tested/read across material
- NM: Released TiO<sub>2</sub> nano particles

## NM: Synthesized TiO<sub>2</sub>

General	Categorization	Physico-chemical characterization	Appearing in life cycle
---------	----------------	-----------------------------------	-------------------------

Identify this nanomaterial by giving it a unique name:

Description:

Raw material as manufactured

How does this nanomaterial relate to the product life?

- as the synthesized nano product itself
- as a nanomaterial in the product
- as a by product
- as a waste product
- as a release
- as transformed
- as exposed
- as used for toxicity testing
- as read across material

What is the physical state of this nanomaterial?

What is the main shape of this solid nanomaterial?

## Nanomaterial (2)

▾ Nanomaterials

- NM: Synthesized TiO<sub>2</sub>
- NM: Titanium Dioxide enabled sunscreen
- NM: Tested/read across material
- NM: Released TiO<sub>2</sub> nano particles

### NM: Titanium Dioxide enabled sunscreen

General

Categorization

Physico-chemical characterization

Appearing in life cycle

Identify this nanomaterial by giving it an unique name:

Description:

How does this nanomaterial relate to the product life?

- as the synthesized nano product itself
- as a nanomaterial in the product
- as a by product
- as a waste product
- as a release
- as transformed
- as exposed
- as used for toxicity testing
- as read across material

What is the physical state of this nanomaterial?

How does the liquid nanomaterial present itself?

What is the viscosity of the fluid?



## Analysis | PhysChem (1)

# NM: Titanium Dioxide enabled sunscreen

General
Categorization
Physico-chemical characterization
Appearing in life cycle

Nanomaterial ISO category: **nanosuspension**

Physico-chemical characteristics
Components

Component(s) in *nanosuspension* | **Titanium Dioxide enabled sunscreen**

	category	description	role of component	conc.	unit	mass perc.	overall conc.
⊖	one phase material	<input type="text" value="another material in the sunscreen"/>	matrix ▼	<input type="text" value="80.0"/>	% <sup>Ⓜ</sup>	~ 80.0	80.0
⊖	nanoparticle	<input type="text" value="the titanium dioxide nano particles"/>	dispersed ▼	<input type="text" value="20.0"/>	% <sup>Ⓜ</sup>	~ 20.0	20.0
+	<input type="text" value="--select--"/> ▼						

## Analysis | PhysChem (2)

Component(s) in <i>nanosuspension</i>   Titanium Dioxide enabled sunscreen							
	category	description	role of component	conc.	unit	mass perc.	overall conc.
☒	one phase material	another material in the sunscreen	matrix ▾	80.0	% <sup>Ⓔ</sup>	~ 80.0	80.0
☒	nanoparticle	the titanium dioxide nano particles	dispersed ▾	20.0	% <sup>Ⓔ</sup>	~ 20.0	20.0
+	--select-- ▾						

▶ one phase material: **another material in the sunscreen**

▼ nanoparticle: **the titanium dioxide nano particles**

Physico-chemical characteristics    Components

Function(s)	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2">Primary size distribution</th> </tr> <tr> <th>diameter</th> <th>particle conc. %</th> </tr> </thead> <tbody> <tr> <td>0 - 10nm</td> <td>2.0</td> </tr> <tr> <td>10 - 30nm</td> <td>15.0</td> </tr> <tr> <td>30 - 100nm</td> <td>65.0</td> </tr> <tr> <td>100 - 500nm</td> <td>15.0</td> </tr> <tr> <td>500nm+</td> <td>3.0</td> </tr> </tbody> </table>	Primary size distribution		diameter	particle conc. %	0 - 10nm	2.0	10 - 30nm	15.0	30 - 100nm	65.0	100 - 500nm	15.0	500nm+	3.0
Primary size distribution															
diameter		particle conc. %													
0 - 10nm		2.0													
10 - 30nm		15.0													
30 - 100nm		65.0													
100 - 500nm		15.0													
500nm+		3.0													
Mass conversion															
Physical info															
Size															
Surface properties															
Chemical info.															
Reactivity info															
Toxicity info															

## Analysis | PhysChem (3)

Component(s) in <i>nanosuspension</i>   <b>Titanium Dioxide enabled sunscreen</b>							
	category	description	role of component	conc.	unit	mass perc.	overall conc.
⊞	one phase material	another material in the sunscreen	matrix ▾	80.0	% <sup>⊞</sup>	~ 80.0	80.0
⊞	nanoparticle	the titanium dioxide nano particles	dispersed ▾	20.0	% <sup>⊞</sup>	~ 20.0	20.0
+	--select-- ▾						

▶ one phase material: **another material in the sunscreen**

▼ nanoparticle: **the titanium dioxide nano particles**

Physico-chemical characteristics    Components

Component(s) in <i>nanoparticle</i>   <b>the titanium dioxide nano particles</b>							
	category	description	role of component	conc.	unit	mass perc.	overall conc.
⊞	elementary matter	the TiO2 particle core	core ▾	84.0	% <sup>⊞</sup>	~ 84.0	16.8
⊞	elementary matter	the coating material	coating ▾	16.0	% <sup>⊞</sup>	~ 16.0	3.2
+	--select-- ▾						

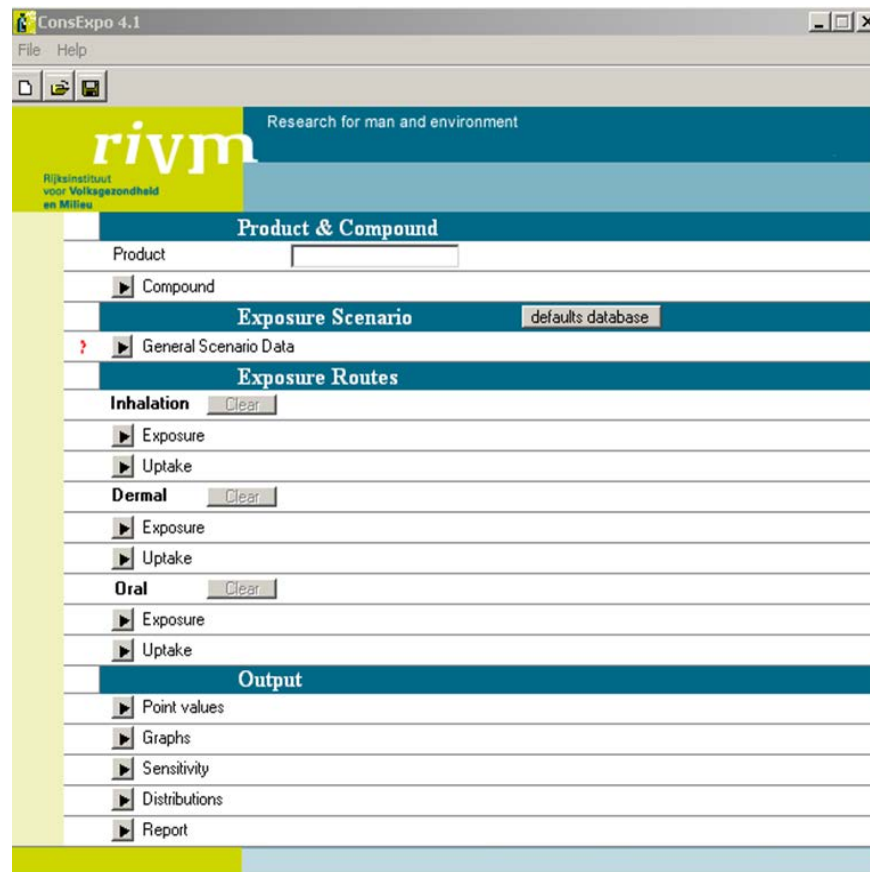
▼ element: **the TiO2 particle core**

Function(s)    molecular formula:

Formula(s)    avarage formula mass in [g/mol] :


Toxicity info

# Exposure | ConsExpo (Dermaal, Oraal)



Cosmeticatool nano | 04-06-2015

# Exposure | ConsExpo nano (inhalatoir)


 Rijksinstituut voor Volksgezondheid  
 en Milieu  
 Ministerie van Volksgezondheid,  
 Welzijn en Sport

**ConsExpo nano**

[About](#)
[Simulation](#)
[Factsheets](#)
[Nanomaterials in consumer products](#)
[Proclaimer](#)
[Help](#)

Welcome to **ConsExpo nano**, the software model developed by RIVM for modeling consumer exposure to nanomaterials in consumer spray products. This model has been developed in the context of the NanoNextNL project "Predictive modeling of human exposure".  
 For more background information on the model and before using the model, we strongly recommend you to read the "About" page carefully.  
[Do not show this text next time](#)
[Go to the "About" page](#)

**Input**

Load default scenario from factsheet > show / hide

Input simulation parameters v show / hide

Product	Nanomaterial	Room	Usage	Simulation
Name or description <input type="text"/>	Name or description <input type="text"/>	Room volume (m <sup>3</sup> ) <input type="text"/>	Spray duration (s) <input type="text"/>	Simulation duration (days) <input type="text" value="365"/>
Mass generation rate (g/s) <input type="text"/>	Density nanomaterial (g/cm <sup>3</sup> ) <input type="text"/>	Room height (m) <input type="text"/>	Exposure duration (min) <input type="text"/>	Deposition model <input type="text" value="ICRP: Male, light exercise"/>
Type of distribution <input type="text" value="Monodisperse"/>	Shape nano particle <input type="text" value="Sphere"/>	Ventilation rate (/h) <input type="text"/>	Spraying towards exposed person <input type="checkbox"/>	Inhalation rate (m <sup>3</sup> /h) <input type="text" value="1.4"/>
Aerosol diameter (median) (µm) <input type="text"/>	Nano particle diameter (nm) <input type="text"/>		Exposure Pattern <input type="text" value="Single event"/>	
Density aerosol (g/cm <sup>3</sup> ) <input type="text"/>	Nanomaterial soluble <input type="checkbox"/>			
Weight fraction nanomaterial <input type="text"/>				
Airborne fraction <input type="text"/>				

**Simulate**

ConsExpo nano RIVM, <http://webw02-int-tv/consexpo-nano/> versie 0.6, 02-05-2015

Print (deze pagina) 100%

## Hazard | limit value

Workflow toxicity for : TiO2 nanoparticles ↗ other substances ○

✓ Should this component (TiO2 nanoparticles) be taken into account for toxicity?  
 Yes  
 No

✓ Is the toxicity/ safety of this component (TiO2 nanoparticles) reviewed by a reliable and relevant institute, like EFSA or JECFA?  
 Yes  
 No

✓ Does a chronic health-based limit value already exist for the component (TiO2 nanoparticles)? ⓘ  
 Yes  
 No

✓ Does the component (TiO2 nanoparticles) have a history of safe use (in the EU)?  
 Yes  
 No

✓ Does the component (TiO2 nanoparticles) become systemically available?  
 Yes  
 No  
 Unknown

✓ Is the percentage known which becomes systemically available?  
 Yes  
 No

✓ Is the component (TiO2 nanoparticles) endogenous? ⓘ  
 Yes  
 No

✓ Does the component (TiO2 nanoparticles) have a specific mode of action?  
 Yes  
 No

## Toxicity studies (1)

[Back to the toxicity workflow](#)

Endpoint	Sub endpoint	Study	Read across	Funct. alerts	Struct. alerts	Critical dose descriptor	Results/Critical dose	OECD	GLP	Accept	Key	Overall Key
Genotoxicity (in vitro)	Gene mutations (in vitro)											
		Bacterial gene mutation test					negative	X	X	Yes	<input checked="" type="checkbox"/>	
	Chromosome aberrations (in vitro)											
Genotoxicity (in vivo)	Gene mutations (in vivo)											
	Chromosome aberrations (in vivo)											
Acute toxicity												
		Acute toxicity, single oral administration, rat				LD50	2150.0 mg/kg bw	X	X	Yes	<input checked="" type="checkbox"/>	
Irritation/ sensitisation												
		Skin irritation/corrosion, Patch test, Rabbit					not irritating	X	X	Yes	<input checked="" type="checkbox"/>	
		Skin sensitisation, Guinea Pig, maximisation test					not sensitising	X		Yes	<input type="checkbox"/>	
Sub-acute/ sub-chronic toxicity												
		Subchronic oral toxicity – Rat 90 day oral (diet)				NOAEL	443.0 mg/kg bw/day			Yes	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Chronic toxicity/ carcinogenicity												
Reproduction/ developmental toxicity	Developmental toxicity/ teratogenicity											
	Reproduction toxicity											
Neurotoxicity												
Immunotoxicity												

## Toxicity studies (2)

### IRRITATION/ SENSIBILISATION ✓

o means mandatory Last saved: Tue Jun 02 2015 13:06

References: [\[i\]](#)

✓ Are there tox-studies available for this endpoint?

- Yes  
 No

✓ Available studies for this endpoint: [\[i\]](#)

study name	OECD study	GLP compliant	Acceptable	Completed
<a href="#">Skin irritation/corrosion, Patch test, Rabbit</a>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
<a href="#">Skin sensitisation, Guinea Pig, maximisation te</a>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

Select one or more studies below.. [\[v\]](#)

Tox study (TiO2 nanoparticles) : Skin irritation/corrosion, Patch test, Rabbit ✓
Skin sensitisation, Guinea Pig, maximisation test ✓

References for this study: [\[i\]](#)

Type of toxicity study: Skin sensitisation

✓ OECD guideline :

Deviations from standard (like additional toxparameters):

✓ Test result:

irritating  
 sensitising  
 not irritating  
 not sensitising

(Critical) effect(s):

Following epidermal challenge neither treated nor control animals showed any changes at 4 the skin. TiO2 regarded as non-sensitiser in maximisation test on guinea pig skin. No systemic effects observed.

Please proceed with the following endpoint or go back to the toxicity workflow for this component.



## Hazard: limit value

### Details on selected overall key study:

Overall key study:	Subchronic oral toxicity – Rat 90 day oral (diet)
Critical dose descriptor:	NOAEL
Threshold limit value animal data:	443.0 mg/kg bw/day
Critical effect(s)	

✓ Is the available animal toxicity information considered sufficient to derive a threshold limit value? i

- Yes  
 No

✓ Safety factor to be used to convert the critical dose from experimental animal data to a threshold limit value for human exposure:  i

Elaboration safety factor:

*The exposure 2.5 [mg/kg bw/day] exceeds the threshold limit value of the experimental data of the overall key study 0.44 [mg/kg bw/day] of this component (TiO<sub>2</sub> nanoparticles).*

*Questions remain and the component (TiO<sub>2</sub> nanoparticles) is in principle unsafe based on the current situation. Assess whether exceeding the toxicological limit value is acceptable or not*

✓ Which data should be used for the threshold limit value?

- Human data  
 Animal data

# Risk Assessment

## RISK CALCULATION

### ALLERGENICITY

product	potential allergenic	allergenic properties	risk assessment required
TiO2 enabled sunscreen			
component(s)			
TiO2 nanoparticles			

product		intake value [mg/kg bw/day]	threshold limit value [mg/kg bw/day]	type of limit value	risk calculation outcome	tox/expo margin
TiO2 enabled sunscreen		10.0				
components	max. concentration					
TiO2 nanoparticles	25.0%	2.5	0.44	experimental data (Subchronic oral toxicity – Rat 90 day oral (diet))	<b>Exceeding the Threshold Limit Value</b>	<b>0.176</b>

## Follow up actions:

### OUTCOME:

- The risk assessment outcome, is 'Exceeding the Threshold Limit Value' proceed with: i
- refine exposure assessment
- additional analytical research
- further toxicity testing

In case further testing might be required due to alerts, safety concerns, legislation etc, in table below an overview is provided of the (OECD-guideline) studies including cost, duration and animal use to perform a cost-benefit analysis for a protocol for further steps to be undertaken.

#### Further testing : TiO2 nanoparticles o

Please note that the studies displayed in **bold** are already performed for the product/ component or its read across candidate. The studies displayed *italic* might be considered for further toxicity testing.

Endpoint	Sub endpoint	Accepted studies/Advised studies	Result	Funct. alerts	Struct. alerts	Cost (EURO)	Duration	Amount animals
<b>Genotoxicity (in vitro)</b>	<b>Gene mutations (in vitro)</b>							
		<b>Bacterial gene mutation test</b>	negative					
	<b>Chromosome aberrations (in vitro)</b>							
		<i>In Vitro Mammalian Cell Micronucleus Test</i>				22000		
		<i>Chromosome aberration test</i>				22000-24420	3 days	
		<i>In vitro Mouse Lymphoma Assay: TK test</i>				14000-22260	1 day	
<b>Genotoxicity (in vivo)</b>	<b>Gene mutations (in vivo)</b>							
	<b>Chromosome aberrations (in vivo)</b>							
<b>Acute toxicity</b>								
		<b>Acute toxicity, single oral administration, rat</b>	2150.0 mg/kg bw					
<b>Irritation/sensibilisation</b>								
		<b>Skin irritation/corrosion, Patch test, Rabbit</b>	not irritating					
		<b>Skin sensitisation, Guinea Pig, maximisation test</b>	not sensitising					

# Reporting

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### 5.3.1.3.1. Acute oral toxicity test

- OECD guideline: *OECD Guidelines 401 and EEC Guidelines 92/32/EEC*  
 - Deviations from standard:

- Critical dose descriptor: *LD50*  
 - Threshold acute limit value: *2150.0[mg/kg bw]*  
 (Critical) effect(s):

*No signs of toxicity recorded during the observation period, no deaths recorded, necropsy 36 showed no alterations, LD50 for male and female rats >2150 mg/kg.*

### 5.3.1.4. Endpoint, Irritation/ sensitisation

Tox-studies available for this endpoint: *Yes*

Available studies for this endpoint:

study name	OECD study	GLP compliant	Acceptable	Completed
Skin irritation/corrosion, Patch test, Rabbit	X	X	X	X
Skin sensitisation, Guinea Pig, maximisation test	X		X	X

#### 5.3.1.4.1. Skin sensitisation

- OECD guideline: *OECD Guidelines 404 and EEC Guidelines 92/32/EEC*  
 - Deviations from standard:

- Test result: *not irritating*  
 (Critical) effect(s):

#### 5.3.1.4.2. Skin sensitisation

- OECD guideline: *OECD Guidelines 406 and EEC Guidelines 84/449/EEC*  
 - Deviations from standard:

- Test result: *not sensitising*  
 (Critical) effect(s):

*Following epidermal challenge neither treated nor control animals showed any changes at 4 the skin. TiO2 regarded as non-sensitiser in maximisation test on guinea pig skin. No systemic effects observed.*

