

Nanotechnology in cosmetics: Opportunities and challenges

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Received : 12-09-11
Review completed : 20-10-11
Accepted : 25-01-12

ABSTRACT

Nanotechnology is the science of manipulating atoms and molecules in the nanoscale - 80,000 times smaller than the width of a human hair. The world market for products that contain nanomaterials is expected to reach \$2.6 trillion by 2015. The use of nanotechnology has stretched across various streams of science, from electronics to medicine and has now found applications in the field of cosmetics by taking the name of nanocosmetics. This widespread influence of nanotechnology in the cosmetic industries is due to the enhanced properties attained by the particles at the nano level including color, transparency, solubility etc. The different types of nanomaterials employed in cosmetics include nanosomes, liposomes, fullerenes, solid lipid nanoparticles etc. Recently, concerns over the safety of such nanocosmetics are raised and have forced the cosmetic industries to limit the use of nanotechnology in cosmetics and for enforcing laws to undergo a full-fledged safety assessment before they enter into the market. In this review, emphasis is made on the types of nanomaterials used in cosmetics by the various cosmetic brands, the potential risks caused by them both to human life and also to the environment and what all regulations have been undertaken or can be taken to overcome them.

KEY WORDS: Dendrimers, health risks, hydrogel, nanocosmeceuticals, safety controls

Nanotechnology is an innovative science that includes the design, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale, which covers the size range from 1 nanometer to 100 nanometer (nm), where 1 nanometer is 1 billionth of a meter. It is not news to cosmetic companies that nanotechnology is the way of the future and is considered as the hottest and emerging technology available. Cosmetic manufacturers use nanoscale versions of ingredients to provide better UV protection, deeper skin penetration, long-lasting effects, increased color and finish quality etc. The global market for cosmetics using nanotechnology is projected to reach an estimated \$155.8 million in 2012.^[1] This widespread use of nanoscale materials in cosmetics is due to the fact that these nanoparticles obtain newer properties which differ from the large-scale particles. These altered properties include color, transparency, solubility and chemical reactivity, making

the nanomaterials attractive to the cosmetics and personal care industries.^[2]

Front-running brands of nanocosmetics

It has been found out from different surveys that almost all the major cosmetic manufacturers use nanotechnology in their various products. Cosmetics giant Estee Lauder entered the NanoMarket in 2006 with a range of products containing “NanoParticles”. L’Oreal, the world’s largest cosmetics company, is devoting about \$600 million dollars, of its \$17 billion dollar revenues, to Nano patents, and has patented the use of dozens of “nanosome particles”. It ranks number 6 in nanotech patent holders in the U.S.^[3] Other examples include Freeze 24/7, DDF (Doctor’s Dermatologic Formula), and Colorescience.^[4] An estimation of how the top 10 cosmetic companies of the world rank in terms of nano-related patents, based on Espacenet database, is depicted in Graph 1.^[5]

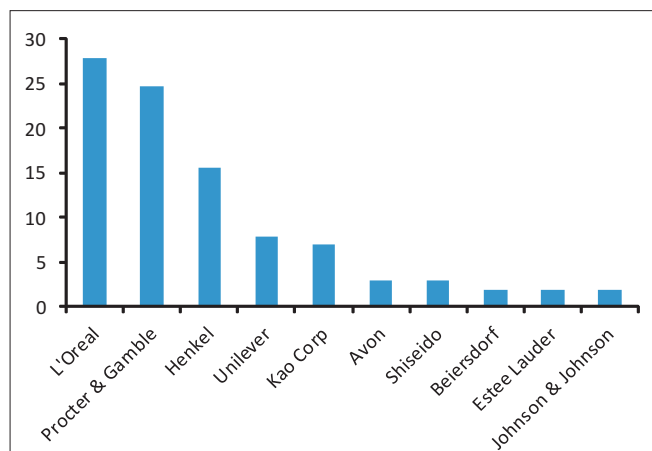
Nano-variegation in cosmetics

Mineral-based cosmetic ingredients with nano-sized dimensions

Some cosmetic products, such as sunscreens, use mineral-based materials and their performance depends on their particle size.

Access this article online	
Quick Response Code: 	Website: www.jpbonline.org
	DOI: 10.4103/0975-7406.99016

How to cite this article: Raj S, Jose S, Sumod US, Sabitha M. Nanotechnology in cosmetics: Opportunities and challenges. J Pharm Bioall Sci 2012;4:186-93.



Graph 1: Ranking of top 10 beauty companies in terms of number of nano-related patents

In sunscreen products, titanium dioxide and zinc oxide, in the size range of 20 nm, are used as efficient UV filters. Their main advantage is that they provide broad UV-protection and do not cause cutaneous adverse health effects.^[6,7]

Other nano-sized materials employed in cosmetics

Many of the leading cosmetic companies claim their products to contain various types of nano-sized materials like fullerenes, nanotubes, liposomes, quantum dots etc.^[6,7]

Types of nanomaterials used in cosmetics are the following

Liposomes

Liposomes are concentric bilayered vesicles in which the aqueous volume is entirely enclosed by a lipid bilayer composed of natural or synthetic phospholipids which are GRAS (generally regarded as safe) products. The lipid bilayer of liposomes can fuse with other bilayers such as the cell membrane, which promotes release of its contents, making them useful for cosmetic delivery applications. Their ease of preparation, enhanced absorption of active ingredients by skin and continuous supply of agents into the cells over a sustained period of time make them suitable for cosmetic applications.^[8] Vesicles, other than liposomes are being used these days that claim to further enhance the penetration of substances across the skin, such as transferosomes,^[9,10] niosomes^[11,12] and ethosomes.^[13]

Nanoemulsions

They are dispersions of nanoscale droplets of one liquid within another.^[14] They are metastable systems whose structure can be manipulated based on the method of preparation. The components used for their preparation are GRAS products and are safe to use. Their smaller particle size provide higher stability and better suitability to carry active ingredients; they also increase the shelf life of the product.^[15,16]

Nanocapsules

Nanocapsules are submicroscopic particles that are made of a polymeric capsule surrounding an aqueous or oily core. It has been found that the use of nanocapsules decreases the penetration of UV filter octyl methoxycinnamate in pig skin when compared with conventional emulsions.^[17]

Solid lipid nanoparticles

They are oily droplets of lipids which are solid at body temperature and stabilized by surfactants. They can protect the encapsulated ingredients from degradation, used for the controlled delivery of cosmetic agents over a prolonged period of time and have been found to improve the penetration of active compounds into the stratum corneum.^[18] *In vivo* studies have shown that an SLN-containing formulation is more efficient in skin hydration than a placebo.^[19] They have also been found to show UV-resistant properties, which were enhanced when a molecular sunscreen was incorporated and tested. Enhanced UV blocking by 3,4,5-trimethoxybenzoylchitin (a good UV absorber) was seen when incorporated into SLNs.^[20]

Nanocrystals

They are aggregates comprising several hundred to tens of thousands of atoms that combine into a “cluster”. Typical sizes of these aggregates are between 10 and 400 nm and they exhibit physical and chemical properties somewhere between that of bulk solids and molecules. They allow safe and effective passage through skin.^[21]

Nanosilver and Nanogold

Cosmetic manufacturers are harnessing the enhanced antibacterial properties of nanosilver in a range of applications. Some manufacturers are already producing underarm deodorants with claims that the silver in the product will provide up to 24-hour antibacterial protection. Nano-sized gold, like nanosilver, is claimed to be highly effective in disinfecting the bacteria in the mouth and has also been added to toothpaste.^[22]

Dendrimers

Dendrimers are unimolecular, monodisperse, micellar nanostructures, around 20 nm in size, with a well-defined, regularly branched symmetrical structure and a high density of functional end groups at their periphery. They contain large number of external groups suitable for multifunctionalization.^[23,24]

Cubosomes

Cubosomes are discrete, sub-micron, nanostructured particles of bi-continuous cubic liquid crystalline phase.^[25] It is formed by the self assembly of liquid crystalline particles of certain surfactants when mixed with water and a microstructure at a certain ratio. Cubosomes offer a large surface area, low viscosity and can exist at almost any dilution level. They have

high heat stability and are capable of carrying hydrophilic and hydrophobic molecules.^[26] Combined with the low cost of the raw materials and the potential for controlled release through functionalization, they are an attractive choice for cosmetic applications as well as for drug delivery.

Hydrogels

They are 3D hydrophilic polymer networks that swell in water or biological fluids without dissolving as a result of chemical or physical cross-links. They can predict future changes and change their property accordingly to prevent the damage.^[27]

Buckyballs

Buckminster fullerene, C60, is perhaps the most iconic nanomaterial and is approximately 1 nm in diameter. It has found its way into some very expensive face creams. The motivation is to capitalize on its capacity to behave as a potent scavenger of free radicals.^[28]

Manufacturers employing nanotechnology in their marketed products as per a study conducted by the 'Friends of the Earth' are shown in Table 1.^[2]

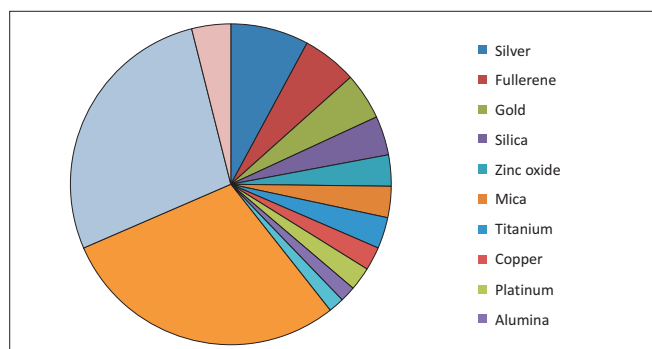
The given Graph 2 shows the principle nanomaterials used in various cosmetics.^[29]

Black-box warnings for nanocosmetics – how and why?

Nanoparticles have been found to cause a large number of risks both to humans as well as to the environment. The toxicity of nanomaterials is affected by their properties, which are attributable to their smaller size, chemical composition, surface structure, solubility, shape and aggregation. The various reasons for this nanotoxicity are summarized below:-

Smaller size of nanoparticles

The main characteristic of nanoparticles is their small size. This can alter their physicochemical properties when compared with their larger counterparts and can create the opportunity for increased uptake and interaction with the biological tissues. Toxicity is mainly concerned with the production of reactive oxygen species, including free radicals which will result in



Graph 2: Principle nanomaterials used in cosmetics

oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA. Because of their size, these nanoparticles can easily gain access to the blood stream via skin or inhalation and from there they will be transported to the various organs. The high dose and long residence time of the nanoparticles in the vital organs can lead to their dysfunction.^[30,31] Carbon nanotubes have been shown to cause the death of kidney cells and to inhibit further cell growth.^[32] Whereas 500 nm titanium dioxide particles have only a small ability to cause DNA strand breakage, 20 nm particles of titanium dioxide are capable of causing complete destruction of super-coiled DNA, even at low doses and in the absence of exposure to UV.^[33] In another study, it was found that mice which were subacutely exposed to 2–5 nm TiO₂ nanoparticles showed a significant but moderate inflammatory response.^[34]

Shape of nanoparticles

Nanoparticles are produced in a variety of shapes like spheres, tubes, sheets etc. and this may be a major cause for the health risks caused by them. A study has shown that exposing the abdominal cavity of mice to long carbon nanotubes are linked with inflammation of the abdominal wall.^[35]

Surface area of nanoparticles

As the size of the particle decreases, their surface area increases leading to an increase in their reactivity. Nanomaterials are also highly reactive due to their high surface area-to-mass ratio, providing more area by weight for chemical reactions to occur. Studies have revealed that because of this increased reactivity, some nanoscale particles may be potentially explosive and/ or photoactive. For example, some nanomaterials—such as nanoscale titanium dioxide and silicon dioxide—may explode if finely dispersed in the air and they come into contact with a sufficiently strong ignition source.^[36]

Penetration of nanoparticles via skin

Scientific studies have shown that nanoparticles can penetrate skin, especially if skin is flexed.^[37] Broken skin is a direct route for the penetration of particles even up to a size of 7000 nm. The presence of acne, eczema and wounds may enhance the absorption of nanoparticles into the blood stream and may lead to further complications. A preliminary study found that nanoparticle penetration was deeper in skin affected by psoriasis than in unaffected skin.^[38] Recently, the base carriers are being modified in order to enhance the skin penetration by incorporating certain penetration enhancers, both physical and chemical, and also by preparing newer vesicular systems with increased skin penetrability like ethosomes and transferosomes. Even flexing and massage can increase the skin penetration of nanoparticles. One study found that even particles up to 1000 nm in size can be taken up through intact skin to reach living cells, when skin is flexed.^[39]

Cellular toxicity of zinc oxide and titanium dioxide nanoparticles

In a study published by Minghong Wu and co-workers at

Table 1: Manufacturers employing nanotechnology in their marketed products^[2]

Nanomaterials	Marketed products	Manufacturer
Zinc oxide and titanium dioxide	Sunforgettable corrector colores SPF 20, unforgettable SPF 30 brush	ColoreScience
	range, wild to mild skin bronzer.	
	Moisturizing dermatone lips 'n' face protection crème	Dermatone
	Solar defence organic moisturizer	Image skincare
	Olay complete UV protective moisture lotion	Proctor and gamble
Fullerenes and fullersomes	Soltan facial sun defence cream	Boots
	Defy: age management exfoliator, EGF complex cocktail, nourish	Bellapelle skin studio
	Dr. Brandt new lineless cream	Dr. Brandt
	Revitalizing night cream	MyChelle dermaticals LLC
	White out / daily under eye care	Sircuit cosmeceuticals
Nanoemulsions	Zelens fullerene C-60 day cream, zelens fullerene C-60 night cream	Zelens
	Coco mademoiselle fresh moisture mist	Chanel
	Calming alcohol-free nanoemulsion	Chanel precision
	Skin caviar ampoules	La prairie
	Pureology COLOURMAX	Pureology
Nanocapsules	Double dose in a box, laser relief, laser tight	Dr. Brandt
	Hydra flash bronzer	Lancome
	Super aqua skin cream range	Enprani
Novasomes	Renutriv range, resilience range	Estee lauder
	Neutrogena line	Johnson and johnson
Nanosomes	Revitalift double lifting, revitalift intense lift treatment mask	L'Oreal
Nano aluminium	Revlon colorstay stay natural powder, revlon new complexion concealer	Revlon
Nano silicon dioxide	Leorex hypoallergenic wrinkle nano remover range	GlobalMed technologies
	Renergie microlift eye, renergie lift makeup	Lancome
	Elixir skin range, pureness matifying compact	Shiseido
Lyphazome nanospheres	Moisturizing sunscreen MAX SPF 29, moisturizing sunscreen spf 30	Dermazone solutions

Shanghai University, they have discovered that zinc oxide (ZnO) nanoparticles used in sunscreens can damage or kill the stem cells in the brains of mice.^[40] To investigate the potential neurotoxicity of ZnO nanoparticles, Wu *et al.* prepared cultures of mouse neural stem cells (NSCs), and treated them with zinc oxide nanoparticles ranging from 10 to 200 nanometers in size. After 24 hours, the cell viability assay indicated that ZnO nanoparticles manifested dose-dependent, but not size-dependent toxic effects on NSCs. Through analysis using confocal microscopy, transmission electron microscopy examination, and flow cytometry, many of the NSCs showed clear signs of apoptosis. This zinc oxide nanoparticle toxicity was found to be the effect of the dissolved zinc ions in the culture medium or inside cells.^[41] In another work by Arnaud Magrez at the NN Research Group, it was found that titanium dioxide based nanofilaments were found to be cytotoxic, which was affected by their geometry and also enhanced by the presence of defects on the nanofilament surface, resulting from chemical treatment. Nanofilament internalization and alterations in cell morphology were observed.^[32]

Occupational risks of nanoparticles

Workers may be accidentally exposed to nanomaterials during the production of nanomaterials or products containing them, as well as during use, disposal or recycling of these products. Exposure may also occur in cleaning and maintaining research, production and handling facilities.^[42] A higher potency of nanomaterials compared to microsized particles was detected by Kaewamatawong *et al.*^[43] At present, there is insufficient information on the number of workers exposed to nanomaterials in the work place or the effects on human health of such exposure, according to the European Agency for Safety and Health at Work. In addition, because nanomaterials have applications in many consumer products and

the use of such materials in products is increasing, consumers have an increasing chance of exposure to these materials.

Route and extent of exposure^[44-46]

The health risks that nanoparticles pose to the humans also depend on the route and extent of exposure to such materials. Nanomaterials enter the body mainly through 3 routes.

Inhalation

It is the most common route of exposure of airborne nanoparticles according to the National Institute of Occupational Health and Safety. For example, workers may inhale nanomaterials while producing them if the appropriate safety devices are not used, while consumers may inhale nanomaterials when using products containing nanomaterials, such as spray versions of sunscreens containing nanoscale titanium dioxide. According to officials at the National Institutes of Health, although the vast majority of inhaled particles enter the pulmonary tract, evidence from studies on laboratory animals suggest that some inhaled nanomaterials may travel via the nasal nerves to the brain and gain access to the blood, nervous system, and other organs, according to studies we reviewed.

Ingestion

Ingestion of nanomaterials may occur from unintentional hand-to-mouth transfer of nanomaterials or from the intentional ingestion of nanomaterials. A large fraction of nanoparticles, after ingestion, rapidly pass out of the body; however, according to some of the studies we reviewed, a small amount may be

taken up by the body and then migrate into organs.

Through skin

Studies have shown that certain nanomaterials have penetrated layers of pig skin within 24 hours of exposure.^[57] According to some of the studies reviewed by the US Government Accountability Office (GAO), concerns have been raised that nanomaterials in sunscreens could penetrate damaged skin.

Environmental risks of nanoparticles

The environment is also at risk due to the exposure of nanomaterials through release into the water, air, and soil, during the manufacture, use, or disposal of these materials. These nanomaterials, if antibacterial in nature and if released in sufficient amounts, could potentially interfere with beneficial bacteria in sewage and waste water treatment plants and could also contaminate water intended for reuse, according to some of the studies reviewed by US GAO. For example, studies have revealed the toxicity of TiO₂ nanoparticles to the main body systems of rainbow trout.^[47] In a study conducted by the University of Toledo, the researchers discovered that nano-titanium dioxide used in personal care products reduced biological roles of bacteria after less than an hour of exposure. These findings suggest that these particles, which end up at municipal sewage treatment plants could eliminate microbes that play vital roles in ecosystems and help treat wastewater.^[48] In one of the studies done on carbon fullerenes, it has been found out that they can cause brain damage in largemouth bass,^[49] a species accepted by regulatory agencies as a model for defining ecotoxicological effects. Fullerenes have also been found to kill water fleas and have bactericidal properties.^[50] Rice University's Centre for Biological and Environmental Nanotechnology has pointed out the tendency for nanoparticles to bind to contaminating substances already pervasive in the environment like cadmium and petrochemicals. This tendency would make nanoparticles a potential mechanism for long range and widespread transport of pollutants in groundwater.^[51,52] Certain studies have even suggested that nanoparticles have the potential for biomagnification.^[53] An interdisciplinary team of researchers at the UC (University of California) Santa Barbara produced a groundbreaking observation on how nanoparticles are able to biomagnify in a simple microbial food chain.^[54]

Toxicity produced by carbon fullerenes (buckyballs)

Various studies have shown that carbon fullerenes, which are currently being used in moisturizers and some face creams, have the potential to cause brain damage in fishes^[55,56] kill water fleas and have bactericidal properties. In a work done by Dhawan *et al.*, he proved that stable aqueous suspensions of colloidal C₆₀ fullerenes have demonstrated genotoxicity with a strong correlation between fullerene concentration and genotoxic response.^[57] Fullerenes have even been found to be toxic to the vascular endothelial cells.^[58]

Characterization methods for safety assessment of nanoparticles in cosmetics

The opinions of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) deals with the risk assessment methodologies available for evaluating the possible adverse health and environmental effects of nanotechnology products^[59] and also on the investigation of nanomaterials.^[60] The specific characteristic of nanomaterials will require new test strategies to determine the mechanisms of potential injury that they may cause. The main parameters that are evaluated for the safety of nanomaterials are the following:

Physical-chemical properties

Physical properties like size, shape, specific surface area, agglomeration state, size distribution, surface morphology, structure, solubility and chemical properties like structural formula/molecular structure, composition of nanomaterial, phase identity, surface chemistry, hydrophilicity/lipophilicity have to be analyzed.^[59]

Mathematical modeling

These predictive models range from simple, empirical algorithms to complex mathematical equations which sometimes require knowledge and estimation of experimentally inaccessible parameters. But, since, in none of these models, data relating to macromolecular compounds or particle structures have been included, they cannot be used with any confidence to predict what might happen when such entities contact the skin.^[61]

Microscopic techniques

More useful information from the *in vitro* studies can be obtained by microscopic examination of the skin posttreatment. While absolute quantification may not be possible, visualization of the tissue to which an active has been applied can provide valuable insight.^[61,62]

The methods used for microscopic evaluation are shown in Table 2.^[61]

In vitro methods

Though there are a number of alternative methods and technologies for studying the molecular mechanisms involved in the biological activity of compounds, only validated methods are permitted for cosmetic products. These validated methods must be used when testing is required, for the safety assessment of cosmetic ingredients.^[61,62]

The different validated *in vitro* tests employed are depicted in Figure 1.^[61]

The relevant toxicological end points considered important for nanomaterials are given in Figure 2.^[61]

Table 2: Methods employed for microscopic techniques^[61]

Techniques used	Advantages
Laser scanning confocal microscopy (LSCM)	<ul style="list-style-type: none"> • 3-dimensional views of the skin can be obtained from relatively thick tissue samples with little or no tissue artefacts • Clearly demonstrate the impact of a nanoparticle formulation on the delivery of a model active • Visualize the affinity of particulate vectors for follicular openings
High-resolution transmission electron microscopy	<ul style="list-style-type: none"> • Visualize individual particles in ultra-thin sections of tissue • Can use X-ray analysis to identify the chemical composition of the visualized vector
Particle induced X-ray emission (PIXE)	<ul style="list-style-type: none"> • Large fields of view • Easy sample preparation • Facile elimination of artefacts
Radio labeling with the positron emitter ⁴⁸ V	<ul style="list-style-type: none"> • Ultra-sensitive • Relatively easy to use • Provides a large field of view • Shows individual positron tracks • Useful for localizing particles to specific structures in/on the skin

Safety requisites for a blooming beauty

Cosmetic manufacturers using nanotechnology confront an uncertain future from both consumer response and a regulatory standpoint. Eminent scientific bodies like the Royal Society, Britain’s most prestigious scientific body, and the US Food and Drug Administration warn that the health risks of nanocosmetics require a thorough investigation before product commercialization.^[63] One of the major problems is that there is no much evidence about how much or what type of safety assessments are done by the various cosmetic manufacturers on their products.

Though there are increasing number of cosmetics and personal care products containing nanomaterials in the market, there are no specific regulations regarding their safety assessment. In Australia, the National Industry Chemicals Notification and Assessment Scheme (NICNAS) regulates the safety of ingredients in cosmetics and personal care products and the Therapeutic Goods Administration (TGA) regulates sunscreens. However these regulators fail to distinguish between nanoparticles and larger sized particles. The EU’s Scientific Committee on Consumer Products (SCCP) looked at the safety evaluation of nanomaterials for use in cosmetic products and considered the implications on animal testing and whether the previous opinions on nanomaterials currently used in sunscreen products would need to be revised.^[64]

The European Parliament approved the amended recast of the EU Cosmetics Directive, introducing the mention of ‘nanomaterials’ into an EU legislation. As requested by the European Parliament, the new regulation introduces a safety assessment procedure for all products containing nanomaterials, which could lead to a ban on a substance if there is a risk to

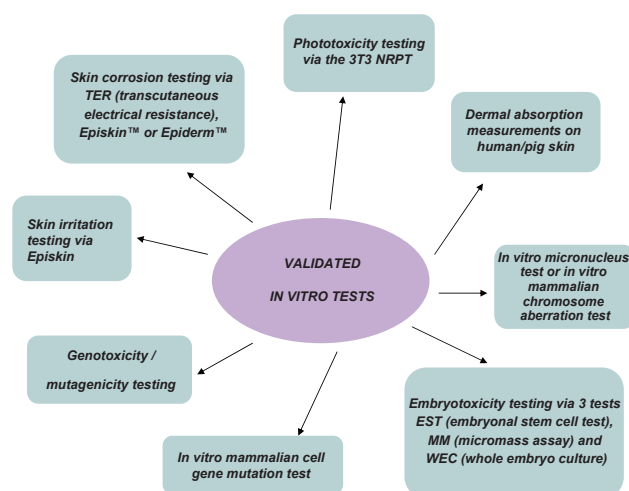


Figure 1: Validated in vitro Methods employed^[61]

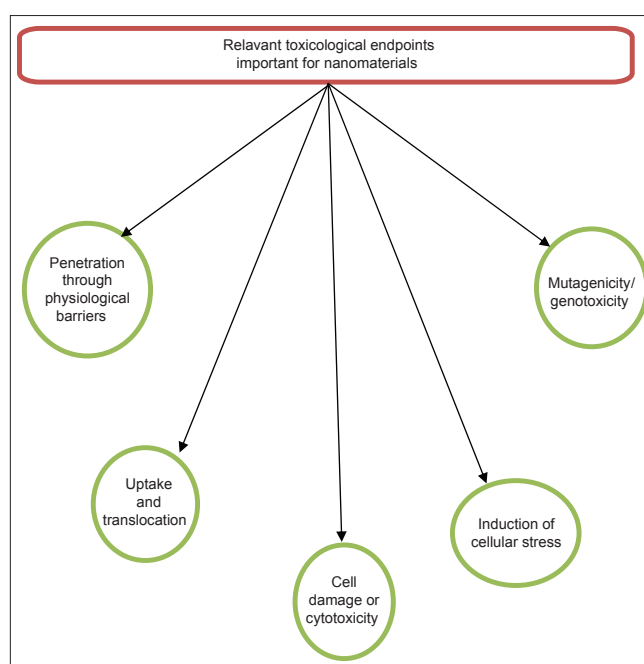


Figure 2: Relevant toxicological endpoints important for nanomaterials

human health.^[65] The major excerpts from the act include the following^[66,67]:-

- The ruling defines nanomaterial as “an insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm”.
- The responsible person shall ensure compliance with safety, GMP, safety assessment, product information file, sampling and analysis, notification, restrictions for substances listed in Annexes, CMR, nanomaterial traces, animal testing and labeling, claims, information to the public, communication of SUE, information on substances.
- Prior to placing the cosmetic product on the market, the responsible person should submit the following information to the Commission:
 - o The presence of substances in the form of nanomaterials

- o Their identification including the chemical name (IUPAC) and other descriptors
- o The reasonably foreseeable exposure conditions
- In case the Commission has concerns regarding the safety of the nanomaterial, the Commission shall, without delay, request the SCCS to give its opinion on the safety of these nanomaterials for the relevant categories of cosmetic products and the reasonably foreseeable exposure conditions.
- All ingredients present in the form of nanomaterials shall be clearly indicated in the list of ingredients. The names of such ingredients shall be followed by the word “nano” in brackets .
- Particular consideration shall be given to any possible impacts on the toxicological profile due to
 - o Particle sizes, including nanomaterials;
 - o Impurities of the substances and raw material used; and
 - o Interaction of substances

In a nutshell

The use of engineered nanomaterials has hiked in today's world. It has also captured the hearts of the cosmetic industries with its enhanced properties and they are shifting their focus from cosmeceuticals to nanocosmeceuticals by incorporating nanotechnology in most of their manufacturing processes. But all these nanocosmetics have raised a great concern regarding their safety for humans and environment. In order to ensure the safety and efficacy of such products, the European Union has incorporated a new amendment in its Cosmetics Directive which will become active from 2012 onwards. This new regulation will allow only the safer nanocosmetic products to enter into the market, safeguarding the beauty and health of the consumers.

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Source of Support: Nil, **Conflict of Interest:** None declared.

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