Zinc oxide – nanosize does not change the toxicological profile

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Introduction

Sunscreen products containing mineral UV filters protect consumers from the harmful effects of UV exposure. Pigmentary grades of metal oxides like ZnO were used in the past, imparting an opaque whiteness as a result of scattering visible light. The transparency of nanosized particles metal oxides like ZnO results in better consumer acceptance and thus improves the protection of human skin against UV-induced damage. In addition, UV light is most efficiently attenuated at a nanosize range of 60–120 nm.

In the last 2 years, the toxicological properties of nanosized ZnO in comparison with pigmentary (non-nano) ZnO were examined. The results of these comprehensive studies, which were performed/sponsored partly by CEFCI LRI and partly by BASF, will be presented.

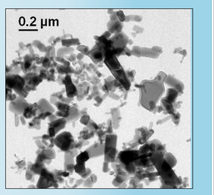
Materials and Methods

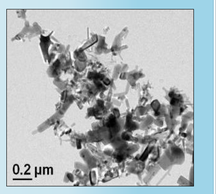
All tests were performed with well characterized nanosize and pigmentary ZnO's of the EU repository.

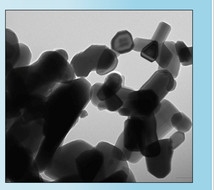
- NM 110 uncoated ZnO (Z-COTE®)
- NM 111 coated* ZnO (Z-COTE® HP1)
- NM 113 uncoated non-nanoscale ZnO

The characterization and test item preparation is published (doi:10.2787/55008)

The testing programme comprised all toxicological endpoints considered to be relevant for nanomaterials including toxicokinetics and dermal absorption. The studies were conducted according to current valid OECD testing guidelines which were modified, especially in regard of substance preparation where appropriate. If no OECD guideline was available, the tests were performed according to accepted scientific standards for nanomaterials.







TEM images of uncoated nano ZnO, coated nano ZnO and pigmentary ZnO

Acknowledgement: The work was partly funded by **CEFIC LRI**

Results

Endpoint	Test substances	Testsystem	Testspecies	Exposure	Testguideline / method	Results
Acute toxicity	coated ZnO	in vivo	rat	dermal	OECD 402	LD50 > 2000 mg/kg bw
Skin and eye irritation	coated ZnO	- Human skin model, isolated bovine cornea (BCOP)		in vitro/ ex vivo	OECD 431, OECD 437	not corrosive
Skin (photo) sensitization	coated ZnO	Photoallery Maximization test , Human Repeat Insult Patch test		in vivo		not sensitizing, not photosensitizing
Repeated dose toxicity	uncoated, coated and pigmentary ZnO	Subacute and subchronic toxicity	rat	inhalation (5d, 14d and 90d)	OECD 412 and 413 incl.BAL, cell proliferation, EM	Local irritation of nasal cavity and respiratory tract , local lung inflammation, all effects reversible within 28d after 90 d exposure , NOAEC (90d) 1.5 mg/m3
Mutagenicity in vitro	coated and pigmentary ZnO	Gene mutation in bacteria	Ames test	in vitro	OECD 471	not mutagenic
	uncoated, coated and pigmentary ZnO	Clastogenicity	CA in V79 cells	in vitro	OECD 473	not mutagenic
	uncoated, coated and pigmentary ZnO	Gene mutation in mammalian cells	Mouse Lymphoma Assay	In vitro	OECD 476	positive
Mutagenicity in vivo	uncoated, coated and pigmentary ZnO	Micronucleus test	- Mouse - Rat	In vivo: - single i.p. injection - inhalative, 14d	OECD 474	not mutagenic
Genotoxicity	uncoated , coated and pigmentary ZnO	- Oxidative comet assay ex vivo in BAL cells - Oxidative damage and local inflammation	rat	inhalation 14d exposure	DNA-strand breaks and oxidative DNA-damage . 8-OH-dG in lungs; cytokines and arachidonic acid metabolites in BAL cells	Increase in pro-inflammatory cytokines (coated ZnO). No evidence of substance specific genotoxic potential
Reproductive toxicity	coated and pigmentary ZnO	Prenatal developmental toxicity	rat	inhalation	OECD 414	Maternal toxicity by increase of lung weights and lung inflammations at 7.5 mg/m^3 No effects on reproductive parameters (conception rate, corpora lutea, implantation sites, pre- and postmplantation loss, resorptions, dead fetuses) , no increase in external and soft tissue malformations and variations NOAEC developmental: 7.5 mg/m^3
Toxicokinetics	uncoated , coated and pigmentary ZnO	ADME	rat	inhalation	OECD 417 (organs and urine investigated)	Dissolution of retained particles , rapid elimination
Percutaneous absorption	[^{65}Zn]-ZnO (nano)	dermal absorption	rat skin	in vitro and in vivo	OECD 427	No systemic absoption, no penetration of nanoparticles through the skin
	coated and uncoated ZnO	dermal penetration	pig skin	in vitro	- Intact skin (OECD 428) - Sunburned skin	No penetration of ZnO nanoparticles through the skin

Conclusion

The two tested nanosized ZnO products showed a toxicological profile similar to a pigmentary, non-nano ZnO grade. Nano ZnO was found to be of low acute dermal toxicity and good local tolerability. Numerous in vitro and in vivo studies do not rise concerns regarding a relevant mutagenic potential. In inhalation studies with exposures ranging from 5, 14 to 90 days, the biological effects and the obtained No-Observed-Adverse-Effect Concentrations (NOAECs) were comparable between the nano ZnOs and the pigmentary grade. A prenatal developmental toxicity study in rats did not reveal any harmful effects to the fetus after inhalation of ZnO nanoparticles. The kinetic studies indicate complete dissolution of the ZnO nanoparticles when taken up into an aqueous physiological environment and there was no evidence that ZnO nanoparticles penetrate through intact or sunburned skin. Overall, there was no indication of a nano-specific toxicity, the observed biological effects are mainly caused by dissolved Zn-ions.