Realistic Exposure Study Assists Risk Assessments of ZnO Nanoparticle Sunscreens and Allays Safety Concerns

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The findings of a new study by Mohammed et al. show that after repeated hourly or daily topical applications typically used for sunscreens, zinc oxide nanoparticles do not penetrate into the viable epidermis or cause toxicity in human skin. This important study confirms that the known benefits of using zinc oxide nanoparticles in sunscreen clearly outweigh the perceived risks of using nanosunscreens.

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Powerful, noninvasive, in vivo analytical techniques were used in a new human study by Mohammed et al. (2018) to investigate the potential for skin penetration and cellular effects after realistic exposure to zinc oxide (ZnO) nanoparticles used in sunscreens. The researchers simultaneously measured a biomarker of exposure in users to indicate skin penetrance (i.e., the levels of ZnO nanoparticles in various layers of skin) and a biomarker of effect (i.e., a biological response to exposure) by using ratios of endogenous fluorescent biomolecules indicative of cellular health. They found that ZnO nanoparticles do not penetrate into the viable epidermis or cause toxicity, even after the repeated hourly or daily topical applications that are typically used for sunscreens.

The safety of nanoparticles used in sunscreens has been a controversial international issue in recent years, in part because previous animal exposure studies generally found much higher skin absorption of zinc from dermal application of ZnO sunscreens than human studies (Wright, 2016). The study by Mohammed et al. (2018) provides long-awaited information about exposure biomarkers during realistic human use of ZnO nanosuncreens, enabling more accurate exposure assessments for evidence-based risk assessments by reducing the uncertainties about estimates of uptake into humans after exposure. The risk assessment process conducted by regulatory authorities for the use of engineered nanomaterials typically involves a whole life-cycle analysis and considers appropriate chemical and physical properties of the nanomaterial to complete the four-step process of hazard identification, dose-response assessment, exposure assessment, and risk characterization (Wright and Jackson, 2016).

The first step in the risk assessment process involves identifying the intrinsic toxicities of the nanomaterial, and the second step requires elucidation of dose-response relationships for potential adverse effects. Such toxicity profiles for these and other ZnO nanoparticles, as well as bulk ZnO particulates, were extensively investigated during the recent internationally sponsored nanosafety testing program of the Working Party for Manufactured Nanomaterials (WPMN), under the auspices of the Organisation for Economic Co-operation and Development (OECD) (Singh et al., 2011). Although the OECD-WPMN program and the numerous (mainly in vitro) studies in the literature have reported useful information for the initial two steps of the risk assessment process, very few studies have directly addressed the third step, that is, the important issue of human exposure under realistic in-use conditions of ZnO nanoparticle sunscreens.

The hallmark human study of Gulson et al. (2010) began to address this knowledge gap by comparing sunscreens with nano and bulk ZnO particulates containing a less abundant stable isotope of zinc, which was repeatedly applied on the backs of volunteers during beach trials. They found little difference in the extremely small amount of zinc absorbed into the body under these conditions between nano and bulk ZnO formulations. Because this study used only single-labeled ZnO (as making dual-rare stable isotope—labeled ZnO is prohibitively expensive), these researchers were unable to provide the essential information about whether zinc had been absorbed through human skin in its ZnO particulate form or as zinc ions due to its partial solubility in sweat. The study by Mohammed et al. (2018) has clearly shown that, for realistic human sunscreen usage scenarios, ZnO nanoparticles do not penetrate through the skin’s outer stratum corneum into the viable epidermis. Furthermore, their ex vivo human skin experiments measured a slight elevation in zinc ion levels in viable epidermis, confirming that the uptake of zinc seen in the study by Gulson et al. (2010) was due to the penetration of zinc ions, and not ZnO nanoparticles, through human skin. Of great significance is their finding that...
Clinical Implications

- A realistic exposure study provides human biomarkers for evidence-based risk assessment of nanosunscreens.
- ZnO nanoparticles do not penetrate human skin with realistic sunscreen use.
- Slight increases in zinc ion levels in viable epidermis did not cause toxicity.

this slight increase in zinc ion concentrations in viable epidermis was not associated with cellular toxicity under conditions of realistic ZnO sunscreen use (Mohammed et al., 2018).

The lack of toxicity from ZnO exposure seen in the new study is not surprising, because zinc is an essential mineral for human nutrition, and its transport and use are strictly controlled within the biological processes of the body. Cytotoxic responses from ZnO nanoparticles are seen at relatively high-exposure concentrations (Feltis et al., 2012), which are at least a magnitude greater than those expected from nanosunscreen use (O’Keefe et al., 2016), even in the case of human phagocytic immune cells that can actively concentrate ZnO nanoparticles (James et al., 2013). Mechanistic studies clearly indicate that ZnO’s cytotoxicity is directly dependent on the extent of cellular uptake of nanoparticles, followed by their intracellular dissolution to zinc ions (James et al., 2013), and is not dependent on extracellular zinc release (Shen et al., 2013).

Although biological properties of nanoparticles may vary within classes of nanomaterials depending on their surface characteristics, the OECD WPoMN safety testing program for engineered nanomaterials and ongoing nanosafety research is providing useful information about the quantitative (surface) structure activity relationships from the growing number of mechanistic toxicology studies of related nanomaterials. For ZnO nanoparticles, surface modification can alter cellular uptake and subsequent cytotoxicity (Luo et al., 2014). In light of this issue, the Mohammed et al. (2018) study also provided an important comparison between coated and uncoated particles to determine whether modification of ZnO nanoparticle surface characteristics commonly used in sunscreens had altered skin penetration. They found that despite having a hydrophobic silane surface-coating (Singh et al., 2011), the coated ZnO nanoparticles behaved in a similar manner to the uncoated pristine ZnO regarding their lack of skin penetration and toxicity and the slight elevation in zinc ion levels in the viable epidermis (Mohammed et al., 2018). This provides further confirmation that the range of ZnO nanoparticles used in sunscreen formulations do not penetrate human skin with realistic use conditions; thus, they have much lower skin penetration than alternative materials used for the same application, such as organic chemical UV filters, which have similar direct in vitro cytotoxicity profiles (O’Keefe et al., 2016).

In conclusion, the findings of the study by Mohammed et al. (2018) confirm that for typical sunscreen usage, ZnO nanoparticles do not penetrate into the viable epidermis or cause cellular toxicity in human skin. This study reinforces the important public health message that the known benefits of using ZnO nanosunscreen clearly outweigh the perceived risks of using nanosunscreens, which are not supported by the scientific evidence. Because of the broad-spectrum UV–filtering characteristics, UV stability, nonirritating nature, hypoproliferative, and visible transparency of ZnO nanosunscreen, it is also the preferred option for people with sensitive skin and allergic reactions to organic chemical UV filters. Furthermore, the public also needs to be educated about the fact that there is little effective difference (actually only ~1%) between sun protection factor 30+ and 60+ and that it is better to use a sun protection factor 30+ sunscreen, especially a ZnO nanosunscreen, as part of their sun protection measures than none at all.

CONFLICT OF INTEREST
The author states no conflict of interest.

REFERENCES