Regulatory Design for New Technologies: Spaghetti Junction or Bauhaus Principles for Regulating Innovative Cosmetic Products

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1. Introduction

Employing cosmetics as a case-study, this article reviews the readiness of the Australian, European Union (EU) and United States (US) regulatory structures to deal with new technologies such as those based on nano-science. Recent developments in the EU regulatory readiness would seem to suggest a development towards inserting nano-anchors in existing regulations, even if no immediate plans have been made to also include tailor-made provisions for those applications. This type of neat and functional design (hence the *Bauhaus* reference in the title) contrasts with the spaghetti junction approach that typifies other jurisdictions (and, until recently, the EU).

The development and commercialisation of nanotechnologies has become an important adjunct for traditional industries due to the increasing consumer demand for improved products. These improvements may be aesthetic or functional in nature, or both, depending on the product itself. Unsurprisingly, consumer demand for cosmetic products that 'renew, restore, and rejuvenate'[1] has resulted in an escalating interest by the cosmetic industry in the use of nanotechnologies within cosmetic formulations. A number of cosmetic products which claim to incorporate engineered nanomaterials have already entered the market and include, for instance, anti-ageing creams, make up, hair care products, cleansers and moisturisers. It is thought that these products contain an assortment of engineered nanomaterials ranging from metal oxides, fullerenes, quantum dots, liposomes and nanospheres. Yet despite the reported wide-spread use of nanomaterials within the cosmetic industry[2], the exact nature and extent to which engineered nanomaterials are being used by the cosmetics industry in their products remains ambiguous[3].

While the use of engineered nanomaterials within cosmetics offers a range of benefits, including increased transparency and solubility, there has been increasing debate over the potential health risks posed by some of the engineered nanoparticles

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currently being incorporated into an array of cosmetic products[4]. While health concerns are not in themselves unique to the cosmetics sector[5], the direct application of cosmetic and personal care products onto the human body, and the general lack of pre-market authorisation requirements for these products, has prompted an increasing number of stakeholders to express their unease over the potential health effects of some nanotechnology-based cosmetics[6]. This is despite the fact that these products are subject to regulatory controls within every jurisdiction in which they are sold.

The effectiveness of regulatory frameworks is increasingly being questioned in terms of their adequacy to safeguard human and environmental health and safety against any potential risks posed by nanotechnologies. This article examines the varying regulatory approaches being employed within three jurisdictions to protect consumers against potential risks posed by one particular class of engineered nanomaterial when used in cosmetics products, specifically nanoscale metal oxides. This family of nanoparticles, which are increasingly being used in make up formulations and sunscreens, are of particular interest to risk assessors, regulators and industry at this time, after the European Commission's (EC) Scientific Committee on Consumer Products (SCCP) expressed their concern over the use of insoluble nanoparticles in topically applied cosmetic products[7].

Their specific concerns, and that of a range of other commentators, relate to the lack of scientifically sound data on:

1. the ability of insoluble nanoparticles to penetrate the stratum corneum, pass into the viable epidermis and enter the vascular system, and
2. the potential consequence, in terms of hazards, should absorption and translocation occur[8].

Questions have also been raised in relation to the adequacy of conventional safety assessment methods for cosmetic ingredients, and the appropriateness of these risk assessment paradigms for insoluble nanomaterials being used in cosmetics[9]. In contrast, soluble nanoparticles, such as biodegradable polymeric nanoparticles[10] which are being increasingly employed as carrier/delivery systems to transport lipophilic drugs across the skin barrier and into the skin[11] appear unlikely to present any new risks to human health[12]. As such, their use in cosmetic products has to date received less attention in the debates.

With the scope of regulatory regimes varying significantly between jurisdictions, this article will focus on the use of metal oxide nanoparticles within cosmetic products and the adequacy of regulatory regimes in three jurisdictions. Cosmetics, such as make up formulations, do not claim to offer a therapeutic benefit, and are therefore used for the primary purpose of modifying the wearer's physical appearance. Such products should not therefore pose any risks to their wearer, and as such, risk/benefit analysis should not be required. This can be contrasted to, for example, topically applied products used primarily for a therapeutic or medicinal purpose, such as sunscreening products. As such, sunscreens will not be considered within the scope of this article, despite being defined as a cosmetic product within some jurisdictions. The relevant regulatory regimes for cosmetics will be assessed and compared within Australia, the

European Union (EU), and the United States (US). Our focus on these three jurisdictions is in part due to the EU and the US being two of the world's largest markets for cosmetics, and in part to the particularly proactive approach taken by government, regulatory agencies, and other stakeholders in these jurisdictions in relation to nanotechnology-related regulatory and policy activities. Within these jurisdictions, for example, a number of government and independent regulatory reviews have already been undertaken, with several of these reviews having already assessed the adequacy of the relevant regulatory frameworks for cosmetics as part of their scope. This article does not therefore seek to re-examine the relevant frameworks per se. Rather, the aim of this article is to draw upon the insights and conclusions of each of the reviews in a comparative manner so as to enable us to review which regulatory regime appears to be the best equipped to deal with the additional challenges posed by these products. It is argued that by highlighting the inherent strengths and weaknesses of these regimes at this time, regulators and governments may take prudent steps so as to address any shortcomings within their own analogous regulatory regimes.

This article is structured as follows. Part II of the article provides an overview of how the cosmetic industry is not only using nanotechnologies to improve existing products, and create superior new products designed to meet the market's needs. A succinct review of the current scientific debate on potential risks posed by metal oxide nanoparticles in topically applied products is provided in Part III. By focusing on several of the most relevant and significant regulatory reviews to date within Australia, the EU and the US, Part IV of the article provides an overview of the current regulatory frameworks for cosmetics within each of the jurisdictions. An assessment of the effectiveness of the current regimes is provided in Part V. The article concludes by arguing that in the absence of firm scientific conclusions as to the safety of nanoparticles in the cosmetic industry, inevitably definitive regulatory frameworks cannot be constructed at this moment. However, given the need to respond quickly should concerns arise in the future (whether near or not), it would already seem worthwhile to provide for regulatory hooks for nanoparticles in the existing legislation, rather than having to conjure a regulatory response form scratch if and when the risks were to be realised.

2. Cosmetics Formulations and Engineered Nanoparticles: Small Ingredients in a Growing Market

As consumer demand for cosmetic and personal care products continues to grow[13], industry has shown considerable interest in developing a range of superior and novel products that improve the skin's appearance and health[14]. Cosmetic products, such as make up products, are typically topical formulations applied to the stratum corneum, the outermost layer of the epidermis. The stratum corneum, which measures between 10-20μm[15], acts as the body's primary protective barrier, preventing water loss as well as the penetration of foreign molecules, including

among other things, cosmetics and drugs[16]. As noted by Moser et al. these '*barrier properties are based on the specific content and composition of the stratum corneum lipids and, in particular, the exceptional structural arrangements of the intercellular lipid matrix and the lipid envelope surrounding the cells*'[17]. Topically applied chemicals may however penetrate the intact stratum corneum and pass through the skin via passive diffusion, or by way of the follicular pathways or sweat glands[18]. The degree of absorption of any such substance will be dependent however on its physio-chemical characteristics[19].

As noted above, one of the early beneficiaries of nanotechnology advances within the cosmetic sector appears to have been make-up compositions[20], which are topically applied to the skin in order to modify the wearer's physical appearance[21]. These products, which may be purchased in the form of lotions, creams, gels and powders, are typically comprised of oil-in-water (o/w) or water-in-oil (w/o) emulsions[22], which are then applied or rubbed into the skin's surface. Principle considerations for all cosmetic formulations, including makeup, include high spreadability, being aesthetically pleasing, having high stability, while being non-irritating to the skin[23]. Importantly while these products are, in general, formulated to stay on the outer layer of the skin, nominal penetration of the stratum corneum may occur[24] regardless of whether or not the formulation incorporates nanoparticles.

Development of cosmetic products that are more visually pleasing, superior colouring, enhanced ease of spreading, and are of a higher quality improves their acceptability to consumers, which in turn increases product sales. To achieve these aims, research within the cosmetic industry has focused not only on developing new products, but also on reformulating and improving existing products. Developments within the cosmetic field have until recently focused on the use of micronized pigment particles within, for example, make-up formulations. However, advances in nanotechnology have more recently enabled manufacturers to mill down particles to the nanoscale (nanopigments); these nanopigments, with a typical diameter of 20nm-200nm[25], are now being incorporated into some formulations. While companies such as Advanced Nano have, for example, focused on using aluminium oxide (alumina) nanoparticles for inclusion in make-up products[26] a range of inorganic and organic nanopigments may be used for this purpose, including calcium silicate (Ca_2SiO_3), carbon black (C) and bismuth oxychloride (BiOCl). Companies have however, to date, primarily opted to incorporate metal oxide nanoparticles into their make-up formulations, specifically titanium dioxide (TiO_2), zinc oxide (ZnO), and iron oxide (Fe_2O_3) due to their ultraviolet (UV) radiation filtering properties[27].

3. Facing Up to the Uncertainty

As outlined above, the use of nanoscale metal oxides within topically applied cosmetic and therapeutic goods has not been without controversy[28]. Of particular concern has been the potential for these metal oxide nanoparticles to penetrate the

stratum corneum and pass into the viable epidermis or dermis, and enter the vascular system[29]. At this early stage it is not known whether these nanoscale particles may pass into the living cells, and if so, under what conditions[30]. Questions over the ability of the insoluble particles to penetrate not only healthy but also physiologically compromised (unhealthy) skin[31] and translocate into viable cells, and the subsequent potential toxicity of these particles have also been raised[32]. In their Opinion, the SCCP believe that '*it [is] necessary to review the safety of nanosized TiO_2 in the light of recent information and to consider the influence of physiologically abnormal skin and the possible impact of mechanical action on skin penetration*'[33]. Moreover, due to the limited publicly available toxicological and ecotoxicological data currently available on these nanoscale materials[34], it is the potential acute and chronic health and safety implications of nanoparticle skin penetration are currently unknown[35].

This view may however be contrasted to that of Therapeutic Goods Administration (TGA), Australia's therapeutic regulator, which in 2006 undertook a review of the scientific literature on the safety of nanoscale titanium dioxide and zinc oxide in sunscreens[36]. While the focus of their review was on sunscreening products, their findings are relevant for the purposes of this chapter. After reviewing twenty four studies, the TGA concluded that '*there is evidence from isolated cell experiments that ZnO and TiO_2 can induce free radical formation in the presence of light and that this may damage these cells (photo-mutagenicity with ZnO). However, this would only be of concern in people using sunscreens if the ZnO and TiO_2 penetrated into viable skin cells*'[37]. Despite a number of limitations related to these studies, the TGA went on to conclude that '*there is no evidence that sunscreens containing these materials pose any risk to the people using them*'[38]. This conclusion has been subsequently supported by leading scientists such as Nohynek et al.[39].

While it should therefore be safe to assume that commercially available cosmetic products incorporating metal oxide nanoparticles are safe when used for the purpose for which they were intended, or under reasonably foreseeable circumstances, the reality would appear to be somewhat ambiguous at this time. Further uncertainty exists in relation to the appropriateness of the conventional risk assessment paradigms used to evaluate potential risks[40]. The European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has stated, for instance, that focus on mass '*rather than particle size [this] may severely underestimate the potential contribution of nanoparticles to overall risk posed by the substance*'[41]. Moreover, in their Opinion on Safety of Nanomaterials in Cosmetic Products, the SCCP suggested that for risk assessment purposes, information on a more comprehensive range of physical and chemical properties, such as shape, surface area, charge and chemistry, may be required[42].

Given that cosmetic products containing these types of engineered nanoparticles have already made their way onto the global market, it is not surprising that a number of commentators have questioned the adequacy of current frameworks to regulate this class of engineered nanoparticle when used as an ingredient in topically applied products such as make up.

4. Regulating Nano-Cosmetics: A Comparative Perspective of the Adequacy of Current Regimes to Regulate Cosmetics Containing Insoluble Nanoparticles

In order to assist in safeguarding public health, cosmetics are regulated by governments around the world. Put simply, the manner and form of the regulatory framework varies between jurisdictions. In Australia, for example, the active ingredients found in cosmetic formulations are generally considered to be an 'industrial chemical', and therefore fall under the regulatory scope of the National Industry Chemical Notification and Assessment Scheme (NICNAS). In contrast, within the EU cosmetics are regulated under a *sui generis* system, as governed by Council Directive 76/768 EEC of 27 July 1976 (the Cosmetics Directive or Directive). This Directive consists of a '*patchwork of more than 45 amendments with no set of definitions and no coherent terminology*'[43]. This can be compared to the US, where, pursuant to the Federal Food, Drug and Cosmetic Act, cosmetics fall under the regulatory scope of the Food and Drug Administration. Despite the differences in the regimes, each will be triggered in varying ways by virtue of a product being defined as a cosmetic product under the relevant Acts, whether or not they contain nanoparticles.

By building on a number of regulatory reviews that have been undertaken in relation to nanotechnologies over the last few years, the purpose of this section is to examine the relative effectiveness of the three regimes when faced with cosmetic products containing insoluble metal oxide nanoparticles. It is argued that a number of relevant lessons may be learnt from such a comparative analysis, including the potential consequences of retaining the regulatory status quo in light of the current scientific uncertainties.

Australia

The most relevant review of Australia's regulations to date for the purposes of this article is that which was undertaken by Ludlow, Bowman and Hodge[44]. Commissioned by the Commonwealth Department of Industry, Tourism and Resources, the primary objective of the review was to assess '… Australia's existing regulatory frameworks to determine if, and under what conditions, nanotechnology-based materials, products and applications, and their manufacture, use and handling, are covered by the existing regulatory frameworks'[45].

Pursuant to s.7 of the Industrial Chemicals (Notification and Assessment Act) 1989, active ingredients in cosmetics imported or manufactured in Australia will generally be considered to be industrial chemicals, and fall under the regulatory scope of the National Industrial Chemical Notification and Assessment Scheme (NICNAS). Ludlow, Bowman and Hodge found that NICNAS exercised control over industry chemicals, including those used in cosmetics, through the listing of chemical substances on a so-called positive list – the Australia Inventory of Chemical Substances (AICS). Importantly the AICS, which operates as 'the legal device that distinguishes new from existing chemicals'[46] differentiates substances on the basis of their chemical formula (based on CAS number) and not their size. With over 30000 chemicals already listed on the AICS, it is unlikely at this time that the

insoluble nanoparticles ingredients in cosmetic formulations will not already be included on the AICS. As such, where a chemical substance such as, for example, TiO_2 is already listed as a chemical on the AICS, it will be deemed to be an 'existing chemical' and may be incorporated into an enormous range of products without, in most instance, triggering further regulatory oversight. The consequence of this is that the regime does not establish any pre-market registration, approval or review requirements for determining the safety of a cosmetic product prior to its entry onto the Australian market where the active ingredients of the cosmetic are considered to be 'existing chemicals'.

The review noted however that '*where the circumstances change in relation to a new or existing chemical that has been previously assessed under the Act, the chemical may be reassessed for hazards under the Secondary Notification provisions of the Act. The changes in circumstances include, for example, that 'the function or use of the chemical has changed, or is likely to change, significantly;...*'[47]. Hence NICNAS may have the legislative power to obtain additional scientific data relating to chemical substances which have been reformulated at the nanoscale and used or is likely to be used in such a way that is different or significantly different from the purpose it was assessed for. However these provisions wouyld seem unlikely to have much traction specifically in relation to cosmetics which have been reformulated to contain nanoscale metal oxide particles, as opposed to macro or micro sized particles of the same chemical substance. In such instances it would appear difficult for the regulator to argue that the '*function or use of the industrial chemical has changed, or is likely to change, significantly;...*' (s 62(2)(a) IC(NA) Act) so as to warrant secondary notification.

The NICNAS may also assess existing chemicals under its Prior Existing Chemicals Assessment Regime. While the Assessment Regime provides the agency with the legislative power scientifically to assess those chemicals which have been declared to be a 'prior existing chemical' (PEC) by the Minister, this may only occur if there are reasonable grounds on which they believe that the chemical presents a risk to human or environmental health. This would appear to be a significant regulatory threshold to overcome, and one that is likely to be dependent on significant scientific evidence.

Importantly, the review highlighted the fact that even where the regulatory agency collects data, undertakes risks assessments or requires a manufacturer or importer to provide information on industrial chemicals to the agency, '*it is unknown whether the notification and testing methodologies, as established under the IC(NA) Act, will be adequate for assessing the human and/or environmental risks of the new nano-scale industrial chemical*'[48]. This is in part due to the fact that NICNAS is not, under its current practices, to collect physio-chemical data pertaining to, for instance, particles size or surface charge. This 'oversight' has been heavily criticised by Friends of the Earth (FoE), who have argued that '*Australian regulation of nanomaterials in personal care products therefore remains based on the flawed assumption that the toxicity of nanoparticles can be predicted from the known properties of larger-sized particles*'[49].

European Union

There is now an extensive body of literature examining the adequacy of currently regulatory regimes for regulating nanotechnologies within the EU, at both the supranational and national levels. These reviews have canvassed not only regulatory frameworks relating to human health and safety, but also environmental health and safety[50], and several specific areas and applications[51]. While a number of these reviews have included within their scope cosmetic products, the most significant review for the purposes of this article is a recently published report by the European Commission[52].

As noted above, within the EU, cosmetic products are regulated under the Cosmetic Directive, which sets out the legal requirements and principles pertaining to cosmetic products within European Union Member States, and provides the European Commission with overall responsibility over cosmetic products. Unlike the situation in Australia and the US, a range of products with therapeutic benefits, such as sunscreens, are considered to be cosmetics under the Directive, and regulated as such. Enforcement of the transposed legislation is the responsibility of each Member State, with States required to assign this function to a competent agency. The Cosmetics Directive may be considered to be somewhat of a 'living legislative instrument', with procedures in place under which Adaptations to the Annexes and Amendments to the Articles may be made. Adaptations to the Annexes, which reflect the evolving state of scientific and technical knowledge and the opinions of the SCCP. Wholesale changes to the Directive are made through Amendments to the Articles, of which there have been seven to date. Due to the regulatory burden associated with adapting or amending the Cosmetic Directive, the EC recently proposed that the Directive be recast as a Regulation[53]. This would not only 'remove legal uncertainties and inconsistencies'[54], but also curtail the 'divergences in national transposition which doe not contribute to product safety'[55]. With the exact nature and content of the proposed recast is unlikely to be known for some time, this article will focus on the current regulatory regime for cosmetics within the EU, as reviewed by the EC itself and the SCCP.

As noted by the EC, the Directive's principle objective is to safeguarding public health, and does this by placing full responsibility for the product's safety on the person placing the product onto the Community market[56]. To achieve this, the Directive sets out significant information and risk assessment hurdles that must be met by manufacturers/importers/marketers of cosmetics productions within the Community, as well as establishing detailed rules over certain ingredients and their use in cosmetics through the establishment of positive, restricted and prohibited lists. Importantly, substances on these lists are listed, and therefore regulated, on the basis of their chemical identify (name); the lists do not, for example, differentiate between substances of the same chemical formula that differ in size. The EC's review found however that, '*on the basis of the obligation to carry out a risk assessment and the possibility to lay down through implementing legislation detailed conditions of use for certain ingredients, risks in relation to nanomaterials and nanotechnologies can, therefore, in principle be dealt with in an appropriate way*'[57]. This conclusion was reached despite the absence of pre-market registration, approval

or review requirements for determining the safety of a cosmetic product prior to its entry on the market, as well as the agency itself noting a number of so-called 'knowledge gaps' In relation to nanomaterials[58].

United States

While there have now been a number of regulatory reviews undertaken in the US, the most relevant to the regulation of cosmetic products containing nanoparticles, including those incorporating insoluble nanoparticles, have been undertaken by Taylor[59] and the FDA[60] itself. As the agency is responsible for regulating drugs, medical devices, food safety, and cosmetics, Marchant, Sylvester and Abbot suggest that '*nanotechnology is expected to result in the manufacture of several different product categories regulated by the FDA*'[61], including cosmetics.

The effectiveness of the agency's framework for regulating cosmetics generally under the FDCA, and more specifically, cosmetics incorporating nanomaterials, has however already been questioned[62]. While the FoE have argued that the '*USFDA has virtually no authority over cosmetics and personal care products and cannot require manufacturers to conduct safety studies*'[63], Davies notes that, '*the FDC Act gives FDA no explicit authority for pre-market oversight of cosmetic ingredients or cosmetic products. FDA has only the standard post-marketing authorities…*'[64]. The absence of pre-market authorisation for cosmetic products, regardless or whether or not they contain nanoparticles of any form is therefore consistent across the three jurisdictions. However, unlike the situation in Australia and the EU, the FDCA does not establish a so called positive-list under which chemical substances are approved. It is perhaps not surprising therefore that in his review, Davies suggested that, '*although the FDCA has a lot of language devoted to cosmetics, it is not much of an exaggeration to say that cosmetics in the United States are essentially unregulated*'[65]. Looking specifically at cosmetics incorporating engineered nanomaterials, Davies has stated that '*although it would be neater legally and bureaucratically to regulate [nanotechnology] cosmetics under the FDCA, the public would be better protected by regulating cosmetics under some alternative regime*'[66].

The FDA's Nanotechnology Task Force has itself recognised a number of challenges associated with nanotechnology-based products that fall under its regulatory umbrella, including cosmetic formulations incorporating free nanoparticles[67]. While the review did not distinguish between the use of soluble and insoluble nanoparticles in cosmetics (or indeed other product categories), and the challenges thereof, the agency's own review noted the limitations associated with the lack of pre-market authorisation regime, in particular data limitations, as well as the current absence of mandatory post-marketing requirements in the event of an adverse event[68]. The adequacy of conventional risk assessment protocols for evaluating risk was similarly highlighted as an area of concern. The Task Force recommended the development of guidance materials for industry and researchers to overcoming some of these challenges, including '*guidance [material] describing safety issues that manufacturers should consider to ensure that cosmetics made with nanoscale materials are not adulterated*'[69]. The report did not however call for the FDA to be

given additional regulatory authority for products containing nanomaterials, including those products which are currently not subject to any pre-market authorisation processes.

5. Flawless or Fallible?

Nanotechnologies have the potential radically to improve a vast range of cosmetic formulations. While enjoying the benefits of these or indeed of any other cosmetic products, consumers must also be assured of the safety-in use of the product when using the product under normal or reasonably foreseeable conditions. It is for this reason that jurisdictions such as Australia, the EU, and the US have established regulatory regimes for cosmetics that are designed for the purpose of safeguarding public health. The mechanisms under which this overarching objective is obtained do however vary between jurisdictions, as highlighted by Part IV above. For instance, while it would appear that cosmetics are more strictly regulated under the *sui generis* system established by the Cosmetics Directive in the EU when compared to the regimes employed in Australia and the US, this is in part due to the fact that a number of products with therapeutic benefits are defined as cosmetics within the EU, and are regulated as such. In contrast these products, including for example, sunscreens, would generally be defined as a therapeutic good or drug with Australia or the US, and regulated as such. This may include the therapeutic good or drug being subjected to a range of additional regulatory hurdles including, for instance, pre-market authorisation procedures, before being allowed onto the market within either Australia or the US.

With scientific debate continuing over the potential benefits and risks posed by products containing insoluble nanoparticles, this section of the article considers the strengths and weaknesses of the current regulatory regimes in Australia, the EU and the US, and the ability of these frameworks to continue to safeguard the publics' health in relation to nanotechnologies.

By virtue of the existence of the regulatory regimes within each of the three jurisdictions*, prime facie* it is possible to assume that all cosmetic products available in the respective markets are safe and do not pose a risk to the health of the consumer when used for the purpose for which they were manufactured. This assumption should extend to all cosmetic products regardless of whether or not they contain insoluble nanoscale materials or not. Failure to comply with this legislative requirement in any of the three jurisdictions will result in the manufacturer or importer being held to be liable for any damage caused by the unsafe cosmetic product or products. For these reasons alone it is in the industry's best interests to only develop and place onto the market in each jurisdiction cosmetic products that are safe and conform to the requirements of that regulatory regime. But is it really that simple?

On first blush it would appear that despite the absence of pre-market authorisation processes in each of the three jurisdictions, and their differing approaches to regulating cosmetics, it is possible to suggest that if it can be unequivocally proven that insoluble nanoparticles do not penetrate the stratum corneum, – under varying conditions – and

enter the vascular system, or that even if this did occur, that the insoluble particles do not pose any health or safety risk, then the current regimes would appear to be adequate in their current form.

However, current uncertainties over the potential toxicity and exposure pathways of many engineered nanoparticles, including insoluble nanoparticles[70], and the appropriateness of the conventional risk assessment methodologies underpinning each of the regulatory frameworks for insoluble nanomaterials[71] would however suggest that it is not this simple. Moreover, with regulatory agencies in Australia, the EU and the US each lacking authority to undertake pre-market reviews on cosmetic products, the question of potential risks remains.

As outlined in Parts II and III, many manufactures of cosmetic products have begun to substitute microsized metal oxide particles, including TiO_2 and ZnO, with their nanoscale equivalents in order to improve the aesthetic and or functional nature of cosmetic products. Within Australia and the EU, the inclusion of these chemicals on so-called 'positive lists' is further suggestive of the safety-in use of these ingredients as otherwise the manufacturer or importer of the cosmetic products would be in breach of their legislative obligations. However, as noted in Part IV, these lists do not differentiate a chemical on the basis of their size. As such, while TiO_2 and ZnO may be safe when used in a cosmetic product at the macro or micro-scale, their inclusion on a positive list cannot guarantee the safety of the ingredients at the nanoscale. In light of the current gaps in knowledge, it would appear that this regulatory mechanism cannot by itself guarantee the safety of cosmetic products which incorporate insoluble nanoparticles, despite the inclusion of the chemical on the positive list.

While the focus on a chemical's name rather than its size appears problematic in relation to the operation of lists in the regulatory frameworks, so too does the focus of these regimes on a substance's mass for risk assessment purposes. Within the European Union, for example, the process by which the safety is assessed of active ingredients within a cosmetic product is set down in the *SCCP's Notes on Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation* (Guidance Notes)[72], which sets out the evaluation regime for end cosmetic products. While the Guidance Notes apply to all active ingredients contained within a cosmetic product, including nanoscale TiO_2 and ZnO, the basic information requirements for the toxicological dossiers to be evaluated by the SCCP for the purposes of the safety evaluation do not expressly include information pertaining to the size of the chemical ingredient being assessed[73]. Rather, the conventional safety evaluation process, which includes a number of toxicological tests[74], relies primarily on the basis of mass metrics. As noted above, reliance on mass may be inappropriate for assessing the potential risks of some nanomaterials.

While one initial step to address this gap could be, for example, to modify the safety assessment frameworks so as to require additional information and risk assessments to be undertaken on insoluble nanoparticles, this in itself does not address the more fundamental issue – that the current risk assessment methodologies may be in themselves inadequate for assessing the risks posed by these particles due to their primary reliance on mass metrics. With the SCENIHR having concluded that 'current risk assessment methodologies require some modification in order to deal with the

hazards associated with nanotechnology and in particular that existing toxicological and ecotoxicological methods may not be sufficient to address all of the issues arising with nanoparticles'[75], it would appear that until validated *in vivo* and *in vitro* risk assessment methodologies are developed for engineered nanoparticles, including insoluble and bio-persistent nanoparticles, and incorporated into the regulatory framework, the potential for certain commercially available nano-cosmetic products to pose a risk to human safety will continue. While consumers and citizens may be prepared to accept a degree of risk in relation to therapeutic applications, it is argued that consumers should not have to be prepared to accept any level of risk of harm, including minimal risk, in relation to their use of cosmetic products.

With its reference to 'particle size' in the proposed recast of the Cosmetics Directive[76], while falling far short of a nano-specific law, the EU would seem the first major jurisdiction to address nanosized applications directly. This may or may not be linked to the length of time it takes to adopt new European legislation. As such, were specific health and safety risks to be realised, such a response would seem preferable than the EC having to, for example, scramble for a nano-specific regulatory response in the face of a potentially hostile European Parliament (and Council of Ministers, if GMO laws in the EU are anything to go by).

6. Conclusions

Availability and use of cosmetic products incorporating different types of engineered nanoparticles appears destined to increase in the coming years. This in turn will lead to consumers of said nano-cosmetic products being increasingly exposed to a range of soluble and insoluble nanoparticles. In light of the current scientific uncertainties associated with the potential risks of some engineered nanomaterials, including their potential uptake and translocation in the human body and potential toxicity, the aim of this paper was to investigate the adequacy and effectiveness of the different regulatory regimes for regulating cosmetic products which incorporate insoluble nanoparticles, which have been identified as a class of engineered nanoparticles which may give rise to health concerns under certain circumstances.

In examining the currently regulatory frameworks for cosmetics within the three jurisdictions, it was evident that the overarching objective of each regime was to safeguard public health. While legislatures and regulators within each of the three jurisdictions utilised different approaches to achieve this objective, each approach was however underpinned by the legal technique of 'manufacturers liability'. By placing the ultimate responsibility for the product's safety on the person/company placing the product onto the market, it is argued that a strong incentive exists for the industry to place only safe products on the market, regardless of whether or not the product or products contain nanoparticles. It is not surprising therefore that the SCCP recently noted that 'in practice, cosmetic products have rarely been associated with serious health hazards…'. This statement was however qualified as follows: 'which, however, does not mean that cosmetics are safe in use *per se*. Particular

attention is needed for long-term safety aspects, since cosmetic products may be used extensively over a large part of the human lifespan'[77]. This caveat is likely to be of particular relevance to cosmetics incorporating insoluble nanoparticles given the current scientific uncertainties associated with their potential risks.

It is however argued that potentially unsafe cosmetic products may enter the market place in jurisdictions such as the Australia, the EU and the US. This is primarily due to the limited pre-market authorisation procedures, which appear to provide a window of opportunity for 'unsafe' products to enter the market place, despite the best efforts of manufacturers/importer and regulators, and the legal consequences thereof. This argument would appear to hold true in relation to all cosmetic products, whether or not they contain nanoparticles, and in particular, insoluble nanoparticles.

Nonetheless, the very fact that the scientific community is still grappling with the fundamental questions relating to characterising accurately the properties of nanoparticles, determining potential exposure pathways and uptake of nanoparticles especially in relation to abnormal skin, and the potential toxicity of these particles, it would appear that at this time there is a risk of potentially unsafe nanotechnology-based cosmetics unknowingly being placed onto the market. Only when we have greater certainty over the adequacy of conventional risk assessment methodologies for nanoparticles, the ability of nanoparticles to penetrate the skin, enter viable cells and translocate, and the hazards associated with this, will we have a greater understanding of the strengths and weaknesses of the current regimes to safeguard public health. It is fundamental that any regulatory regime is therefore able to evolve and adapt so as to take into account the evolving state of scientific knowledge, and those which are able to evolve quickly are likely to provide a higher level of public safety than those which are not.

That being said, if it can be shown that insoluble nanoparticles do not penetrate the stratum corneum and enter viable cells (and are therefore not translocated around the body) or that even when such an event occurs, the nanoparticles did not pose a risk to the biological system, then the current regulatory regimes in Australia, the EU, and the US, would appear to be adequate for safeguarding the public's health, regardless of the varying regulatory approaches adopted within each of the jurisdictions, and there inherent strengths and weaknesses thereof. Of concern however is that it appears that a definitive answer on this issue will not be reached for some time yet, despite the best efforts of industry, scientists, and regulators. With public opinion and Parliaments holding regulators to much greater scrutiny than ever before, a neat and pre-established regulatory structure, *Bauhaus* fashion, would seem preferable to spaghetti junction type solutions for filling up the potholes.

Notes

[1] Lupo, 2001, p. 467.
[2] Environmental Working Group, 2006, p. 1.
[3] See for instance Scientific Committee on Consumer Products, 2007, p. 13.
[4] Davies, 2006.

[5] See for example Aitken, Creely and Tran, 2004, pp. 51-57; and Maynard et al., 2006, pp. 267-269.
[6] Kimbrell, 2006, pp. 366 and FoE, 2006, p. 2.
[7] SCCP, 2007, p. 5.
[8] See generally Bowman and Fitzharris, 2007, pp. 382-384; Hoet, Bruske-Hohlfeld and Salata 2004, pp. 1-15; Swiss Re, 2004; and Oberdörster, Oberdörster and Oberdörster, 2005, pp.823-839.
[9] SCCP, 2005, p. 2.
[10] Alvarez-Roman et al., 2004, p. 53.
[11] Muller, Mader and Gohla, 2000, pp. 164-171.
[12] SCCP, 2007, p. 5.
[13] Mowad, 2001, p. 188; Euromonitor International, 2007.
[14] Lupo, 2001, p. 467.
[15] Foldvari, 2001, p. 417.
[16] Hadgraft, 2001, p. 1. See also Suhonen, Bouwstra and Urtti, 1999, p. 149; and Morganti et al., 2001, p. 489.
[17] Moser et al., 2001, p. 103.
[18] See Michaels, Chandrasekaran and Shaw, 1975; Morganti et al., 2001, p. 494.
[19] Guterres, Alves and Pohlmann, 2007, p. 149.
[20] SCCP, 2008, p. 12-15.
[21] Cunningham, 1996, p. 149.
[22] Tadros, 1992, p. 94.
[23] Tadros, 1992, p. 94; Lupo, 2001, p. 471; Moranti et al., 2001, p. 496.
[24] In relation to the topical application of sunscreen and subsequent skin penetration, some secondary systemic exposure is also likely. See Cross et al., 2007.
[25] Cross et al., 2007.
[26] Advanced Nanotechnology Limited, *Products*, 2007.
[27] Nohynek et al., 2007, p. 254; Hoet, Bruske-Hohlfeld and Salata, 2004, p. 9.
[28] See generally FoE, 2006, 2007.
[29] Swiss Re, 2004, p. 18; Environmental Working Group, 2006; Tsuji et al., 2006, pp. 44-45.
[30] In their review of the scientific literature relating to the use of nanoscale TiO_2 and ZnO in sunscreens, Australia's Therapeutic Goods Administration concluded that, "There is evidence from isolated cell experiments that ZnO and TiO_2 can induce free radical formation in the presence of light and that this may damage these cells (photo-mutagenicity with ZnO). However, this would only be a concern in people using sunscreens if the ZnO and TiO_2 penetrate into viable skin cells. *The weight of current evidence is that they remain on the surface of the skin and in the outer dead layer (stratum corneum) of the skin*" (emphasis added) (TGA, 2006a, p. 15).
[31] Nohynek et al., 2007.
[32] See for instance Tsuji et al., 2006.
[33] SCCP, 2007, p. 6. See also the Committee's discussion relating to the uptake of nanoscale particles by abnormal skin at p. 27.
[34] See generally Kandlikar et al., 2007; Maynard, 2006; Oberdörster, Stone and Donaldson, 2007.
[35] See SCCP, 2007. This can be contrasted to the views of Nohynek et al., 2007.
[36] TGA, 2006b.
[37] TGA, 2006b, p. 15.
[38] TGA, 2006a, p. 1.
[39] Nohynek et al., 2007, pp. 251-277; and Nohynek, Dufour and Roberts, 2008, pp. 136-139.
[40] Chaudhry, Bouwmeester and Hertel, 2008, Publishing.
[41] SCENIHR, 2006, p. 47.
[42] SCCP, 2007, pp. 35-36.
[43] EC, 2007, p. 2.
[44] Ludlow, Bowman and Hodge, 2007.
[45] Department of Industry Tourism and Resources, 2006, p. 5.
[46] NICNAS, 2005.
[47] Ludlow, Bowman and Hodge, 2007, p. 76.
[48] Ludlow, Bowman and Hodge, 2007, p. 81.
[49] FoE, 2006, p. 15.

[50] Royal Society and Royal Academy of Engineering, 2004; Chaudhry et al., 2006; Chaudhry, George and Watkins, 2007, pp. 212-238; and Fuhr et al, 2006.
[51] Chaudhry, et al., 2008, pp. 241-258; Food Standards Agency, 2006.
[52] EC, 2008a.
[53] EC, 2008a.
[54] EC, 2008a, p. 2.
[55] EC, 2008a, p. 2.
[56] The EC refers to this principles as the "manufacturer's responsibility".
[57] EC, 2008a, p. 17.
[58] EC, 2008a.
[59] Taylor, 2006.
[60] FDA, 2007.
[61] Marchant, Sylvester and Abbott, 2007, pp. 189-211.
[62] Kimbrell, 2006, pp. 329-338; FoE, 2006, and International Centre for Technology Assessment, 2006.
[63] FoE, 2006, p. 15.
[64] Davies, 2006, p. 28. The one exception to this is in relation to colour additives.
[65] Davies, 2006, p. 13.
[66] Davies, 2006, pp. 7-9 and pp. 29-30.
[67] FDA, 2007, pp. iiii, noted that 'the agency's authorities are generally comprehensive for products subject to premarket authorization requirements, such as drugs, biological products, devices and food and color additives, and that these authorities give FDA the ability to obtain detailed scientific information needed to review the safety and, as appropriate, effectiveness of products. For products not subject to premarket authorization requirements, such as dietary supplements, cosmetics, and food ingredients that are generally recognized as safe (GRAS), manufacturers are generally not required to submit data to FDA prior to marketing, and the agency's oversight capacity is less comprehensive'.
[68] FDA, 2007.
[69] FDA, 2007, p. 34.
[70] See Oberdörster et al., 2005, p. 6.
[71] SCCP, 2007, p. 4.
[72] SCCP, 2006. The legal basis for the Guidance Document is provided by the Cosmetic Directive. See in particular Articles 2, 4a1 and 7a(d).
[73] SCCP, 2006. See 3-3 Chemical and Physical Specifications of Cosmetic Ingredients, at p.18.
[74] Including acute toxicity, irritation and corrosivity, skin sensitisation, repeated dose toxicity, mutagenicity/genotoxicity, carcinogenicity, reproductive toxicity, toxicokinetic studies, phot-induced toxicity, and human data testing (SCCP, 2006. See 3-3 Chemical and Physical Specifications of Cosmetic Ingredients, Sections 3-4.1 to 3-4.11)
[75] SCENIHR, 2006, p. 4.
[76] EC, 2008b, pp. 56-59. See, generally Part A, Section 6 of Annex I which states that, 'particular consideration shall be given to any possible impacts on exposure due to particle sizes'.
[77] SCCP, 2006, p. 1.

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