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Chapter 41

One-way Communication...

One of the funny things about writing columns like these is the fact that you write whatever you want to write about but there is hardly any reaction. But when I meet people during my trips all over the world, it is clear that you folks are reading my columns. You may violently disagree (I admit to be as provocative as I can be to get you to jump off your chairs and write to me that "this time I have gone too far") but your level of tolerance is infinite and despite whatever I try, I cannot enthuse you to react. But the point is that you do read what I write. That, in fact, is the power of the written word.

You might be wondering where this is going. I want to talk this time about communication as I have been wondering a lot about this lately. We communicate a lot, we organize conferences and we talk to each other. We fill an enormous amount of cosmetic journals and cosmetic magazines and cosmetic periodicals with our writings that, strangely, are also read by cosmetic people like yourself, but are you buying my products? If we want to sell—and what is the objective of any industry when push comes to shove—should we not be talking to our customer, the user of our products instead of to each other? It is obvious that the marketers of the suppliers talk to their customers, the manufacturing world (ideally the techies), and that the marketers

If we want to sell, should we not be talking to our customer, the user of our products instead of to each other?

of these manufacturing companies talk to our ultimate customer, per definition a non-techie. So, I embarked on a process that is going to make me very unpopular and decided to investigate the effectiveness of one-way communication.

I recently attended the SCS Cosmetic Science Symposium in Chepstow, Wales. Or was it Chepstow, England? The border was somewhere on the grounds of the golf course that surrounded the hotel and even the staff was not sure where the border was. It felt like the perfect place to discuss the boundaries between cosmetics and drugs and "us and them." We, the cosmetic scientists, were of course the good ones, and them, the cosmetic consumer, was the bad one as they were brainwashed by those horrible tabloid journalists. As many of you won't be living in the United Kingdom, I honestly have no idea how well-spread the terminology tabloid is, but it is not a classy newspaper, normally with a sparsely dressed girl on page three and not the front page so that you can walk with that newspaper in public without being caught with your trousers down. It is the newspaper that you and I do not read but is exclusively read by our neighbors. And because we all have neighbors, we are also neighbors to someone else and therefore, we all read these things. Of course, we never look at the page three girls but we carefully read the highly interesting articles that inform us that we should buy natural cosmetics, that chemicals are bad for you, that our products should be chemical-free and if that is not possible, they should be at least fragrance-free, preservative-free and paraben-free. In short, a quality newspaper!

Because you and I are both cosmetic scientists, we know that this is a lot of BS and I do not mean Bible Studies, but a purely organic and 100% natural excrement of a solely plant-fed animal. But where does this excrement come from? It must be from those horrible journalists that write nasty and utterly incorrect pieces about our industry and how you and I do everything wrong. But here I claim that we are wrong ourselves. These holy Bible Studies comes from us! And we love it!

Wait a minute … are we responsible for our own mess? Yes, of course. Let's take the paraben issue as an example. Someone who was trying to sell an alternative to parabens did do a study in which they

showed some oestrogenic activity of a paraben. I will not even go into whether the study was performed right or not, but did you know that with a single piece of sashimi drenched in soy and wasabi, you actually get more oestrogenic activity inside your body than from a life-time use of parabens? Whereas the Japanese happily (and rightly so) continue to enjoy their sashimi and sushi rolls and have continued to produce offspring, we immediately jump the bandwagon of commercial success and decided to ban these products because a scientist with a not-so-hidden objective (to sell his or her alternative to parabens) decided to tell the public press that they were feminized by the outrageous exposure to these very dangerous parabens. Instead of telling the cosmetic world and our cosmetic marketers that someone is talking 100% natural and organically-certified excrement, we allow them to insist on paraben-free products! We give them what they want, and in doing so, indirectly admit that we were wrong for all these years. A comparison with the normal world would be that we should now close zoos, as tigers and lions and snakes could break out of their cages and do us harm. But whereas in the case of these animals, the hazard is high but the exposure is zero, in the case of parabens the exposure is high but the hazard is zero. But in both cases the risk (the product of exposure and hazard) is zero.

You've got an idea about the problem by now. Journalists are not cosmetic scientists and therefore we do not tell them the correct information because they would not understand it anyway. So, they will start looking for themselves because there is a story in the air and it needs to be written. They would like to have the correct information but we are not willing to give it to them, simply because they would not understand. Is it that when you failed everything in school you can still become a journalist? These people are not stupid but sometimes write stupid things simply because we as an industry do not want to give them the correct information. We as cosmetic scientists need to stand up and take the time to explain things to them. Journalists can be our best friends and it is perfectly OK for them to be critical. Even better, you should want them to be critical. If we would start telling these people what we really do to make better products every day, don't you think that they would write differently?

How many journalists for the general public are members of the SCC, the SCS and similar IFSCC-affiliated member societies? I think if only 1% of us cosmetic scientists would care to speak to the general public and explain what we are doing, we could avoid most of the unjustified scare stories that currently dominate the cosmetic public news. Am I alone or are you with me? Is it one-way traffic or will we all drive the same road and in the same direction? You, colleague cosmetic scientists, are all my buddies, but so are journalists. Don't you think it is time to start talking to them instead of ignoring them? Communication is the first step to education. And that is what is needed. Let's talk, let's educate and embrace, maybe in the beginning selected ones, as our friends and companions. Or am I having yet another non-effective one-way communication?

Modified from a column "One-way communication" previously published in *Cosmetics & Toiletries* magazine's Newsletter, May 7, 2008

Chapter 42

Infinitely Big or Infinitely Small?

"It's green and it flies. What is it?" is a typical question that you may get from your four-year old child and you better answer something like a flying cucumber, a jet-engine-fuelled frog or Batman in a disco-outfit although the latter answer is a little bit too old-fashioned and outdated for this age group. If you think, this is a silly opening for a column, hold your breath and try to answer this one: "It is infinitely small and has infinite opportunities. What is it?" I am sure that you, in contrast to the questions asked by your four-year old son or daughter, will immediately know the answer to be nanotechnology. We all know about nanotechnology and we all know that we know nothing about nanotechnology. We all know that it has infinite possibilities but also that there is infinite safety issues associated with it. We all know that we should be working on it in order not to miss this opportunity and we know that we therefore have to call everything mega-small. Mega XXL is out, nano XXXXS is in, is hot and is cool (in teenager language).

What is nanotechnology actually? According to Maynard, "Nanotechnology is a catch-all term for techniques, materials, and devices that operate at the nano-meter scale. Being defined as the design, characterization, production, and application of structures, devices, and systems by controlling shape and size at the nano-scale,

The use of [nanoparticles] does not sound too smart an idea, as they would never reach the viable epidermis, let alone the dermis.

it represents one of the most promising technologies of the 21st century, and has been considered to be a new industrial revolution." Really important therefore, but are we using it in cosmetics? Nohynek et al. write, "Today, nanomaterials are increasingly used in sporting goods, tires, catalysts, electronic components, window sprays, paints, varnishes, coatings, foods, sunscreens, cosmetics, antimicrobial and antifungal preparations and are expected to be increasingly applied to the medical field in diagnosis, imaging, and drug delivery." So, that's good. It is already used in cosmetics and sunscreens. How come I don't recall it? What did I miss while I was comparing the structure of fullerene to a molecularly-sized football?

Nanoparticles are indeed used in cosmetics and particularly in sunscreens and antimicrobial products. "Nanoparticles are a subset of nano-materials, and were defined as single particles with a diameter below 100 nm, although their agglomerates may be larger," according to Maynard. In sunscreens the nanoparticle diameter is normally between 20 nm and 50 nm. Until now, I'd called that ultrafine inorganic sun filters, but obviously that vocabulary is missing out on a new gigantic opportunity. And the opportunity is indeed gigantic. The global production of nanoparticles for sunscreen products was estimated to be approximately 1,000 tons during 2003/2004 and principally consists of titanium dioxide $(TiO2)$ and zinc oxide (ZnO) particles.

Obviously, we use enough but what are then the exact benefits of these nanoparticles over conventionally sized TiO_2 and ZnO? It sounds strange but the benefit is the fact that you cannot see them. "You cannot see it but it works, what is it, Daddy?" "That's my love for you, my little one!" "No wrong, Daddy, that's nanosized zinc oxide!!" I don't have to explain to you that if the particle size of an inorganic sun filter is getting in the order of magnitude of 35 nm, sunscreen formulations are transparent while the nanoparticles are being just still big enough to scatter UV radiation. But one obvious question has been, if the particles are that small, do these particles then penetrate the skin? The short answer to this question is a simple no, but you are fully right in asking for a little bit more flesh on these bare bones. Gerhard J. Nohynek, Jürgen Lademann, Christele

Ribaud and Micheal S. Roberts recently reviewed all available literature describing skin penetration of sunscreen agents in a magnificent review in *Critical Reviews in Toxicology*, 37: 251-277, 2007, with the beautiful title "*Grey Goo* on the Skin? Nanotechnology, cosmetic and sunscreen safety." They reviewed literally every paper that has been published in this field and reach the same conclusion as I had done by reading roughly half of the papers over the years, namely that nanoparticles will penetrate into the stratum corneum layers of the skin, but will never reach the deeper layers, the viable epidermis, let alone the dermis. I already saw on the web that the next issue of *Skin Physiology and Pharmacology* will contain the sequel to this article and I can't wait to read it. If you can do a sequel to such a long review within a year, it shows that the number of new publications that is emerging in the field of nanotechnology is enormous.

So, in sunscreen technology, the benefit of size reduction is the transparency although too small is also not too good, as you lose the capability to scatter and reflect UV light. But where is nanotechnology used in the rest of cosmetics? I have not really seen it (although some argue that even things like liposomes are now nanotechnology), but if size really matters and therefore, let's say, an antiaging nanoparticle product would penetrate to the same depth as a sunscreen nanoparticle (and that is not beyond the stratum corneum), then the use of such particles for such applications does not sound too smart an idea, as they would never reach the viable epidermis, let alone the dermis, which are exactly the regions where the majority of biologically active ingredients is supposed to work. Of course, other tricks could be thought of to ensure that this would still happen but if I would see nanoparticles being advertised in antiaging products, I would be asking for two different types of evidence. First of all, evidence that it works (and therefore that it penetrates the skin as all available skin penetration evidence indicates the opposite) and secondly, for evidence that there is a benefit of the size reduction, i.e., does a non-nanosized particle not give you exactly the same result? I'm sure that we, cosmetic scientists, will come up with a couple of smart ideas to still get them to penetrate the deeper layers of the skin

but the advantage of that would be that it only happens if we want them to do so.

And if you are still concerned about the potential skin penetration of these particles, read the work of Mike Roberts at the University of Queensland in Brisbane, Australia, that you can find on *www.fda.gov/ohrms/dockets/dockets/06n0107/06n-0107-ts00003-roberts.ppt*. He calculated on theoretical grounds that the skin penetration of 30 nm nanoparticles is in the order of magnitude of 10^{-18} nmol/mL! If the safety hazard is zero (not discussed here but in the review quoted above) and the exposure is zero (as discussed here), then the safety risk has to be zero as well.

Whereas we still need to do a lot more work to fully identify and exploit the opportunities of nanotechnology in cosmetics, simply renaming ultrafine inorganic sun filters as nanosized inorganic sun filters may not be enough. If that is all we do, I have to quote another question to which I could not provide the answer although the questioner, my good friend and former Uniqema colleague Chris Dederen, was much more than four years old when he posed the question: "Is all this nanospeak just meganoise to extract teradollars from the gullible taxpayer or consumer with femtoreturn on investment?" With the benefit of hindsight, let me respond with Special Agent Fox Mulder who said that, "If we fail to anticipate the unforeseen or expect the unexpected in a universe of infinite possibilities, we may find ourselves at the mercy of anyone or anything that cannot be programmed, categorized or easily referenced." We have infinitely big expectations from infinitely small particles. Let's get nanotechnology to work for us in other applications than sun care too.

Modified from a column "Infinitely small or infinite possibilities" previously published in *Cosmetics & Toiletries* magazine's Newsletter, May 20, 2008

Chapter 43

Dry Skin or Skin Cancer, is that the Question?

Everybody recognizes the need for moisturizing your skin. But at the same time, almost every chemical that I have measured in my cosmetic life turned out to be moisturizing human skin. Maybe I was lucky, maybe I was smart and only picked good moisturizing molecules to measure, but I often jokingly said that if I would grind up the hard disc of my computer, even that would moisturize my skin. From this you could conclude that moisturizing human skin would and should be easy.

That was exactly one of my problems when I wanted to select my benchmark chemicals, a positive and a negative control for skin moisturization. As everything moisturizes human skin, what do you select as the negative control? The only thing needing moisturization was human skin itself, so I chose untreated skin as a negative control and glycerin as a positive control. I applied a product and expressed the result of that as a relative performance moisturization (RPM) where untreated skin had value of 0% and glycerin-treated skin a value of 100%. Measured at 6 hours, the worst moisturizer of all chemicals tested turned out to be water!

Water and glycerin are interesting molecules if you talk about skin moisturization. We have buckets full of water within our

Let's do our science properly and completely before we come up with new claims and completely confuse ourselves, our regulatory bodies and our consumers.

bodies that stay inside our body thanks to an efficient barrier called the stratum corneum. But the barrier itself dries out towards the surface as the environment is significantly less moist than the inside of our bodies. We keep it moisturized via the production of the natural moisturizing factor (NMF) which is a mixture of amino acids, urea, lactate and other polar hygroscopic molecules. One of the most hygroscopic molecules is glycerin, but that is not part of the NMF. This is something we apply in large quantities in cosmetic products to give back to our skin its youthful appearance, and allowing it to be flexible. We have to apply it from the outside as there is no "natural" glycerine present within the skin.

That is what we thought until we realized that the phospholipids that are present in the cell membranes of actively proliferating keratinocytes are broken down during the transformation of these cells to terminally differentiated keratinocytes and glycerin is left over. This glycerin will penetrate into the cells and act as a skin moisturizer. But what regulates uptake of glycerin into cells? Aquaporins.

Aquaporins is a word that is underlined with red wriggles in my Word documents. Bill Gates therefore does not know what it means. And with him many consumers of cosmetic products! It might be even new for you but you are excused. In the second edition of "Dry Skin and Moisturizers – Chemistry and Function" of Marie Lodén and Howard Maibach published in 2006, there are only two references in the index to aquaporin-3, the epidermal water/glycerol transporter. In a very recent article in the *Journal of Investigative Dermatology* (Mariko Hara-Chikuma and Alan S. Verkman, Roles of Aquaporin-3 in the Epidermis, *J. Invest. Dermatol.*, 128 (2008) 2145-2151), aquaporin-3 (AQP-3) is being reviewed and we learn that it is involved in skin hydration, wound healing and skin tumorigenesis.

By comparing skin hydration levels of normal mice and AQP-3 knockout mice, it is obvious that the skin of mice lacking AQP-3 is very dry and not elastic. Interestingly, if you measure the level of glycerin, also these levels are significantly reduced in the absence of AQP-3. In short, AQP-3 is good for you and we have seen the emergence of new cosmetic ingredients that that stimulate AQP-3 expression, which (should) result in more skin hydration.

In wound healing, it was observed that wounds in AQP-3 deficient mice healed significantly slower due to the role of AQP-3 in the proliferation of keratinocytes during wound healing but its involvement in skin tumorigenesis is the one that makes you raise your eyebrows. It was shown that AQP-3 was strongly over-expressed in basal cells in human skin squamous cell carcinomas. Moreover, AQP-3 knock-out mice do not develop skin tumors following exposure to a tumor initiator and phorbol ester promoter, a well-established multistage carcinogenesis model. Subsequently, in May 2008 Alan Verkman published, "A cautionary note on cosmetics containing ingredients that increase aquaporin-3 expression" (*Experimental Dermatology*, 17 (2008) 871-872), in which he states that "Though the available data show prevention of skin tumorigenesis with AQP-3 deletion, it is not unreasonable to postulate an increased propensity for tumor formation when AQP-3 expression is up-regulated. Further studies are thus indicated in testing the relation between epidermal AQP-3 up-regulation and skin tumorigenesis as well as epidemiological evaluation of the incidence of squamous cell carcinomas and other skin cancers in subjects using cosmetics containing AQP-3 expression-enhancing ingredients."

While Verkman is right in what he says, we are dealing here of course with the famous question of what was first, the chicken or the egg. If there is more AQP-3 in basal squamous cell carcinoma, this does not automatically mean that increased AQP-3 levels lead to basal squamous cell carcinoma. Every cow is an animal but not every animal is a cow. Having money makes many people happy, but that does not mean that you can only be happy if you have money. Squamous cell carcinoma is associated with increased AQP-3 but that does not automatically mean that increased AQP-3 leads to more squamous cell carcinoma. It could, as Verkman says, and therefore we agree that we need to be careful and investigate. He then continues: "Perhaps, cosmetic testing in animals, which has fallen into disfavor among cosmetic companies and regulatory agencies, should be reinstituted at least in selected cases such as this." Although very controversial, I prefer this reaction over the advertisement that I saw for a product on the internet as a "*moisturizer that allows the body to*

produce approximately 50% less AQP-3" (claiming that it makes your skin more resistant against cancer would clearly be medical claim, but I wonder how well this moisturizer moisturizes human skin).

Let's do our science properly and completely before we come up with new claims and completely confuse ourselves, our regulatory bodies and our consumers. By coming out too early with nonsense claims, we run the risk of missing out on great product opportunities as we will have turned the public opinion against a new technology before we even mastered it as is happening right now with nanotechnology. Will we ever learn to keep our mouths shut while we do our investigations? That question, right now, is equally difficult to answer as whether down- or up-regulation of aquaporins leads to dry skin or skin cancer, but those questions definitely need a technical answer before our marketers get involved.

Modified from a column "Opening the watersheds" previously published in *Cosmetics & Toiletries* magazine's Newsletter, June 27, 2008

Chapter 44

Really, It's All About Sex!

With these opening words, a marketing colleague of mine once opened his speech to our senior management and he was right in two aspects. Yes, it is really all about sex, and yes, he had grabbed their attention in the same way as I now have yours. And if not, you can still claim to be senior management and needing to think more about this. Actually, what my marketing colleague did say—to quote him correctly—is that in our personal care industry, "We were all working in the sex industry."

Although I hate to admit this to a marketing guy, he was actually right! The cosmetic industry is an industry that helps people to look good. From a purely evolutionary point of view, our only purpose in life is to produce offspring, something that can be done rather clinically via in vitro fertilization but just like the modern user of cosmetics, most people prefer the natural (but not necessarily safer!) way of creating offspring. But, again I stress to be speaking in purely evolutionary terms, before a man would decide to separate from his precious sperm, he will carefully evaluate whether his offspring will be well off with his new children's mother-to-be. Whereas the modern man could ask for a genetic footprint of the lady in question before making up his mind, the early

Sex hormones definitely play a role in skin moisturization and even in the lab with our NIR equipment we could prove that it is!

hominid hunters that once inhabited the plains of what is now northern Kenya around Lake Turkana did have neither the time nor the technology. The place nowadays is a perfect breeding ground for the Nile crocodile, the hippopotamus and a variety of venomous snakes and I guess the situation was not much better 1.8 million years ago. All our hominid hunters could rely on was their instinct and that simply had to be good. If a woman had a symmetrical face, she was well built and if she had the right proportions, she should be able to carry a child, give birth to it and survive, and nurse and raise it. So beauty was simply essential for staying alive.

But of course, I need to have a point in my columns and my regular readers know that there always is one. This one is actually quite dramatic. I will try to link bodily beauty to our sex hormones but beware! You might be in for some disturbing surprises!

For years I have been investigating skin moisturization, placing my Corneometer on more or less every surface I could put my hands on. I measured neat raw materials applied to female and sometimes male skin; I measured formulations and even the influence of production procedures (such as the influence of droplet size) on skin moisturization. The conclusion was a bit worrying. Almost everything turned out to moisturize human skin.

But we know that there is a distinct correlation between beauty and skin moisturization. If everything moisturizes human skin, we should all be less wrinkly and there should not be a problem in finding partners. Aagh, but there you forget to think evolutionary. Most women produce their offspring before they get wrinkly, so anti-aging cosmetics and being beautiful when you are past your sell-by date is—again, I stress this—from an evolutionary point of view a waste of your time and money. Your productive life is over when you hit menopause (although, to please my female readership, a new phase in life is starting where you, female human beings, are different from any other animal species in this world, in caring for our own children that go through childbirth and help them out with the upbringing of their children).

Lots of stuff on evolutionary biology but no cosmetic science, so let me now discuss some skin moisturization experiments I used to

do with near infrared spectroscopy. My colleagues and I were able to measure water in the skin noninvasively but we found that there was a link with some other peaks that we had not yet identified. Because one was more dominant in all spectra originating from men and another was more dominant in all spectra obtained on women, we ordered some estrogen and testosterone and measured these chemicals. Low and behold, the peak more prominent in the spectra of the male volunteers coincided with the peak of testosterone whereas the peak more prominent in the spectra of the female volunteers coincided with that of estrogen. But remember that we were interested in water in the skin and not primarily in sex hormones levels. That changed when we tried to correlate the presence and surface area of the water peak to that of other peaks. We found that in men there was a good correlation between his estrogen levels and the amount of water in his skin (especially for the non-smokers), whereas the correlation with his testosterone levels was reasonable at best. Sorry blokes, your femininity determines your skin hydration levels and your skin hydration levels subsequently determine amongst others how well you look. If you smoke, your testosterone levels go up and your estrogen levels go down and your skin gets worse by roughly 15 years. For women, the picture was very different. Their water levels in the skin correlated reasonably with their estrogen levels (but the correlation was not as high as for men). But strangely enough, the correlation with testosterone was completely absent: Diddly squat, *niente*, zero! In evolutionary terms, women never liked the macho guys. A little bit of feminism in a man is good, as it ensures women that he will not go crazy and try to kill that lion in front of his male friends. The ancient women preferred to have a caring bloke that would defend his family over a guy trying to impress his friends. But it also explained why women have their sell-by date at menopause. When this hits, estrogen levels hit rock bottom and skin moisturization goes out of the window. Wrinkles emerge. Why? You don't need your perfect skin any longer. Why? You can't have children any longer anyway, so your body is no longer wasting its energy on looking good. Your body shape is changing and your body is preparing for the time that you have to spoil the grandchildren.

Sex hormones definitely play a role in skin moisturization but the title of this column is that it is really all about sex. And even in the lab with our NIR equipment we could prove that it is! How? We also measured seven pregnant ladies in the laboratory; there must have been something in the water at that time. And water they had! These lovely ladies must have had the best moisturized skin we ever measured. Strangely enough, their water levels were not correlated to their estrogen levels (like in men or to some extent in non-pregnant women), nor to the levels of testosterone, but to the ratio of estrogen over testosterone.

So, finally I am there. The best skin moisturizer turns out to be sperm that gets you, pre-menopausal ladies, pregnant. Really, it's all about sex. But as a bloke, I will never get pregnant and I will never look as good as a pregnant lady. All I can do is keep on using cosmetic products to look better. All I can do is dream; after all, it's all about sex, or to be more accurate sex hormones!

Modified from a column "It's all about sex" previously published in *Cosmetics & Toiletries* magazine's Newsletter, July 19 2008

Chapter 45

All That is Good is Bad...

Picture this. It is summer 2008 and the Wiechers family is going on holidays by car to Spain. Having left Gouda, Netherlands, early in the morning, we spend the night in Limoges somewhere in the middle of France. In the morning of our second day, we soon see signs to Sarlat, a beautiful little French town in the Dordogne where we spent our holidays a couple of years back. One evening in Sarlat in 2004, we strolled through the medieval town after a good meal with *fois gras* and a beautiful local wine (my wife is a vegetarian and does not drink any alcohol, so I had double portions of both; we're indeed a perfect match) and we ran into a couple of folk musicians that played in the streets of Sarlat lit by candlelight. The group was called Paris-Londres as the violin-playing lady Sophie Read is originally from London and the guitar-playing and singing troubadour Bruno Vatys is originally from Paris. One particular song struck us as very beautiful and we listened for more than one hour, which in the busy holiday schedules of the Wiechers' family is actually quite a long time. But hey, that is why it is called holidays.

No, I am not paid by the French tourist board in an attempt to attract more cosmetic scientists to the Dordogne Valley although I can highly recommend it. Until now, the story so far only cost me money as we decided to buy their

More absurd, how can 35-day-old pig skins mimic the skin of menopausal ladies suffering from cellulite?

then latest CD of this folk group called *Dans un pré*. So, when we saw the town Sarlat signposted on our way to Spain, I grabbed that CD to relive the memories as we had already done so many times. As every other time, the whole family and I were waiting for track 4, the song that we listened to three times that evening in Sarlat. It's called "La Santé (Health)" in which Bruno declares that he loves sausages, beer and strong coffees. Worse, he also loves cigarettes, Bourgogne wines and French fries much more than apples or a liter of milk. Health, as he concludes, is actually not very complicated at all, all that is good is bad. I admit that it sounds rather banal but in French, especially in their grammatically incorrect way, it sounds enchanting: *La santé, c'est pas compliqué, tout ce qui est bon est mauvais* … .

As always, you are wondering what this has got to do with cosmetic science. I know from feedback that I received on an earlier column in which I described how I improved my analytical knowledge during my holidays by reading forensic pathology novels of Patricia Cornwell, that you love to hear what I am doing during my holidays, but do *fois gras*, beautiful local wine and health fit in the same sentence as Paris-Londres wants us to believe? And moreover, what has it got to do with cosmetic science?

In case you had very bad holidays (or a very good memory or desperately need your next holidays), you may remember that I wrote last time how my colleague and I could measure testosterone and estrogen in your skin and link it to skin moisturization. Using the same technique, we were able to show that the skin of people that smoke is on average about 15 years older than that of their non-smoking counterparts. *Tout ce qui est bon est mauvais*, all that is good is bad … .

People love to do all that God has forbidden. At least that is what they like to do in the Netherlands but considering the number of tourists coming to Amsterdam every year, they like it just as much anywhere else. We all love meat, fat, sugar, alcohol and sun, sex and the beach. Meat has cholesterol and fat which is not good for you. Most fat is saturated and certainly not the good conjugated linoleic acid that we put in our cosmetic products. Sugar can act as a skin moisturizer but is normally adding more carbohydrates than water.

Sun is so bad that we need to protect ourselves from its UV radiation with large SPFs! Sex, I already discussed last time when I said that our industry is all about sex. And all these oh so joyful but horrible things take place on the beach, so our preferences are not only a Sodom and Gomorra for our health as Paris-Londres says but also for our beauty. After all, beauty is the ultimate outcome of good health, also in evolutionary biology.

While we are passing the exit to Sarlat on our way to Spain, this is all running through my brain as cocaine running through my cerebral vein and I am asking myself how bad Bruno's preferences really are for my health and my beauty. Have people been making this up or is there really some benefit to be obtained from all that God has forbidden? I therefore decided to have a look in the very recent scientific literature (abstracts that popped up in my inbox only last week as electronic alerts) about what is said about the cosmetic effects of all that God forbids.

The first article I found was entitled "Sun protection by red wine?" (For an abstract: *http://www3.interscience.wiley.com/journal/121358652/abstract?CRETRY=1&SRETRY=0*.) Although I must admit, being a rather weak individual that needs every argument to convince his non-drinking wife that he needs his daily portion of the magic red elixir, I read with interest that 15 healthy male physicians (probably equally weak individuals married to equally strong non-drinking wives) participated in an investigation in which wine was applied to their back under occlusion as well as 12% alcohol. The systemic effect was tested by ultraviolet irradiation immediately prior to oral intake. What was the result? There are no topical effects and 'wine baths' will not have any sun protective properties. A significant rise of the MED following oral intake of the wine with the highest level of polyphenols content, however, might be due to these substances. The authors conclude that further research is needed to clarify the role of polyphenols content, dose and duration of wine consumption. Needless to say that Bruno Vatys and myself have already contacted the authors to participate in the next trial. We're even willing to sign two Informed Consent Forms to get double portions!

The second article I found this week on the topic of what God forbid dealt with was, "The effect of topical caffeine on the morphology of swine hypodermis as measured by ultrasound" (see: *http://www3.interscience.wiley.com/journal/121371172/abstract*). This is a rather bizarre study in which 35-day-old pigs received to their dorsal skin gel, gel plus ultrasound, gel plus 5% w/w caffeine, and gel plus caffeine plus ultrasound daily for 15 days. A fifth area receiving no topical application served as control. The authors found that ultrasound treatment was only effective in increasing the cutaneous permeation of caffeine, as evidenced by the reduction in thickness of the hypodermis and number of adipocytes. Why do I think this study is bizarre? First of all, they use ultrasound to enhance the topical penetration of caffeine which is often used as a model penetrant in skin delivery studies because of its ease of skin penetration and they need ultrasound to get it in. Thirty-five days old pigs must have very tough skins! More absurd, how can 35-day-old pig skins mimic the skin of menopausal ladies suffering from cellulite? After all, they call it orange skin but maybe it is really behaving like pig skin! But as I am not suffering from cellulite, I continue to take my coffee black, just like my good friend Bruno Vatys takes his double espressos, but I am starting to wonder whether my wife should continue to drink her coffee caffeine-free. Maybe I should give her an ultrasound machine for her next birthday instead of the espresso machine that I would like her to have for some obscure personal reasons!

The third and last article I found last week has the intriguing title of "Passive cigarette smoke exposure inhibits ultraviolet B-induced skin tumors in SKH-1 hairless mice by blocking the nuclear factor kappa B signaling pathway." (Available at: *www3.interscience.wiley.com/journal/120174231/abstract?CRETRY=1&SRETRY=0*).

In this study, the investigators subjected groups of mice to one of the following treatments: control, smoke (the equivalent of 40 cigarettes a day for 20 weeks), UV (0.1 J/cm2 of UVB five times a week for 20 weeks), or smoke and UV. Oxidative DNA damage was investigated and it could be shown that while UVB exposure resulted in an average of four squamous cell carcinomas (SCC) and 15 smaller papillomas per mouse, exposing the mice to both UVB and passive

cigarette smoke completely prevented SCC formation and averaged less than one small papilloma per mouse. Well Bruno, there you have it my friend, passive cigarette smoking prevents UVB-induced SCC in mice and dramatically reduces the incidence of non-malignant papillomas by altering the NF-κB signaling pathway of tumorigenesis!

I should stop, but I would like you to know that I did have some great holidays. I drank plenty of wine in the shade after having had my coffee in the morning whilst the neighbors in the adjacent mobile home smoked their 40 cigarettes a day. Maybe that Bruno Vatys needs to change his chanson and start to sing that all that is bad is good for you (and your beauty)! If you see Paris-Londres in Sarlat, give Bruno Vatys my regards, a bottle of wine and a cigarette to his lovely wife Sophie Read, the English violin-playing lady! To listen to their beautiful blues and country music, visit www.paris-londres.com, click *entrez*, click albums and enjoy (it's all in French but *c'est la plus belle langue, n'est ce pas*?). We still enjoy it four years later, so it can't be that bad and look at my excellent skin! Bruno and Sophie, maybe not all that's good is bad.

Modified from a column "All that is good is bad" previously published in *Cosmetics & Toiletries* magazine's Newsletter, September 1, 2008

Chapter 46

Much Ado About Nothing...

Yes, I admit. It was my wife's idea to write about nothing. She always has the brilliant ideas in our household but when the topic is nothing, you've got nothing left to argue about. At least that is what I thought until I looked closer into the topic of today's column, the placebo.

We all know what a placebo is, correct? You'll be surprised! Officially, the word "placebo" comes from Psalm 116, verse 9, where it is written (in the Latin version) "*Placebo domino in regione vivorum*" (literally, "I will please the Lord in the land of the living"; also described as "I will walk before the Lord in the land of the living"). These words formed the beginning of what the congregation had to respond to the clergy during the prayer for the dead that was sung at funerals in the Middle Ages. In France, food was provided for the relatives after a funeral and soon it became customary for distant relatives and other, unrelated, parasites to attend the ceremony, simulating great anguish and grief in the hope to obtain their share of food and drink. The latter practice was so widespread that these parasites were soon recognized as the personification of all things useless, and were considered to be archetypical simulators. Because the grief simulators' first collective act was to chant "*Placebo Domino in regione vivorum*,"

What do you do if there is no active ingredients in your formulation? Is everything active?

they were collectively labeled (in French) as either "placebo singers" or "singers of placebo"; they were so labeled because they sang the word "placebo," *not* because they were "choral placaters," using their song to please.

The modern meaning of the word "placebo" has, however, also been surrounded by lamentations. In 1939, the Italian physician Fieschi introduced a technique for patients with angina pectoris in which he blocked two internal mammary arteries so that more oxygen would become available to the heart. Dramatic improvements were seen: three quarters of the patients showed an improvement and one quarter of the patients was cured. Due to this success, this technique became the standard surgery practice for the next 20 years. In 1956, the American surgeon Leonard Cobb had doubts about the technique and decided to check the validity of this intervention by performing two types of surgery. In a group of nine patients, he made the incisions but did not do anything more than that, whereas in a second group of eight patients, he performed the full Fieschi technique. Again, the results were dramatic. Similar improvements were seen in both groups. That was the end of the Fieschi technique and the beginning of the documented surgical placebo effect.

Ever since these days, every decently performed clinical study must be placebo-controlled. In addition, it must be performed double-blind. Both the investigator as well as the subject should not know which treatment is received to eliminate any form of bias, so that we can be completely sure about the true biological effect of a treatment and do not confuse our data by allowing a suggestive component to play a role. This is indeed important as, after all, Henry K. Beecher, in his 1955 paper "The Powerful Placebo," attributed a rough percentage of 30 percent of the overall therapeutic benefit to the placebo effect. And that paper published in *JAMA, the Journal of the American Medical Association*, described medicinal research, and we're working in cosmetics where suggestion is definitely and deliberately a part of the equation!

Recently I was called in as an expert witness for a case in which the cosmetic effects of a product was measured. Modest claims were made that were fully justified by the data. Yet, it was argued that the

study results were not valid as the test was not performed against a placebo but against untreated skin. Was this proper science or not? This is, however, an impossible question. It is the same as asking you how long a flight to New York is. For me, living in the Netherlands, it is about 7 hours, but for my Allured colleagues living near Chicago, it is only two hours or so, whereas for my Aussie friends... You get the point. It depends on your starting position. And the starting position for a clinical cosmetic efficacy trial is always the cosmetic claim that you (want to) make. If you claim that your product is better in providing X than the leading product in the market, then you need to test it against that product and measure the development of X in both cases. If you claim that your active ingredient is causing X (as is often done by suppliers), you should test it against the placebo, so that the only difference between the active formulation and the placebo formulation is indeed the active ingredient. But if you claim that your complete formulation is causing X, then X should be tested with and without the use of the product for which the claim is made. In other words, it should be tested against nothing or if you want to make things more difficult for yourself, against the current usual routine of the volunteers (without defining or describing it). And this is exactly what some people do not get. They claim that every product should be tested against a placebo, i.e., the same formulation without the active ingredient, irrespective of the circumstances (read the claim). Understandable but wrong.

So, such people keep on pressing that I should test against a placebo. But that raises another interesting issue. What do you do if there is no active ingredient in your formulation? Is everything active (because, after all, the formulation does have an effect)? Is isopropyl myristate or mineral oil an active if it helps to moisturize the skin but that activity is not claimed? What do we do if an active is incorporated in an emollient that helps to moisturize the skin and in doing so, increases the skin penetration of this active? Has the emollient now become an active? One thing is clear, such a base without actives is not without efficacy but what is the placebo? That base will definitely have a measureable placebo effect. But how you design your test depends on your claim and not the other way round.

The same happened to me when I submitted an article to an academic journal with a high impact factor. I compared two formulations with different compositions and showed that the penetration from one vehicle was significantly better than from another by changing the polarity of the oil phase in which the active was incorporated. In addition to my skin penetration results, I was able to show that you could get more clinical efficacy while using less active ingredient. In a clinical study! The claim that I made was that I could manipulate the clinical effect by changing the polarity of the emollients. And subsequently reduce the dose without losing the clinical efficacy. Naively I thought that that would make an impact in that high impact-factor journal. But it was rejected because—according to the reviewers—I should have tested it against placebo. No, highly-esteemed reviewers, this is wrong as I was not claiming that my active was causing the effect (I had already done that in previous clinical trials) but that the clinical efficacy of an active is determined by the remainder of the formulation. When I pointed out to the reviewer that (s)he had probably misunderstood the objective of my studies, the answer was authoritative: "In proper research, everything is tested against a placebo." I argued that I could not test it against a placebo because every formulation was— that was the whole purpose of my paper—different. Testing against a placebo is completely correct if you want to show that a drug or an active is responsible for the effect. But if you are testing whether or not a complete formulation that you are selling is effective (unless you are a supplier selling an active ingredient), you should be testing against untreated skin. Against nothing. *Rien*. *Niente*. *Niets*. *Nichts*. Diddly squat.

And as always my wife is absolutely right. I do get upset about nothing. Is the difference between dermatology and cosmetics that cosmetic testing is really much ado about nothing? Placebo means I'll please. But who are we pleasing? Regulatory bodies, lawyers, scientists or our customers? Indeed, too much ado about nothing!

Modified from a column "Neutraceuticals and nanoparticles" previously published in *Cosmetics & Toiletries* magazine's Newsletter February 16, 2009

Chapter 47

Organized Chaos...

Today's title could refer to almost everything. Our business and private lives are nothing else but organized chaos, our financial state is organized chaos, our offices are in a dynamic state of organized chaos and if not, you've probably got nothing else to worry about than to clear your desk! Chaos seems to be *the* natural state for our mind, our surroundings and our lives. As a counterargument to "green" seeming to be the only natural thing in cosmetics nowadays, I investigated whether "chaos" could be truly the one and only natural thing in cosmetics. Or was it just only me?

So I looked up what the meaning could be of chaos theory. "Could be" and not "is" as I looked it up in Wikipedia, a free encyclopedia on the Internet that is in a dynamic state of flux. What's true today in Wikipedia could be incorrect tomorrow. *Panta rhei*, everything is in a state of flux. According to the version of Wikipedia that I looked at, on April 11, 2009, it said, "In mathematics, chaos theory describes the behavior of certain dynamica systems–that is, systems whose states evolve with time–that may exhibit dynamics that are highly sensitive to initial conditions (popularly referred to as the butterfly effect). As a result of this sensitivity, which manifests itself as an exponential growth of

Mechanisms of action may be very complex and seem chaotic, but you can create your own order in this chaos and only then, this chaos comes to life.

perturbations in the initial conditions, the behavior of chaotic systems appears to be random. This happens even though these systems are deterministic, meaning that their future dynamics are fully defined by their initial conditions, with no random elements involved. This behavior is known as deterministic chaos, or simply *chaos*." I must admit that these sentences did not make me overflow with joy, especially as it then continued to speak about natural systems: "Chaotic behavior is also observed in natural systems, such as the weather. This may be explained by a chaos-theoretical analysis of a mathematical model of such a system, embodying the laws of physics that are relevant for the natural system."

By this time, I was starting to wonder whether there might be a differentiation between chaos theory in physics and biology. Strangely enough, I would describe the physical world as something strictly regulated with low margins of error, yet–according to today's version of Wikipedia–chaos theory rules by seemingly random processes that are dictated by the initial conditions. Biology on the other hand may seem very chaotic (e.g., survival of the fittest and that type of stuff) and is typically characterized by much higher margins of error that we conveniently call biological variability but is, in fact, strictly regulated. In case you're wondering where I am going in this rather chaotic column, let me tell you that it is about mechanisms, biological mechanisms. How, why and what for?

Very recently I finished writing a chapter for the book, *Aging Skin: Contemporary Knowledge and Future Directions* that will be published shortly (now I am finally finished) by Allured Business Media. The editor is my friend Dr. Linda D. Rhein, former president of the SCC. She asked me to write a chapter on the mechanisms of skin whiteners. As I could think of at least a few, I decided to accept the invitation and signed the necessary paper work in which you promise to submit your work on time (which I subsequently never do for the simple reason that my life is too chaotic, a euphemism for saying that I don't plan properly enough). But what I need when writing a chapter is some structure, my "coat-hanger," to be able to explain what I want to say. So, I looked at all the different mechanisms from various angles; from a physical side, from a chemical perspective,

from an enzymatic side, from a physiological angle, but never did I get a clear answer. From whatever viewpoint I looked at the mechanism of skin whiteners, a clear-cut subdivision was not possible. Let me show you.

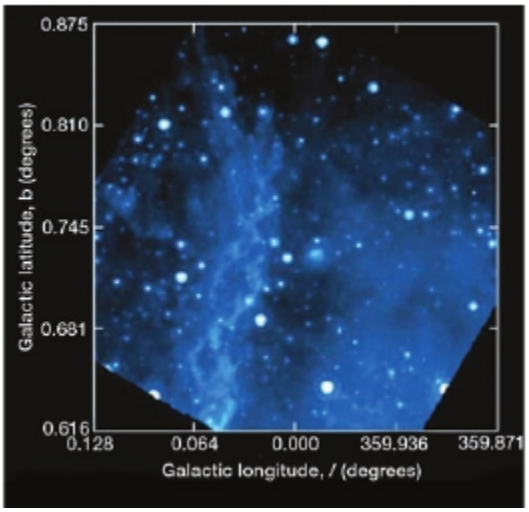
We all know only too well that tyrosinase inhibition is involved in skin whitening. Tyrosinase is the enzyme that catalyzes the rate-limiting first two steps of the skin melanogenesis process. Both eumelanin and pheomelanin production are reduced when blocking this enzyme. This is clearly an enzymatic mechanism and you don't have to look too long to find a few more, such as TRP 1 and 2, tyrosinase related protein 1 and 2. Another mechanism of action of skin whiteners is a hormonal one, involving different hormones of which melanocyte-stimulating hormone (α-MSH) is probably the most well-known representative. A third mechanism of skin whiteners is a strictly chemical one where cupper ions are extracted from the tyrosinase enzyme, rendering them inactive. A fourth mechanism of skin whiteners is a biochemical or molecular biological one, where a whole series of growth factors is involved in inducing changes in skin melanogenesis. But when we come to the fifth mechanism of skin whiteners, my beautiful ordering of the various mechanisms of skin whiteners is starting to fall apart. This is the physical mechanism of skin whiteners. A sun tan, for instance, is nothing more than an inflammatory reaction to sunlight. It comes from a physical effect (sunlight), resulting in a biochemical effect (the up-regulation of interleukin-1α (IL-1α)), which induces enzymes (tyrosinase) to work harder and steers a physiological effect (melanin being transported to the dendritic ends of the melanocyte and taken up by neighboring keratinocytes) to create a sun tan. Although this may all sound rather chaotic, these processes are all strictly regulated and definitely not random!

Melanin is not the only chaotic process that is highly regulated. As we look more and more at skin barrier formation, we also find that there is a lot of order in that chaos too. In June 2009, I will publish an article in *Cosmetics & Toiletries* magazine in which I describe a new mechanism of skin moisturization: the stabilization of the orthorhombic skin lipid phase. But again, this biophysical mechanism

is only one aspect of skin moisturization. You can also improve skin barrier function and therefore skin moisturization via enzymes, chemistry, biochemistry and molecular biology.

By this time, I am starting to ask myself whether chaos is the right word. The borderline between chaos and order is very slim. Many of you would call my office extremely chaotic but for others (mainly with a similar office) this is normal. Mechanisms of action of active ingredients may be very complex and therefore seem chaotic, but once you get to know them, you can create your own order in this chaos and only then, this chaos comes to life. And isn't that what we all would like to have? A dynamic vibrant life? A chaotic life where we are in full control? There's definitely more order in this chaos of ours than we think.

My friend Dr. Gavin Greenoak from the University of Sydney and the next president of the IFSCC sent me the following picture of a nebula in the middle of the Milky Way Galaxy. If you look carefully, you can see an 80 light-years-long double helix structure. Just like DNA! And if you come to think of is, does a cell not look like a solar system? Are we nothing more than a cell within another mechanism? That is–in turn–part of a much bigger structure? Or that our cells contain complete galaxies? Simply too many chaotic questions without any ordered answers.



Enough of this, I need to clear out my room and create some order in my office, my mind, my conscience to be creative again next week!

Modified from a column "The organized chaos of biological mechanisms" previously published in *Cosmetics & Toiletries* magazine's Newsletter, April 11, 2009

Chapter 48

In the Land of the Blind, the One-eyed Man is King

Sometimes you have to go to the other side of the world to find something local. I had this with the expression above, for instance. I needed to know whether the expression "In the land of the blind, the one-eyed man is king" that I know from the Dutch language also exists in English. When I asked this question to my colleague Angela Kozlowski of Allured Business Media, I was told that it was an expression recorded by a Dutch humanist author who collected more than 3,000 proverbs mainly from the classic literature, including this one, in a book called *Adagia*. The Dutch humanist was Desiderius Erasmus. At this time, I started to feel a little bit embarrassed as Erasmus was probably the greatest philosopher we ever had in the Netherlands (others are Spinoza and Hugo de Groot, although I am only saying that to correct the image that I know absolutely nothing of my own history). Having gone to the United States to check the expression out, it was now getting terribly close to home as Erasmus was the unlawful son of a priest that lived in Gouda (the place where I live). He was figuratively speaking conceived in my very own backyard, and subsequently born close to what is now called the Erasmus Bridge in Rotterdam. Clearly, in the land of the

Regulatory bodies claim that everything should be tested against a placebo, but they should also learn to see that there is a difference between fundamental science and applied science.

blind, the one-eyed man is king! I was completely blind and Angela Kozlowski was the one-eyed queen!

What has this got to do with cosmetic science? Nothing of course, although... . Following the positive feedback I received on the previous column on the placebo effect, I want to talk once again about clinical study design in relation to cosmetic claim substantiation. This time, I would like to discuss when to perform double-blind studies and when single-blind studies. Double-blind studies are studies in which both the subject participating in the trial and the investigator judging the outcome don't know whether or not the subject received an active formulation or a placebo. So both the subject and the investigator don't know whether the treatment should have any effect, taking away any form of bias. When one is trying to obtain an objective result on the effectiveness of an active in a formulation, this is the preferred study design in clinical trials.

The essential words in the sentence above are "the effectiveness of an active in a formulation." This means that most clinical studies performed by suppliers of active ingredients will be performed double-blind as they often want to show the effectiveness of an active in a formulation. Assuming the active is active, the supplier will supply the active to a manufacturer of cosmetic products. Now the situation changes. The end manufacturer is not interested in showing the effectiveness of the *active* in its formulation, but will, on average, be interested in the effectiveness of the formulation! What is the difference, you may ask? The supplier tries to get an answer on the question whether an active is active; the end manufacturer tries to get an answer on the question whether its formulation is active. And that changes the clinical trial design fundamentally. Now a single-blind study is required. A single-blind study is a study in which either the investigator or the subject knows which treatment was received or judged. In most cases, it is the investigator who knows and then it is called a subject-blinded trial; in the opposite case, it is the subject that knows and it is called an investigator-blinded trial. Here, some degree of bias would be possible but often only in theory as we will see later.

The necessity for a single-blinded trial is the fact that your placebo is different. I already discussed this last time. If you want to know

that your active is active, you must compare the active in a formulation to the same formulation without the active. This is called the placebo. Logically, if you want to know that your formulation is active you must compare the formulation to the same formulation without the formulation. But what is that, a formulation without a formulation? That is nothing. As I said last time, zero, *riente*, *niets*, *nichts*, diddly-squat! You test against untreated skin.

Regulatory bodies claim that everything should be tested against a placebo ("in proper science, you always test against a placebo"), but they should also learn to see that there is a difference between fundamental science and applied science. In fundamental science, you would like to know whether your active is active (and how it works). In applied science, you would like to know whether your formulation works. Finding out how much of the effect is caused by the active and how much by the formulation itself is again fundamental science. How can you easily differentiate between fundamental science and applied science? By answering the question: "As a consumer, do I care?" A scientist would like to know what the effect is and why and how it comes about. A consumer wants a product to do what it is supposed to do. He wants a car to drive, a CD to function in his computer or her stereo and a moisturizing cream to moisturize. Leaving personal interests of the individual consumer aside, he doesn't care about the details of fuel combustion, the width of a laser beam or the stabilization of the orthorhombic phase of skin lipids. In such cases, a single-blind trial should be used because the subject in such a trial will always know whether he applied a product or not, or in case the subject serves as his own control on which side of his body a product was applied.

Wrong, according to the regulatory bodies. Everything needs to be tested in a double-blind trial. Because otherwise, we will have the so-called Clever Hans effect. Who is Clever Hans, you may ask? Clever Hans was a horse that was claimed to have been able to perform arithmetic and other intellectual tasks. After formal investigation in 1907, psychologist Oskar Pfungst demonstrated that the horse was not actually performing these mental tasks, but was watching the reaction of his human observers. Pfungst discovered this artifact in

the research methodology, wherein the horse was responding directly to involuntary cues in the body language of his human trainer, who had the ability to solve each problem. The trainer was entirely unaware that he was providing such cues. In honor of Pfungst's study, the anomalous artifact has since been referred to as the Clever Hans effect and has continued to be important knowledge in the observer-expectancy effect and later studies in animal cognition.

Can this happen in a single-blind clinical study? Of course, it can but with the horse Hans it took years of practice. Years of social interaction to learn to read the signals from the trainer. And that was a *clever* Hans. It took humans centuries to discover the effect, admittedly because it is subtle. But to address the question whether the Clever Hans effect happens in a single-blind clinical study, we have to realize that the reality of a clinical study is different. I've monitored many of these trials. For the investigator who does not even know the subject, that volunteer is nothing more than another test tube, something to measure a reaction on. There is no social interaction between the subject and the investigator. The professional evaluator is behaving as a professional and does not speak to the subject, hardly acknowledges his or her presence. Social interaction is necessary for the Clever Hans effect to occur and that is lacking in clinical trials. And if it would happen once in a whole trial, that would be a lot. It simply cannot happen in every volunteer and in that way explain the complete results. Volunteers are not trained horses. They are not trained. They are not horses. They are not clever and they are not called Hans. OK, I admit that the latter may not be true.

Single-blind trails are very well possible and scientifically justified under specific conditions that frequently apply for the manufacturing cosmetic industry. Some regulatory bodies understand that perfectly whereas others want a uniform response to whatever claim you are trying to substantiate. Maybe *they* are double-blind. To those regulatory bodies judging cosmetic claim substantiation I would like to say: Wake up and stop closing your eyes for the reality of what the cosmetic industry is testing. Get off your Clever Hans horse and stop applying fundamental research principles to applied research. Open your eyes to the differences. Imagine how clever you would be if you

would have an open mind towards different claims needing different study designs. You can be a single-eyed king called Hans or a double-blind Clever Hans stumbling in the dark. The choice is yours. As a cosmetic scientist with a visual impairment, I know which one I would prefer to be.

Modified from a column "In the land of the blind: Applying single-blind study to finished products?" previously published in *Cosmetics & Toiletries* magazine's Newsletter, October 13, 2009

Chapter 49

Nessie and The Precautionary Principle

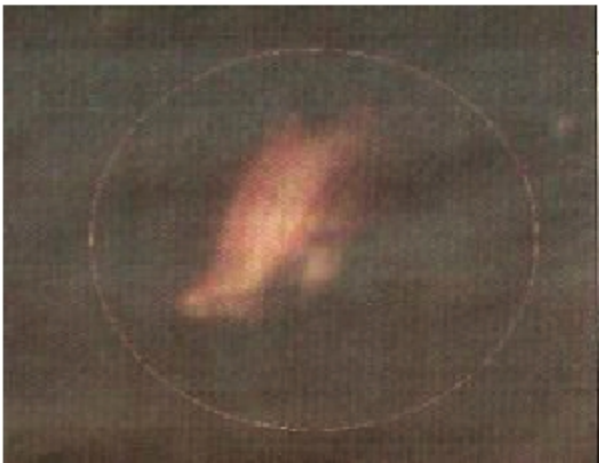
Democracy is a good thing. Absolutely. No doubt about that in my mind, but you can take things too far. The word democracy comes from the Greek, *demos* meaning "people," and *krátos* meaning "rule or strength." The Ancient Greek city-states experimented with this system where all the people had the same access to power and all members enjoyed universally recognized freedoms and liberties. So, what can you take too far in this democratic context then?

No, I am not talking about an initiative of one of the Dutch political parties that wants absolute freedom of speech, including the right to state that the Holocaust never happened. Not that they even want to suggest for a second that it did not happen, but, in their mind, weird ideas can only be changed if they can be discussed, hence there needs to be an absolute freedom of speech. The limit is reached when your words instigate hatred and violence. But if *you* would have absolute freedom of speech right now, you would probably ask me whether this is a political column or one about cosmetic science. The latter, of course, but I need to warm you up as there is so much politics involved in this cosmetic subject.

Agreement exists that the valid legal regulations are suitable and adequate to market safe products in accordance with the current knowledge levels.

A little while back, I published a story on the use of nanotechnology

in cosmetics in *Cosmetics & Toiletries* magazine. In short, I argued that the majority of purpose-made, i.e., engineered nanoparticles is used for the production of sunscreen actives that are incorporated in sun care formulations. They have to be nano-sized because our customers want to apply a transparent film on their skin. We're talking here about micronized zinc oxide and titanium dioxide. Concerns have been raised that these particles might penetrate the skin and a plethora of studies (about 70) have been executed that failed to show that these particles penetrate beyond the stratum corneum into the living layers of our skin. A few studies did show somewhat deeper penetration but in these cases, this could be attributed to the methodology used. So, in approximately seventy studies there was no experimental evidence for the skin penetration of nanoparticles. I even applied all the theoretical knowledge of skin penetration onto these particles (guided by the deductions made by Prof. Dr. Michael Roberts of the University of Queensland, Australia) from which it could be concluded that it is physically simply impossible for these particles to penetrate normal healthy human skin. Yet, the concerns remained because the safety of these particles could not be irrefutably shown. Safety never can. Why? Because you cannot demonstrate the presence of an absence. You can show that something is there, but not that something is not there. It is like proving that Nessie, the official monster of Loch Ness, does not exist, despite the existence of clear photographic evidence (see picture).



Nessie, the famous monster of Loch Ness was photographed by Ian and Tracey (see: *http://www.nessie.co.uk/htm/searching_for_nessie/search7.html*)

And with that, we have reached an impossible situation. Our academic friends keep on doing experiments in which they demonstrate that nanoparticles do not penetrate into the deeper layers of the skin. But nano-skeptics such as the Friends of the Earth do not accept this evidence. They stress the impossibility of stating that something is completely safe. In that statement, they are absolutely right. Water may be the safest place for Nessie to hide herself in, but we can drown in it. In fact, it is terribly dangerous. Not convinced? See *www.dhmo.org* for incriminating evidence! And we, cosmetic scientists, therefore need to continue experimenting until we find skin penetration, in the same way as we, the general public, need to continue looking for Nessie to find her. The nano-skeptics at the same time keep informing the public about the grave dangers the industry is exposing us to. Whereas it is true that there are safety issues associated with the inhalation of nanoparticles from the air (and please keep in mind that I am not referring to that route of entry into the body, we don't inhale our sunscreens!), skin penetration of topically applied particles is theoretically and experimentally shown to be impossible. So, we have two camps with opposing opinions that are both right. The scientists cannot unambiguously state that something that *is* not there *could* not be there. The nano-skeptics argue that if we don't know these facts, we should not use the technology. But with that mentality, we would still be living in caves. A true Catch-22 situation! The generally accepted answer out of such situations (that you see quoted at the end of almost every scientific paper) is that further research is necessary to resolve the remaining uncertainties.

Instead of doing nothing, the real world behaves differently. Faced with a situation where the absolute safety of irrespective what cannot be guaranteed, toxicologists make an estimation of the risk, build in a safety margin and from that reach a conclusion that something can or cannot be used in the market place. This is also what happened for micronized Zinc Oxide and Titanium Dioxide. The general public

has been using these nano-sized products for years already without health risks that I have heard of.

We need to do further research to identify whether skin penetration of nanoparticles happens or not. But by the laws of science, we can never demonstrate that it did not happen. Hence, the uncertainty will always remain and the general public is continuously informed about this lack of information and therefore the feeling that there is something wrong with nanotechnology remains or even grows. Worse, a recent television program in the Netherlands discussing nanotechnology even left the impression that we, the industry, hardly know anything about the safety issues associated with nanotechnology. How safe is my tennis racket with nanoparticles, my self-cleaning window, my sunscreen product? In these programs, we publicly promise to do more research in such fields, knowing that it will be insufficient as the conclusive answer cannot be given. Again a Catch-22 situation but this time, more research is not going to help.

So far the science, now the politics. If science cannot solve the problem, give it to the politicians. And they did solve it, but how? In a presentation at the Cosmetic Science Conference held during the In-Cosmetics show in Munich last month, Dr. Andreas Reinhart, a lawyer, told the audience that soon (January 2013) the presence of nanoparticles in cosmetic products will need to be declared. When asked for the reasons for this, he commented that "there continues to be no certainty concerning health risks. There is, therefore, the uniform view that further research should be undertaken. Agreement exists also to the extent that the valid legal regulations are suitable and adequate to market safe products in accordance with the current knowledge levels. That in the new EC Cosmetics Regulation there will be nano-specific legal provisions is therefore at first glance somewhat surprising. Wide-ranging significance is attached to the wish for comprehensive consumer protection, which is why the precautionary principle is increasingly being applied also in the field of cosmetics. The EC Commission (Regulatory Aspects of Nanomaterials, 17.06.2008) correspondingly declared that the measures must be founded on the precautionary principle, 'where the full extent of a risk is unknown,

but concerns are so high that risk management measures are considered necessary, as is currently the case for nanomaterials.'"

What he is saying is that because science cannot give the absolute answer but only show a lack of incriminating evidence, the public remains concerned. We will therefore put a label on the nanoparticle-containing product stating "contains purpose-made nanoparticles," and the general consumer can make up his or her own mind. This is democracy gone too far. If the scientist can state that no skin penetration of nanoparticles can be sufficiently shown but not conclusively demonstrated (simply because you cannot demonstrate the presence of an absence), why should we ask the general public to make up his or her own mind? What would they know? As safety can *never* be shown in absolute terms, are we going to apply this to every product entering the consumer market? Lawyers call this the precautionary principle but what it really means is that your democratically chosen representatives cannot make a decision for you and ask you to make your own decision. Is this normal? If you would hire someone to do a job for you and (s)he tells you that (s)he cannot do it, you fire that person and hire a new one. The Europeans have that choice on June 4th to vote for the new Members of the European Parliament but nowhere can you read the various parties' vision on nanotechnology. It is about time we elected some (cosmetic) scientists into the European Parliament, rather than hundreds of Nessie-searching individuals that want to stay friends with everybody, take no risk and therefore ask us to do their job.

To my European friends, don't forget your democratic right to vote on June 4th. I need to go now, Nessie's calling. I hope I can find her, she's penetrated again into the dark waters of Loch Ness and is probably only as big as a nanoparticle. I could be gone for quite a while. But I am only saying that just in case, out of precautionary principle ... .

Modified from a column "'Nessie' and the precautionary principle" previously published in *Cosmetics & Toiletries* magazine's Newsletter, June 1 2009

Chapter 50

Too Often, Too Hot and Too Long...

Now, that title did get you wondering what I am up to today, am I right? No, I am not talking about your Thanksgivings' turkey. That turkey was courteously released by President Obama and it is not Thanksgivings too often, the turkey is never too hot and the day definitely does not last too long. No, I am talking about something that everybody with adult kids will certainly recognize. And that is the fact that while you cannot get pre-teenagers to go into the shower, you can't get teenagers out of the shower. For quite a while, we had three teenagers in the Wiechers' household and with only one shower in the house (come on folks, it is a European house!), I woke up every morning because one of my children was thinking (s)he was the Netherlands's next *Idol*. Needless to say, that single shower is next to our bedroom. After having been cruelly awoken with the firm realization that they are not even a mere 5% of Susan Boyle, I grudgingly come out of bed to tell them that it is too often, too hot and too long. That's it, I am talking about showering. Not the quick, 3 minutes and 19 seconds shower that you and I do every day, but the "I don't care if my brother or sister is waiting for me" shower. And if this would happen only once a week, but no, around 11 am when working in my office (on the other side of the

If you extract too much NMF, you damage your barrier function and when that happens, skin penetration of whatever is applied onto the skin increases.

bathroom), I can again hear the shower. It is one of my sons stating that he is already back from school and so dirty that he urgently requires a second shower. While I am glad to find out that they make him sweat in school, I am not sure whether a second shower is really necessary. This is the same son that takes his third shower after he comes back from his soccer practice where he certainly sweats a lot. Just looking at him doing his exercises opens my floods of transpiration! No complaints there. But in the evening I hear the shower again, this time because of the relaxing and stress-releasing properties of dihydrogenmonoxide at elevated temperatures. Because those elevated temperatures are my last complaint; we have such a shower system where the water can only be above your body temperature if you push a certain lever to allow the temperature to be raised to dangerously hot levels. Every time I am in the shower, I find that the previous user has been steam-stripping his or her skin. Not only his or her skin, I almost need to replace the tiles in our bathroom because even the mortar is steamed off. Just in the same way—and in this context maybe more important than my house refurbishment necessities—as they strip their natural moisturizing factor (NMF) away from their skins.

Since the advent of confocal Raman microspectroscopy, we know for certain what we had always expected. Our levels of NMF, our natural moisturizing factor, diminish towards the skin surface. NMF is a complex mixture of many amino acids, lactate and ions that are all water-soluble, so they should be easy to extract from the skin by water. And when are we surrounded by water? When we swim and when we take a bath or a shower.

Somewhere I read that the skin of long-distance swimmers was not badly affected by their sportive behavior but I did not manage to find it. I remembered it to be at the ISBS Conference held on October 28-30, 2004 in Orlando, Florida, immediately after the IFSCC Congress, so looked up the abstracts but all I could find it an abstract stating the opposite: “The results suggest that recreational swimming can induce significant modifications in some skin biophysical properties related to skin hydration.” This abstract was published this month as a full paper in *Skin Research and Technology* (Vol 15, 2009, 427-432) under

the intriguing title, “Variations of skin biophysical properties after recreational swimming”. In this article, Sophie Gardinier et al., describe a study in which they measure skin hydration, skin pH, transepidermal water loss (TEWL), skin temperature and sebum casual levels at different time points after the start of the study (0, 4, 24, 48 and 72 hours). The study was repeated a second time, but now the subjects were swimming for 1 hours between the first and second measuring point. During the control period, none of the skin parameters showed any significant variation over time on all body sites that were measured. In contrast, during the swimming period, significant changes were found 1.5 hours after swimming for skin pH (increased), sebum casual levels (reduced on upper chest but not on the forehead), while TEWL and skin temperature remained unaffected. From the next measuring point (t= 24 hours) onwards, all changes had disappeared.

Where does this scientific backing of my arguments leave me in my “battle” with my children? First of all, they argue that their shower water is not chlorinated (true), to which I argue that the water in our city is hard which increases the irritancy effects of water. My daughter is doing competitive synchronized swimming (currently her team is in third place in all of the Netherlands) and swims between 7 and 14 hours a week. Each time is followed by extensive showering. And indeed her whole team is suffering from dry skin.

The point that I would like to raise to your attention is not my family life but the consequences of excessive showering. If you extract too much NMF, you damage your barrier function and when that happens, skin penetration of whatever is applied onto the skin increases. This is not only your washing up liquid but also your ever-so-mildly formulated cosmetic products. But who is subsequently blaming our industry for producing cosmetic products that cause irritancy reactions? Our customers. The same customers that would have nothing to complain about if they did not shower too often, too hot and too long. So for some of the problems of which the cosmetic industry is accused, the consumers only have themselves to blame. But how we do explain to our customers that contradiction that water

dries them out, whereas we cannot even convince our own children to be more careful with their showers that actually damage their skin?

If anyone knows the answer to do this question, please let me know. It will save me (shower) money, it will save my children's NMF, it will reduce the skin irritancy of customers and reduce product complaints for our industry. Definitely a hot issue that we may have left too often for too long.

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